BOOK OF ABSTRACTS

ID	Título Trabalho	NOME
5	Convergent Synthesis of Proline-Functionalized Pyrazolopyrimidines as Anti-T. cruzi Bioactive Compounds	JOÃO PEDRO NOGUEIRA BONESCONTO
6	Synthesis and antimicrobial activity evaluation of coumarin-3-carboxylic acids obtained via Knoevenagel Condensation using chitosan as catalyst	PALOMA GOMES DE ABRANTES
7	Synthesis of 2-amino-4H-chromenes catalyst-free and evaluation of biological activity in tumor cells	POLIANA GOMES DE ABRANTES
8	Synthesis and anti-leishmanial activity evaluation of isatin adducts obtained via Knoevenagel Condensation using chitosan-EDTA as a catalyst	JULIANA ALVES VALE
10	Strain-Release Pentafluorosulfanylation	CODY ROSS PITTS
11	Lipase from Burkholderia cepacia (BCL) immobilized in Chitosan/EDTA applied to the resolution of rac-1-phenylethanol	RENATA RODRIGUES MAGALHÃES
12	Harnessing Glyco-Compounds: Effective Anti-Fungal Biofilm Agents Against Candida sp.	LUCAS LOPARDI FRANCO
13	Silver Sacrificial Electrodes in Electrosynthesis: Enabling Regioselective Cyclization for Isochromenes and Dihydroisobenzofurans	PEDRO PÔSSA DE CASTRO
14	Autobench-RX: A software for automatic reaction barrier calculations	RODRIGO CORMANICH
15	One-Pot Diastereoselective Synthesis of Highly Functionalized γ-Lactams via Sequential Ugi-4CR and Intramolecular Michael Addition	ARLENE GONÇALVES CORRÊA
16	Synthesis of substituted coumarins from 2-hydroxyaldehydes, maleimides and tributylphosphine via microwave and continuous flow	FERNANDO ALVES BARRETTO
17	1,3-Diazepane-2,4-diones: bench-stable, bifunctional and customisable isocyanate precursors	JAKE PAINTER
18	Photocatalytic synthesis of 1-pyrrolines under continuous flow conditions	LUCAS GIANI FURNIEL
19	Synthesis and evaluation of quinazolinone-eugenol hybrids as new compounds with trypanocide and leishmanicide potential	DIOGO TEIXEIRA CARVALHO
20	Building a Microscale Parallel Synthesis (MPS) platform linked to phenotypic assays against a parasitic panel	DANIEL GEDDER SILVA
21	Enantioselective Synthesis of Dihydrobenzofurans derivatives by Merging Intramolecular Heck-Matsuda Reactions from Anilines with Redox-Relay Process	EDSON LEONARDO SCARPA DE SOUZA
22	Highly Enantioselective Lewis Acid Catalyzed Conjugate Addition of Imidazo[1,2-a]pyridines to α,β-Unsaturated 2-Acylimidazoles under Mild Conditions	MARIA EDUARDA CANDIDO THEDY
23	Selenium dioxide in the synthesis of oxazole-5-carbaldehydes	GABRIELA TRISCH DE QUADROS
24	Multisite-Sequential Cyclization to Construct 1,2,3-Triazole-Based Se,N-Fused Heterocyclics	RICARDO SAMUEL SCHWAB
25	Functionalization of Sulfoxonium Ylides with molecular iodine: Synthesis of α-(Xanthates, Dithiocarbamates, Thiocyanato)-α-Carbonyl Sulfoxonium Ylide	KAUÊ CAIRES CAPELLARO
26	Employing substituted pyrazoles as stoppers in rotaxanes	FELLIPE FREIRE SANTOS DE FARIAS
27	Selenation of 2-arylimidazo[1,2-a]pyridines promoted by visible light using arylseleninic acids	CAROLINE SIGNORINI GOMES
28	New Chitosan Beads as Efficient Organocatalysts for Accessing 1,2,3-Triazoles	INGRID CARDOSO OLIVEIRA
29	Copper-Catalyzed β-Hydroxylation of Abietanes: Synthesis of a C5 Bridgehead Alcohol	LARISSA JAROCZINSKI
30	Late-stage, C—H oxidation/decarboxylation via non-heme iron catalysis diversion	MILENA CRISTINA VIEIRA FERNANDES
31	Copper-Mediated C—H Bond Oxidation in Synthetic Studies of Complex Diterpenes	LUCAS DIAS PIRES GONÇALVES
32	Revisiting the Reactions of Sulfur Ylides with Acetylenic Esters: Facile and Stereoselective Synthesis of Electron-Deficient Trisubstituted 1,3-Dienes, α-Carbonyl Vinyl Sulfoxides and α-Carbonyl Vinyl Sulfoxonium Ylides	MATHEUS PEREIRA DE JESUS
33	Rhodium Catalysed Deconstruction of Epoxy Resin in Water	EMIL VINCENT SCHWIBINGER
34	Synthesis of chalcones and in vitro and in silico evaluation for Helicobacter pylori and gastric adenocarcinoma cells	RODRIGO REZENDE KITAGAWA
35	Asymmetric Dihalogenation from Sulfoxonium Ylides	MARCIO HAYASHI
36	Ruthenium(II)-Catalyzed C–H Alkenylation of SuFEx-Functionalized Quinones: A Mechanistic Approach	ESTHER REGINA SILVA PAZ

37	$Ce(SO4)_2.4H_2O$ promotes the synthesis of carbazole derivatives through Michael addition and Diels-Alder reactions	OCTAVIO LISBOA GUTERRES FERNANDES
38	Experimental studies and in silico approaches in evaluating the effect of solvent on the Se-77 NMR chemical shift profile of diphenyl diselenides	LUCAS EMANUEL BELUZZO IAROCZ
39	Benzylation of Phenol Catalyzed by Diphenyl Ditelluride	PHILIPE RAPHAEL OLIVEIRA CAMPOS
40	Alternative synthesis of intubation drugs propofol and etomidate	ALVARO TAKEO OMORI
41	From biomass to natural flavonoids: Studies for total synthesis of Podocarflavone A	GABRIEL DOS SANTOS RAMOS
42	Synthesis of new triazolic thionaphthoquinones with trypanocidal potential	LEONARDO GOMES CAVALIERI DE MORAES
43	Organocatalyzed synthesis of 1,5-diaryl-1H-1,2,3-triazolyl pyridines from α-2-pyridinyl-acetophenones and aryl azides	LÍVIA DRAWANZ JESKE
44	Synthesis of selenylated derivatives of acetanilide	ARIANA SILVEIRA LIMA
45	A Multi-Step Synthesis Approach to a Functional [2]Rotaxane	GUSTAVO HENRIQUE WEIMER
46	Integrating Hydroformylations into a Methanol Economy	ANDREAS BONDE JENSEN
47	Ru-catalyzed Disconnection of C–O Bonds in Epoxy Resins	GABRIEL MARTINS FERREIRA BATISTA
48	Synthesis of new aminocoumarin derivatives and investigation of antioxidant activity.	JOÃO FELIPE SILVA OLIVEIRA
49	Efficient Synthesis of Mono- and Diselenylated Fluorescein Derivatives: Arylseleninic Acids as Selenylating Agents to Prepare Fluoroprobes	KETHELYN MACHADO DA ROSA
50	A one-pot C-H functionalization protocol for the synthesis of (hetero)chalcones	FRANCO JAZON CAIRES
52	The use of type-MCM-48/TiO2 mesoporous materials in the Betti Reaction to synthesize hybrids 1,3-oxazines-4-methyl coumarins, potential anticancer hit	VERA LUCIA EIFLER LIMA
53	Synthesis of polyfunctionalized molecular hybrids of isatin	LEONARDO ANTONELLI NASCIMENTO DE JESUS
54	Functionalization of eugenol as strategy to amplify the chemical space: sustainable synthesis of new thioureas and 2-aminobenzoxazoles	JAQUELINE ROSA CARDOSO BARBOSA
55	Auronas based on dihydroeugenol: attempts to synthesize new potentially antifungal compounds	LEONARDO SCALIONE TEMPESTA
56	Synthesis of O-sulfonylated derivates of phenylpropanoid Mannich bases as potential antifungal agents	JORYS CESAR HEGEDUS FILHO
58	Photoactive formyl benzimidazoles: New molecular scaffolds for optical sensing	LILIAN CAMARGO DA LUZ
59	Synthesis of Adenine and 1,3-Diphenylurea Hybrids as Potential Kinase Inhibitors for Cancer Treatment	FRANCISCO PAULO BUCHAILLOT
60	Squaramide-Dihydropyrimidinone as a New Class of Hybrid Compounds	SAMUEL JOSÉ SANTOS
61	Modeling and synthesis of 6-imidazolylquinazoline-2,4-diones as potential SARS-CoV-2 Mpro inhibitors	JOÃO CÂNDIDO PILAR MAYER
62	Photoredox-catalysed nucleophilic a-functionalization of carbonyl compounds via destabilised carbocations	ARUNPRASATH DHANARAJAN
63	4-amino-1,2-Naphthoquinone triazoles as potential anti-SARS-CoV-2	EDSON DE OLIVEIRA LIMA FILHO
64	Sustainable Synthesis of Zwitterionic Bases for CO_2 Capture	RAFAEL DALAROSA ZINK
65	Heterogenized palladium pincer complexes for the cross-coupling reaction of styrenes and iodonium salts	DAVI DOS SANTOS LEITE
66	Reaction of 1,3-diynes with Pentaphenylborole: A straightforward route towards phenyl-substituted Borirenes	PEDRO HENRIQUE RAMOS DE OLIVEIRA
67	Enantioselective palladium-catalyzed Heck-Matsuda reaction for desymmetrization of N-protected 2,5-dihydro-1-H-pyrroles with aryldiazonium salts	SERGEI GORBATOV
68	Photoprecursors of arynes in visible-light promoted cycloaddition and nucleophilic coupling reactions	VINÍCIUS VIEIRA DE SOUZA
69	Stereoselective Synthesis of N-Containing Heterocycles via Ir-Catalyzed Intramolecular α-Alkylation of Carbonyl Compounds	ROMI AGGARWAL
70	The preferential crystallization of chiral isoxazoline cycloadducts from the (3+2) cycloaddition reaction of arylnitrile oxides and chiral monoterpe	BRUNA THATISE BATISTEL
71	Trans-Anethole isolated from Star Anise for (3+2) Cycloaddition Reaction Applications	HÉRICA DA SILVA SILVEIRA
73	TBA($FeCl_3Br$) complex as photocatalyst in the Csp^3- bond activation in alcohols for the synthesis of N-based heterocycles	LUIZ HENRIQUE DAPPER

74	Visible Light Photoalkylation of 2-Arylimidazo[1,2-a]pyridines on C3 Position via EDA Complex Formation with Katritzky Salts	LUIZ PAULO DE AZEVEDO BELLI
75	Redox-Neutral Stereospecific Deoxyalkylation of Alcohols Enabled by an Interrupted Appel Reaction	ISABEL WOOD
76	Antiproliferative activity of novel triazole scaffold	MARIA CAROLINA THEISEN
77	Efficient N-arylation and N-alkylation of quinazolines using PEG-400 as green solvent	GABRIEL DE PAULA BUENO
78	New series of Schiff bases for lanthanide luminescent sensitization	LUCÍA GALEAZZI
79	Efficient synthesis of pharmaceutical relevant N-nitrosamines under flow reaction conditions	FABRÍCIA NUNES DA SILVA
80	Synthesis of new marinoquinoline derivatives with potential antimalarial activity	WELLINGTON DA SILVA
81	Use of the Suzuki-Miyaura coupling reaction in the synthesis of chrysin biarylic derivatives for the investigation of their neuroprotective activities	RAVIR RODRIGUES FARIAS
82	Synthesis and antibiofilm and antibacterial activity evaluation of Tetrahydroindolone-Dihydropyrimidinone hybrids	VINICIUS VENDRUSCULO
84	Photoinduced Thiol-Ene “Click” Reaction	SERGIO HERNAN SZAJNMAN
85	Transition Metal-Free Hydroformylation Through A Combined Radical-Ionic Process	LAURA BLAIR
86	Towards the synthetic optimization of (3aR,6aR)-6-((benzyloxy)methyl)-2,2-dimethyl-3a,6a-dihydro-4H-cyclopenta[d][1,3]dioxol-4-one	SHEILA IRINA DE DIEGO SAADIA
87	Nb_2O_5/H_2O_2 as an efficient catalyst for primary alcohols oxidation under visible-light conditions	JOY NWACHUKWU EGBUCHA
88	Towards the Total Synthesis of Psilocybin/Psilocin: A Known Natural Psychoactive Compound with Prominent Therapeutic Properties	RENATO LÚCIO DE CARVALHO
89	Selectivity in the Photo-Fries rearrangement reaction of Aryl Esters carried out in micro heterogeneous media	VALENTIN LUCENA
90	Aromatization of betanin promoted by trimethylsilyldiazomethane	ALEXANDRE BARROS BARBOSA
91	Synthesis of Selenium and Tellurium-Containing Sulfonamides Derived from Lupeol	LEILA RENAN OLIVEIRA
92	Selenium-Functionalized Ionic Liquids: Synthesis and Biological Activity	MARIANA FERREIRA SOARES
93	Development of 3,5-O-di-tert-butylsilylene-D-galactofuranoside analogues for the synthesis of arabinogalactans from M. tuberculosis	TAMILA PAVLIVNA GALAKA
95	Attempts to synthesize a benzofuran-3(2H)-one from eugenol, a key intermediate to potentially antimicrobial aurones	MICAELA MARINA BARBOSA NOGUEIRA
96	Telescopic one-pot synthesis of pyrido[2,3-a]phenazin-5-amines	IGOR SANDE DE SANTANA
97	Silver(I)-catalyzed b-hydride migration from a-diazo esters: mild and stereoselective synthesis of (1E,3E)-dienes and mechanistic insights	PEDRO AUGUSTO MAROCCO MORO
98	Synthesis of enantioenriched helical complexes	LUCAS DOS SANTOS CUNHA
99	Methodological Study for the Synthesis of Symmetric and Unsymmetrical Sulfides from Bunte Salts	ROGÉRIO APARECIDO GARIANI
100	Telescoped CO_2-Mediated Amide Synthesis from Nitroarenes in a Continuous Flow Regime	BRUNO GONZÁLEZ IAÑES GERALDO
101	Enantioselective Heck-Matsuda Reaction Coupled to Organotin Transmetalations	LUIZ PAULO MELCHIOR DE OLIVEIRA LEÃO
102	Synthesis of a new series of 1,2,3-triazole-4-yl-phosphonates	GABRIEL TAVARES DE ALMEIDA PINTO
103	Synthesis of new polyurethanes from biomass-derived diols	JORGE ANDRÉS MORA VARGAS
104	TiO2-catalyzed direct diazenylation of active methylene compounds with diazonium salts	YURI PEREIRA VIDAL DE CARVALHO
105	Organocatalytic Mannich reaction as key step for the synthesis of a series of L-pentofuranose-mimetic iminosugars with potential anti-trypanosomal act	DANIELA GAMENARA
106	New Insights on the Reactivity and Selectivity of Nucleophilic Fluorination Mediated by Hydrogen Bonding Solvation	ELOAH PEREIRA ÁVILA
108	New Aromatics from a Chitin-based Nitrogenated Furanic Platform	BRUNA BUTKE DE SOUZA
109	STD-NMR Applied to Study Intermolecular Organization of PolymersIonic Liquids Hydrogels	CAROLINE RAQUEL BENDER
111	Synthesis of 1-D-Glucal Amides Derived from 1-Iodo-D-Glucal Through Carbonylative Cross-Coupling Reaction	PAMELA MONIZ SILVA
112	Synthesis of a series of Quinone-Fused Pyrrole Derivatives	ANA BEATRIZ MESTRE BOTELHO

113	Synthesis, optical emission, redox and thermal properties of 2,8-diaryl-imidazo[1,2-a][1,8]naphthyridines	HELIO GAUZE BONACORSO
114	Synthesis and anti-tumoral activity of N,N-dipropargylaminopyrimidines and bistriazole derivatives against C6 glioma cell line	FABIANE GRITZENCO
115	Telescopic one-pot synthesis of chromene derivatives from lawsone, aldehydes and Meldrum's acid in water.	GEIZIANE ALVES SANTOS
116	Palladium(II)-Catalyzed C–H Arylation of 1,4-Naphthoquinones, α-Tetralones and Benzophenones Derivatives	JOSÉ MANUEL DA CRUZ TAVARES JUNIOR
118	Imidazo[1,2-a]pyridine-tetrazole hybrids: phytotoxic and photophysical properties	VICTOR HUGO JUSTINO GARCIA PRACIANO
119	A green synthesis of 2,5-disubstituted thiophenes from terminal alkynes: a telescopic approach	MARCIO CONTRUCCI S. DE MATTOS
120	Rufinamide® Luminescent Hybrids: Design, synthesis and photophysical properties of news 3-(1-aryl-1H-1,2,3-triazol-4-yl)-1,1-difluoro-1H-1λ4,9λ4-pyrido[1,2-c][1,3,5,2]oxadiazaborinines	FÁBIO MULAZZANI DA LUZ
121	Radical C3-alkylation of coumarin via Pd-photocatalyzed Heck reactions	CAMILA PELIZZER DE OLIVEIRA
122	Remote radical alkylation of silyl dienol ether by palladium-photoredox catalysis: a direct access to γ-alkylated α,β-unsaturated ketones	CLARICE ALVES DALE CAIUBY
123	Synthesis and thermal and structural characterization of novel Ionic Liquids with imidazolium cations and carboxylate anions.	JOSÉ LÚCIO BAUER VIEIRA
124	2-(((4-(Trifluoromethyl)quinolin-6-yl)amino)methyl)phenols: Synthesis and optical properties	INAIÁ OLIVEIRA DA ROCHA
125	Selective fluorination reactions in 5-aryl(heteroaryl)-7-(trifluormethyl)-2methylpyrazole[1,5-a]pyrimidines	JULIANE NASCIMENTO ARAUJO
126	Exploring the reaction of sulfoxonium ylides with allylic carbocations	VIKTOR SARAIVA CÂMARA
127	Design and Synthesis of 1,2-Nphthoquinones Derivatives	SEARITHA COUTO RODRIGUES
128	Synthesis, derivatization and radiolabeling of carbasugars for the detection of hidden infections	CAROLINA BRINDISI
129	Telescoped Continuous Flow Photochemical and Electrochemical Synthesis of Butyrolactones	LUCAS GONÇALVES ROCHA
130	Synthesis of 2-phenyl-1H-benzo[d]imidazole-derived fluorescent G-quadruplexes ligands	MILENA DE NARDIN
131	Metal-free Synthesis of Isoquinoline Derivatives Via Intramolecular Cyclization Through C-C(sp) Bond Activation	ELIAKIN SATO DE BORBA
132	Oxazoline-based dyes for fluorescent enantioselective differentiation of carbohydrates in solution	NATALÍ PIRES DEBIA
133	Au nanoparticles decorated with derivatized thiols: synthesis, characterization and applications	GUSTAVO SEOANE
134	Direct Selenization of the C(sp^2)-H Bond of Quinoline via Electrosynthesis	MANOELLA DE LIMA
135	Eletrochemical Diselenation of BODIPY Fluorophores for Bioimaging Applications and Sensitization of 1O2	ÍCARO ANTÔNIO OLIVEIRA BOZZI
136	Electrochemical Halogenation of Naphthoquinones: A Modular and Sustainable Strategy towards Trypanocidal Compounds	EDUARDO FRANCISCO DA SILVA GUIMARÃES
137	Generation and Capture of Naphthoquinonynes: A New Frontier in the Development of Trypanocidal Quinones via Aryne Chemistry	LUANA ALVES MACHADO
138	Ruthenium-Catalyzed C–H Alkenylation of Quinones to Introduce SuFEx Functionalization: A Potential Building Block for Bioactivity Valorization	JOYCE CRISTINA DE OLIVEIRA
139	Multicomponent reactions in the synthesis of phenytoin derivatives for formation of products with potential anticonvulsant activity	DANIEL MEDEIROS DE LIMA
140	Design and Synthesis of a New Series of Pyrido[3,4-b]carbazole Derivatives	MARIA TEREZA MIRANDA MARTINS
141	Synthesis and optimization of MMV1788223 as new anti-Malarial agent	THAÍS HELENA MACIEL FERNANDES
142	Electrosynthesis of Benzofurans and Benzofuranols derivatives using sacrificial silver electrode	WILLIAM ANTONIO BRITO SANTOS
143	Reactivity study of isopiperitenol and p-mentha-2,8-dien-1-ol for the synthesis of cannabidiol and cannabidiolic acid methyl esther	MARCOS ACCIOLY PEREIRA JUNIOR
144	Exploring the Antidepressant Potential of Dihydropyrimidin-2-thiones with Sertraline-like Substitution Patterns	ITAMAR LUÍS GONÇALVES
145	Batch and Continuous Flow Total Synthesis of Cannabidiol	FELIPE CAMARGO BRAGA

146	Synthesis of the Pheromone of Duponchelia fovealis Zeller, 1847 (Lepidoptera, Crambidae) for Pest Control in Strawberry Crops	ALICE DOBRYCHTOP CORREA
148	Exploring the reactivity of glycals in photocatalytic reactions	THAIS GOULART SILVA
150	Silver-Catalyzed Intramolecular Cyclization of Guanidine Motifs onto Alkynes	ROBERTO DO CARMO PINHEIRO
151	Scaling up the Synthesis of p-mentha-2,8-dien-1-ol Under Continuous Photoflow Conditions	TIAGO DE OLIVEIRA RAMOS
152	Synthesis of a BODIPY-dihydropyrimidinone derivative	CARINE DE ARRUDA
153	Telescoped Synthesis of N-Substituted 8H-Indeno[1,2-d]thiazol-2-amine Promoted by Tribromoisocyanuric Acid	JAIME CRISPIM NETO
154	Linear Free Energy Relationships of Organocatalyzed Asymmetric Michael Additions	NATAN DE MOURA UCHIYAMA
156	An Expedient Synthesis of tetra-ortho-fluoro-azobenzenes via Nucleophilic Aromatic Substitutions (SNAr)	MATHEUS YAGO GOUVEA WATANABE
157	Visible Light-Mediated Diastereoselective Synthesis of Novel C Glycopeptides	JEIMY ALEJANDRA CHAVARRO VELEZ
158	Novel D-π-A Iminocoumarin-Based Molecules: Synthesis, Photophysical Properties, and Preliminary Evaluation as Photosensitizers for DSSCs	AMANDA DE ANDRADE BORGES
159	Asymmetric Synthesis of 1,4-Oxachalcogenanes and 1,4-Azochalcogenanes	PEDRO JORGE HAUY
160	Synthesis of 9,10-bis(organochalcogenyl)phenanthrenes by cyclization of (biphenyl-2-alkyne)chalcogenides	ANGELITA MANKE BARCELLOS
161	Photocatalysis as a tool for the development of certified reference materials: a case study in university technology transfer	MARIANA DOS SANTOS DUPIM
162	High-throughput screening of new Iron catalysts for Enantioselective Reductions by Online ESI-MS	FABIANE MANKE NACHTIGALL
163	Electrosynthesis of Benzothiazole Derivatives Using Sacrificial Electrodes	LAÍS APARECIDA PIAZ
164	Chiral Monothiosquaramides as Efficient Catalysts for the Enantioselective Imine Reduction of Dihydro-β-carbolines	LEONARDO SILVA SANTOS
165	ANO-catalyzed multicomponent synthesis of 3-alkyl-N-substituted pyrroles	VIVIANE TESSMER MENA
166	Reductive Amination Reactions under Electrosynthesis Conditions	GABRIEL HIROSHI SEKI ROSA
167	Visible Light and Triselenium Dicyanide (TSD): New Horizons in the Selenocyanation of Enamino Compounds	JOÃO MARCOS ANGHINONI
168	Visible light-promoted synthesis of 3-selanylthiochromenones	SABRINA SOUZA FERREIRA
169	A French Connection in Organic Synthesis	EMMANUEL GRAS
170	Synthesis and biological prospecting of 4-quinolone-3-acylhydrazone derivatives as potential anti-HIV-1 candidates	YURI INÁCIO MARQUES SILVA
171	Photochemically-promoted C-H insertions of N-heterocycles with aryldiazoacetates	RONEI MESSIAS SILVA SOUZA
172	Synthesis of new analogs of an anti-malarial agent in a hit-to-lead phase	NATÁLIA GOEDTEL MEDEIROS
173	Enantioselective Synthesis of Pyrroloindolines Bearing Heteroaromatic Side-Chains	BEATRIZ GONÇALVES RODRIGUES
174	Tunable Divergent Reactivity of Aziridinium Ylides in the Synthesis of Complex Piperidines and Azetidines	GIULIANA PAVANELI
175	Photocatalytic strategies for the synthesis of C-nucleoside analogues	BRUNO MAIA DA SILVA SANTOS
176	Solvent-Controlled Selective Synthesis of 1,4-Benzodithiins and 1,4-Benzodithiafulvenes via Cyclization and Ring Contraction	DOUGLAS BERNARDO PAIXÃO
177	Selenoesters acting as benzoyl donors on lipase-catalyzed reactions	ANA LETÍCIA WASZAK DA SILVA
178	Iodine-catalyzed synthesis of pyrido/benzo[b][1,4]selenazines	RICARDO FREDERICO SCHUMACHER
179	Mechanochemical synthesis of aromatics from biomass derived terpenes	JHULLY ANNE BARROS CARVALHO RIBEIRO
180	Small molecule drugs: Synthesis of SePh-benzocaine	MARIA JULIA MILETO DA SILVA
181	Synthesis of 4-quinolone-α-aminophosphonate derivatives with antiviral profile	MAYRA SILVA COUTINHO
182	Ru(II)-Catalyzed Asymmetric Transfer Hydrogenation of Aryl(1-aryl-1H-1,2,3-triazol-4-yl)methanones: A Novel Strategy for Developing CFTR traffic Corr	SAMUEL BENTO RIBEIRO
183	Tribromoisocyanuric acid-mediated telescopic synthesis of selenazoles	GUILHERME FURTADO BOTELHO
184	Synthesis and biological prospection of new derivatives 4-quinolone-3-hydroxamic acids with potential activity anti-HSV	FERNANDA DA COSTA SANTOS BOECHAT
185	Difluoro-triazaborinines containing benzo-fused imidazo-, oxazolo-, and thiazolo-pyrimido fragment as new luminescent frameworks	RICARDO RAMOS CORREA CASSOL

186	Dynamic kinetic resolution of benzylic amines with palladium supported on dolomite and ionic liquids with microwave heating. A new approach.	JOSÉ CARLOS QUEIROZ ARÊAS
187	Telluride-Based Pillar[5]arene: A Potent and Recyclable Catalyst for Alkylation Reactions in Water	PATRICK CARVALHO NOBRE
188	Synthesis of [1,2,3]triazolo[1,5-a]quinolines promoted by organocatalyst and base	GABRIEL PEREIRA DA COSTA
189	Visible-Light-Mediated Cyclization of 1,3-Diones and Chalcogenoalkynes: A New Regioselective Method for Polysubstituted Chalcogenofurans	BIANCA THAÍS DALBERTO
190	CuAAC reaction promoted the synthesis of promising selenyl-dihydropyrimidinones (DHPMs)	AMANDA REBELO DE AZEVEDO
191	Synthesis of N-aryl Azacoumestanes with potential antileishmanial and antibreast cancer activity	RACHEL DE CAMPOS VILAS NOVAS
192	Potential Bioactive N-Heterocyclic/Spirocyclic Sulfonamides Building Blocks	EDNA FARIA DE MEDEIROS
193	Sustainable chemical synthesis of high added-value aromatic compounds through the photochemical valorization of lignin	PEDRO DOMINGUEZ BRANCO
194	Biaryl-4-hidroxi-1,2,3-triazoles as a platform for new fluorene-triazole hybrids	DAVID CHAFI ZEITUNE
195	Dual-Catalysis Approach to Stereoselective [2 + 2] Cycloaddition of Erlenmeyer-Plöchl Azlactones	GIOVANNI WILSON AMARANTE
196	Synthesis and Neuroprotective Potential of Carvacrol-Derived Selenides-1,2,3-Triazoles for Alzheimer's Disease	LUANA DA SILVA GOMES
197	Synthesis of 4-arylchalcogenyl-1H-pyrazoles catalyzed by copper	HECTOR CEZAR RIBEIRO
198	Synthesis and Characterization of Highly Efficient Anticorrosive Organoselenium Derivatives Containing 1H-Tetrazole Nucleus	VICTOR HUGO MENEZES COSTA
199	Electrosynthesis of 2,3,5-trisubstituted selenium-chalcogenophenes from (Z)-chalcogenenynes and diselenides	DAVI LEONARDO DE SOUZA SIMPLICIO
200	Electrochemical Synthesis of E-Vinyl Chalcogen Halides	RODRIGO COSTA E SILVA
201	4-acyl-1,2,3-triazoles as a platform to synthesize fused quinolonetriazole hybrids through oxidative C−H Amination	MARCELO FOLHADELLA MARTINS FARIA AZEVEDO
202	Continuous flow enatioselective synthesis of α-amino acid derivatives through asymmetric photoredox catalysis	MARCELO STRAESSER FRANCO
203	Synthesis of 4-(Phenylchalcogenyl)tetrazolo[1,5a]quinolines: A novel bicyclization approach	NICOLE CRISTINA MARTINS ROCHA
204	Convergent synthesis of 2-iminothiazoles containing α-diazo carbonyl groups from 4-haloacetoacetates and thioureas	CINARA TEIROBA DE ÁVILA
205	Synthesis, in vitro and in vivo antitumoral effect against oral squamous cell carcinoma of new dithioethers based on catalyst-free Michael addition of	THAÍS BARRETO SANTOS
206	Theoretical and Experimental approach to visible light-catalysed 6π-photoelectrocyclization	ERICK HENRIQUE DE SOUZA ALVES
207	Efficient Synthesis and Iodine-Functionalization of Pyrazoles using KIO3/PhSeSePh System	JOÃO PEDRO SENNA SILVA CARDOSO THOMAZ
208	Ru(II)-Catalyzed Asymmetric Transfer Hydrogenation of alpha-Alkyl-beta-Ketoaldehydes via Dynamic Kinetic Resolution	DAIENE DE PAULA LAPA
210	Exploring the reactivity of unsaturated organoboron compounds in cycloadditions and related reactions	SILVINA PELLEGRINET
211	Synthesis of N-Heterocyclic functionalized arylselanyl benzenes	LUIZA HEPP DE AZEVEDO
212	Synthesis new hypervalent heterocyclic Tellurium compound containing Te-N bond	BERNARDO ARIEL SCHORR ZOTZ
213	Direct amination of selenium containing α-cyanohydrin acetates	MARIA CLARA DA SILVA DURIGON
215	Developing a sustainable approach for the synthesis of Phosphorus-containing amino acids	KARINA DE SOUZA QUAGLIO
216	PEC-NH2 as a novel organocatalyst for the synthesis of 2-arylselanyl-1,3-diketones	LIVIA CONCEIÇÃO LIMA VALENTE
217	Potassium Persulfate Promoted the One-Pot Seleno-Functionalization of Pyrazoles under Acidic Conditions	THIAGO JACOBSEN PEGLOW
218	Biocatalytic oxidation of glycerol carbonate promoted by laccase-mediator system	VINÍCIUS BERTONCELLO MOLON
219	BAICALEIN DERIVATIVES AS PROMISSING ANTICANCER AGENTS	JOÃO PEDRO NEVES DE MELLO
220	Orange Peel Ashes as Catalyst for Glycerol Carbonate Synthesis	LAURA ABENANTE

221	Design, synthesis and biological activity of menadione-1,2,3-triazole chalcogenides	NATHÁLIA LESSA BOTELHO SANTOS
222	Electroreduction of elemental Sulphur for the synthesis of 2,5-disubstituted thiophenes	EDUARDO GIOVANNI DE OLIVEIRA SOARES
223	Synthesis of Tetrahydroimidizalone-Dihydropyrimidinone hybrids	DENNIS RUSSOWSKY
224	One-Pot Synthesis of (+)-Nootkatone via Photooxidation of (+)- Valencene	SAMUEL DA SILVA CONSTANCIO
225	Benzo[f]indole-4,9-dione derivatives: synthesis and evaluation as potent antitumor agents to suppress the growth of triple-negative breast cancer	FLAVIANA RODRIGUES FINTELMAN DIAS
226	Ruthenium-Catalyzed Chemo- and Regioselective Alkenylation of Flavones with Alkenes through C-H Activation	NATHÁLIA SANTOS DE OLIVEIRA
227	Mechanistic investigation of Pd-photocatalyzed Heck reaction	MATEUS OLIVEIRA COSTA
228	Base mediated divergent intramolecular cyclization of β-enamino diketones: a diversity-oriented synthesis of N-heterocycles	JULIA POLETTO
229	Molecular docking and dynamics of AKT1 and N-heterocycles on the search for novel anticancer compounds	HELENA DOMINGUES DE SALLES
230	A Visible Light-Mediated Strategy for the Cyclopropenation of Ynamides with Aryldiazoacetates	TALES ANTONIO CAMARGO GOULART
232	Development of organocatalyst-loaded electrospun nanofibers to improve heterogeneous catalysis	CAROLINE FORTUNA
233	Synthesis of new eugenol derivatives using microwave and ultrasound irradiation.	THIAGO FERREIRA LEÃO LOESER
234	Molecular Docking of new eugenol derivatives with selenium like Catechol O-methyltransferase inhibitors	ELTON DE LIMA BORGES
237	Synthesis Arylselanyl Acrylates promoted by Electrosynthesis	PAULO HENRIQUE MANZI DE SOUZA
238	Synthesis of fluorescent supramolecular complexes containing pillar[5]arenes and benzothiadiazoles	DÉBORA KÉLEN SILVA DA CONCEIÇÃO
239	Chalcogen Bond-Mediated Alkylation Catalysis: Selenoxide-Pillar[5]arene as a Recyclable Catalyst in Aqueous Solutions	PÂMELLA DA SILVA CORDEIRO
240	Synthesis and Photophysics of novel 4-aryl-polyhydroacridinodiones: Fluorescence confinement effect	RICARDO FERREIRA AFFELDT
241	Scope of the Diels-Alder reactions of potassium furanyl trifluoroborates	FEDERICO DEZOTTI
242	Study of the reactivity and the selectivity of the Diels-Alder reactions of furanylboron compounds with maleimides	MARIEL ANTONELLA LAMBRI
243	Ru(II)-Catalyzed Asymmetric Transfer Hydrogenation of Polymethoxylated 3-Arylidene Chromanones via Dynamic Kinetic Resolution	MARCOS VINICIUS DE OLIVEIRA DA SILVA
244	Sulfonic Acid-functionalized Chitosan as a Biodegradable Heterogeneous Organocatalyst in O-alkylation and A3 coupling Reactions	VITOR FRANCISCO FERREIRA
245	Expanding the Chemical Space of Electrophilic β-Glycosyl β-Lactams through Photoinduced Diastereoselective Functionalization	LUCAS LOSS BALDASSARI
246	Fast and efficient one-pot ultrasound-mediated synthesis of solid state (full color tunable) fluorescent indolizine derivatives	MANOELA DO SACRAMENTO
247	Synthesis and In Vitro Studies of Chalcogenophenes Containing Quinoline.	MATIAS EZEQUIEL VICTORY
248	Synthesis of new derivatives of salicylic acid with potential bioactivity	WARLEY DE SOUZA BORGES
249	Copper Catalyzed Direct Chalcogenylation of Chalcogenophenes C(sp2)- H Bonds Using a 2-Amino Oxazole Directing Group	GUL BADSHAH
250	Design, Synthesis, and Structure-Activity Relationship Study of Thiohydantoin Derivatives	TÁRSIS AUGUSTO ALEXANDRE CHAGAS
251	Towards greener MCRs: use of renewable reactants in Ugi and Passerini reactions	ALEJANDRO PEIXOTO DE ABREU LIMA

SEPTEMBER 23-27 2024
19BMOS
BRAZILIAN MEETING ON ORGANIC SYNTHESIS
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Convergent Synthesis of Proline-Functionalized Pyrazolopyrimidines as Anti-*T. cruzi* Bioactive Compounds

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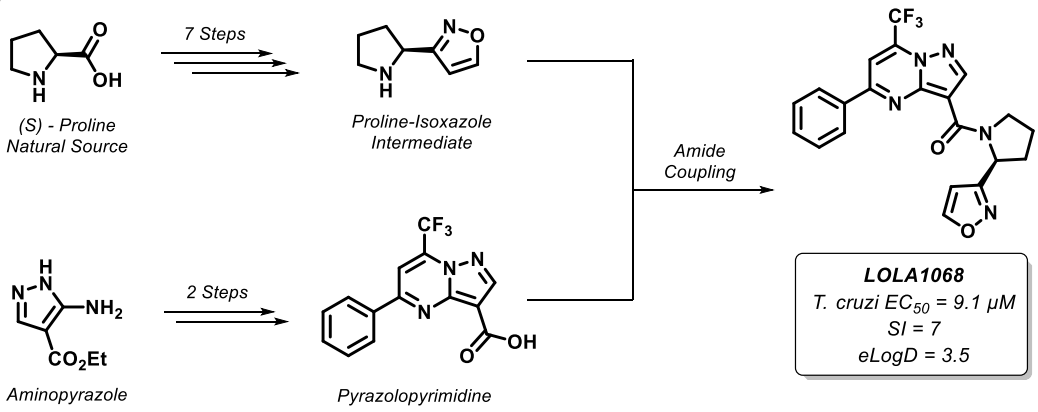
Keywords: *Chagas Disease, Convergent Synthesis, Hit Assessment.*

ABSTRACT

Chagas disease is a chronic and parasitic malady, endemic to Latin-America, which affects around 7 million people worldwide. Caused by the protozoan *Trypanosoma cruzi*, this Neglected Tropical Disease (NTD) may lead to cardiac, digestive, and even neurological disorders, often associated with sudden death. Currently, only two drugs – effective exclusively in the initial stages of infection – are available for the treatment of Chagas disease, underscoring the need for new treatments. Herein, the LOLA consortium arises as a Drug Discovery project for NTDs devised by the Drugs for Neglected Diseases initiative (DNDi). This work consists of the obtention and biological evaluation of proline-functionalized pyrazolopyrimidines via convergent synthetic route starting from natural enantiopure proline and 3-amino-4-carbethoxypyrazole as a key step in the Hit Assessment phase of new anti-*T.cruzi* drugs. After 10 steps, the compound LOLA1068 was obtained in good purity, exhibiting a micromolar concentration activity against Tulahuen LacZ *T.cruzi* strains, and adequate lipophilicity.



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IQ Instituto de Química
Laboratório de Química Orgânica Sintética

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SEPTEMBER 23-27 2024
19BMOS
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Synthesis and antimicrobial activity evaluation of coumarin-3-carboxylic acids obtained via Knoevenagel Condensation using chitosan as a recyclable catalyst

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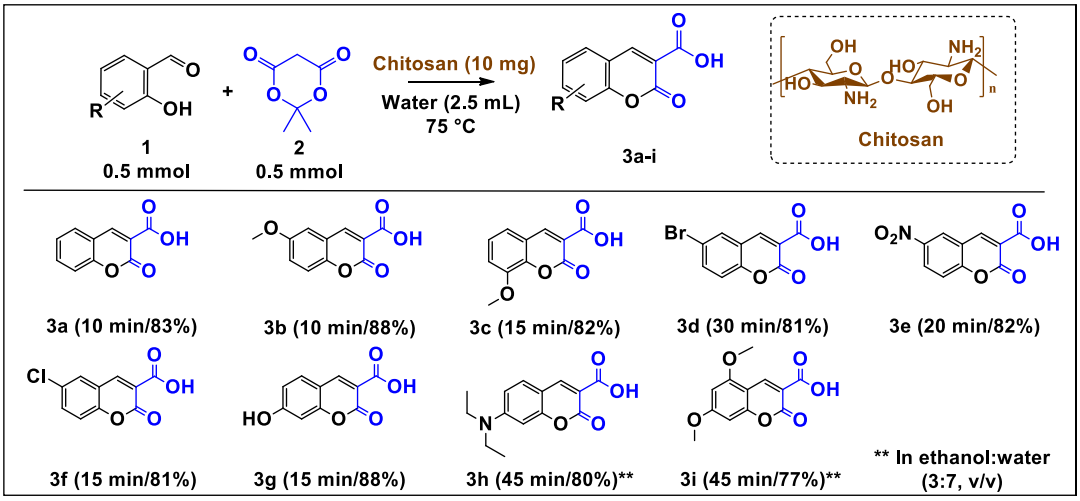
Keywords: *Chitosan; Coumarin-3-carboxylic acids; Antimicrobial activity; Knoevenagel condensation.*

ABSTRACT

Commercial chitosan was used as a catalyst for the efficient synthesis of coumarinic-3-carboxylic acids in water at 75°C via Knoevenagel condensation. The reaction between substituted salicylaldehydes (**1**) and Meldrum's acid (**2**) under mild conditions yielded high yields (77-88%) of coumarin-3-carboxylic acids (**3a-i**) in short reaction times (10-45 minutes) without the need for extensive purification (Scheme 1). This method associated the benefits of homogeneous catalysis with the recovery and reuse of the catalyst up to four times, maintaining its catalytic activity and structural integrity [1].



Scheme 1. Application of substituted salicylaldehydes to obtain various coumarin-3-carboxylic acids using commercial chitosan as recyclable catalyst.

In antimicrobial evaluations against 12 strains of fungi and bacteria, coumarin-3-carboxylic acids **3c-e**, **3h** and **3i** showed significant inhibitory effects (1024-256 µg/mL). Notably, product **3d** exhibited the lowest minimum inhibitory concentration (MIC) against fungal and bacterial strains (256 µg/mL), suggesting its potential as a bactericidal and fungicidal agent [2].

ACKNOWLEDGEMENTS

The authors are grateful to the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq, 170183/2023-8), and the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES, 88887.659769/2021-00) for their financial support.

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SEPTEMBER 23-27 2024
19BMOS
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Synthesis of 2-amino-4H-chromenes catalyst-free and evaluation of biological activity in tumor cells

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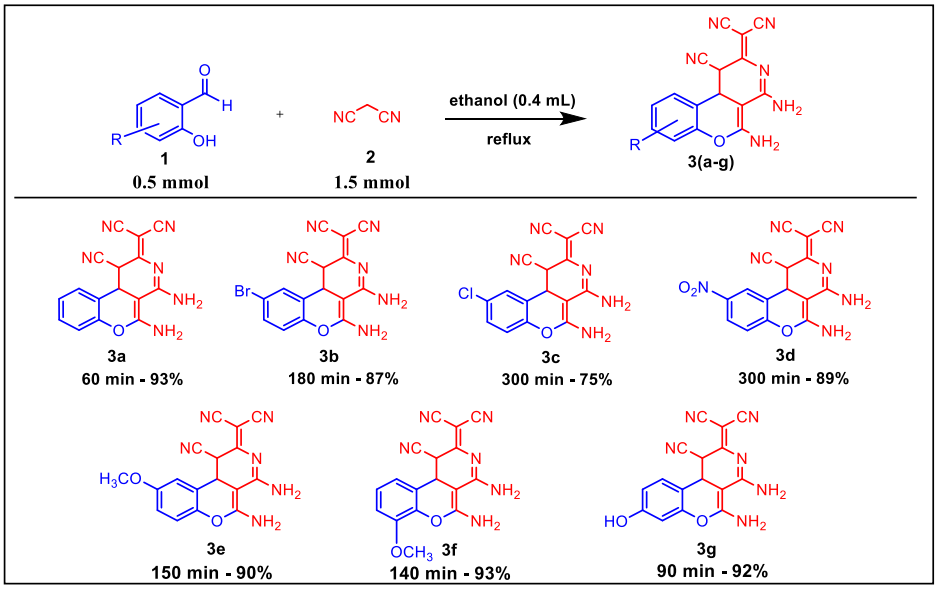
Keywords: *2-amino-4H-chromenes; Knoevenagel-Michael; Anticancer activity; Virtual screening; Molecular docking.*

ABSTRACT

This study focuses on the selection of solvents for the catalyst-free synthesis of 2-amino-4H-chromenes from salicylaldehydes (1) and malononitrile (2) via the sequential Knoevenagel-Michael (**Scheme 1**). Ethanol under reflux was the solvent that provided the highest yield and the shortest time to obtain 3a (60 min – 93% yield). Several 2-amino-4H-chromenes 3(b-g) were obtained under these optimized conditions with high isolated yields (75-93%) and short reaction time (90-300 min), including four new compounds (3b, 3d, 3e, 3g) [1].



Scheme 1. The synthesis of 2-amino-4H-chromenes 3(a-g) from salicylaldehydes and malononitrile in ethanol under reflux.

Virtual screening on H-116 and K-562 cells identified 3e as most promising in antitumor activity. In vitro assays confirmed its potential, in line with in silico results. Molecular docking suggested inhibition of the T315I Abl mutant protein, linked to imatinib resistance in chronic myeloid leukemia. This pioneering study explores the biological activity of these compounds, indicating potential for new antitumor agents.

ACKNOWLEDGEMENTS

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SEPTEMBER 23-27 2024
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Text

Synthesis and anti-leishmanial activity evaluation of isatin adducts obtained via Knoevenagel Condensation using chitosan-EDTA as a bifunctional heterogenized catalyst

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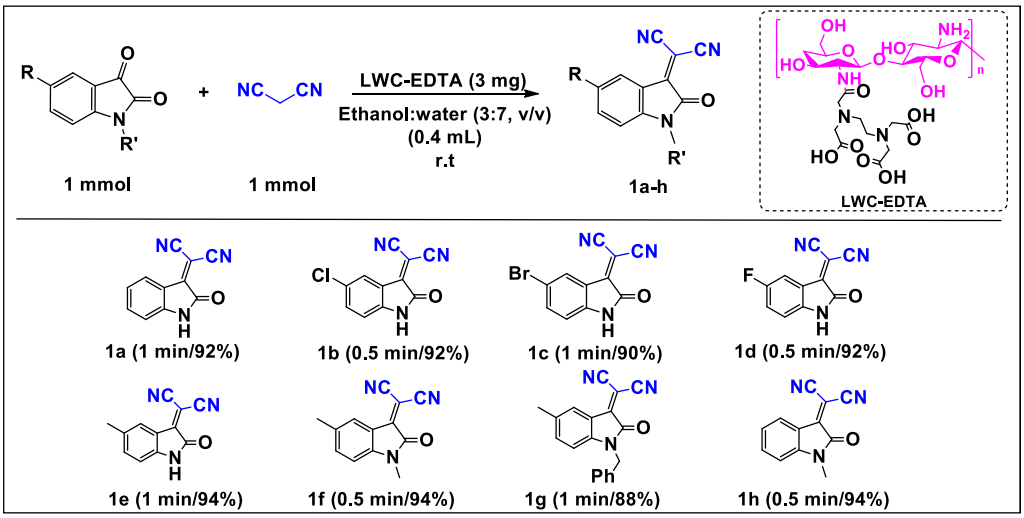
Keywords: *Chitosan; Catalysis, Isatin adducts; Knoevenagel condensation; Anti-leishmanial activity.*

ABSTRACT

Low molecular weight chitosan functionalized with EDTA (LWC-EDTA) was applied as a bifunctional heterogenized catalyst [1] between several isatin derivatives and malononitrile, providing the obtaining of isatin adducts (**1a-h**) via Knoevenagel condensation in short times (0.5-120 min) and excellent isolated yields (88-94%). The catalyst can be recovered and reused for six cycles without considerable loss of catalytic activity.



Scheme 1. Application of isatin derivatives to obtain various isatin adducts using LWC-EDTA as a bifunctional heterogenized catalyst.

In evaluations against leishmaniasis, isatin adducts **1b** and **1g** exhibited IC_{50} of 12.09 and 10.90 μM, respectively, proving to be effective against the promastigote phase of the microorganism. In the cytotoxicity test, isatin adducts **1b** and **1g** showed hemolytic activity similar to the negative control, that is, none of the compounds were toxic to human red blood cells. Consequently, it was not possible to calculate the selectivity index (SI).

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SEPTEMBER 23-27 2024
19BMOS
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Strain-Release Pentafluorosulfanylation

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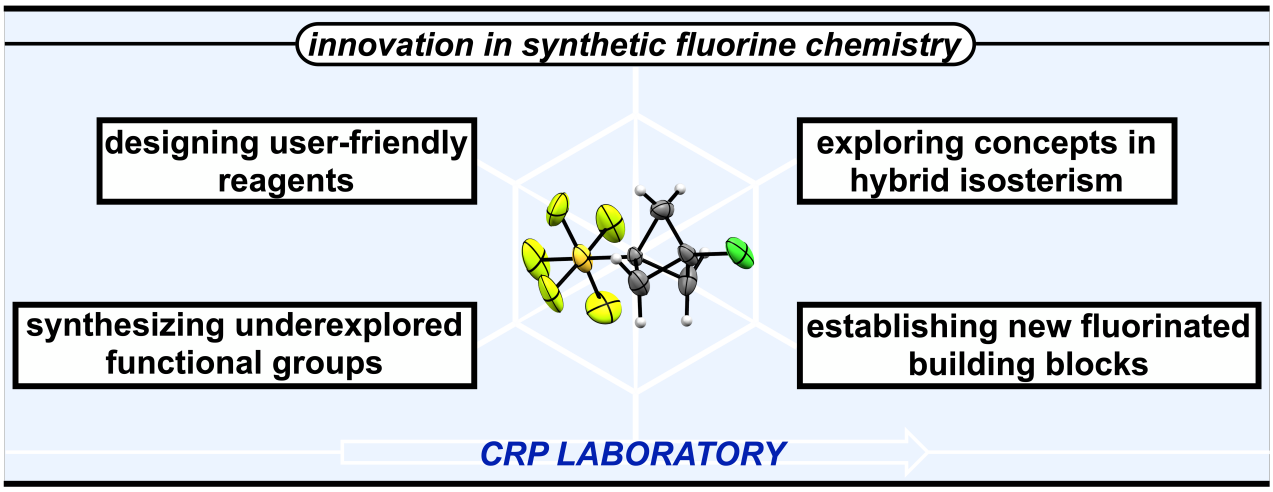
Keywords: *fluorinated functional groups, strain-release functionalization, radical chemistry.*

ABSTRACT

This presentation details recent progress in our laboratory toward the synthesis and evaluation of underrepresented fluorinated functional groups that have been made more accessible using the TCICA/KF approach to oxidative fluorination.[1] A major theme will be our recent merging of SF_5 radical chemistry with strain-release functionalization of [1.1.1]propellane[2] and [1.1.0]bicyclobutanes.[3] Structural consequences of making these SF_5-based "hybrid isosteres" and preliminary mechanistic insight will be discussed. Aside from being a topic of fundamental interest, we believe this work affords an unusual and subtle type of flexibility in molecular design that could prove useful in increasing availability of building blocks containing $C(sp^3)$–SF_5 bonds to medicinal chemists, agrochemists, and in the materials community.



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SEPTEMBER 23-27 2024
19BMOS
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Lipase from *Burkholderia cepacia* (BCL) immobilized in Chitosan/EDTA applied to the resolution of rac-1-phenylethanol

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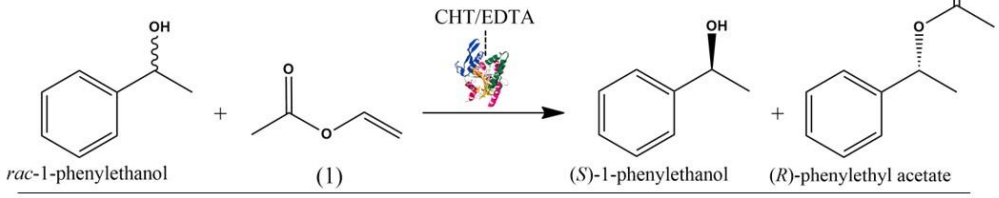
Keywords: *Lipase Immobilization, Chitosan/EDTA, Enantioselectivity.*

ABSTRACT

This work evaluated the immobilization between several lipases and chitosan functionalized with EDTA (CHT/EDTA) [1]. Enzymatic activity and stability of different lipases before and after immobilization were analyzed in different conditions (pH and temperature). The results showed better stability for immobilized *Burkholderia cepacia* (BC-CHT/EDTA), for example against the temperature range, which it kept 75% of its activity, while the free form only kept 21%. The biocatalysts BC-CHT/EDTA synthetized was applied to the resolution of 1-phenylethanol (1) with vinyl acetate (2) in different weights of biocatalyst and reaction temperature [2]. The datas were compared with the free lipase applied in the same conditions (table below).



rac-1-phenylethanol (1) (*S*)-1-phenylethanol (*R*)-phenylethyl acetate

Entry	Lipase	Weight (mg)	Temperature(°C)	ee_A (%)	ee_E (%)	C (%)
1	BCL	5,6	r.t	20	99,9	16,7
2	BCL	5,6	60	11	99,9	10
3	BC-CHI/EDTA	50*	r.t	15,3	99,9	13,3
4	BC-CHIT/EDTA	50*	60	32	99,9	24,2
5	BCL	11,4	r.t	48	99,9	33
6	BCL	11,4	60	44	99,9	30
7	BC-CHIT/EDTA	100*	r.t	46	99,7	31,6
8	BC-CHIT/EDTA	100*	60	82	99,9	45

* 50 and 100 mg of BC-CHT/EDTA corresponds to 5,6 and 11,4 mg of BCL, respectively.

Using 100 mg of BC-CHIT/EDTA at 60°C was achieved 100% of enantiomeric excesses of ester (ee_E), 82% of enantiomeric excesses of alcohol (ee_A), and a 45% of conversion rate. These results demonstrate the potential of BC-CHIT/EDTA for the resolution of racemic compounds.

ACKNOWLEDGEMENTS

The authors express their gratitude to the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq, 170183/2023-8) and the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES, 88887.614830/2021-00) for their generous financial support.

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SEPTEMBER 23-27 2024
19BMOS
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Harnessing Glyco-Compounds: Effective Anti-Fungal Biofilm Agents Against *Candida sp.*

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Keywords: *glycol-triazole, metronidazole, antifungal*

ABSTRACT

Fungi are one of the main causes of disease in humans and their way of life generally involves the formation of biofilm, which consists of a strong and dynamic structure that provides a range of advantages to its members, such as: low energy demand and low oxygen demand[1]. That said, we can look to metronidazole mechanism of action, that function as a prodrug that is activated by the bioreduction of its nitro group in low oxygen concentration environments. The metronidazole itself does not work as antifungal agent, but we can build derivative of that, such as glyco-compounds, to furnish new molecular structure exploring this mechanism of action as new antifungal agents[2]. In this study, we hereby presente the synthesis and antibiofilm fungal study of the eight unprecedent glyco-compounds prepared by non-classical glycosylation, to explore the impact on the pharmacokinetics and pharmacodynamics offered by glycosides, additionally to the potential enhancement provided by the triazole ring. To study the chiral pool provided by carbohydrates, as well as their relationship with size and polarities, we explored four different glyco-compounds of D-glucose, D-galactose, *N*-acetylglucosamine and D-lactose, with interesting activities in in vitro assays, in addition to a satisfactory selectivity index. To study the chiral pool provided by carbohydrates, as well as their relationship with size and polarities, we explored four different glyco-compounds of D-glucose, D-galactose, *N*-acetylglucosamine and D-lactose,[3] All glyco-compounds showed both interesting antifungal and antibiofilm activities, with lacto-mentronidazole standing out for its significantly higher activity compared to the reference drug fluconazole.

ACKNOWLEDGEMENTS

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SEPTEMBER 23-27 2024
19BMOS
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Silver Sacrificial Electrodes in Electrosynthesis: Enabling Regioselective Cyclization for Isochromenes and Dihydroisobenzofurans

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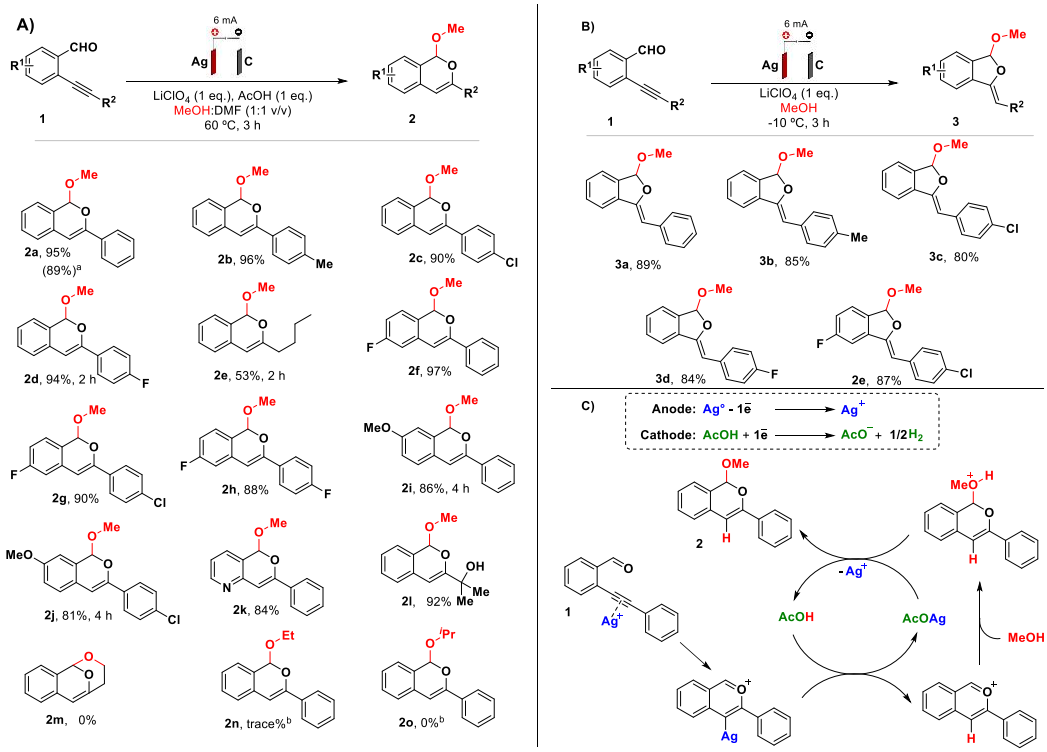
Keywords: *Electrosynthesis, regioselective cyclization, silver.*

ABSTRACT

Isochromenes and dihydroisobenzofurans are heterocycles with great importance in organic synthesis and medicinal chemistry.[1,2] In this context, an efficient method for synthesizing isochromene and dihydroisobenzofuran analogues through electrochemical regioselective cyclization of 2-ethynylbenzaldehyde, employing silver as sacrificial electrodes is described. Remarkably, after careful optimization of the reaction conditions, the reaction presented an exceptional regioselectivity towards 5-exo-*dig* or 6-endo-*dig* cyclization, allowing the preparation of a diverse scope of products in up to 97% isolated yield (Scheme 1a and 1b), without the need for external oxidants or transition metal catalysts. The role of silver(I) and acetic acid additive in controlling the regioselectivity was investigated through control experiments and density functional theory (DFT) calculations, allowing the proposal of a plausible reaction mechanism, as shown in Scheme 1c for isochromene formation.

Scheme 1. A) Scope of isochromenes; B) Scope of dihydroisobenzofurans; C) Plausible reaction mechanism.



[a] Reaction carried out using a 5 mmol scale for 22 hours at a constant current of 6 mA; [b] Using etanol or isopropanol as solvent instead of methanol.

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Autobench-RX: A software for automatic reaction barrier calculations

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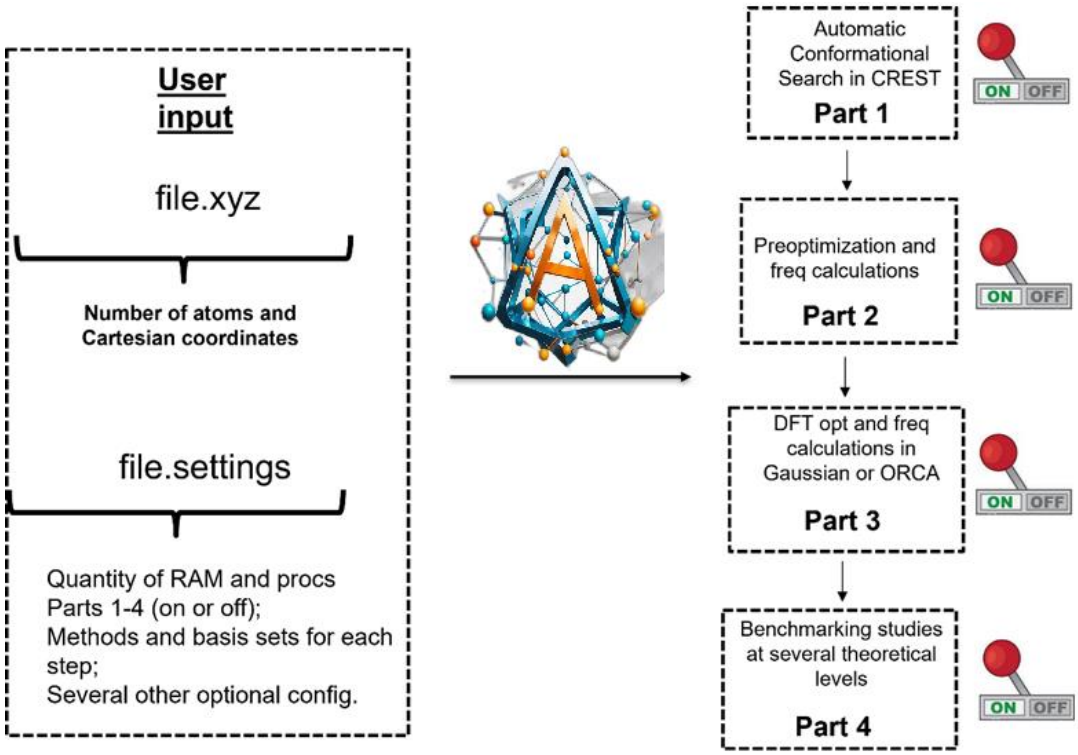
Keywords: *Physical Organic Chemistry, Computational Chemistry, Organic Reaction Mechanisms*

ABSTRACT

This work reports on new software for automatic reaction barrier calculation and benchmarking. This is a new version of Autobench[1] for reaction barrier calculations, coined as Autobench-RX. As its previous version, Autobench-RX workflow consists of four parts (Figure 1): conformational search for transition states, preoptimization, optimization and frequency calculations at a higher level and lastly calculations using several theoretical levels. The software was written to be user friendly and versatile to be used by non-experts in computational chemistry. Any theoretical levels available in either Gaussian 16 or ORCA 5 may be applied in the benchmarking study. The workflow will automatically run conformational search calculations and deal with conformers that converge to the same minimum and those that do not show a single imaginary frequency. At the end of the workflow, the user will have the intrinsic reaction coordinate and Gibbs free energy barriers for several theoretical levels that can be used to compare with experimental data for the reaction of interest.



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SEPTEMBER 23-27 2024
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One-Pot Diastereoselective Synthesis of Highly Functionalized γ-Lactams via Sequential Ugi-4CR and Intramolecular Michael Addition

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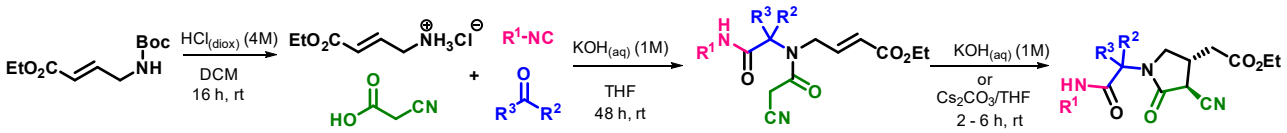
Keywords: *multicomponent reaction, Michael addition, γ-lactam, diastereoselective synthesis*

ABSTRACT

The γ-lactam is a conspicuous scaffold in medicinal chemistry, and due to their important properties, the synthesis of this ring has attracted the attention of the scientific community.[1] In this sense, we have recently reported a simple one-pot diastereoselective synthesis of new γ-lactams from ketoaziridines, via the Horner-Wadsworth-Emmons reaction.[2] The range of γ-lactams includes the 2-oxopyrrolidine-3-carbonitrile derivatives, a versatile synthon in organic chemistry that can be easily converted into other functionalities such as carboxylic acids, amines, amines, and aldimines, for instance.

Herein, an efficient one-pot diastereoselective protocol for the synthesis of highly substituted γ-lactams is described. The Ugi reaction was carried out with an appropriated γ-amino α,β-unsaturated ester, 2-cyanoacetic acid and different isonitriles and carbonyl compounds. The Ugi product was then cyclized via a Michael addition using a base. By employing the optimized conditions, a representative reaction scope was performed with 10 different isocyanides being the desired γ-lactams obtained in moderate to good overall yields over three steps. For our delight, only one diastereoisomer was observed and the relative configuration was determined by x-ray crystallography of one of the γ-lactams. However, when different carbonyl compounds were used only the Ugi products were isolated. We have then screened other bases to promote the 1,4-addition of the isolated Ugi products and Cs_2CO_3 showed the best result, providing the desired γ-lactams in good yields.



Next, we will investigate the intramolecular asymmetric Michael addition by screening different chiral organocatalysts.[3]

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SYNTHESIS OF SUBSTITUTED COUMARINS FROM 2-HYDROXYALDEHYDES, MALEIMIDES AND TRIBUTYLPHOSPHINE VIA MICROWAVE AND CONTINUOUS FLOW

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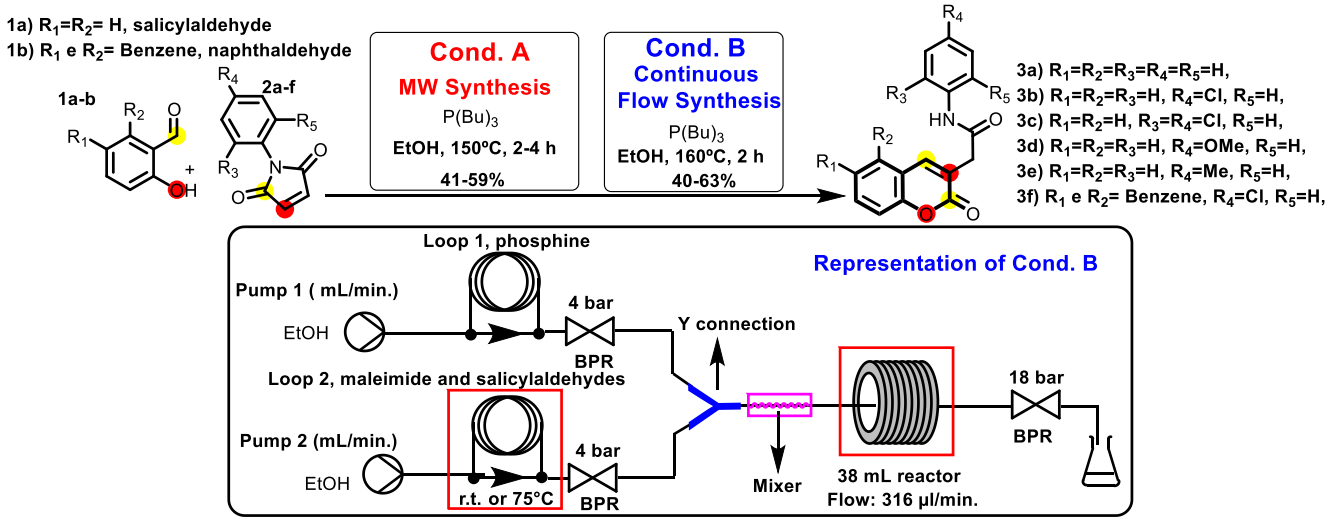
Keywords: *Coumarins, Microwave, Continuous Flow synthesis.*

ABSTRACT

Coumarins have an aromatic ring condensed to a pyran-2-one with uses in several research areas such as cosmetics, food additives, and medicinal chemistry due to its pharmacological properties.[1] They can be obtained through classical synthetic routes such as Knoevenagel and Pechmann condensation[2], Perkin, Wittig and Reformatsky reactions.[3] Continuous flow chemistry is characterized as an enabling technology with advantages over batch synthesis, such as high precision on heat and mass transfer, reproducibility, sustainability and easy scale-up[4] In this study, coumarins were synthesized using salicylaldehydes **(1a-b)**, arylmaleimides **(2a-f)** and tributylphosphine through the synthetic transposition from microwave to continuous flow, as a new methodology. Initially, coumarins **(3a-f)** were obtained using **condition A** in the microwave heating. Then, under continuous flow conditions (**condition B**), two solutions of the reagents were introduced into the flow reactor using two loops and two independent pumps. The loop containing the solution of maleimide and salicylaldehyde was heated to 75°C in some cases. A total flow of 316 µL/min., BPR, Y connection, static mixer and EtOH were used. The coumarins **(3a-f)** were isolated in 40-63% yields via simple vacuum filtration and washing with cold EtOH.



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SEPTEMBER 23-27 2024
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1,3-Diazepane-2,4-diones: bench-stable, bifunctional and customisable isocyanate precursors

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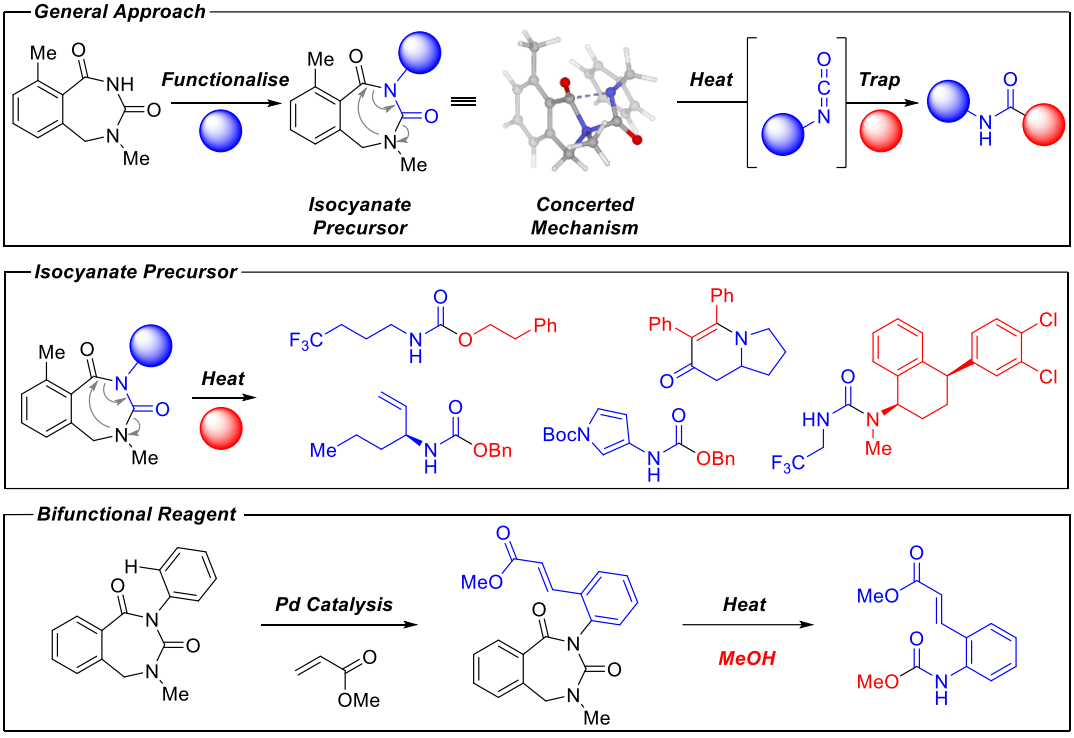
Keywords: *Isocyanate precursor, Ring-contraction, Metal-free*

ABSTRACT

Isocyanates are extremely useful reagents in the synthesis of ureas, carbamates and *N*-heterocycles which are ubiquitous amongst bio-active molecules.[1,2] However, accessing novel isocyanates on a scale relevant to the analogue synthesis of bio-active compounds can be synthetically challenging. Furthermore, commercially available isocyanates can be expensive, limited to aliphatic carbon chains/substituted aromatics and toxic and/or volatile to handle. The work presented addresses these issues by utilising the DFT-directed design of 1,3-diazepane-2,4-diones reagents which undergo a metal-free ring contraction acting as bench-stable isocyanate precursors.[3,4] A series of mild functionalisation techniques such as Chan-Lam, Mitsunobu, S_N2-alkylation and asymmetric allylic amination were developed yielding a diverse set of isocyanate precursors which could be utilised to form unsymmetrical ureas, carbamates and thio-carbamates, as well as *N*-heterocycles *via* Rh-catalysed cycloaddition and electrocyclic ring closure. The reagents also exhibit bifunctionality by directing C-H activation before acting as an isocyanate precursor.



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Funding Source: University of Liverpool; **Computation:** Neil G. Berry; **Crystal Structure:** Craig M. Roberston

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Photocatalytic synthesis of Δ^1-pyrrolines under continuous flow conditions

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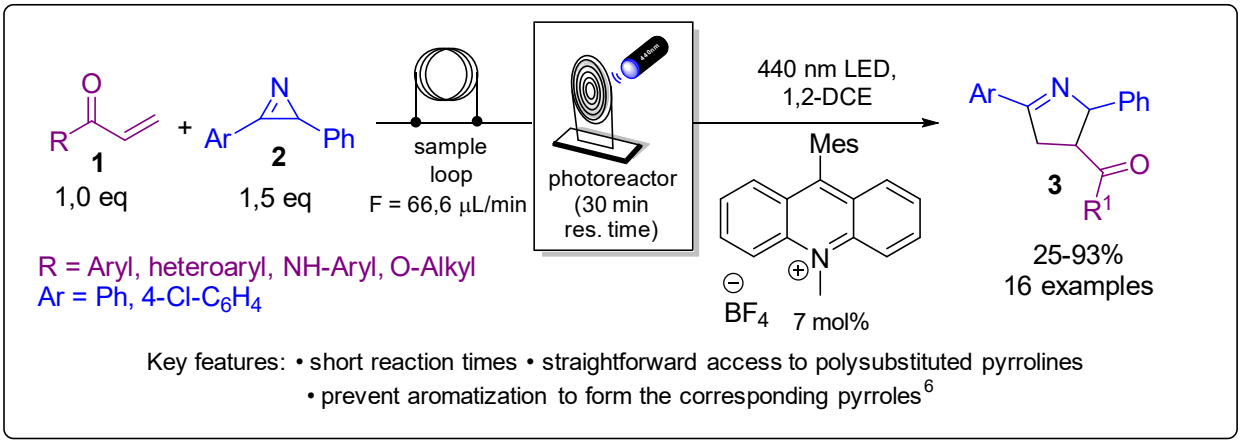
Keywords: *Photocatalysis, pyrrolines, flow chemistry*

ABSTRACT

Five-membered *N*-heterocycles are ubiquitous substructures in drugs and biologically active natural products.[1] With the resurgence of organic photochemistry[2] and the recent development of flow chemistry[3], there is a growing interest in developing methods combining these technologies, since flow chemistry can enhance the efficiency and scalability of photocatalytic reactions.[4] The inherent reactivity of three-membered rings makes them a valuable building block for the synthesis of other heterocyclic motifs of biological relevance.[5] In this sense, herein, we report a continuous flow photocatalyzed formal (3+2) cycloaddition of *2H*-azirines **2** and enones **1** to afford Δ^1-pyrrolines **3** (Scheme 1).



Scheme 1. Photocatalytic formal (3+2) cycloaddition of *2H*-azirines and enones.

Several conditions, starting materials, and catalysts were screened, and the best combination is displayed in Scheme 1. Up to this point, 16 examples of Δ^1-pirrolines **3** have been prepared with yields ranging from 25 to 93%. Studies to further evaluate the scope and limitations of this method are underway.

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Synthesis and evaluation of quinazolinone-eugenol hybrids as new compounds with trypanocide and leishmanicide potential

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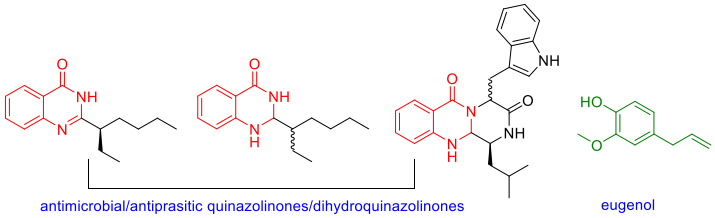
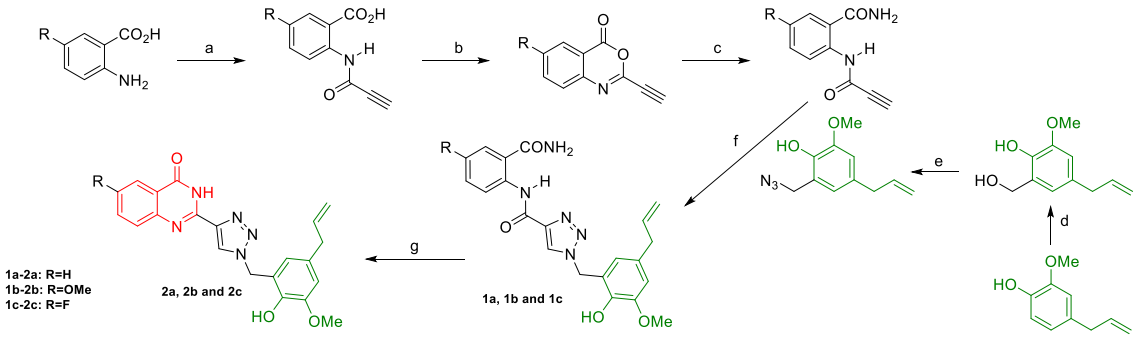
Keywords: *molecular hybrids, natural products, tropical neglected diseases.*

ABSTRACT

The search for new therapeutic agents against neglected tropical diseases is one of the most frequent branches of academic research for new drug candidates. Natural products are a very rich source for obtaining new compounds with therapeutic potential[1]. Very often, they are explored in the construction of hybrids that may bring together the potential of the individual compounds. Then, given the need of better drugs against trypanosomiasis and leishmaniosis, we designed new molecular hybrids based on marine quinazolinones and eugenol, a natural phenolic compound[2]. Following reports on the antiparasitic and antimicrobial activity of quinazolinones[3] and eugenol derivatives, we expected that the union of these pharmacophores could generate biologically relevant substances.



The designed compounds were obtained by classical synthetic procedures and using triazole click chemistry to link both pharmacophores. Nine intermediates and final products were then evaluated *in vitro* against *Trypanosoma brucei* and *Leishmania infantum.* Three compounds (**1b**, **1c** and **2c)** showed activity against *T. brucei* with IC_{50} 11.7-16.4 μM. Intermediate **1c** showed anti-*Leishmania* activity (IC_{50} 7.5 μM) and was six times less cytotoxic against normal cells. The antiparasitic potential of these compounds indicates that their structural framework may be interesting for future optimization.



a) propinoyl chloride, TEA, DCM, 0°C; b) Ac_2O, 130 °C; c) NH_4OH, EtOH, 25 °C; d) NaOH, H_2CO, H_2O, 25°C; e) $SOCl_2$, K_2CO_3, DMF, 0°C, then NaN_3, DMSO, 25°C; f) $CuSO_4.5H_2O$, sodium ascorbate, THF/ H_2O, 25°C; g) NaOH, H_2O, EtOH, reflux, 1 hour.

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SEPTEMBER 23-27 2024
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Building a Microscale Parallel Synthesis (MPS) platform linked to phenotypic assays against a parasitic panel

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Keywords: Anti-infectives, heterocyclic, medicinal chemistry

ABSTRACT

A large number of new heterocyclic compounds having different ring systems were synthesized using condensation, Mannich and C−H activation reactions. Following, the fused rings were decorated with many functional groups, giving rise to a structurally diverse set of analogs, which demonstrate high antitrypanosomal activities on parasite cultures and show significant promise for trypanosomiases drug discovery.[1] However, guiding structural modification through structure-activity relationships (SARs) is essential, but laborious using conventional synthesis methods. A MPS approach allows rapid access to libraries of compounds. This platform linked with Medium-Throughput Screening (MTS) were explored using the urea bond formation reactions in a 96-well plate (**Figure 1**). To test whether unpurified reaction mixtures can give useful screening results against parasite panels, identified hits were resynthesized, purified and further characterized and retested. The implementation and validation of the MPS method shows that large compound libraries can be produced without purification to an initial biological screening.

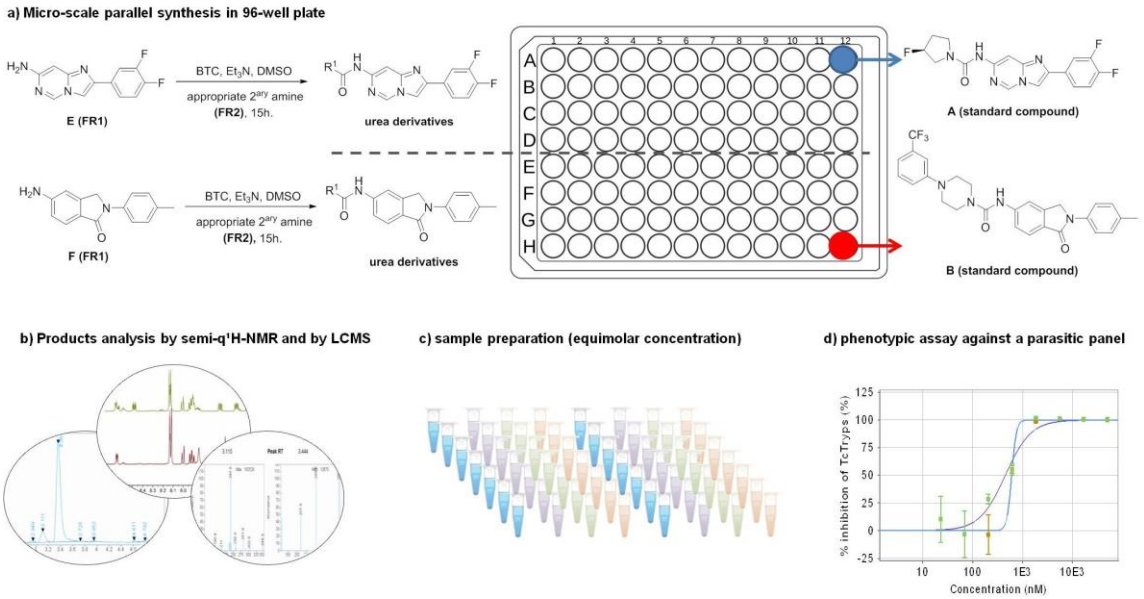

Figure 1. Overview of the overall workflow of the microscale parallel synthetic (MPS) approach combined with phenotypic assays against a parasitic panel. The core ring and the amine derivatives are denoted as FR1 and FR2, respectively.

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SEPTEMBER 23-27 2024
19BMOS
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Enantioselective Synthesis of Dihydrobenzofurans derivatives by Merging Intramolecular Heck-Matsuda Reactions from Anilines with Redox-Relay Process

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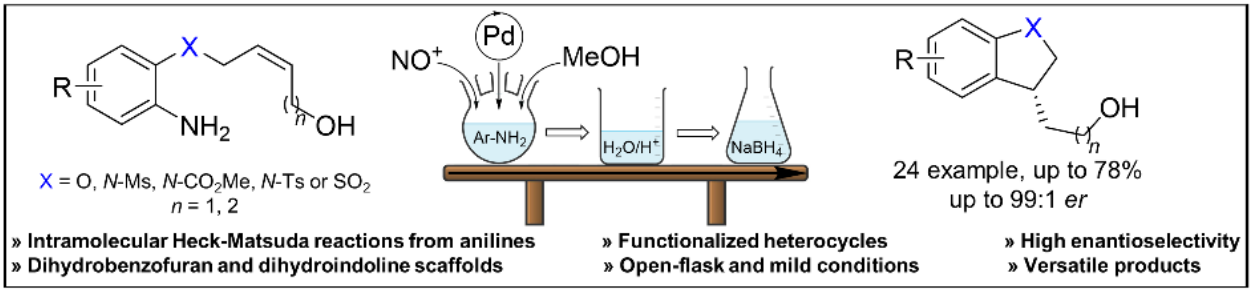
Keywords:*Catalysis, Enantioselectivity, Intramolecular Heck reactions.*

ABSTRACT

Heteroaromatic compounds are scaffolds present in a variety of important natural products, and they are building blocks in the synthesis of several biologically active molecules, agrochemicals, and drugs. Dihydrobenzofuran and indolines are relevant heterocyclic compounds, and the literature lacks effective protocols for their enantioselective synthesis.[1] Since our first enantioselective Heck-Matsuda reaction in 2012,[2] we have been focusing on the expansion of the reaction to the construction of more complex heterocycles.[3]

Herein, we report the efficient and practical protocol for the homogeneous Pd-catalyzed synthesis of dihydrobenzofuran, dihydroindole, and dihydrobenzosulfone scaffolds with high enantioselectivity in a Heck-Matsuda reaction with aryldiazonium salt generated *in situ* directly from anilines, or nitro compounds, in a tandem, one-pot, process. Derivatizations of the versatile acetal intermediate allowed the construction of more than 20 hydroxylated heterocycles and methyl esters in overall yields up to 78% over 5 steps, in an enantiomeric ratio of up to 99:1.[4] Those functionalized heterocycles represent valuable building blocks in organic synthesis.



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Highly Enantioselective Lewis Acid Catalyzed Conjugate Addition of Imidazo[1,2-*a*]pyridines to α,β-Unsaturated 2-Acylimidazoles under Mild Conditions

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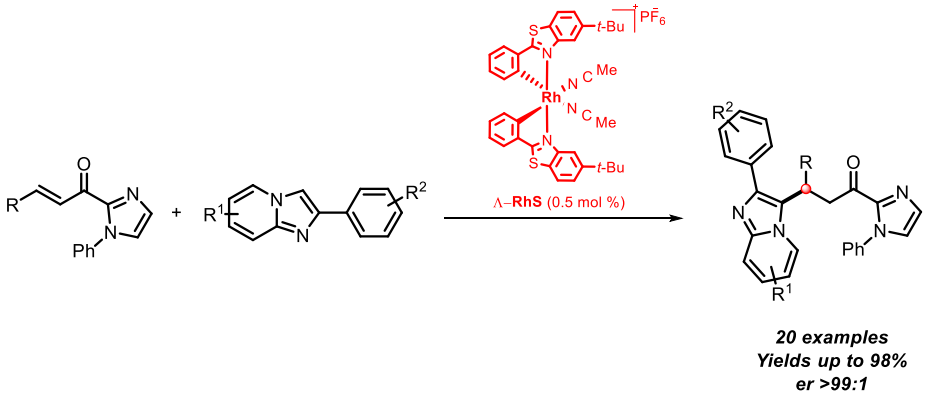
Keywords: *asymmetric catalysis, enantioselective synthesis, rhodium catalyst.*

ABSTRACT

Chirality is of great relevance for the drug development processes; however, the enantioselective synthesis of chiral compounds remains a challenge nowadays. In this context, asymmetric catalysis is an emergent and attractive tool for the enantioselective synthesis of chiral molecules.[1] Additionally, new synthetic methods that prioritize the use of mild reagents along with smooth, safe, and practical reaction conditions are also very desirable.[2] In this work, we describe a simple and robust catalytic asymmetric conjugate addition of 2-arylimidazo[1,2-*a*]pyridines to α,β-unsaturated 2-acylimidazoles in the presence of a rhodium-based chiral Lewis acid catalyst, using mild reaction conditions with very high stereoselectivity. Our method provided the corresponding adducts in yields of 25–98% with enantioselectivities up to *er* > 99:1.[3] The imidazo[1,2-*a*]pyridine moiety is embedded in the structure of many commercial drugs and can be associated with a wide range of biological activities, which make them an interesting study skeleton in organic synthesis.[4]



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SEPTEMBER 23-27 2024
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Selenium dioxide in the synthesis of oxazole-5-carbaldehydes

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Keywords: *oxazole, selenium dioxide, propargylamide.*

ABSTRACT

Heterocyclic systems are a prominent class of compounds, which are widely found in nature and extensively applied in different industrial segments.[1] Among them, oxazole derivatives are a class of biologically privileged structures, which play an important role in the prospection of new drugs in the pharmaceutical industry, being the core of important bioactive molecules.[2] Among the pharmacological properties of oxazoles are antitubercular,[3] anticancer,[4] antibacterial,[5] antifungal,[6] and antidiabetic.[7]
In this work it was developed a simple and efficient methodology to access 2-substituted oxazole-5-carbaldehydes. In this strategy, intramolecular cyclization reactions of *N*-propargylamide **1a-i** were performed, using selenium dioxide (1.5 equiv.) as the oxidant and acetonitrile as a solvent. The reactions were conducted at 80 °C for 4 h, leading to the respective oxazoles **2a-i** in good to excellent yields (Scheme 1).

Scheme 1. Synthesis of 2-substituted oxazole-5-carbaldehydes.

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SEPTEMBER 23-27 2024
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Multisite-Sequential Cyclization to Construct 1,2,3-Triazole-Based Se,N-Fused Heterocyclics

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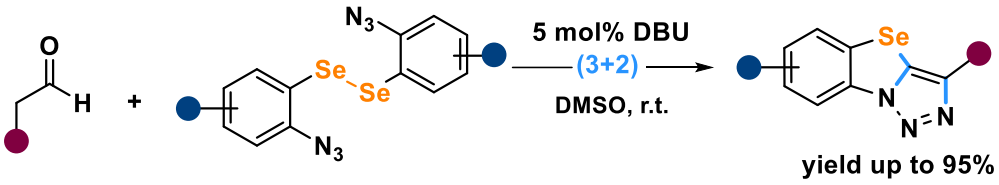
Keywords: *1,2,3-triazoles, cascade reaction, organocatalysis, organoselenium.*

ABSTRACT

The construction of complex polyheterocyclic molecules, such as pharmaceuticals, polymers, agrochemicals and dyes, which are integrated into everyday life, has been in the spotlight of organic synthesis.[1] Cascade reactions offer an ideal and efficient approach to constructing such compounds, building molecular complexity in a single transformation.[2] In particular, 1,2,3-triazoles fused with heterocycles at the 1,5-positions represent a ubiquitous type of core substructure that has attracted enormous interest since they have been frequently found in synthetic molecules, biologically active substances, and pharmaceutical targets. Among the established strategies,[3] the interrupted version of copper(I)-catalyzed azide−alkyne cycloaddition (CuAAC) stands out as one of the most direct and straightforward synthetic approaches for accessing 1,2,3-triazoles fused at the 1,5-positions with different heterocyclic moieties. In the last few decades, organocatalysis has emerged as a powerful tool for synthesizing diversely functionalized 1,2,3-triazoles that are inaccessible by other means.[4] Based on our continuing interests in developing elegant approaches for constructing 1,2,3-triazoles and on the organoselenium compounds chemistry, we reported here a novel method for constructing selenium-cycle-fused 1,2,3-triazoles by combining the organocatalyzed (3+2)-cycloaddition of aldehydes with 1,2-bis(2-azidoaryl)diselenides followed by an intramolecular cyclization reaction (Scheme 1).



Features:
- cascade reaction; - metal-free; - three new bonds C-N, C-N, C-Se; - mild reaction; - broad scope;

Scheme 1.

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SEPTEMBER 23-27 2024
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Functionalization of Sulfoxonium Ylides with molecular iodine: Synthesis of α- (Xanthates, Dithiocarbamates, Thiocyanato)-α-Carbonyl Sulfoxonium Ylides

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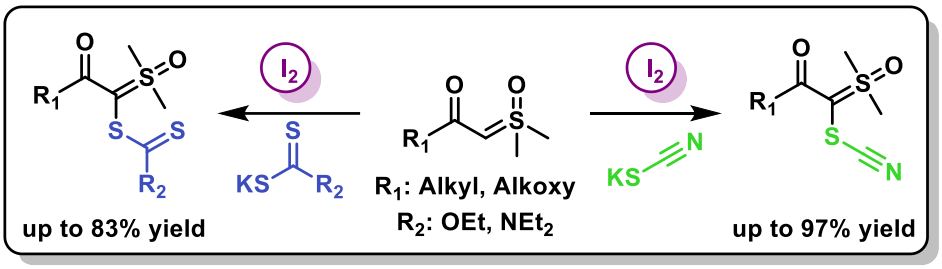
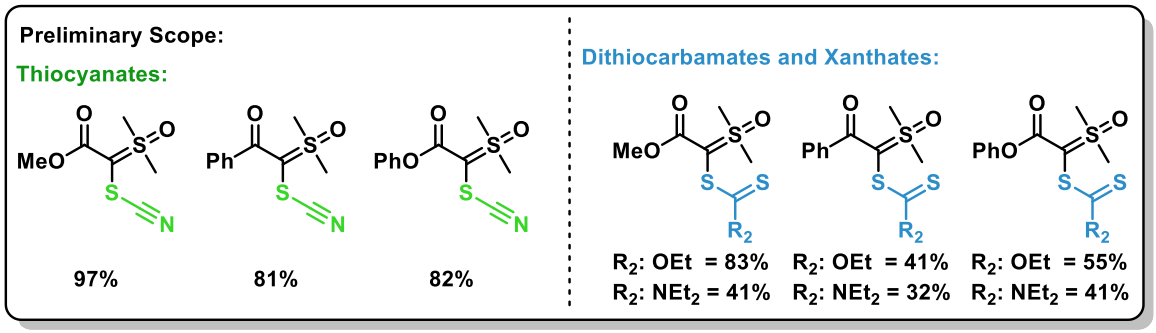
Keywords: *Sulfoxonium, ylides, radical chemistry, xanthate, dithiocarbamate, thiocyanate.*

ABSTRACT



Sulfoxonium ylides have captivated the attention of chemists since their emergence in the 1960s[1], gaining even greater interest in recent years[2]. This attention has brought forth significant advancements in ylide chemistry, including known reactions with molecular iodine[3]. Here, we present a novel and distinctive method for functionalizing both ester and keto sulfoxonium ylides using molecular iodine and sulfur-based nucleophiles such as xanthates, dithiocarbamates, and thiocyanates. This approach yields α- (xanthates, dithiocarbamates, thiocyanato)-α-carbonyl sulfoxonium ylides. The functionalization is a topic of interest as these reactions are uncommon, and new methods to synthesize more complex ylides are still necessary[4]. Furthermore, both dithiocarbamates and thiocyanates are reported to be present in different molecules with biological activity[5]. Nine examples were prepared in a preliminary study, achieving yields of up to 97%[6]. Additionally, experiments using TEMPO suggests a radical mechanism, which provides insight into the formation of functionalized sulfoxonium ylides rather than functionalized ketones.



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SEPTEMBER 23-27 2024
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Employing substituted pyrazoles as stoppers in rotaxanes

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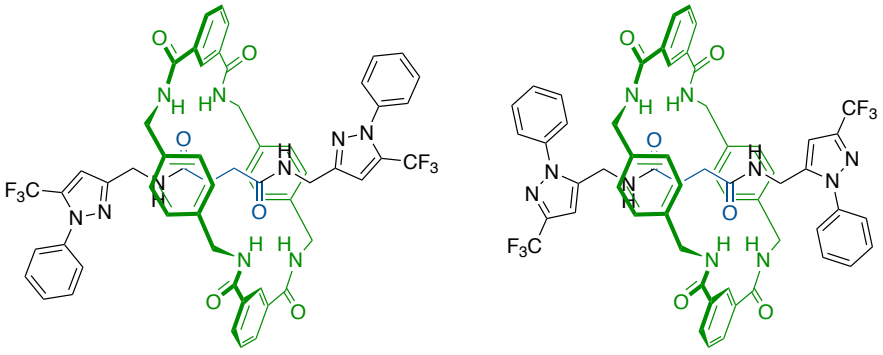
Keywords: *Pyrazoles, Rotaxanes, Intercomponent interactions.*

ABSTRACT

[2]Rotaxanes consist of two main components: a linear 'thread' with bulky end groups called stoppers, and a cyclic component called 'macrocycle'.[1,2] These molecules serve as excellent supramolecular models, displaying a range of interactions observable in both solution and solid states.[3,4] Substituted pyrazoles can be synthetized as different regioisomers and their use as bulky groups may assist to recognize how intercomponent interactions reflect in the movements performed by rotaxanes.[5,6] Based on our research group's expertise in pyrazoles synthesis, we propose the construction of novel threads and rotaxanes by exploring different regioisomers of pyrazoles as bulky groups. To synthesize the rotaxanes, several synthetic processes were used including acylation, allylic halogenation, nucleophilic substitution, cyclocondensation, organic reduction, nucleophilic addition and intramolecular cyclization. A multicomponent reaction was also employed to form a tetralactam macrocycle. Two rotaxanes (**1** and **2**) designed for this project are shown in Figure 1 as initial goals.



1 **2**

Figure 1. Rotaxanes **1** and **2** design for this study.

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Selenation of 2-arylimidazo[1,2-*a*]pyridines promoted by visible light using arylseleninic acids

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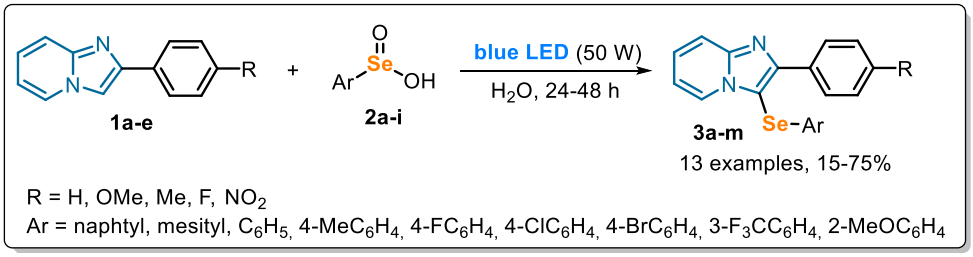
Keywords: *organoselenium, imidazopyridines, photochemistry*

ABSTRACT

The imidazo[1,2-*a*]pyridine derivatives are considered key structures due to their applications in materials science, medicinal chemistry and organometallics.[1] In particular, imidazo[1,2-*a*]pyridines functionalized at the position 3 have a variety of pharmacological activities, such as anticancer, antibacterial, and antifungal.[2] Due to this, efforts have been made to develop new methodologies to prepare this class of compounds. On the other hand, organoselenium compounds are known for their synthetic and pharmacological applications, presenting, for example, anticancer, antimicrobial, antioxidant, and antidepressant activities.[3] Furthermore, in recent years, we have dedicated our efforts to developing light-mediated reactions for the synthesis of organochalcogen compounds, through environmentally friendly strategies.[4] Therefore, as a continuation of our efforts, we report an alternative and mild method for the synthesis of 2-phenyl-3-(phenylselanyl)imidazo[1,2-*a*]pyridines starting from different 2-aryllimidazo[1,2-*a*]pyridines and arylseleninic acids as selenylating agent, under 50 W blue LED irradiation and water as solvent. Using this method, thirteen products were obtained with yields ranging from low to moderate (15-75%) in reaction times of 24 h to 48 h (Scheme 1). The presented method does not require the use of metals, oxidants nor heating. Diaryl diselenide, which can be recovered converted to arylseleninic acid, and water are formed as by-products in the reaction.



Scheme 1. Selenation of 2-aryllimidazo[1,2-*a*]pyridines using arylseleninic acid.

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We thank to the CAPES, CNPq, FAPERGS, and UFPel for financial support.

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New Chitosan Beads as Efficient Organocatalysts for Accessing 1,2,3-Triazoles

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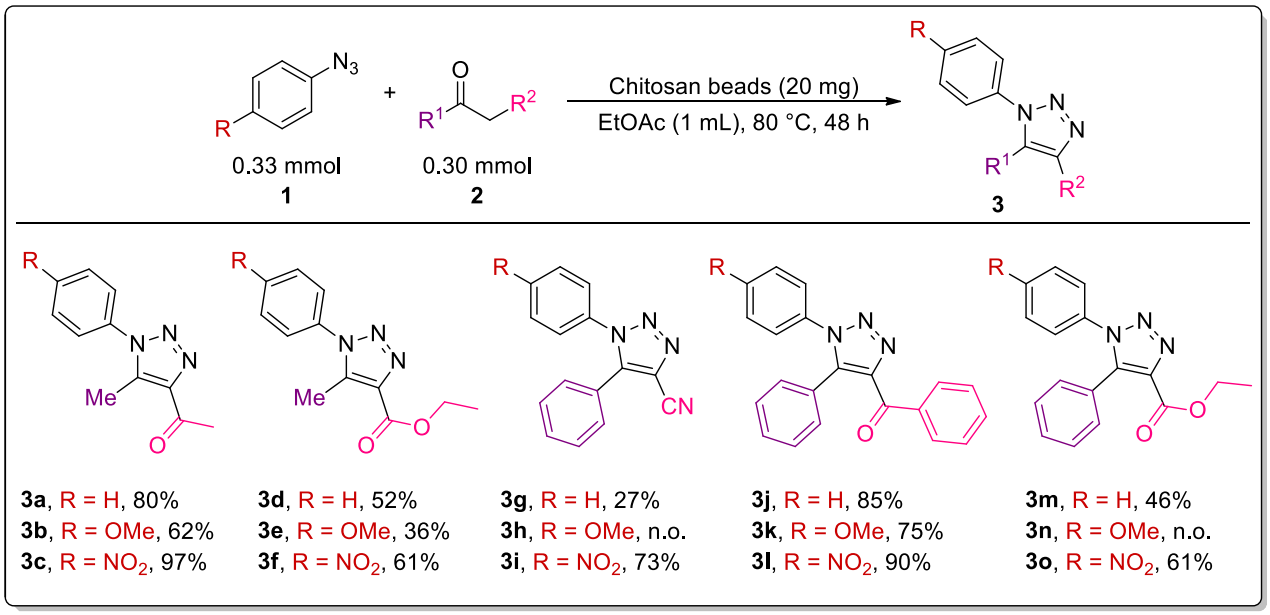
Keywords: *1,2,3-triazoles, organocatalysis, chitosan beads.*

ABSTRACT

1,2,3-Triazoles constitute a relevant class of *N*-heterocyclic compounds. They are widely found in pharmaceuticals due to their various biological activities. One of the most common methodologies for their synthesis is the [3+2] cycloaddition reaction using azides.[1]

Concomitantly, modified chitosan emerges as an organocatalyst because of its environmental advantages. Chitosan is a low molecular weight organic molecule with exceptional qualities, including non-toxicity, biodegradability, biocompatibility, and low cost.[2]

Based on this, we report a new methodology to validate the performance of developed chitosan beads as an organocatalyst in azide-ketone [3+2] cycloaddition reactions for the synthesis of 1,2,3-triazoles. The best reaction conditions for this synthesis use 0.33 mmol of azide **1**, 0.30 mmol of ketone **2**, 20 mg of chitosan beads as the catalyst, and ethyl acetate as the solvent, at 80 °C for 48 hours. Using this protocol, thirteen compounds were obtained, with yields ranging from 27% to 97% (Scheme 1).



Scheme 1. Scope of the reaction of azides **1** with ketones **2** to form 1,2,3-triazoles **3**.

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We thank CAPES, CNPq, FAPERGS and UFPEL.

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Copper-Catalyzed β-Hydroxylation of Abietanes: Synthesis of a C5 Bridgehead Alcohol

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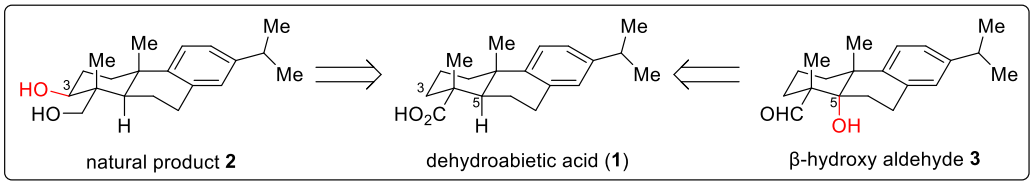
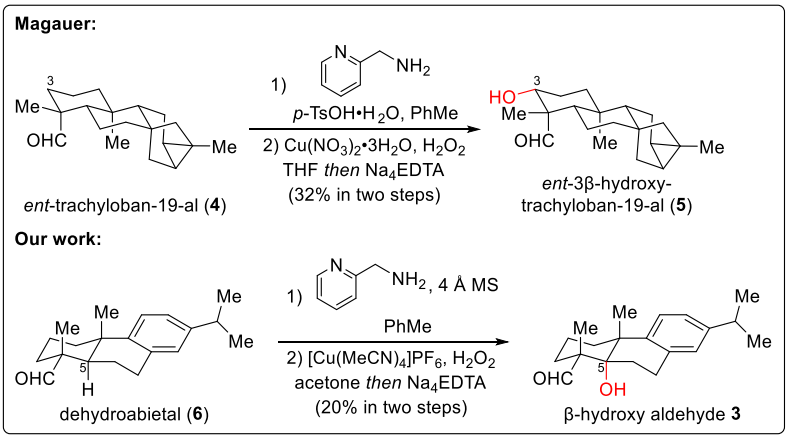
Keywords: *Natural Products, Diterpenes, C-H oxidation.*

ABSTRACT

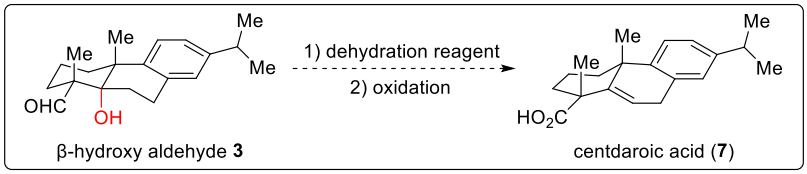
This study investigates a synthetic approach to obtaining complex natural products through the oxidation of C—H bonds. Using a copper-mediated oxidation,[1] we aimed to oxidize the C3 position in dehydroabietic acid (**1**) as a key step to achieve the natural product **2**. Surprisingly, the reaction yielded a bridgehead alcohol, an interesting product for further diversification.



In a recent study,[2] Magauer and co-workers used a copper-catalyzed oxidation to functionalize the C3 position in a natural product derivative. Applying this method to dehydroabietal (**6**), we obtained a bridgehead alcohol at the C5 position. While the directing group in the study of the Magauer group was in axial, ours was equatorial, directing the C—H oxidation towards the C5 position, forming the β-hydroxy aldehyde **3**.



With the oxidized product in hands, we plan a dehydration followed by an oxidation to a carboxylic acid, to yield centdaroic acid (**7**), enabling further functionalization of **1** and other diterpenes.



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We are grateful to São Paulo Research Foundation (FAPESP), for the financial support for this work (grant 2018/04837-6) and fellowships to L. Jaroczinski (grant 2023/06648-4) and L.D.P. Gonçalves (grant 2023/13162-0), FAEPEX, CNPq, and CAPES.

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Late-stage, C–H oxidation/decarboxylation via non-heme iron catalysis diversion

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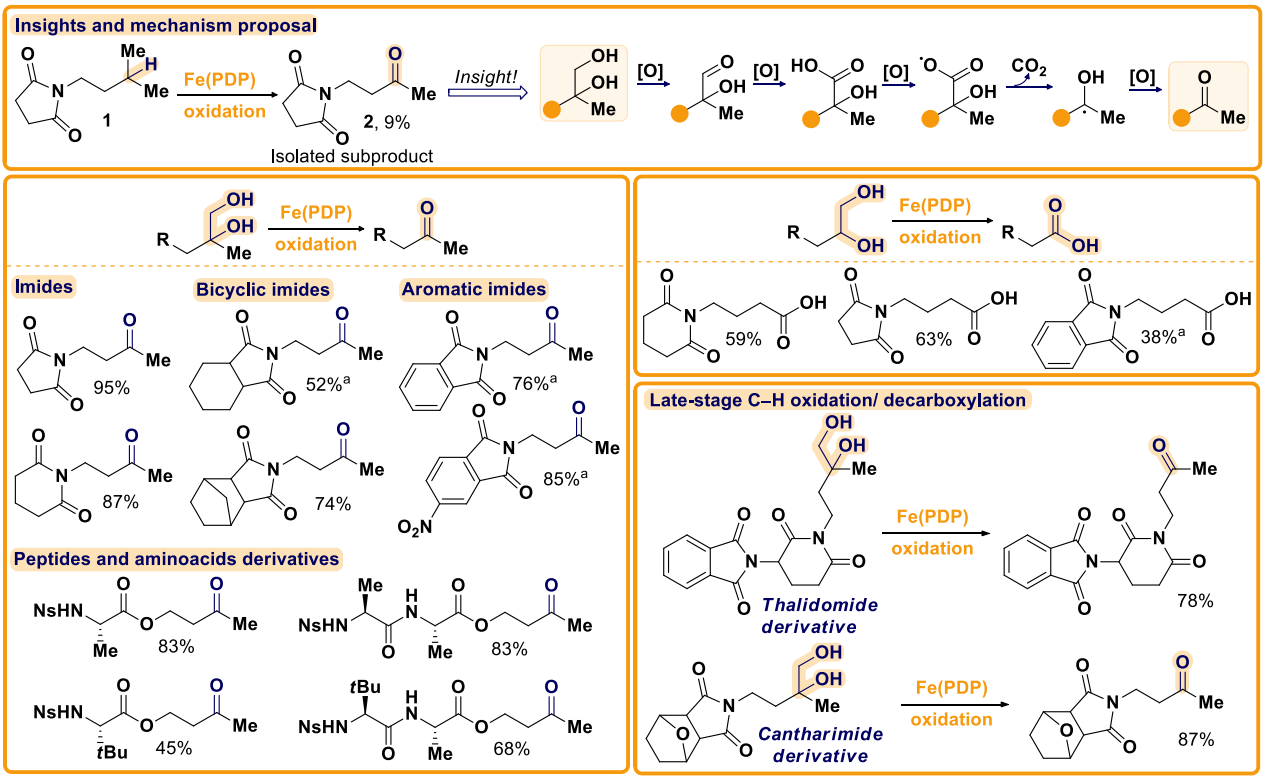
Keywords: *C–H oxidation, decarboxylation, iron catalysis*

ABSTRACT

Understanding what byproducts a reaction condition forms can provide good insights into the development of new reactivites. Recently, an unexpected product was observed by our research group in the oxidation of compound **1**, which is known to form only a tertiary alcohol.[1] Besides the methine oxidation, we observed the formation of the methyl ketone **2** in 9% yield (Scheme 1). Therefore, a cleavage of a C–C bond must have occurred. This result urged us to study more closely this reactivity.
Thus, a new method has been developed that allows the oxidation of an aliphatic C–H bonds followed by a decarboxylation using Fe(PDP). This new reactivity using non-heme iron catalysis expands the scope of C–H bond oxidation beyond hydroxylations and desaturations, and facilitates late-stage diversification of complex molecules.



Scheme 1. Scope and complex examples. *Reactional condition: 15 mol% Fe(PDP), 5 eq. AcOH, 9 eq. H_2O_2, MeCN, rt, 90 min. [a]Using 4.5 eq. H_2O_2.*

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SEPTEMBER 23-27 2024
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Copper-Mediated C—H Bond Oxidation in Synthetic Studies of Complex Diterpenes

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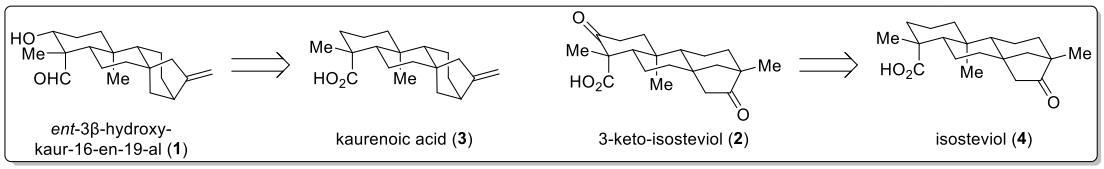
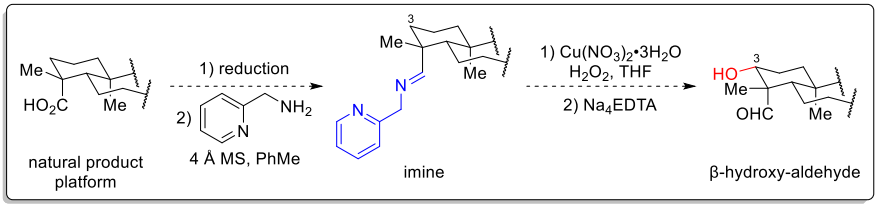
Keywords: *Natural products, Diterpenes, C—H oxidation.*

ABSTRACT

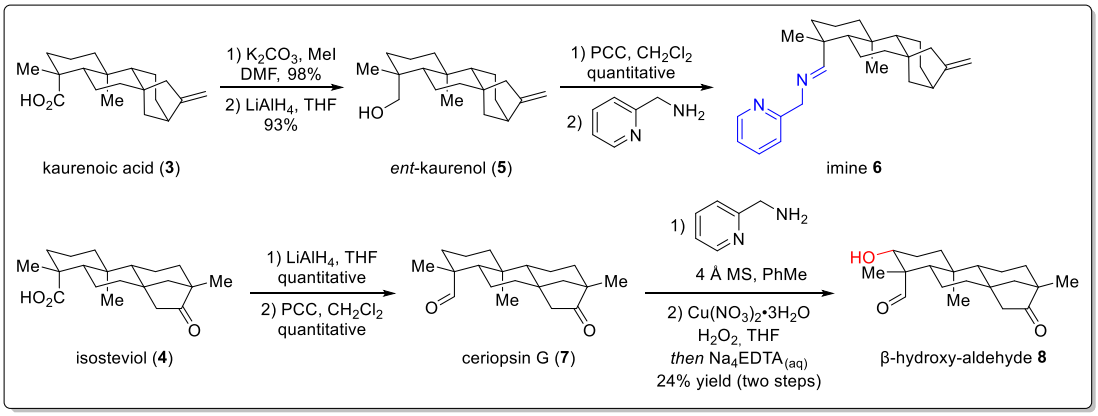
This study aims to investigate a synthetic route to obtain the natural products **1** and **2**,[1] through an oxidation of C—H bonds as the key step. Since these natural products have an *ent*-kaurene (**1**) and *ent*-beyrane (**2**) carbon skeleton, we propose synthesizing them from kaurenoic acid (**3**) and isosteviol (**4**), respectively.



In view of recently reported synthesis of *ent*-trachylobanes through a copper-mediated oxidation of a C—H bond,[2] we propose to use this strategy in the synthesis of natural products **1** and **2**.



By employing these reactions, we have progressed in our efforts to synthesize the natural products. The next steps involve the oxidation of a C—H bond using the kaurenoic acid imine derivative **6**, and the correction of oxidation states to obtain the proper natural products.



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Revisiting the Reactions of Sulfur Ylides with Acetylenic Esters: Facile and Stereoselective Synthesis of Electron-Deficient Trisubstituted 1,3-Dienes, α-Carbonyl Vinyl Sulfoxides and α-Carbonyl Vinyl Sulfoxonium Ylides

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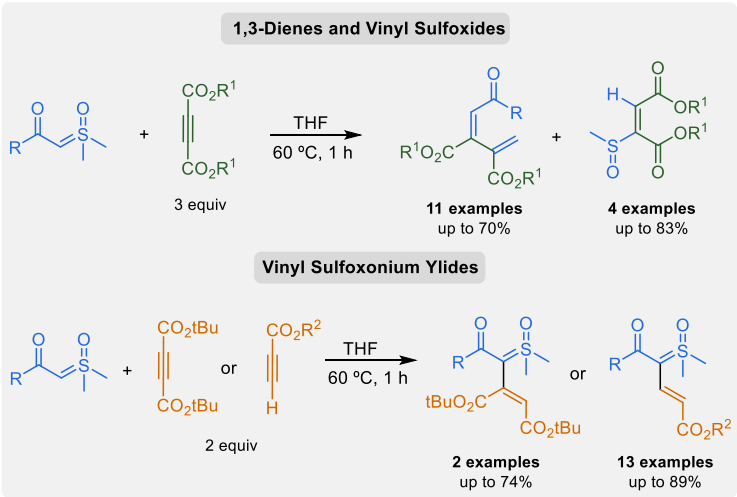
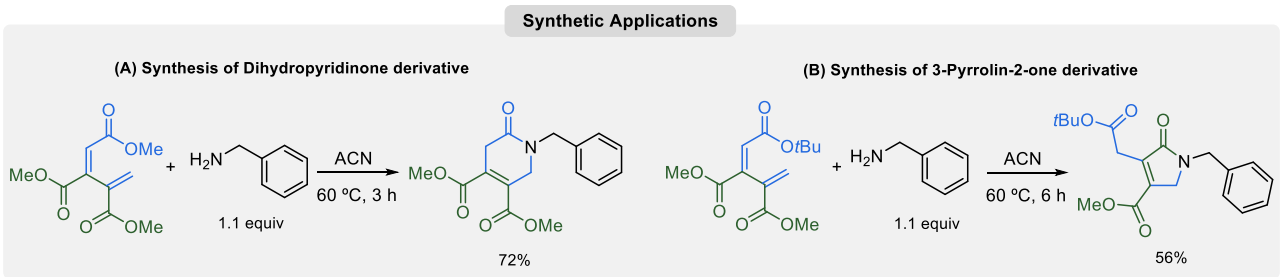
Keywords: *1,3-Dienes, vinyl sulfoxides, vinyl sulfoxonium ylides*

ABSTRACT

1,3-dienes and vinyl sulfoxides constitute the framework of numerous bioactive natural and synthetic compounds, often playing a crucial role as intermediates in total synthesis.[1-4] Continuing our previous study of conjugate additions using α-carbonyl sulfoxonium ylides,[5] we came across an interesting transformation when dimethyl acetylenedicarboxylate (DMAD) was employed as a Michael acceptor. Trisubstituted electron-deficient 1,3-dienes and α-carbonyl vinyl sulfoxides were obtained for the first time from these sulfur ylides, in a stereospecific manner, achieving yields of up to 70% and 83%, respectively. The proposed mechanism involves two sigmatropic rearrangements and the generation of sulfenic acid, leading to the formation of both products. Selected dienes were subsequently utilized in the synthesis of novel nitrogen heterocycles through conjugate addition reactions. On the other hand, when di-*tert*-butyl acetylenedicarboxylate (D*t*BAD) or alkyl propiolates were evaluated, the isolated product arose from the classical Michael addition, yielding α-carbonyl vinyl sulfoxonium ylides in yields of up to 89%.





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FAPESP · Research Centre for Greenhouse Gas Innovation · CAPES · CNPq · IQSC

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Rhodium Catalysed Deconstruction of Epoxy Resin in Water

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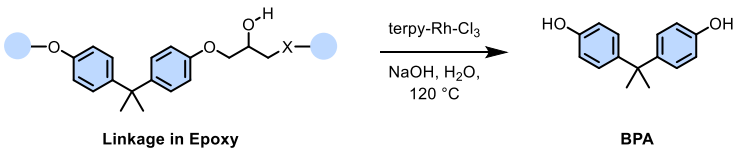
Keywords: *Catalysis, C-O bond activation, polymer recycling.*

ABSTRACT

Thermoset epoxy resins and their fibre reinforced composites have excellent resistances to chemical exposure and mechanical stress. Meant for structures designed to last, such as coatings, airplanes, or wind turbines, deconstruction and recycling of epoxy is highly challenging, and thus underdeveloped[1]. To achieve circular economies for plastics, which reduce waste accumulation and resource consumption, efficient depolymerisation strategies are necessary, which optimally adhere to the principles of green chemistry, such as atom efficiency and the use of green solvents[2]. For the valorisation of lignin, terpy-Rh complexes have been shown to be efficient depolymerisation catalyst in water[3].
Here, we present a rhodium catalysed approach to selectively cleaving C(Alkyl)–O bonds in epoxy resins in mild conditions with water as sole solvent. The reactivity was investigated on model compounds mimicking the linkages of epoxy polymers. Furthermore, we demonstrate the recovery of the polymer building block bisphenol A from commercially used thermoset epoxy polymers.



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Synthesis of chalcones and *in vitro* and *in silico* evaluation for *Helicobacter pylori* and gastric adenocarcinoma cells

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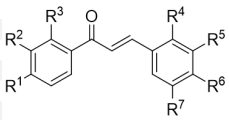
Keywords: *Claisen-Schmidt condensation, chalcones, Helicobacter pylori.*

ABSTRACT

Helicobacter pylori is a gram-negative bacterium that colonizes the human stomach and is a major risk factor for the development of inflammatory gastrointestinal diseases, including cancer[1,2], which is why it is classified as group 1 carcinogen by World Health Organization[3]. NF-kB and MAPK pathways are triggered by *H. pylori* infection[4–6], specially cagA$^+$ strains, and are usually overexpressed in cancer. The objective of this study was to synthesize 10 hydroxylated and methoxylated chalcones and evaluate their anti-*H. pylori* and gastric antitumor effects. The chalcones were synthesized through *Claisen-Schmidt*[7,8] condensation within yields of 15-52%, then characterized by ^{1}H and ^{13}C Nuclear Magnetic Resonance and Mass Spectrometry. Predictive *in silico* data revealed possibility of anti-*H. pylori*, anti-inflammatory and MMP-9 inhibition for the chalcones. Three of the ten chalcones (**1**, **6**, **7**) showed strong *H. pylori* growth inhibition results (MIC and MBC ranging from 1-2 µg/mL). Compound **7** also presented significant MMP-9 inhibition docking score and CI_{50} for AGS cells (32.25 ± 5.43 µM). Then, these results reveal that compound **7** is promising as a possible drug for *H. pylori* treatment, that may act synergically reducing the inflammatory response and the possibilities for developing gastric tumor.

Compound	R^1	R^2	R^3	R^4	R^5	R^6	R^7	MIC (µg/mL)	MBC (µg/mL)	L929 IC_{50} (µM)	AGS IC_{50} (µM)	SI	S (kcal mol^{-1})
1	-OH	-H	-OH	-H	-H	-OMe	-H	1	2	177.30 ± 6.81 ****	48.21 ± 1.04	3.60 **	-7,26
2	-OMe	-H	-OH	-OMe	-H	-H	-H	4	8	352.05 ± 7.46 ****	55.92 ± 12.84	6.30 ****	-7,37
3	-OMe	-H	-OH	-H	-H	-OMe	-H	2	4	92.19 ± 16.21 ****	108.58 ± 16.36 ****	0.85	-7,63
4	-OMe	-H	-OH	-OMe	-H	-OMe	-H	2	4	135.81 ± 9.35 ****	186.39 ± 14.70 ****	0.73	-7,75
5	-OMe	-H	-OH	-OMe	-H	-H	-Br	4	8	233.58 ± 28.69 ****	32.49 ± 0.36	7.19 ****	-7,82
6	-OMe	-H	-OH	-Cl	-H	-H	-H	2	2	100.34 ± 10.15 ***	53.89 ± 3.88	1.86	-7,03
7	-OMe	-OMe	-OMe	-H	-H	-H	-H	2	2	84.03 ± 1.01 ***	32.25 ± 5.43	2.61	-7,91
8	-H	-	-	-	-	-	-	4	8	95.55 ± 0.36 ***	25.34 ± 0.47	3.77 **	-7,31
9	-OMe	-	-	-	-	-	-	8	16	43.18 ± 9.46	135.74 ± 12.35 ****	0.32	-7,31
10	-Cl	-	-	-	-	-	-	8	8	303.67 ± 9.36 ****	28.70 ± 14.22	10.58 ****	-7,40
amoxicilin	-	-	-	-	-	-	-	0.0625	0.125	-	-	-	-
cisplatin	-	-	-	-	-	-	-	-	-	24.05 ± 6.04	39.59 ± 0.66	0.61	-
marimastat	-	-	-	-	-	-	-	-	-	-	-	-	-6,00

MIC: minimum inhibitory concetration; MBC: minimum bactericidal concentration; IC_{50}: Half-maximal inhibitory concentration; SI: selectivity index; ****: p < 0.0001; ***: p < 0.001; **: p < 0.01 compared to cisplatin; S: Ligand/receptor interaction energy of compounds against MMP-9 (lower is better);



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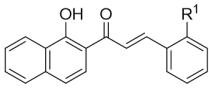

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19BMOS
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Asymmetric Dihalogenation from Sulfoxonium Ylides

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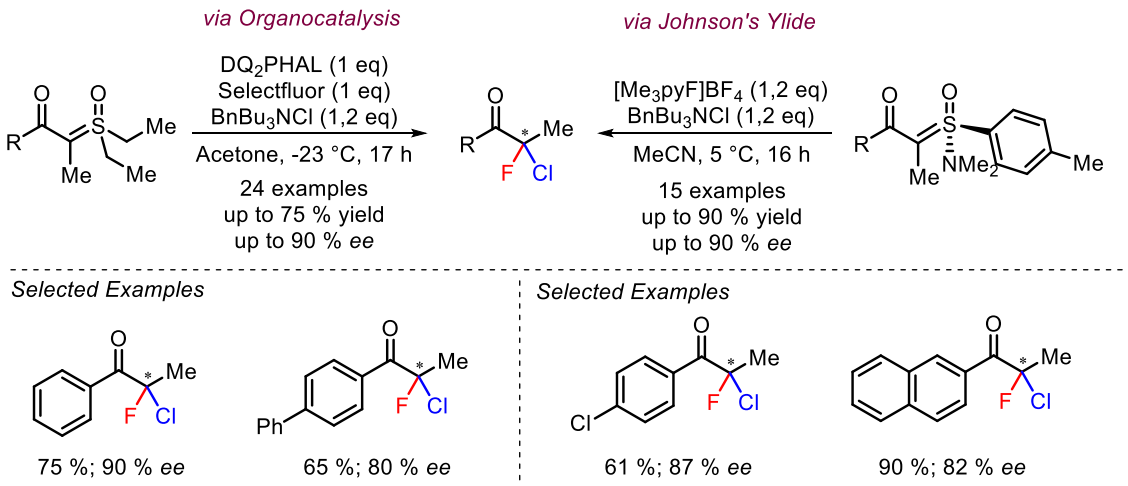
Keywords: *Sulfur Ylides, Dihalogenation, Enantioselective*

ABSTRACT

Optically activated fluorinated compounds are vital in medicinal and agricultural chemistry, with chiral *gem*-chlorofluorinated carbon centers being key building blocks for biologically active compounds.[1] Existing synthesis methods for these chiral centers often involve multiple steps or require starting materials containing halogens.[2] In this context, sulfoxonium ylides offer a promising alternative, capable of generating *gem*-disubstituted compounds in a single step.[3]

We developed two strategies to synthesize *gem*-chlorofluorinated compounds from sulfoxonium ylides under mild conditions. The first strategy, utilizing organocatalysis (Scheme 1, left), achieved the dihalogenated products with good yields and high enantioselectivity. The second strategy, employing Johnson's Ylide (Scheme 1, right), also produced the target compounds efficiently, with good yields and enantioselectivity. These methods streamline the synthesis process, offering a more efficient route to these important chiral building blocks.



Scheme 1. Asymmetric Dihalogenation from Sulfoxonium Ylides via: Left-Organocatalysis; right-Johnson's Ylide.

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Ruthenium(II)-Catalyzed C–H Alkenylation of SuFEx-Functionalized Quinones: A Mechanistic Approach

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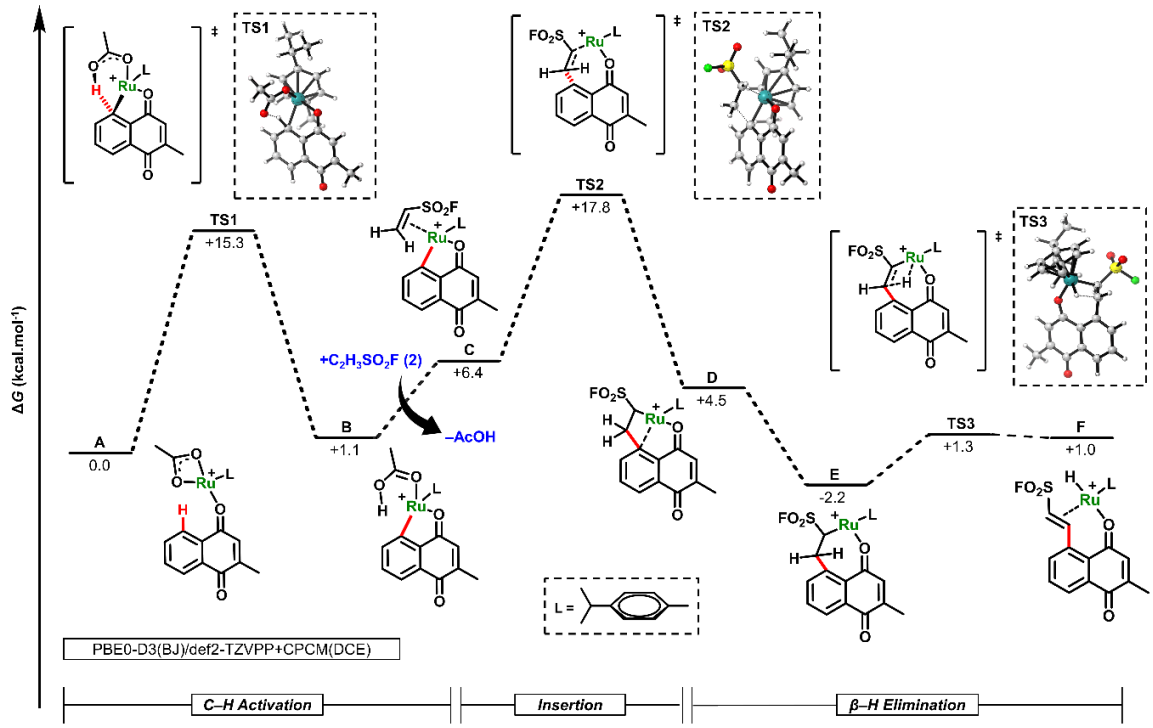
Keywords: *SuFEx, C–H activation, catalysis, naphthoquinones, reaction mechanism*

ABSTRACT

In the 21st century, the development of sustainable, selective, and modular click-reactions has revolutionized chemistry, enabling the rapid and efficient connection of molecular building blocks.[1] Within this concept, sulfur(VI) fluoride exchange (SuFEx) emerged as a second-generation click-type reaction, providing a protocol to obtain hypervalent sulfur derivatives under metal-free conditions.[2] Therefore, in pursuit of new C–H activation methodologies to afford direct functionalization of quinone motifs employing organometallic catalysis, our group has developed a ruthenium(II)-catalyzed C–H alkenylation route to access 1,4-naphthoquinone-based SuFEx–hybrids. In this work, aiming to investigate the alkenylation mechanism, we focus on a detailed computational approach using density functional theory (DFT). All free energies (ΔG) were computed at the PBE0[3]-D3(BJ)/def2-TZVPP+CPCM level of theory, following geometry optimizations and harmonic vibrational frequencies at PBE0-D3(BJ)/def2-SVP. Intrinsic reaction coordinate (IRC)[4] calculations were performed to verify the connectivity of transition states (TS), resulting in the proposed reaction pathway for the mono-methylated derivative.



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$Ce(SO_4)_2.4H_2O$ promotes the synthesis of carbazole derivatives through Michael addition and Diels-Alder reactions

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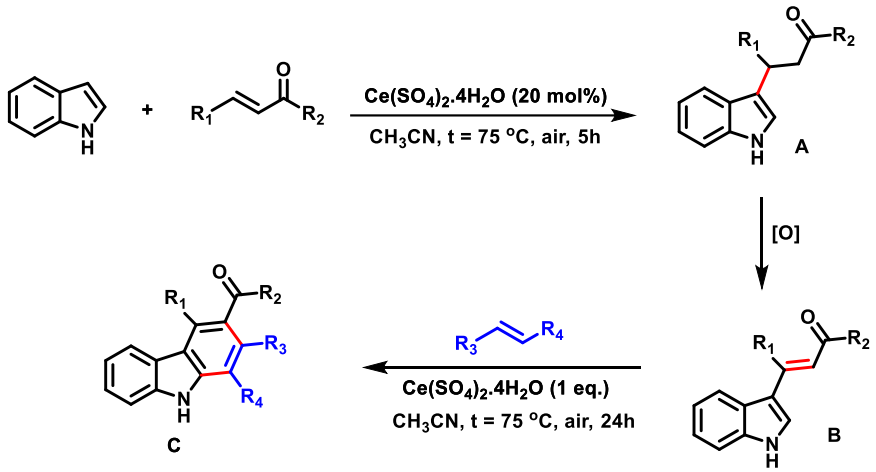
Keywords: *Catalysis, Michael addition, carbazole.*

ABSTRACT

Michael's addition reaction (MAR) is a versatile method to access numerous building blocks in organic synthesis such as the access to 3 substituted indole obtained from indole and α,β-unsaturated carbonyls [1–3]. Because of their biological relevance[4], it is still a rewarding task to search for new catalytic conditions to produce these alkaloids. We hereby report the synthesis carbazole alkaloids promotes by $Ce(SO_4)_2.4H_2O$ (**CAT1**) through Michael addition of indole to α,β-unsaturated ketones (chalcones) and the Diels–Alder reaction (DAR) (**Scheme 1**). Different catalysts were used among them **CAT1** turned out to be the best that enabled the preparation of 12 examples of A with yields up to 97% while 8 examples of C were produced with yields up to 30% in optimized conditions.

Scheme 1. Synthesis of Michael addition and the Diels-Alder reaction



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Experimental studies and *in silico* approaches in evaluating the effect of solvent on the ^{77}Se NMR chemical shift profile of diphenyl diselenides

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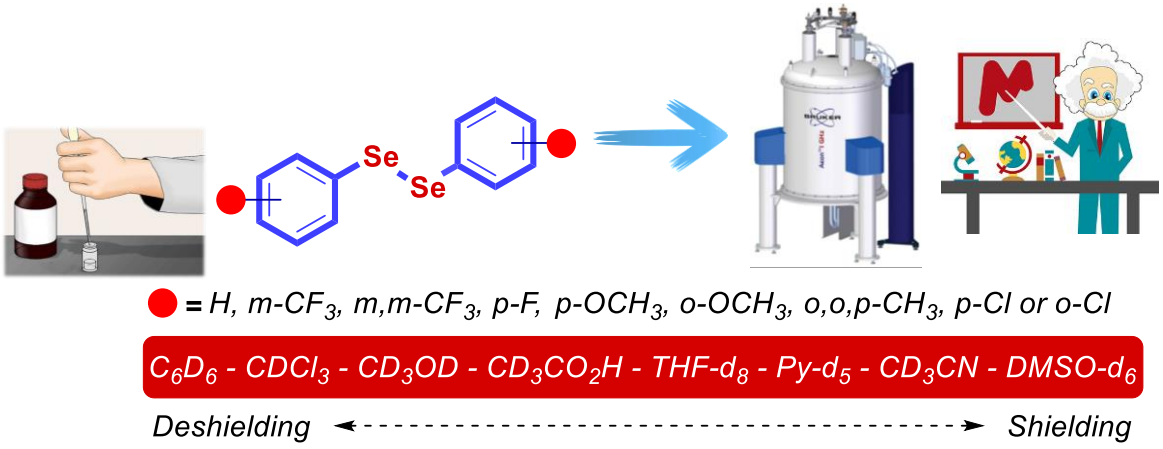
Keywords: *Diselenides, NMR, Solvents*

ABSTRACT

Nowadays, the chemical[1a-c] and pharmacological[2a-d] relevance of organoselenium compounds makes it imperative to know the behavior of the ^{77}Se nucleus in NMR analyzes under different experimental conditions, especially of the compounds used to provide the reference signal in the spectra. Diphenyl diselenide has been widely used as an internal reference standard due to its stability and ease of handling.[3a,b] However studies on the effect of experimental conditions on chemical shift in ^{77}Se NMR analyzes are scarce.

Therefore, we have prepared some common diphenyl diselenides and we evaluated the effect of solvent on the ^{77}Se NMR chemical shifts. Thus, ^{77}Se NMR spectra of diphenyl diselenides containing electron-withdrawing (EWG) or electron-donating (EDG) groups were recorded in eight different deuterated solvents with distinct polarities. The effects of temperature and concentration were also assessed and were found to play a minor role in the precise value of ^{77}Se chemical shifts. Finally, a computational study was performed to rationalize the ^{77}Se NMR chemical shifts behavior and to highlight the limits of standard approaches (Scheme 1)[4].



Scheme 1. Graphical abstract of this work

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Benzylation of Phenol Catalyzed by Diphenyl Ditelluride

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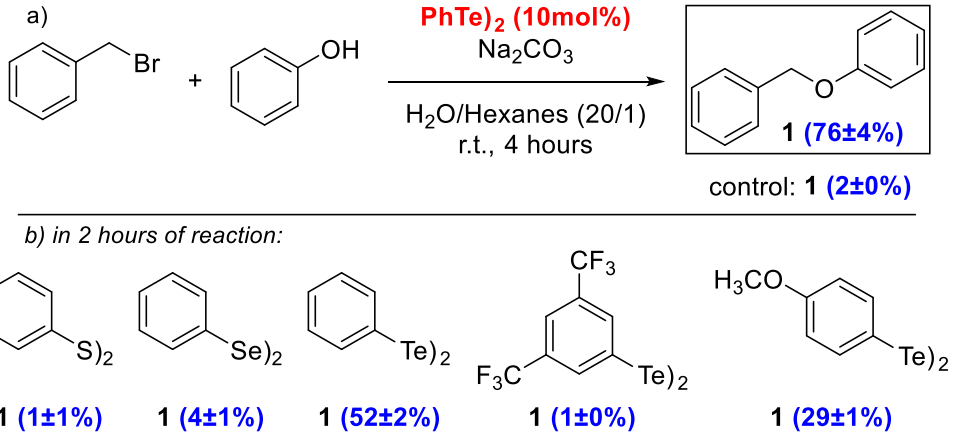
Keywords: *Organocatalysis, Alkylation, Chalcogen.*

ABSTRACT

In this work, we disclose our initial findings on the benzylation of phenols under a biphasic system catalyzed by ditellurides. Benzyl phenol ether **1** has been prepared using benzyl bromide, Na_2CO_3, and 10 mol% of PhTeTePh in a water/hexanes mixture (Scheme 1a). The reaction involves the *in situ* activation of benzyl bromide, resulting in an active species that transfers the benzyl group to the phenolate.[1-3] We optimized the reaction by varying the base, organic cosolvent, and catalyst. The results using different catalysts are described in Scheme 1b.



Scheme 1. Alkylation reactions catalyzed by $PhTe)_2$.

Currently, we are exploring the scope of substrates (phenols and bromides) that are suitable for this transformation and conducting control experiments to shed light on the reaction mechanism.

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Alternative synthesis of intubation drugs propofol and etomidate

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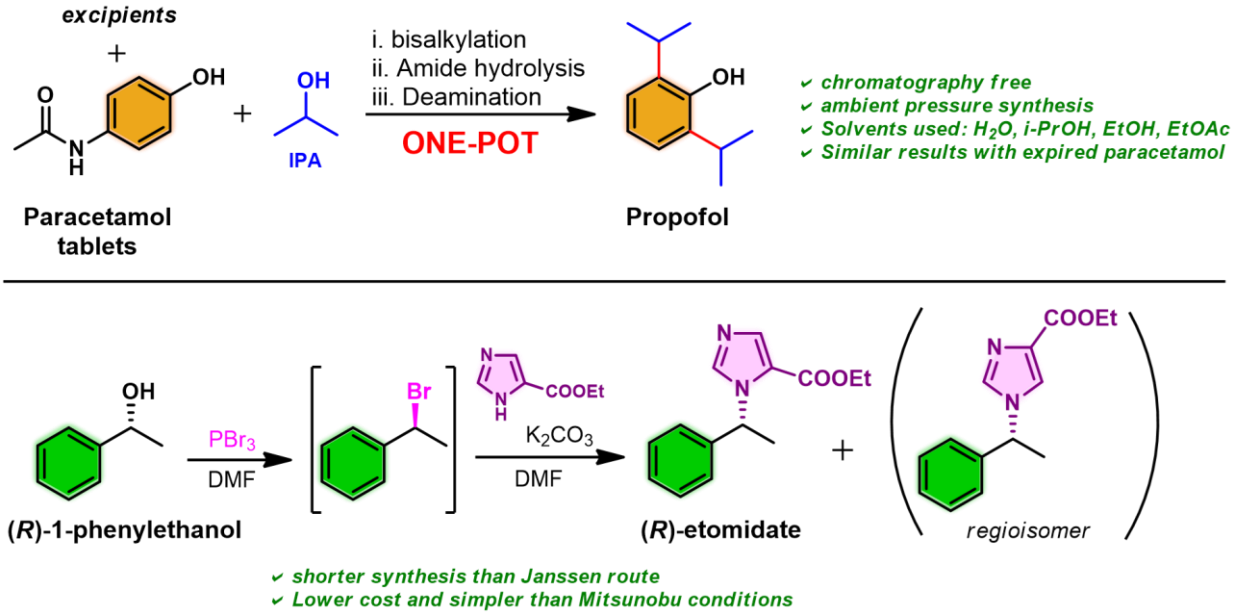
Keywords: *intubation drugs, one-pot synthesis, covid-19*

ABSTRACT

The COVID-19 pandemic has affected millions of people in the entire world and temporarily caused a shortage of several intubation drugs, including propofol and etomidate.[1] Herein, we present alternative synthesis of both sedative drugs with different approaches. The propofol was synthesized in a one-pot protocol starting from paracetamol, a very common and abundant active pharmaceutical ingredient. This presented process afford propofol in 47% isolated yield with high purity.[2] In the case of etomidate, a shorten route in comparison to the Janssen group[3] was developed. Starting from the commercially available (*R*)-1-phenylethanol, (*R*)-etomidate was synthesized by two SN_2 reactions. Substitution of the alcohol to the corresponding bromide followed by addition of ethyl imidazole-4-carboxylate in the presence of K_2CO_3 afforded etomidate in 30% overall yield.[4] Studies to minimize the regioisomer formation are in progress.



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From biomass to natural flavonoids: Studies for total synthesis of Podocarflavone A

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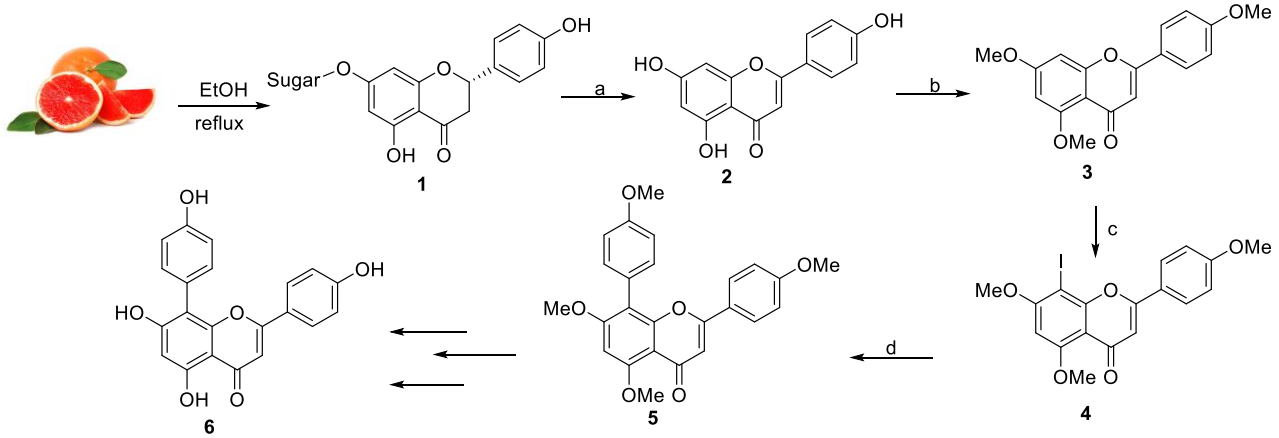
Keywords: *flavonoid, total synthesis, Suzuki-Miyaura Cross Coupling.*

ABSTRACT

Natural products are secondary metabolites produced by plants for various functions.[1] Flavonoids, a class of these metabolites, are polyphenolic compounds vital for plant metabolism, defense, and cellular signaling.[2] Podocarflavone A (**6**), a natural flavonoid, was first isolated from *Podocarpus macrophyllus* in 2014.[3] Few studies have evaluated its biological activities due to its recent isolation. Only one total synthesis has been reported, by Puranik and coworkers[4] in 2022, using a linear route from commercial materials. Our aim is to synthesize Podocarflavone A from grapefruit (*Citrus paradisi*) biomass wastes using an environmentally friendly extraction method.[5] The synthetic route developed includes five steps after extracting the O-glycosylated flavone: oxidation of natural flavonoid naringin **1**, followed by hydrolysis, full protection of apigenin **2**, regioselective halogenation, and a not-optimized microwave-mediated Suzuki-Miyaura coupling to compound 5. We will apply a demethylation protocol to obtain Podocarflavone A (**6**).



Scheme 1: Synthetic route to synthesize Podocarflavone A **6**.(a) i) I_2, pyridine, 100 °C, 16h, ii) H_2SO_4, glycerol, 120 °C, 1h, **74%** (over 2 steps); (b) $(CH_3)_2SO_4$, K_2CO_3, acetone, 16h, **70%**; (c) NIS, DMF, 70 °C, **65%**; (d) 4-methoxyphenylboronic acid, $Pd(OAc)_2$, K_3PO_4, toluene, MW, 150 °C, 2h, **26%**.

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SEPTEMBER 23-27 2024
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Synthesis of new triazolic thionaphthoquinones with trypanocidal potential

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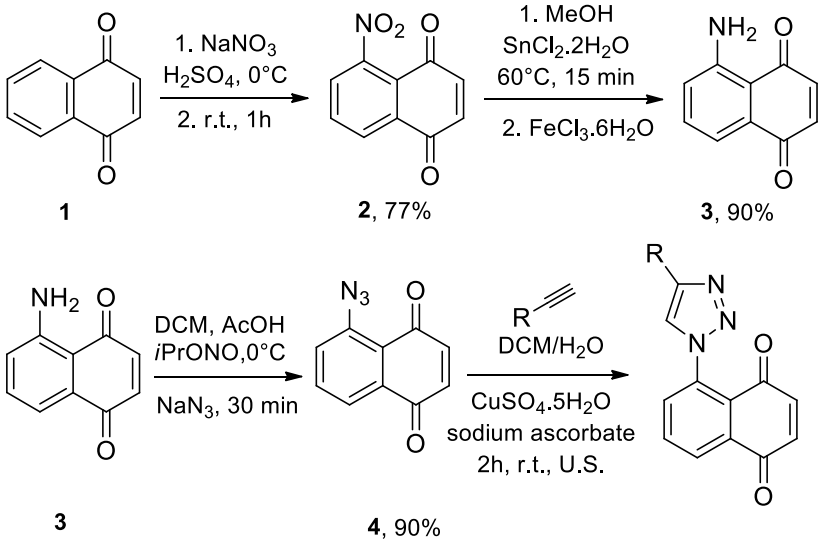
Keywords: *heterocycle, click chemistry, neglected disease.*

ABSTRACT

Naphthoquinones are a class of substances widely studied in the literature due to their wide variety of biological activities. Among these activities, it is possible to mention an enormous potential for the trypanocidal activity of triazole naphthoquinones.[1] In this context, this work aims to synthesize a series of thionapthoquinones linked to the triazole ring directly by the naphthoquinone aromatic ring. The synthetic route began with the nitration of **1**, producing intermediate **2**.[2] Then the nitro group was reduced using stannous chloride, obtaining intermediate **3**.[2] This intermediate underwent diazotization followed by a nucleophilic aromatic substitution with sodium azide producing intermediate **4**. Finally, a cycloaddition catalyzed by copper I occurred between **4** and different commercial and synthetic alkynes producing triazole derivatives **5**.[3] We synthesized 17 derivatives of the type **5**, 16 of which are new, that are currently in the prospecting phase for their trypanocidal activity.



5a, R= CH_2S(4-Me-Ph), 24%
5b, R = CH_2S(Ph), 53%
5c, R = CH_2S(2,5-diCl-Ph),47%
5d, R = CH_2S(4-Br-Ph), 56%
5e, R = CH_2S(2-benzotiazole), 47%
5f, R = CH_2S(3-Me-Ph), 21%
5g, R = CH_2S(2-Me-Ph), 27%
5h, R = CH_2S(4-NO_2-Ph), 58%
5i, R= CH_2S(4-Cl-Ph),62%
5j,R= CH_2S(4-F-Ph) 54%
5k,R= CH_2S(4-OMe-Ph), 32%
5l, R = Ph, 51%
5m, R = Pr, 37%
5n, R = But, 46%
5o, R = Pent, 41%
5p, R = 4(Pent)Ph, 46%
5q, R = CH(Me)(OH)CH_2CHMe_2, 39%

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Organocatalyzed synthesis of 1,5-diaryl-1*H*-1,2,3-triazolyl pyridines from α-2-pyridinyl-acetophenones and aryl azides

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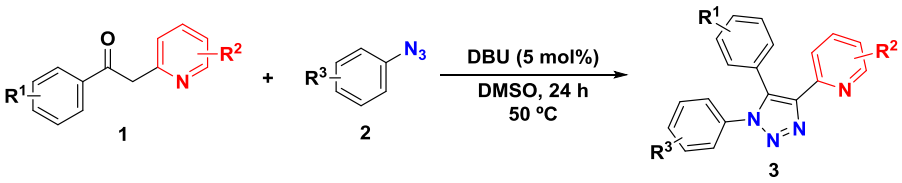
Keywords: *Cycloaddition, 1,2,3-triazoles, organocatalysis.*

ABSTRACT

1,2,3-Triazoles are significant nitrogen-based heterocycles studied extensively for drug and material synthesis.[1] Recent research aims to develop metal-free methods, including organocatalytic [3+2]-cycloaddition, for functionalized 1,2,3-triazole synthesis.[2] Designing an efficient and environmentally friendly synthesis using accessible substrates remains a challenge in organic chemistry. To date, organocatalytic synthesis of 1,2,3-triazolyl-pyridines has not been explored. This study focuses on synthesizing 1,5-diaryl-1H-1,2,3-triazolyl pyridines 3 via the reaction of α-2-pyridinyl-acetophenones 1 with aryl azides 2, utilizing DBU as an organocatalyst (Scheme 1).



Scheme 1. General scheme of the reaction.

Scheme 1 outlines the optimal synthesis conditions for 1,5-diaryl-1H-1,2,3-triazolyl pyridines 3: α-2-pyridinyl-acetophenones 1 (0.3 mmol), aryl azides 2 (0.375 mmol), and DBU (5 mol%) in DMSO (0.5 mL), stirred at 50°C for 24 hours under ambient air. This method yielded various 1,2,3-triazolyl-pyridines with yields ranging from 7% to 93%. Notably, the reaction demonstrated excellent tolerance to diverse electron-donating and -withdrawing groups on the aromatic ring, underscoring its potential utility in organic synthesis.

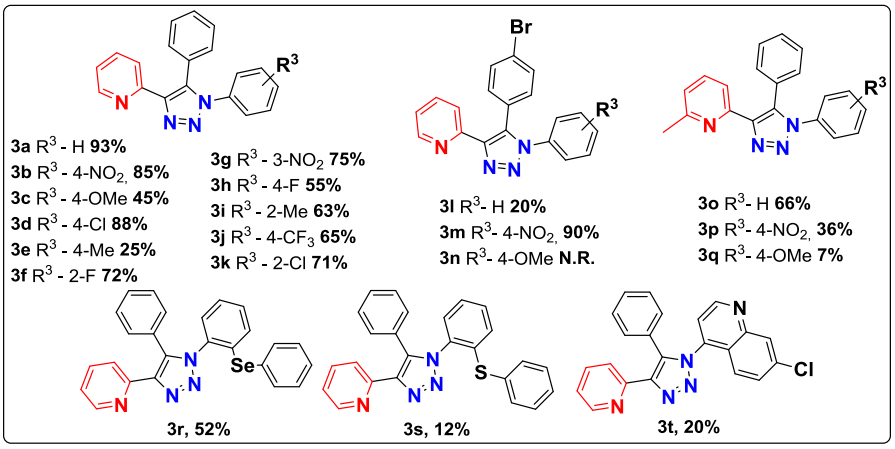


Figure 1. Synthesis of 1,5-diaryl-1*H*-1,2,3-triazolyl pyridines 3a-t.

ACKNOWLEDGEMENTS

LaSOL, CNPq, CAPES, FAPERGS and UFPel.

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Synthesis of selenylated derivatives of acetanilide

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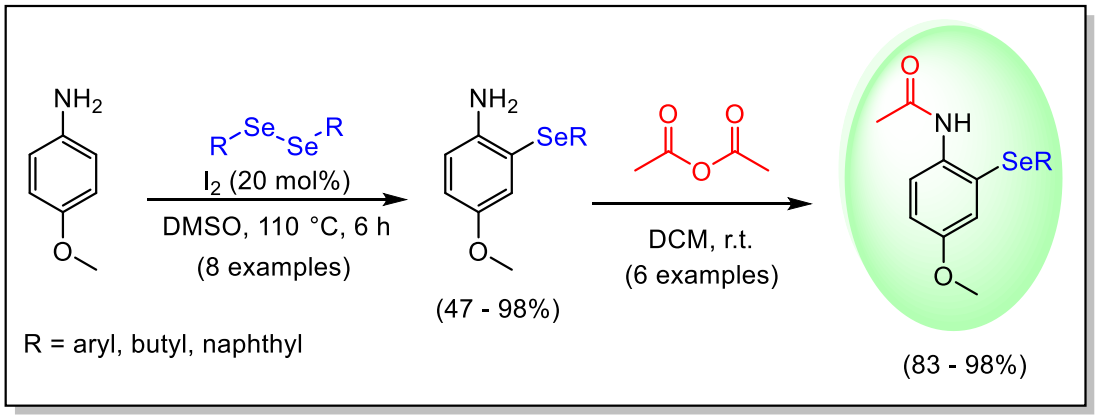
Keywords: *Selenium, synthesis, drugs.*

ABSTRACT

In drug development, an effective strategy is synthesizing molecules with multiple functional groups to target different biological profiles. Developing molecules containing selenium atoms is promising due to their synthesis potential[1] and pharmacological properties.[2] Aromatic amines acetylated at the nitrogen atom are commonly used as analgesics or antipyretics, such as acetanilide, phenacetin, and acetaminophen, and are available over the counter.

This work aims to synthesize acetanilide derivatives containing organic selenium groups to enhance pharmacological activities. Using a method with molecular iodine (20 mol%),[3] six compounds with aryl, butyl, and naphthyl substituents were obtained, yielding 47-98%. These compounds were then acetylated to convert the amino group to the amide group, resulting in acetanilide derivatives with yields of 83-98% (Scheme 1).



Scheme 1: Synthesis of selenylated derivatives of acetanilide

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LaSOL, CNPq, CAPES, FAPERGS, PPGQ and UFPel.

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A Multi-Step Synthesis Approach to a Functional [2]Rotaxane

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Keywords: *Molecular machines, rotaxanes, molecular dynamics*

ABSTRACT

Mechanically Interlocked Molecules (MIMs) are characterized by the presence of mechanical bonds,[1] consisting of one or more components interconnected through their intrinsic topology.[2] Rotaxanes, a subclass of MIMs, typically comprise a linear molecule with bulky end groups (thread), and a cyclic molecule (macrocycle), connected by a mechanical bond.[3] The controlled and reversible translational and rotational movements of the macrocycle in relation to the thread can classify these compounds as molecular machines.[4,5] In this context, this study aims to present the synthesis of a [2]rotaxane molecule with two stations on the thread, enabling both rotational and translational movements. The synthesis of the target [2]rotaxane **1** involved several synthetic steps, including nucleophilic additions reactions, SN_2, [3+2] cycloaddition (CuAAC), multi component reactions applying the clipping methodology.

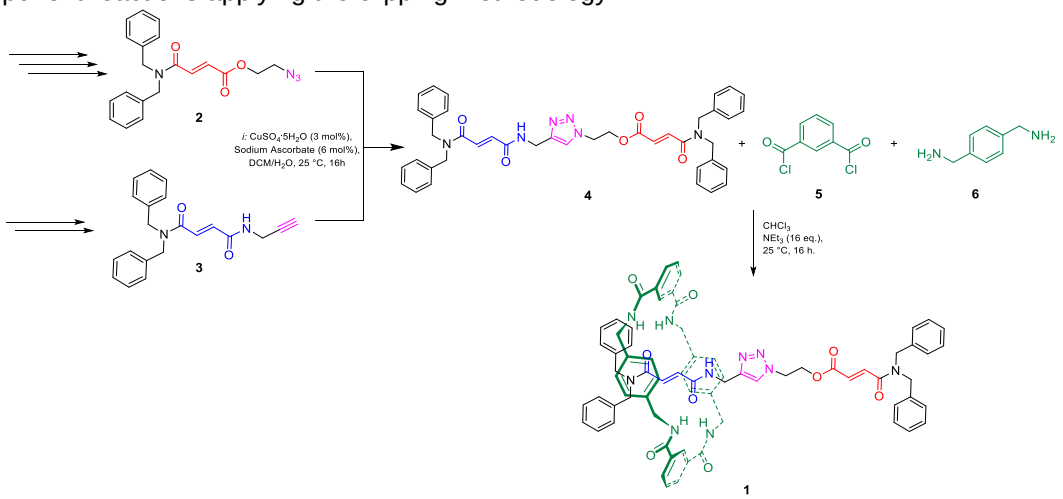

Figure 1. Reaction scheme for the synthesis of [2]rotaxane **1**.

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Integrating Hydroformylations into a Methanol Economy

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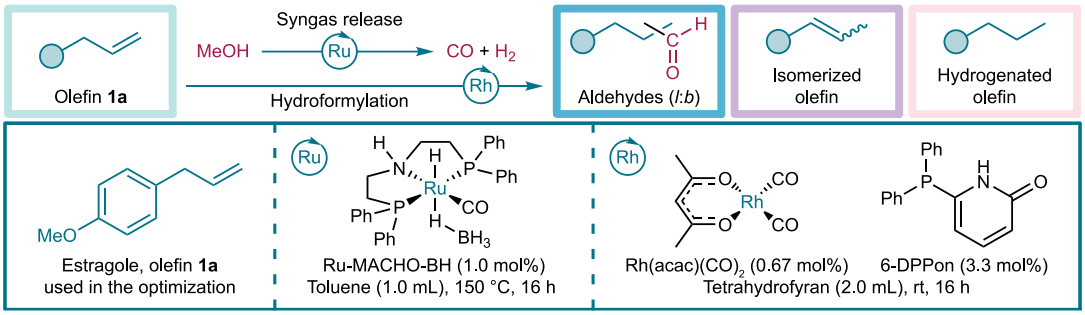
Keywords: *Catalysis, Hydroformylation, Methanol Economy, Methanol-to-Syngas*

ABSTRACT

In almost all man-made chemical products, the carbon skeletons originate from unsustainable fossil resources. As a green transition gains traction, introducing CO_2 as a feedstock for organic synthesis will be one of the keys to a carbon-neutral chemical industry. However, redesigning large scale processes for alternative feedstocks is challenging. Methanol sourced from CO_2 is presently becoming available, linked to the emergence of a methanol economy utilising it as circular fuel. This presents an ideal entry point to rethink the highly interconnected chemical production chains.

Here, we report that interlocking a ruthenium-catalysed methanol-to-syngas reforming with a low-pressure rhodium-catalysed hydroformylation in a two-reactor setup affords oxo products in high yields and selectivity. This study elucidates the kinetics and selectivity of syngas formation and their key role in matching both catalytic cycles. If combined with methanol-to-olefin processes and green methanol production, oxo-products could thus be generated using solely CO_2 as the carbon feedstock through a methanol platform.



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Ru-catalyzed Disconnection of C–O Bonds in Epoxy Resins

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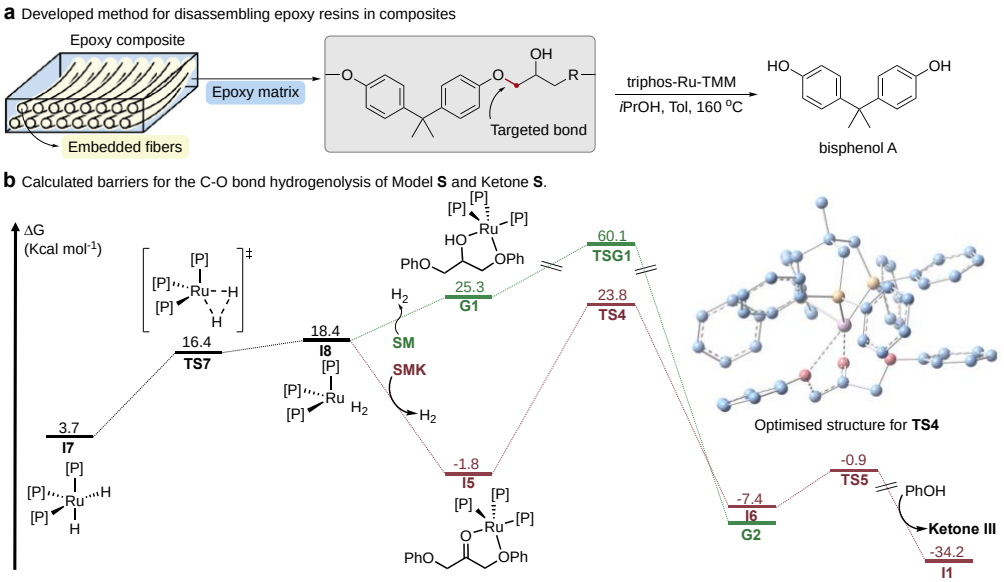
Keywords: *Epoxy resins, Ruthenium, Catalytic depolymerization.*

ABSTRACT

Epoxy resins, when combined with carbon or glass fibers, form lightweight, inert, high-performance composites extensively used in the marine, aerospace, automotive, and wind turbine industries.[1,2,3] To date, there are no industrial closed-loop recycling technologies for this thermoset polymer, leading to landfilling and incineration as primary disposal methods.[1,2,3] Innovative chemical recycling and depolymerization strategies are needed to recover monomers from end-of-life thermoset plastics, making these materials sustainable.[1,2,3] In 2023, we published the first process capable of disassembling epoxy resins in composites, liberating intact glass fibers, and recovering bisphenol A, a key component of the epoxy polymer.[4] This was followed by a detailed mechanistic investigation of this catalytic disassembly process, which has been recently published.[5]



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Synthesis of new aminocoumarin derivatives and investigation of antioxidant activity.

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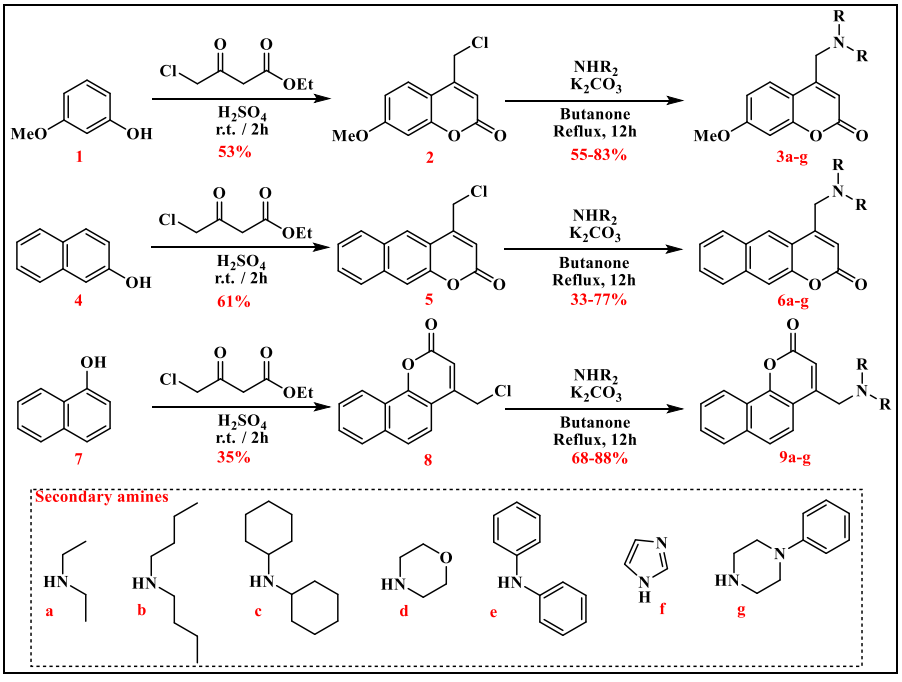
Keywords: *Coumarin, N-alkylation, antioxidant.*

ABSTRACT

Coumarin derivatives are widely explored due to their diversity of applications in the pharmacological field. The synthetic methodologies remain an efficient strategy to access the coumarin moiety, considering the low coast, and time of reaction. It is important to highlight the structural modification of coumarins employing easy organic synthesis, which allows obtaining new compounds[1,2].

In this work, 3-methoxyphenol (**1**), β-naphthol (**4**) and α-naphthol (**7**) were the substrates to obtain 4-chloromethylenecoumarins (**2**, **5**, and **8**), through Pechmann cyclization[3]. Then, secondary amines (**a-g**) were employed to promote N-alkylation on the halogenated carbon of coumarins[4]. The three series of analogue products, 4-aminomethylenecoumarins (**3a-g**, **6a-g**, and **9a-g**), were obtained with yields ranging between 33 and 88%. After spectrometric characterization, the products were evaluated on the antioxidant activity, against the DPPH radical. However, in comparison with gallic acid standard, the compound **3a** showed a slight activity, which not exceeded 25 % under 250 µg.mL^{-1} concentration.



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Efficient Synthesis of Mono- and Diselenylated Fluorescein Derivatives: Arylseleninic Acids as Selenylating Agents to Prepare Fluoroprobes

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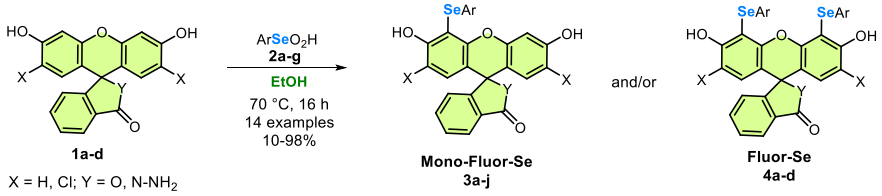
Keywords: *Fluorescence, Fluorescein, Arilseleninic acid.*

ABSTRACT

Benzeneseleninic acids (BSA), are bench-stable selenium(IV) species that can be used as a selenylating agent in reactions under thermal or photochemical conditions. They selectively form C-Se bonds with electron-rich species, producing only water as a byproduct.[1] Considering the structure of fluorescein (**1**) with electron-rich sites, its reaction with BSA (**2**) resulted in mono- and (bis)selenylated fluorescein derivatives (**3** and **4**), using ethanol as a green solvent, thus avoiding the use of unstable and harmful reagents (Scheme 1). A total of 14 derivatives, of which 9 are new, with yields ranging from 10% to 98%. Furthermore, complementary studies were carried out on the photophysical properties of compounds **3a** and **4a** (Ar = Ph) to explore new applications (Figure 1). In addition, fluorescence emission occurs when the molecules are subjected to an oxidizing medium, indicating that the molecules can act as indicator probes in redox environments (Scheme 2).[2]



Scheme 1. General synthesis of products **3a-j** and **4a-d.**

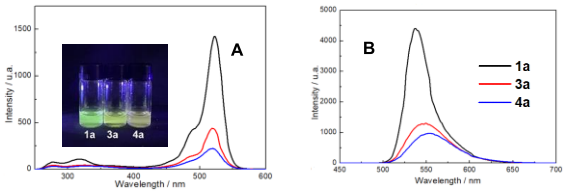
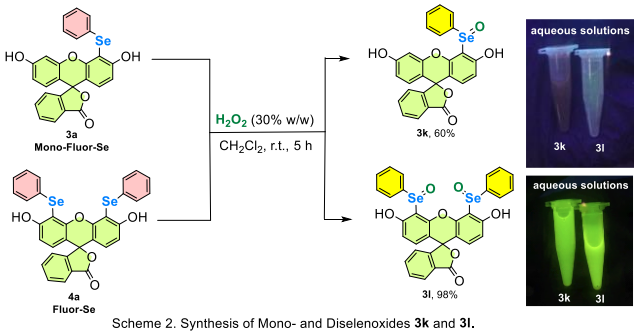


Figure 1. Excitation (A) and emission (B) spectra of **1a**, **3a**, and **4a** in DMSO in the presence of 0.1 mol L of TEA. The inserts show solutions of the probes exposed to UV light (λ_{exc} = 365 nm). The concentration of the probes was 3.0 ×10-6 mol L-1. The excitation spectra were carried out λ_{em} = 550 nm and the emission spectra were collected using λ_{exc} = 550 nm.



Scheme 2. Synthesis of Mono- and Diselenoxides **3k** and **3l.**

ACKNOWLEDGEMENTS

We thank the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – Brasil (CAPES), FAPERGS, CNPq and FINEP for financial support. CNPq is also acknowledged for fellowships to VGM and EJL.

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SEPTEMBER 23-27 2024
19BMOS
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A one-pot C-H functionalization protocol for the synthesis of (hetero)chalcones

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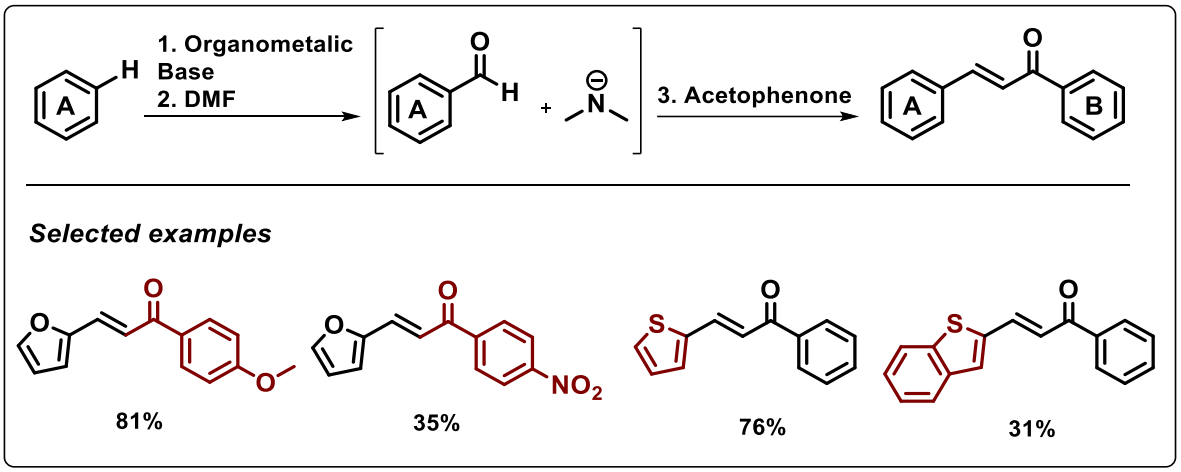
Keywords: *metalation, chalcones, C-H functionalization.*

ABSTRACT

Chalcones comprehend an interesting class of organic compounds which have been studied in several works.[1] They can be obtained from natural sources as important precursors of secondary metabolites and, not restricted to biosynthetic roles, chalcones can also be synthetized and employed in different fields such as optical devices[2] and medicinal chemistry, exhibiting a wide range of relevant biological activities.[3] A variety of synthetic methodologies are available to provide chalcones like classical Claisen-Schmidt aldol condensation[4] or more recent ones, using C-H activation.[5] In our study, a number of (hetero)aromatic chalcones displaying interesting drug-like structural features could be synthesized in a one-pot approach, using a novel organometallic base-mediated protocol, that explores a direct C-H functionalization of readily available aromatic and heterocyclic substrates.



ACKNOWLEDGEMENTS

The authors gratefully acknowledge financial support for this work by the Brazilian foundations Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP), Conselho Nacional de Desenvolvimento e Tecnológico (CNPq) and Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES).

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The use of type-MCM-48/TiO_2 mesoporous materials in the Betti Reaction to synthesize hybrids 1,3-oxazines-4-methyl coumarins, potential anticancer hits.

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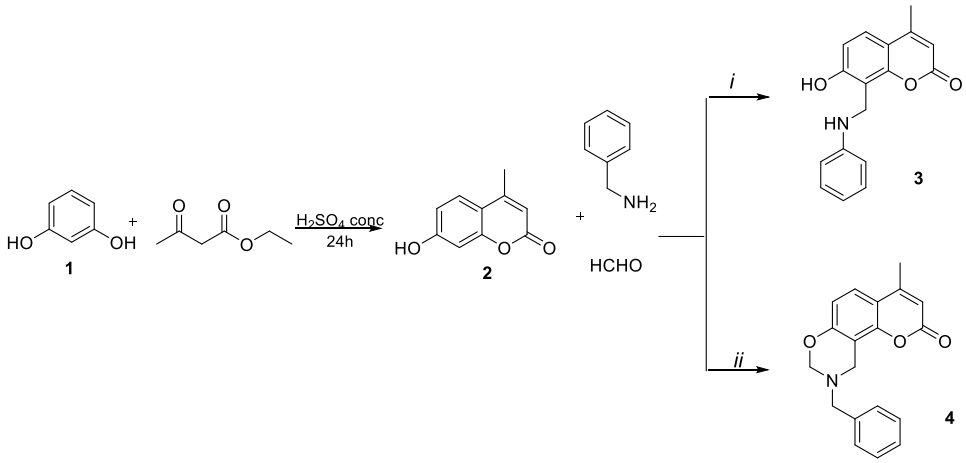
Keywords: *Betti Reaction, Cumarins, MCM-48*

ABSTRACT

Coumarins are oxygenated heterocycles, widely distributed in nature, that have several pharmacological activities, including anticancer. These facts attract medicinal chemists to the synthesis of compounds containing this fragment.[1] The Betti reaction is a multicomponent reaction that consists of a α-aminomethylation of phenolic compounds. In this work, we used Betty reaction with coumarin **2**, HCHO and benzylamine or propylamine in various situations. The following three components conditions were tested: a) reactions at room temperature (7 days), under reflux (overnight) or in microwaves (7 minutes) b) in water or water:ethanol mixture c) without catalyst d) with catalyst (zeolites). The conditions that provided the 1,3-oxazine-coumarin hybrid **4** and compound **3** was the use of type-MCM-48/TiO_2 mesoporous materials, ethanol in reflux (overnight) as depicted in Fig.1. Initial yields are moderate (<50%) but we are optimizing the reaction conditions as well as performing with other aldehydes and amines.



Conditions: i) MCM-48/TiO_2, 10%, EtOH, reflux, overnight, cumarin1 (1 equiv.), benzylamine (1 equiv.), HCHO (1 equiv.) ii) MCM-48/TiO_2, 10%, EtOH, reflux, overnight, cumarin1 (1 equiv.), benzylamine (1 equiv.), HCHO (2 equiv.)

Figure 1

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SYNTHESIS OF POLYFUNCTIONALIZED MOLECULAR HYBRIDS OF ISATIN

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Keywords: *Isatin; Mechanochemistry; Molecular Hybridization.*

ABSTRACT

In this work, molecular hybrids of isatin were synthesized from chemical transformations involving its aromatic ring, aiming to obtain potentially bioactive compounds for future evaluation of its biological activities. Among these compounds, nine enaminones, six thioureas, three diazonium salts, one 2-pyrrolinone, one tetronamide and seven molecular hybrids of isatin with bioactive phenolic compounds using the diazene group as linker for connecting the fragments. All the 27 isatin synthesized derivatives (Figure1) are novel and were obtained in moderate to good yields, providing through this study methodologies for the synthesis of drug candidates that may have their biological activity evaluated in the future.

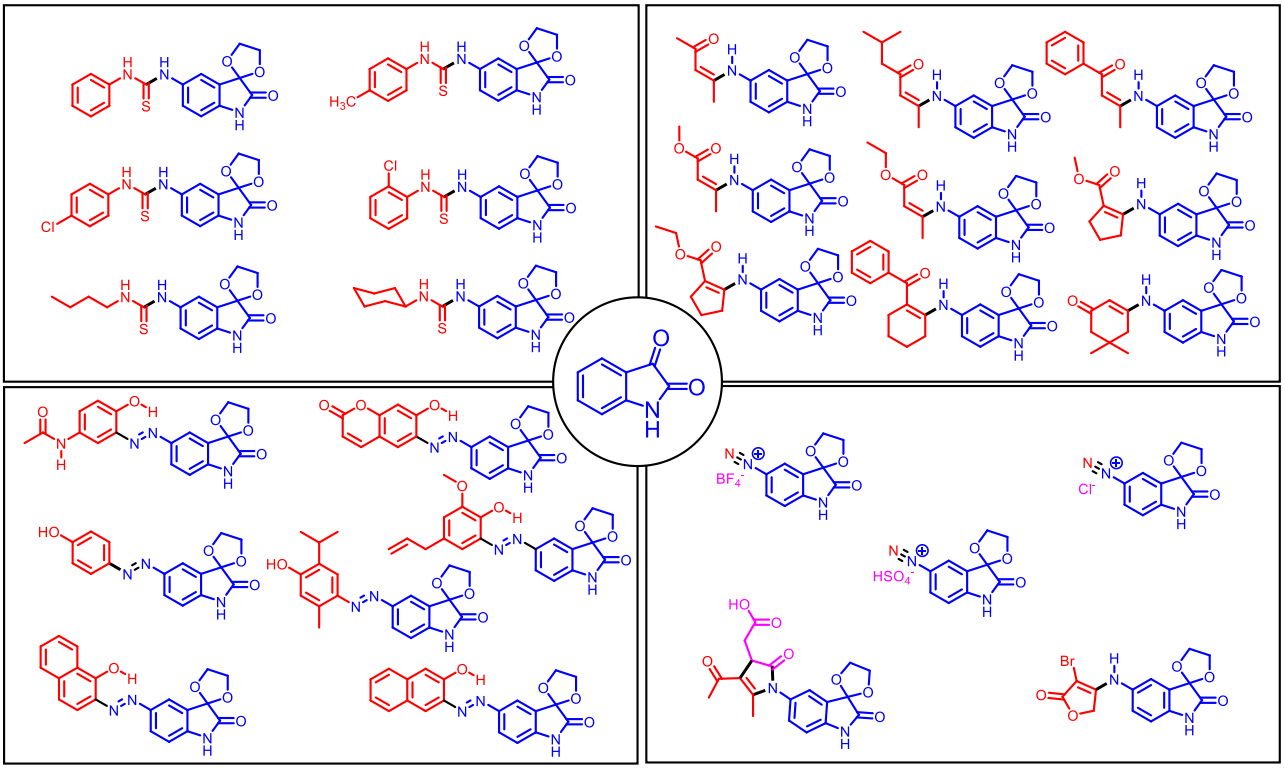

Figure 1. Synthesized isatin derivatives in this work.

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SEPTEMBER 23-27 2024
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Functionalization of eugenol as strategy to amplify the chemical space: sustainable synthesis of new thioureas and 2-aminobenzoxazoles Synthesis of thioureas and 2-aminobenzoxazoles derived from eugenol

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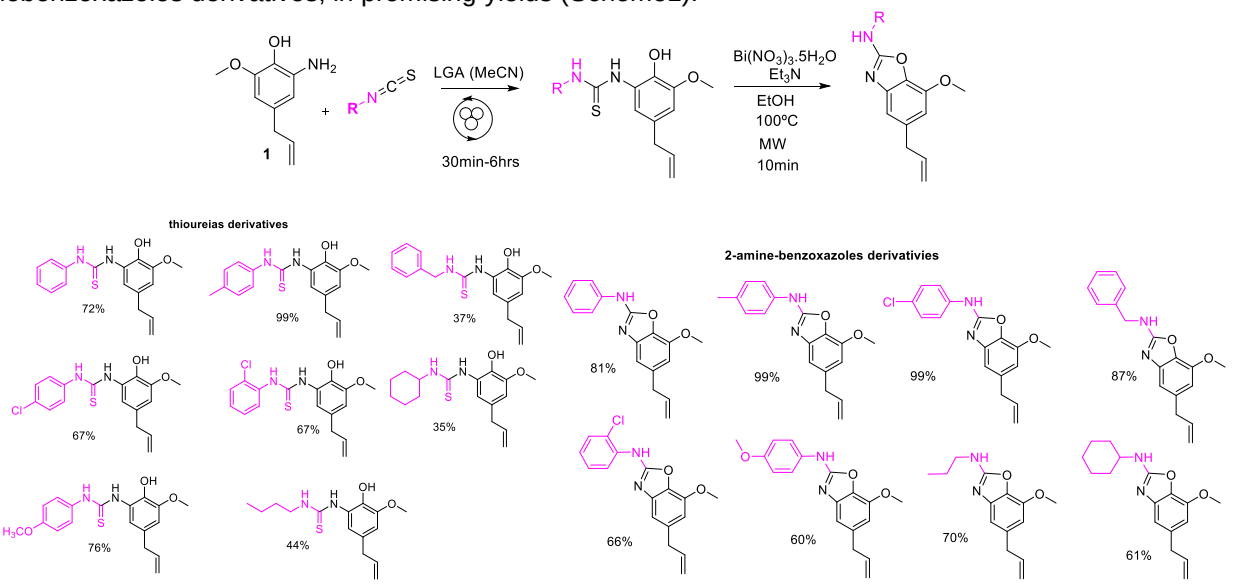
Keywords: *eugenol, 2-aminobenzoxazoles, thioureias.*

ABSTRACT

Eugenol is a natural phenylpropenoid obtained mainly from cloves[1]. It is widely used for diverse applications due to its anesthetic, cytotoxic, antifungal, and anticancer potential. Benzoxazoles are a class of heterocycles that has shown extensive chemotherapeutic activity[2], among these derivatives are the N-substituted benzo[d]oxazol-2-amines (2-aminobenzoxazoles) which broad pharmaceutical applications are of great importance[3]. An efficient and widespread method to obtain 2-aminobenzoxazoles would be a treatment of 2-aminophenols with isothiocyanates to synthesize the derivative thioureas, which subsequently undergo cyclodesulfurization with the assistance of diverse desulfurizing agents[4]. Strategies that lead expansion chemical space of natural product-based compounds is important to enable new drug discovery[5]. In this work 6-aminoeugenol (1) was obtained after a study to modify the aromatic ring of eugenol [6], and sustainable methods as mechanochemistry and microwave were applied in view to reach thioureas and 2-aminobenzoxazoles derivatives, in promising yields (Scheme1).



Scheme 1. Synthesis of thioureas and 2-aminobenzoxazoles derived from eugenol.

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Auronas based on dihydroeugenol: attempts to synthesize new potentially antifungal compounds

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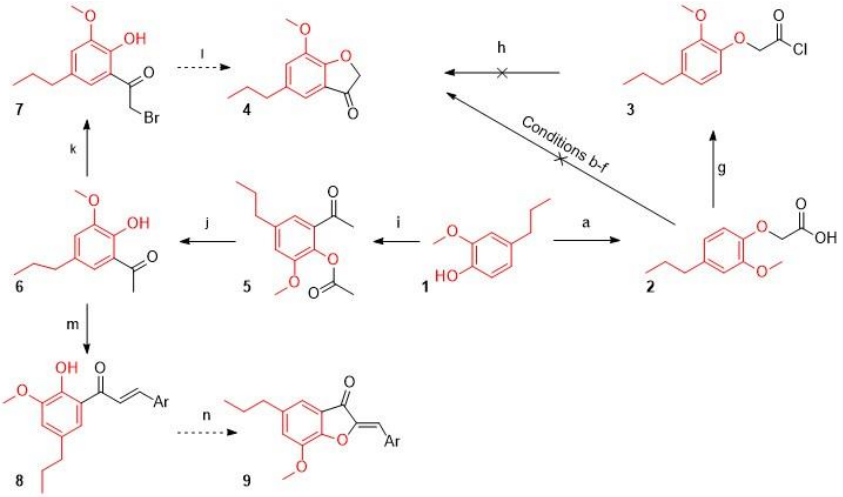
Keywords: *natural products, phenylpropanoids, aromatic acylation*

ABSTRACT

Aurones are heterocyclic compounds related to flavonoids that are found in nature or are obtained by synthesis. They present a myriad of biological activities (*e.g.*, antimicrobial, antiparasitic, antineoplastic, anti-inflammatory etc.), so several works report the creation of aurones with the most diverse structural patterns aiming at optimized properties[1]. Starting from findings not yet published concerning to antifungal activity, our working group has dedicated itself to the synthesis of new aurones with the general structure shown as **9** in the Scheme 1. Thus, it seemed feasible to use dihydroeugenol (**1**) as a starting compound, which could, by different routes, lead to the key intermediate benzofuranone (**4**) or to the aurones themselves (**9**). Based on a traditional methodology[2], **1** was converted to the acetic intermediate (**2**) which, as such or via its corresponding acid chloride, was tentatively subjected to intramolecular aromatic acylation conditions based on the available reagents at that time (steps **b**-**h**), but none of them led to the desirable product or even to a mixture of products accessible to separation. On the other hand, **1** could be led to the acetophenone **6** in two steps by aromatic acetylation reaction with acetic anhydride and zinc chloride followed by methanolysis of the ester. This ketone intermediate (**6**) followed two paths, one that led to the α-bromo ketone intermediate (**7**) by reaction with $CuBr_2$ and the other, through condensation with the respective aldehydes, to the corresponding chalcones (**8**)[3,4]. The next steps will be the formation of the benzofuranone intermediate (**4**) by cyclization of **7** in a basic medium or the final aurones (**9**) by oxidative cyclization of **8**.



a: NaH, Chloroacetic acid, DMF, 25 °C; b: Amberlite IR 120, $CaCl_2$, $CHCl_3$, 25 °C; c: H_2SO_4, 25 °C; d: PPA, 80 °C; e: MSA, 25 °C; f: PTSA, Graphite, 100 °C; g: $SOCl_2$ 70 °C; h: $AlCl_3$, $CHCl_3$, 0 °C or 150 °C; i: Ac_2O, $ZnCl_2$, 25 °C; j: $NaHCO_3$, MeOH, 25 °C; k: $CuBr_2$, EtOAc/CH_2Cl_2, 80 °C; l: TEA, ACN, 70 °C; m: NaOH, EtOH, Ar-CHO, 25 °C; n: $Hg(AcO)_2$, Pyridine, 25 °C.

Scheme 1: Synthesis route to new potentially bioactive aurones (Ar is an aromatic unit not yet to be disclosed).

ACKNOWLEDGEMENTS

Thanks to FAPEMIG (APQ-00686-18; APQ-00352-18, APQ-00544-23, RED-00110-23 and APQ-01455-24).

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Synthesis of *O*-sulfonylated derivates of phenylpropanoid Mannich bases as potential antifungal agents

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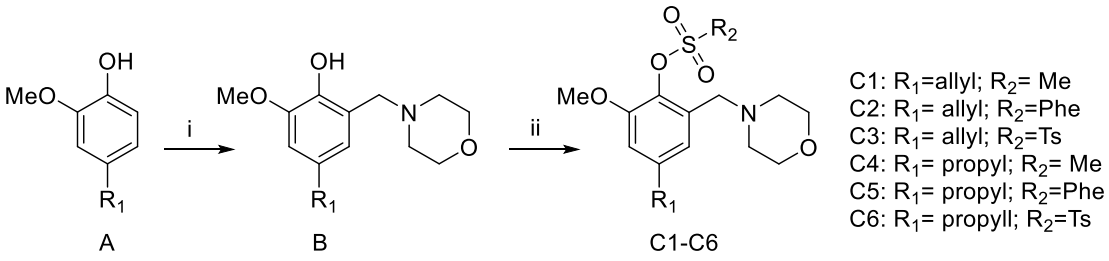
Keywords: *sulfonate ester, molecular hybridization, natural products.*

ABSTRACT

This research focuses on the synthesis and characterization of a series of sulfonate esters from a Mannich base prepared previously and known for its antifungal activity[1, 3]. This starting compound was synthesized from eugenol and morpholine, exhibiting fungistatic properties against various *Candida* spp.[1, 3]. Now, inspired by the work of Ahmad and co-workers[2], who reported significant antimicrobial activity of sulfonate esters derived directly from eugenol, we aimed to functionalize that Mannich base as sulfonates, expecting to discover promising products as antifungals. We also used dihydroeugenol to compare the influence of side chain in biological activity. The synthesis route used was as follows (Scheme 1):



i: morpholine, formaldehyde, EtOH, HCl_{cat}, reflux; ii: respective sulphonyl chloride, TEA, THF, 25 °C

Scheme 1: Synthesis route to the *O*-sulfonylated derivatives C1-C6.

The products were evaluated *in vitro* against *Candida* spp. and *Criptococcus* spp. and fluconazole was used as the control drug. Compounds C3 and C6 demonstrated good activity against *Candida krusei* and *Criptococcus neoformans.* When compared to the starting molecules, eugenol and dihydroeugenol, an excellent improvement was observed in potency, being at least 5-10 times higher than the starting materials, it is worth noting that there was no significant difference between eugenol and dihydroeugenol compounds in antifungal activity. These sulfonate derivatives are good candidates for further optimization.

ACKNOWLEDGEMENTS

Thanks to FAPEMIG (APQ-00686-18; APQ-00352-18, APQ-00544-23, RED-00110-23 and APQ-01455-24).

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Photoactive formyl benzimidazoles: New molecular scaffolds for optical sensing

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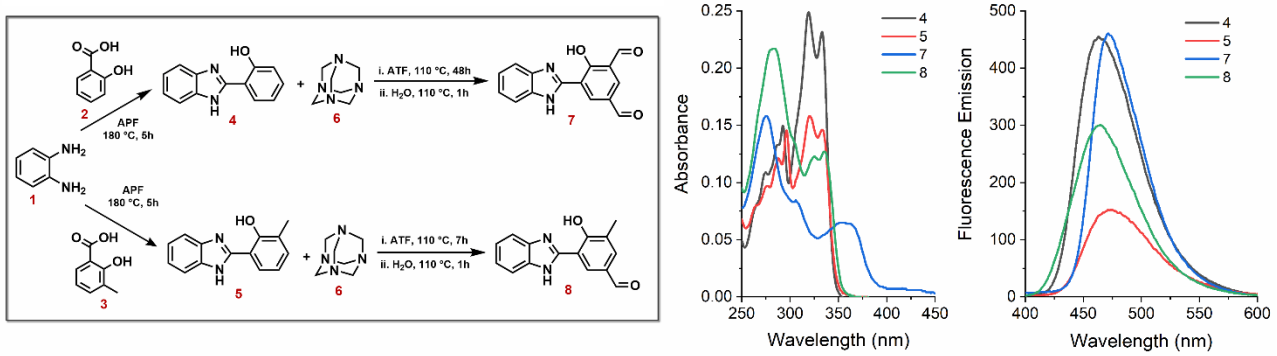
Keywords: *benzazoles, formyl derivatives, proton transfer, fluorescence, optical sensors.*

ABSTRACT

Excited-state intramolecular proton transfer (ESIPT) is a photochemical process that results in the formation of a tautomer with an electronic structure different from that of the initial conformer. ESIPT-responsive fluorophores exhibit remarkable photophysical properties, such as large Stokes shifts and intense fluorescence emission.[1,2] This work presents the synthesis and photophysical characterization of photoactive compounds via ESIPT, specifically substituted hydroxyphenyl benzazolic heterocycles, obtained through the classical condensation reaction methodology between a functionalized aromatic amine and a salicylic acid derivative.[3] From these precursors, the Duff formylation methodology enabled the synthesis of mono- and biformylated benzazolic heterocycle derivatives. This modification preserved important photophysical characteristics, such as absorption in the UV-region and fluorescence emission in the visible region, with a large Stokes shift (~150 nm), while causing a significant increase in the fluorescence of these molecules if compared with their precursors. Notably, the presence of a formyl group in an aromatic system facilitates the design of new fluorescent compounds.[4]



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Synthesis of Adenine and 1,3-Diphenylurea Hybrids as Potential Kinase Inhibitors for Cancer Treatment

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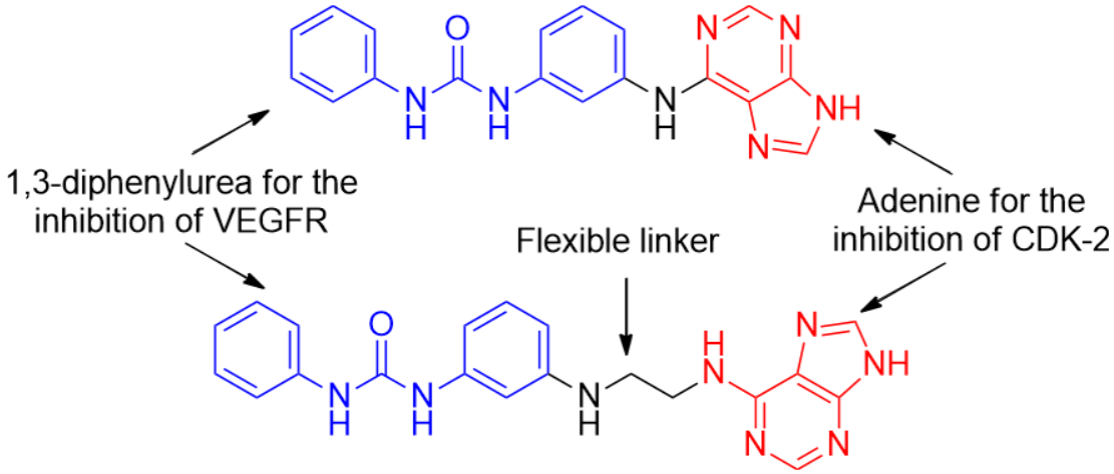
Keywords: *Cancer; Targeted Anticancer Therapy; Hybridization.*

ABSTRACT

According to the estimation of the International Agency for Research on Cancer[1] it is predicted there will be 28 million new cancer cases worldwide each year by 2040, if incidence remains stable and population growth and aging continues in line with recent trends. Therefore, there is a constant need for development of new targeted drugs that are potent and selective to cancer cells. In this context, heterocyclic compounds form the structural scaffold of contemporary anticancer therapy that has led to the development of roughly 40 kinase inhibitors that received FDA approval over the past 3 decades.[2] The 1,3-diphenylurea nucleus is present in the drug Sorafenib, an oral multikinase inhibitor that can suppress tumor cell proliferation,[3] angiogenesis and induce cancer cell apoptosis. In this work, we look to synthesize potential kinase inhibitors by hybridization of 1,3-diphenylurea and adenine by linking them directly or through a flexible linker.



Scheme - Structure of hybrid target molecules and their potential inhibition activity.

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Squaramide-Dihydropyrimidinone as a New Class of Hybrid Compounds

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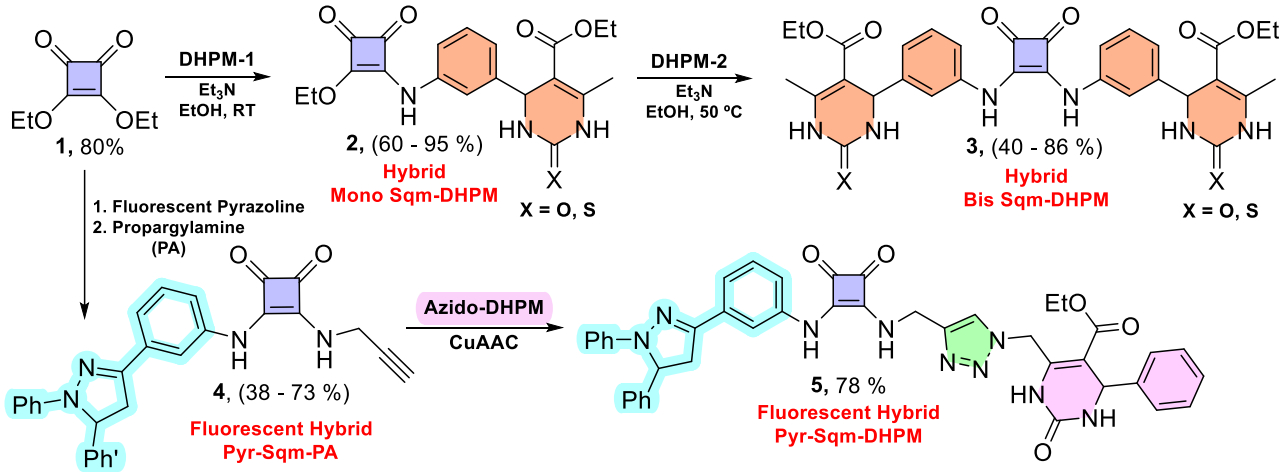
Keywords: *Hybridization, Squaramides, Dihydropyrimidinones*

ABSTRACT

Squaramides (Sqm), besides their use as organocatalysts, exhibit bioisosteric properties[1] and many of them have anti-cancer activity.[2] The connection of two bioactive entities can lead to multifunctional hybrid compounds, aiming at the discovery of more potent drugs with fewer side effects.[3] In this work, we present the synthesis of conjugated dihydropyrimidinones (DHPM) and squaramides as new linkers for mono and bis *Sqm-DHPM* hybrid compounds (**2** and **3**, respectively), designed for possible anti-cancer activity (Scheme 1).



Scheme 1. Hybrid Squaramide-based Compounds

Additionally, a fluorescent hybrid can be used as a fluorescent molecular probe, allowing the direct observation of compounds in the intracellular environment by confocal microscopy.[5] Thus, Squarate **1** was transformed into the hybrid *Pyr-Sqm-PA* (**4**) in two steps. After that, a Click-type CuAAC reaction with an azido-DHPM led to the fluorescent hybrid *Pyr-Sqm-DHPM* (**5**). Evaluation of cytotoxic activity against tumoral cell lines is in progress.

ACKNOWLEDGEMENTS

The authors are in debit with CAPES, FAPERGS and CNPQ for the financial support.

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Modeling and synthesis of 6-imidazolylquinazoline-2,4-diones as potential SARS-CoV-2 M^{pro} inhibitors

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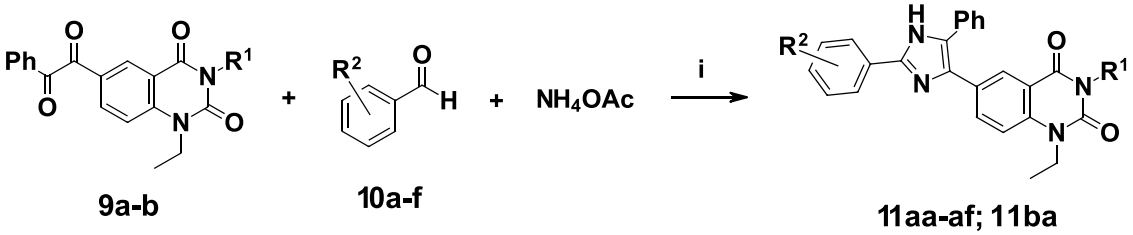
Keywords: *Imidazoles, quinazolines, molecular modeling.*

ABSTRACT

Given the importance of the *N*-heterocycles imidazole[1] and quinazoline[2] in Medicinal and Synthetic Chemistry, we modeled a series of potential inhibitors of SARS-CoV-2 Main Protease with the aid of Molecular Docking and Semi-empirical Quantum Mechanics (SQM). Initially, PM6-optimized structural models of the proposed M^{pro} inhibitors were docked into the enzyme's active site.[3-4] The three highest-ranked different positions were submitted to a further PM6-D3H4X/COSMO optimization in a protein globular model.[5] Debus-Radziszewski imidazole synthesis by reacting quinazolinylethanediones with ammonium acetate and aldeydes in acetic acid at 100 °C for 2 h[6] furnished the final products in good to excellent yields (65 - >95 %) after extraction and recrystallization. The obtained compounds were predicted to favorably bind to the enzyme, while quinazoline core and diarylimidazole moiety both fitted within its active site. Anti-SARS-CoV-2 assays are being carried out in collaboration with partner research groups at our institution.

* Synthesis
* Molecular Docking
* Semiempirical Quantum Mechanics



R^1 = *i*-Pr, Ph. R^2 = H, 2-OCH_3, 2-Cl, 4-OCH_3, 4-Cl, 1-Naph (-C_4H_4-).
i) Acetic acid, 100 ºC, 2 h.

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We gratefully acknowledge CNPQ, CAPES and FAPERGS for financial support.

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Photoredox-catalysed nucleophilic α-functionalization of carbonyl compounds via destabilised carbocations

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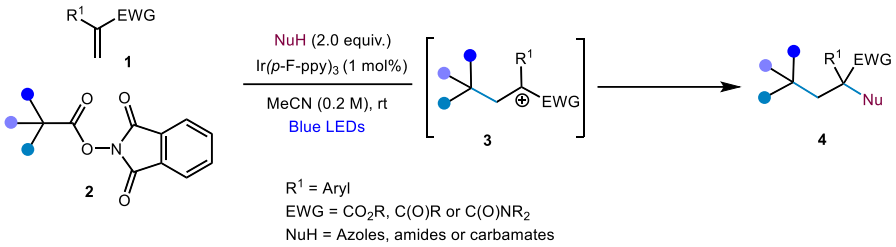
Keywords: *Photoredox catalysis, destabilised carbocations, alkene difunctionalization.*

ABSTRACT

Destabilised carbocations, such as those substituted with electron-withdrawing groups, are underexplored majorly due to their inaccessibility under mild reaction conditions.[1,2] While the α-position of carbonyl compounds is known for nucleophilic reactivity,[3] exploiting umpolung α-carbonyl carbocations under a new mechanistic strategy could be valuable to expand the reaction space. Here, we report a photoredox-catalysed *C*-centred radical addition to Michel acceptors **1** that generates an α-carbonyl carbocation **3** upon oxidative radical to polar cross-over by a photocatalyst. These destabilised intermediates were successfully trapped with weak nucleophiles including azoles and amides. This reaction provides a direct method for making valuable α-functionalised carbonyl compounds **4** including α-amino acid derivatives. Readily accessible redox-active phthalimide esters **2** served as precursors for reductively generating 1°, 2° and 3° nucleophilic carbon radicals under mild reaction conditions using Ir-based photocatalyst. Moreover, Michael acceptors other than acrylates can also be used in the transformation, including α,β-unsaturated ketones, and amides.



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4-amino-1,2-Naphthoquinone triazoles as potential anti-SARS-CoV-2

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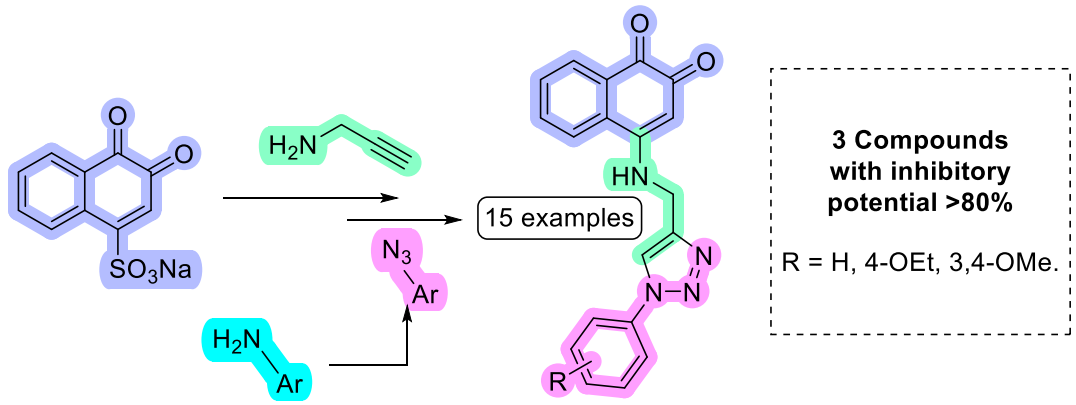
Keywords: *anti-SARS-CoV-2, 1,2,3-triazole, 1,2-naphthoquinone.*

ABSTRACT

COVID-19 disease promoted by the SARS-CoV-2 virus caused more than 6.6 million deaths between 2019-2022.[1] Therefore, research groups have been trying to find new drugs or small molecules to be produced as medicines that can inhibit the virus.[2] Quinones are promising COVID-19 drug candidates to be explored, due may inhibit M_{pro}, enzyme responsible for replication.[3] Santos and coworkers employed computational study of naphthoquinones against SARS-CoV-2, herewith experimental evaluation getting micromolar to nanomolar range for M_{pro}.[3] Here, we developed a new method to obtain 1,2,3-triazole from sodium 1,2-naphthoquinone-4-sulfonic acid (β-NQSNa) to afford 15 unpublished examples of naphthoquinones derivatives (33-66% yield) *via* microwave. All compounds were initially tested in a 10 μM screen for SARS-CoV-2 replication inhibition assays. That were performed in Calu-3 cells, infected with an MOI of 0.1 of SARS-CoV-2 for 1h at 37 ºC. After 48h, virus-containing supernatants were collected for quantification of viral replication using plaque formation assay. After quantification, the percentage of inhibition of the compounds was calculated, where three compounds show inhibitory potential anti-SARS-CoV-2 above 80% (**Scheme 1**).



Scheme 1. Triazole derivatives with promissory structures anti-SARS-CoV-2.

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Sustainable Synthesis of Zwitterionic Bases for CO_2 Capture

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Keywords: *CO_2 capture, zwitterionic bases, DFT.*

ABSTRACT

Carbon dioxide (CO_2) capture is essential for reducing emissions and mitigating climate change effects. Developing new materials for CO_2 capture is crucial for enhancing efficiency and reducing energy costs. Zwitterionic bases are promising due to their high water solubility, thermal stability, recyclability, and low absorption enthalpy. This study explored an alternative synthesis route for zwitterionic bases using dimethyl carbonate (DMC) as a green alkylating agent. Various reaction conditions were tested. Extended reaction times (>4 hours) predominantly yielded fully alkylated products with high purity (93% ^{1}H NMR), whereas shorter times (30 minutes) resulted in mixed products, highlighting the need for optimized reaction conditions. Density functional theory (DFT) calculations elucidated the reaction mechanisms, revealing insights into transition states and energy profiles. These findings supported experimental results and deepened the understanding of the processes. This work demonstrates DMC's potential as a sustainable alkylating agent, advancing green chemistry and sustainable practices in environmental remediation.

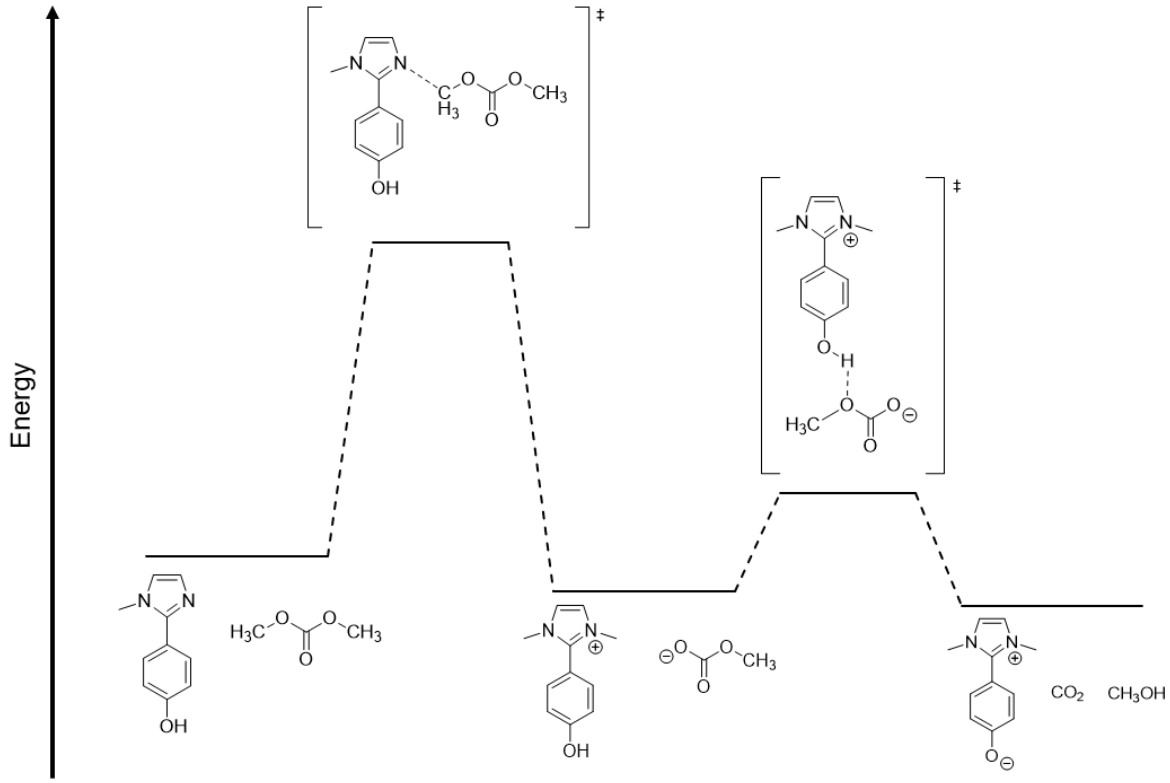

Figure 1 – Calculated energy profile for the reaction between DMC and 1-methyl-2-(4-hidroxiphenyl)-imidazole.

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Heterogenized palladium pincer complexes for the cross-coupling reaction of styrenes and iodonium salts

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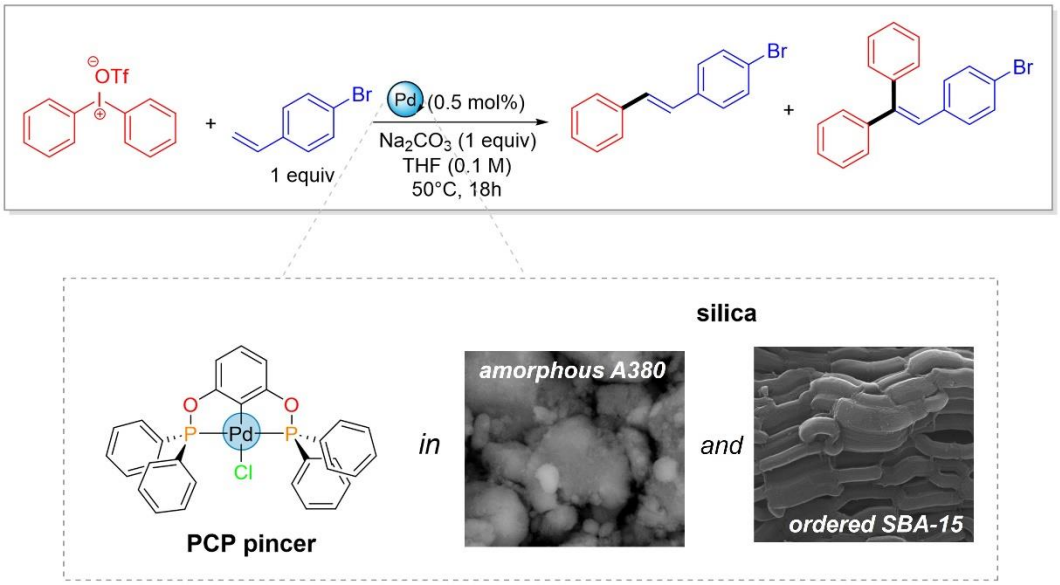
Keywords: *Heterogeneous catalysis, organometallics, cross-coupling reactions.*

ABSTRACT

Phosphine-based palladium pincer complexes were initially thought of as readily steric- and electronically controllable, conferring a suitable balance between thermal stability and reactivity[1]. When submitted to the mild reductive conditions of typical Heck and Suzuki couplings, however, these were shown to easily decompose to metal nanoparticles (NP), the active form of the catalyst[2]. To take advantage of the NP formation, air- and moisture-stable phosphinite PCP Pd-pincer complexes were supported at 1 wt.% Pd in both amorphous and ordered silica by wet impregnation and evaluated in the coupling of styrenes and iodonium salts, which would follow a Pd(II)-Pd(IV) cycle in a homogeneous phase[3]. The best heterogeneous catalyst afforded 97% conversion and 17:3 selectivity to the monoarylated product by GC analysis, while both homogeneous and physical mixtures of support + complex yielded only traces of products. Further support pore structure and charge of the complex are also under evaluation and will be presented.



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Reaction of 1,3-diynes with Pentaphenylborole: A straightforward route towards phenyl-substituted Borirenes

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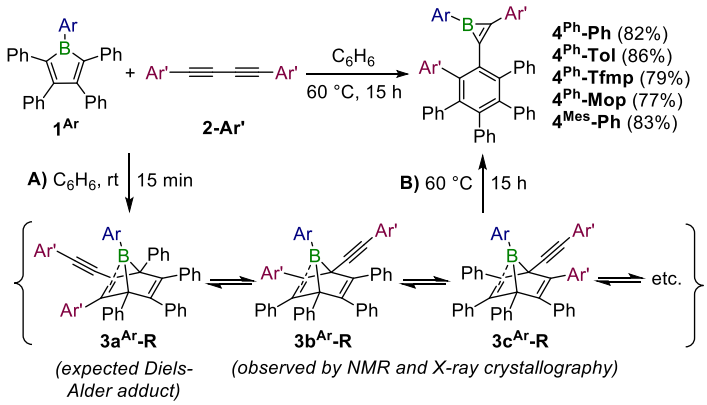
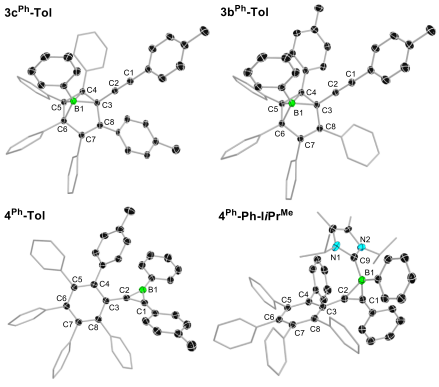
Keywords: *Boron Chemistry, Boroles, Borirenes, Cycloaddition*

ABSTRACT

Borirenes are isoelectronic to cyclopropenylium cation, thus representing the smallest type of boron-containing aromatic heterocycle.[1] Among different methods to synthesize borirenes the [2+1] cycloaddition of alkynes with in-*situ* generated borylenes has become a reliable strategy to access these compounds.[2] In recent years there has also been significant progress in the synthesis of boron-containing conjugated heterocycles by the ring expansion of borole precursors. The high reactivity of boroles, arises from their highly Lewis-acidic boron center and antiaromatic character, making them particularly prone to the insertion of multiple bonds generating more stable heterocycles.[3] Considering previous studies between boroles and alkynes and the influence of the eletronics and sterics of alkynes we describe a straightforward strategy for the synthesis of novel perarylated borirenes by combining pentaarylboroles with various 1,4-diarylbuta-1,3-diynes and explore the mechanism of these reactions both experimentally and computationally.





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Enantioselective palladium-catalyzed Heck-Matsuda reaction for desymmetrization of N-protected 2,5-dihydro-1-H-pyrroles with aryldiazonium salts

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Keywords: *Desymmetrization, enantioselective Heck-Matsuda reaction, lactam synthesis*

ABSTRACT

Desymmetrization reactions are a powerful and refined strategy for asymmetric synthesis, enabling many valuable chemical modifications to increase the complexity of molecules.[1] The Heck-Matsuda reaction has an important role in this strategy, involving the desymmetrization of cyclic systems.[2] Despite previous results in this area, the desymmetrization of 2,5-dihydro-1*H*-pyrroles led to some challenges due to substrate instability and undesirable side reactions. Herein, we report the palladium-catalyzed Heck-Matsuda desymmetrization of *N*-protected 2,5-dihydro-1*H*-pyrroles with aryldiazonium salts using the *N*,*N*-ligand (*S*)-PyraBOx to provide several 4-substituted lactams in an enantioselective fashion, with yields up to 85% and *er* up to 93:7 (**Figure 1**). The methodology was shown to be robust, allowing the use of different protecting groups of the nitrogen of the 4-pyrroline substrate. Two of the chiral aryl-lactams were further derivatized to provide phosphodiesterase-4-inhibitor (*R*)-rolipram[3] (61% overall yield, 3 steps, 82:18 *er*), and the commercial drug (*R*)-baclofen[4] (49% overall yield, 4 steps, 90:10 *er*).

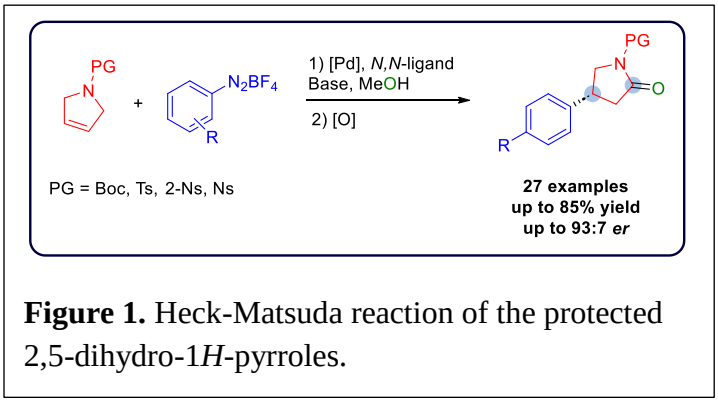

Figure 1. Heck-Matsuda reaction of the protected 2,5-dihydro-1*H*-pyrroles.

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Photoprecursors of arynes in visible-light promoted cycloaddition and nucleophilic coupling reactions

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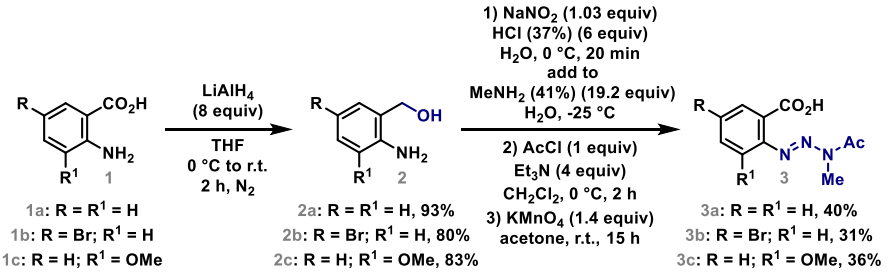
Keywords: *Benzyne chemistry, photochemical reactions, compact fluorescent light.*

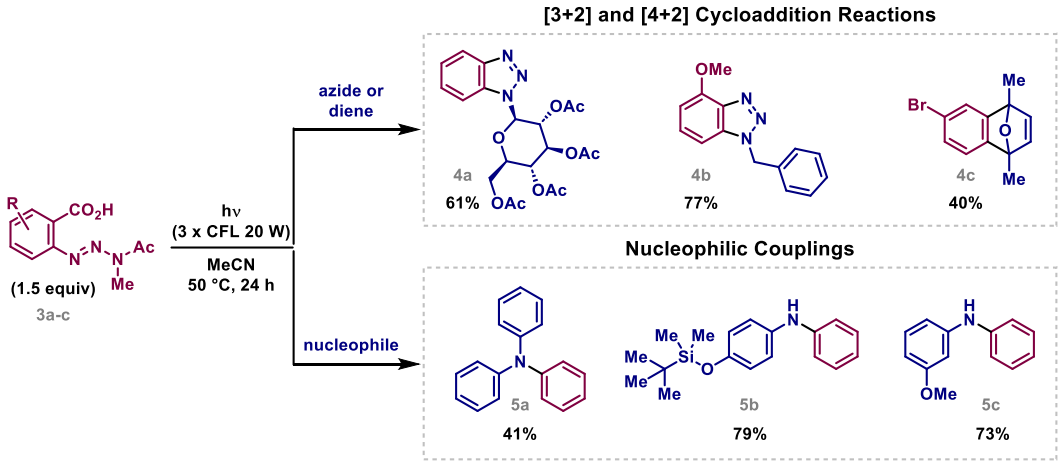
ABSTRACT

2-(3-Acetyl-3-methyl-1-triazen-1-yl)benzoic acids (**3a-c**) are understudied benzyne and aryne precursors, which are prepared from commercially available anthranilic acids (**1a-c**) in four reaction steps (**Scheme 1**).[1,2]



Scheme 1. Synthesis of compounds **3a-c**.

After extensive optimization of the reaction conditions, compounds **3a-c** promoted the formation of arynes with white light, which were used in cycloaddition reactions to provide cycloadducts **4a-c** in yields of 40-77% and in nucleophilic couplings to give coupling products **5a-c** in yields of 41-79% (**Scheme 2**).



Scheme 2. Preparations of compounds **4a-c** and **5a-c**.

Twenty-two compounds were isolated in yields from 13% to 85% using aryne photoprecursors **3a-c**. It is noteworthy that this chemistry is compatible with functionalized groups containing sulfur, boron, and silicon. These groups are not tolerated under the conditions required to generate arynes via Kobayashi precursors.[3] A mechanistic investigation using TEMPO and mass spectrometry suggests a radical mechanism for the photogeneration of arynes.

ACKNOWLEDGEMENTS

We thank the FAPESP and the CNPq for their financial support. V.V.S. thanks the CNPq and M.A.Jr thanks the CAPES for their scholarships.

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SEPTEMBER 23-27 2024
19BMOS
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Stereoselective Synthesis of *N*-Containing Heterocycles via Ir-Catalyzed Intramolecular α-Alkylation of Carbonyl Compounds

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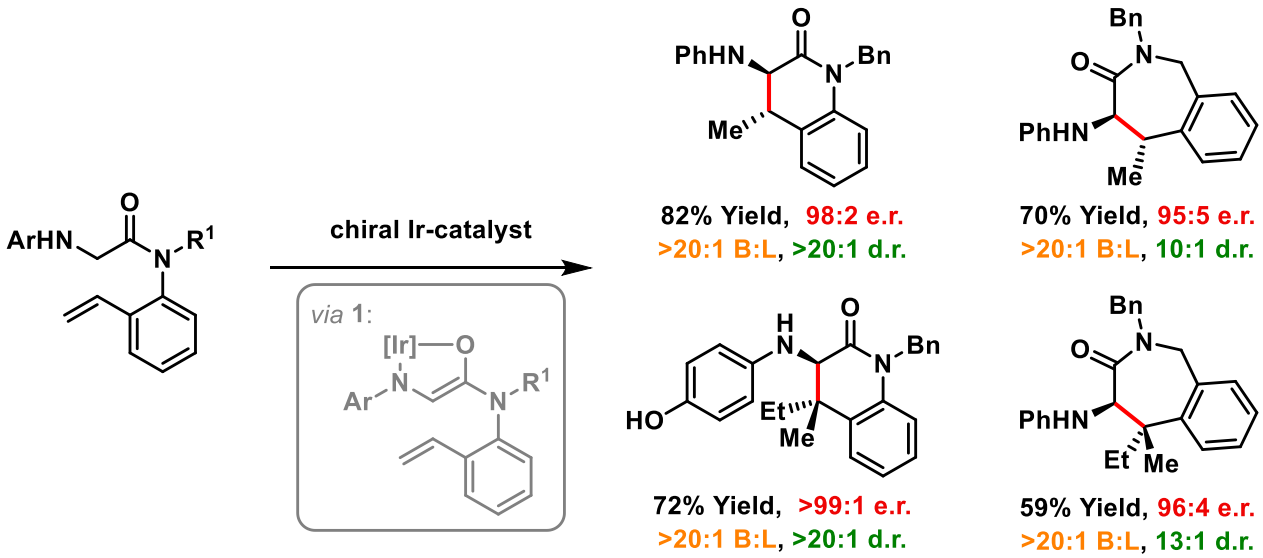
Keywords: *Heterocycles, Stereoselective Catalysis, C-H activation.*

ABSTRACT

Chiral nitrogenous heterocycles are prevalent in many biologically active molecules, with 59% of U.S. FDA approved small-molecule drugs possessing a nitrogen-containing heterocycle.[1] Many synthetic methodologies have been developed to access these scaffolds.[2] However, the asymmetric synthesis of highly substituted *N*-containing heterocycles from achiral, acyclic starting materials is still extremely limited.[3] Here, we demonstrate an intramolecular iridium-catalyzed cyclization of α-amino amides onto unfunctionalized alkenes, installing adjacent stereocenters. This method utilizes the directing group ability of a glycine-derived N–H unit to facilitate Ir-catalyzed enolization of the carbonyl unit (**1**).[4] The resulting stereodefined enolate undergoes branch-selective C–C bond formation with complete regioselectivity. The process occurs with complete atom economy and excellent diastereo– and enantiocontrol (up to >20:1 d.r. and >99% e.r.), which is retained when accessing sterically challenging contiguous stereocenters. This method allows 6– and 7– membered *N*-containing heterocycles and 5– and 6– membered carbocycles to be constructed stereoselectively.



- unique directing-group-based strategy
- high regio-, enantio- and diastereoselectivity
- contiguous stereocenters
- complete atom economy
- non-activated alkenes
- different ring sizes (n = 5–7) and ring classes accessible

ACKNOWLEDGEMENTS

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SEPTEMBER 23-27 2024
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The preferential crystallization of chiral isoxazoline cycloadducts from the (3+2) cycloaddition reaction of arylnitrile oxides and chiral monoterpenes.

Bruna Thatise Batistel[1*], Hérica da Silva Silveira[1], Adailton João Bortoluzzi[2], Sidnei Moura[3], Aloir Antonio Merlo[1], Itamar Luís Gonçalves[1,4]

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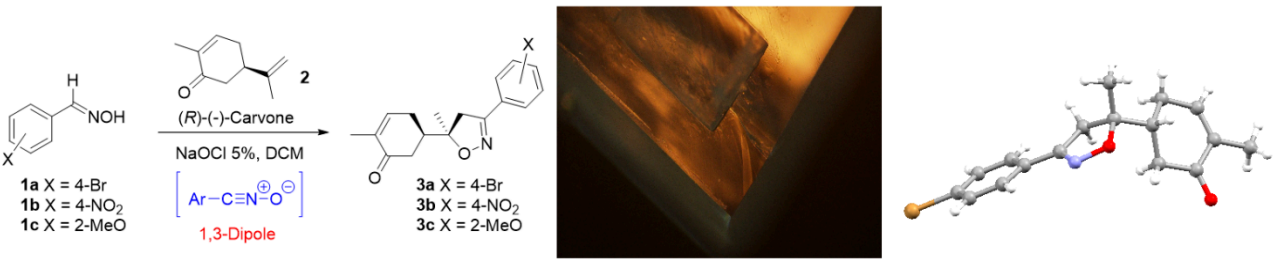
Keywords: *(3+2) 1,3-dipolar cycloaddition, Chiral isoxazolines, Carvone dipolarophile, Preferential crystallization*

ABSTRACT

In this communication, we report our partial results on competitive crystallization process of the synthesis of 3,5-disubstituted isoxazolines solids using aryl nitrile oxides derived from **1a-c** with (*R*)-(-)- and (*S*)-(+)-carvone (**2**) in DCM and a 5% aqueous NaOCl solution. The cycloadducts are formed by the capture of the reactive intermediate arylnitrile oxide by carvone present in solution. The cycloadducts were isolated as pale white solids, and the ^{1}H and ^{13}C NMR spectra show typical signals indicating the formation of two respective diastereoisomers. For the reaction with oxime **1a**, the competitive crystallization of the cycloaddition reaction products showed interesting stereoselective results that will be discussed in detail. Scheme 1 illustrates the synthesis, appearance of the chiral single crystal of **3a** observed under light polarized optical microscope, and the crystal structure determined for diastereoisomer **3a** by single-crystal X-ray diffraction experiments (SC-XRD).



Scheme 1. Synthesis, texture of single crystal and ORTEP drawing for (*R,R*)-**3a**

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SEPTEMBER 23-27 2024
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Trans-Anethole isolated from Star Anise for (3+2) Cycloaddition Reaction Applications.

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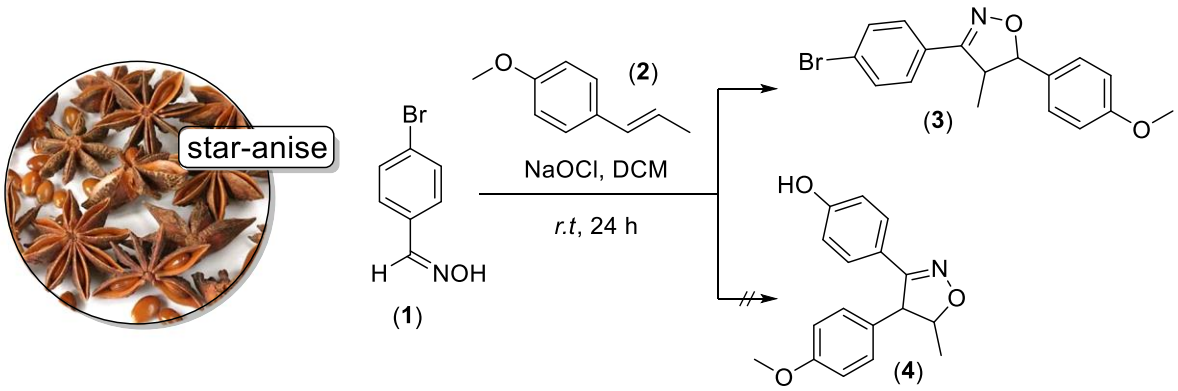
Keywords: *Anis Stellati Fructus; trans-anetole; 1,3-dipolar cycloaddition; isoxazoline*

ABSTRACT

In this report, an experimental classroom through extraction, characterization, and application of *trans*-anethole from raw star-anise oil was conducted by undergraduate students. Initially, the star-anise oil was extracted by hydrodistillation in a Clevenger apparatus, yielding an oil yellowish material with a high *trans*-anethole content. The extracted oil was then characterized by RMN, FT-IR, and HRMS. The oil with higher content of *trans*-anethole (**2**) was utilized as a dipolarophile in a dipolar (3+2) 1,3-dipolar cycloaddition reaction with 4-bromobenzaldoxime (**1**) to afford a new highly functionalized 3,5-isoxazoline cycloadduct (**3**) with regioselectivity in favor of **3**. This sequence of experimental steps allowed the students to gain hands-on experience in the extraction techniques in raw natural materials, its comprehensive characterization using spectroscopic techniques, and its subsequent use in as a green building block in an organic synthesis to produce 5-membered heterocyclics. This study highlights the educational value of engaging undergraduate students in research-oriented projects, providing them with skills and insights into the field of natural product chemistry and organic synthesis.



Scheme 1. Synthesis of isoxazoline from *trans*-anethole

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SEPTEMBER 23-27 2024
19BMOS
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TBA($FeCl_3Br$) complex as photocatalyst in the Csp3- bond activation in alcohols for the synthesis of *N*-based heterocycles¶

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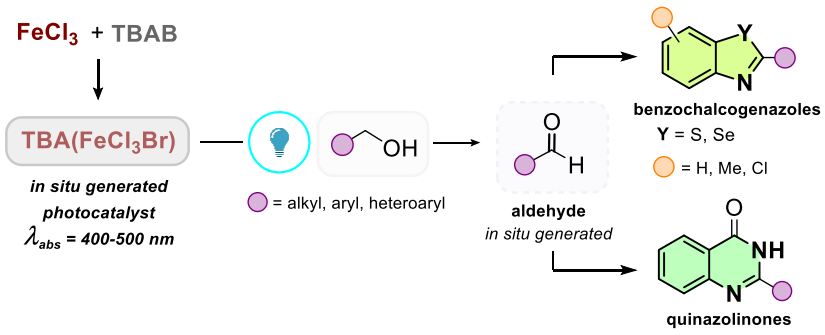
Keywords: *TBA($FeCl_3Br$) complex, visible-light, benzochalcogenazoles, quinazolinones*

ABSTRACT

Green chemistry is a crucial tool for fostering sustainable chemical processes.[1] Additionally, *N*-based heterocycles, including benzochalcogenazoles and quinazolinones, represent an important class of compounds in pharmaceutical industry.[2] Given their significance, the development of efficient and eco-friendly methods to obtain these compounds is essential. In this context, TBA($FeCl_3Br$) complex, formed *in situ* by the mixture of $FeCl_3$ and tetrabutylammonium bromide (TBAB) in MeCN, has been proven to be an outstanding photocatalyst to promote the selective oxidation of alcohols to aldehydes under blue-light irradiation. Here we describe the synthesis of benzochalcogenazoles and quinazolinones by the reaction of *ortho*-substituted anilines and alcohols under mild conditions following some of the green chemistry principles. Among them, the developed procedure reduces the need of derivatization circumventing the use of aldehydes as substrate and allows the isolation of the quinazolinones by precipitation after washing the crude with ethyl ether, avoiding the need of purification by column chromatography.



34 examples *up to 98% yield* *scale-up* *good substrate tolerance*

column chromatography avoided for the QZN derivatives

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SEPTEMBER 23-27 2024
19BMOS
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Visible Light Photoalkylation of 2-Arylimidazo[1,2-*a*]pyridines on C3 Position via EDA Complex Formation with Katritzky Salts

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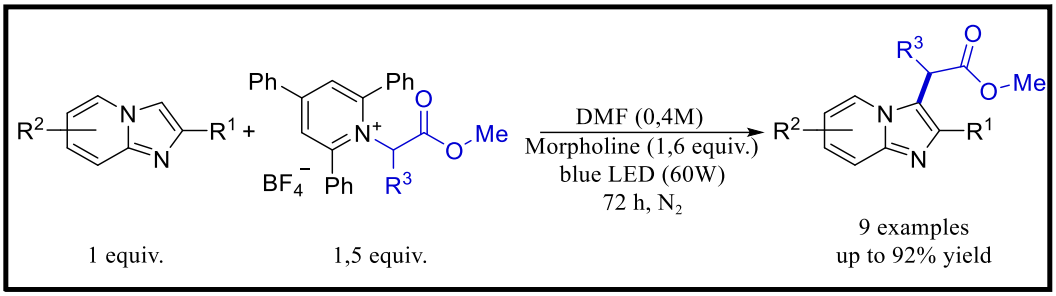
Keywords: *Imidazo[1,2-a]pyridine, Katritzky Salt, EDA Complex*

ABSTRACT

The use of visible light-driven photochemical reactions has become increasingly frequent in organic synthesis, as it usually allows for good selectivity, safety and mild conditions. Unfortunately, most organic systems do not absorb visible light[1,2] requiring the addition of a photocatalyst or the formation of an Electron Donor-Acceptor (EDA) complex as a way of activating the system[3]. The formation of EDA complexes alters the region in which the organic compounds absorb, making it possible for them to be activated by visible light[4]. In the present study we explored the C3-alkylation[5] of 2-aryllimidazo[1,2-*a*]pyridines derivates in the presence of Katritzky salts and morpholine under visible light. Optimization of the reaction conditions was conducted and substrate scope valuation is ongoing, with 9 examples accomplished so far, with up to 92% yield. Among the compounds obtained is a known precursor of Zolpidem[6,7], a sedative-hypnotic drug[8]. This may represent an alternative synthesis for this pharmaceutical.



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SEPTEMBER 23-27 2024
19BMOS
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Redox-Neutral Stereospecific Deoxyalkylation of Alcohols Enabled by an Interrupted Appel Reaction

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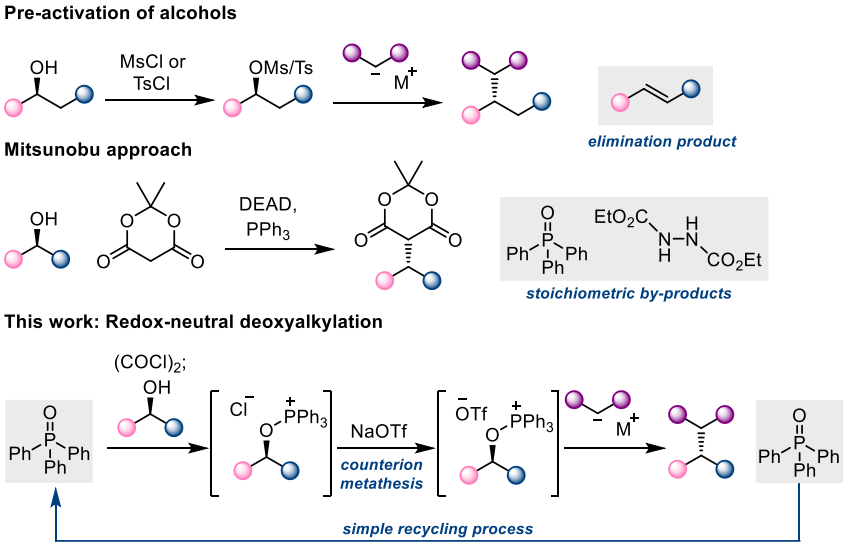
Keywords: *organophosphorus chemistry, stereoselective synthesis, alkylation.*

ABSTRACT

Strategies to forge sp^3–sp^3 carbon linkages are integral to the field of synthetic organic chemistry.[1] Alcohols are abundant and generally easy to handle in the laboratory which makes them ideal partners for cross-coupling and alkylation.[2] Unfortunately, there are limited methods for direct, stereospecific, nucleophilic substitution of alcohols with carbon nucleophiles, despite the advantage of avoiding a discrete activation step.[3] Mitsunobu-based protocols using Brønsted acidic carbon nucleophiles have been shown to be efficient, yet often require the use of high energy diazodicarboxylates as oxidants, which limits their application.[4-8]

We have developed a direct, redox-neutral phosphorus(V)-mediated approach in which alkoxyphosphonium intermediates, generated from phosphine oxides, undergo coupling with exogenous carbon nucleophiles. This process is driven by an Interrupted Appel reaction, eliminates the need for hazardous oxidants, and allows for recycling of the phosphine oxide, the waste product of conventional approaches.[8]



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Antiproliferative activity of novel triazole scaffold

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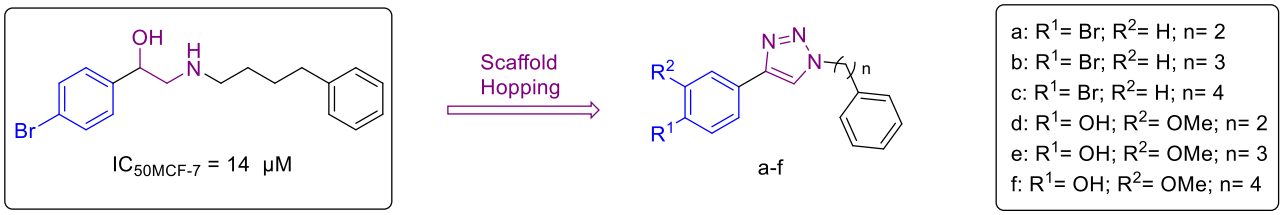
Keywords: *Bioisosterism, scaffold hopping, antitumoral.*

ABSTRACT

The 1,2,3-triazole scaffold has a widespread occurrence on several bioactive compounds, such as antimicrobials[1], antitumorals[2], and antivirals[3]. Previously, a promisor β-amino alcohol compound had shown antiproliferative activity against two cell lines of breast cancer[4]. In this work, 1,2,3-triazole was used to replace the core structure of this β-amino alcohol prototype. A metal-free synthesis method was applied using primary amines (1.4 equiv), enolizable ketones (1 equiv), and 4-nitrophenyl azide (1 equiv)[5]. The obtained yields were 28-93%. All products demonstrated some antiproliferative activity, but the *p*-Br substituted compounds presented a higher activity than their equivalents with the guaiacol portion. The chain extension from two to three methylenes has improved activity, but the same improvement was not observed from three to four. Further studies are needed, but this work demonstrated that the 1,2,3-triazole scaffold has the potential for the development of new antitumoral candidates, and it is a promising bioisostere for β-amino alcohol.



Compound	Cellular viability (%) in 60 μM
a[1]	65.94±3.74
b[1]	30.12±1.10
c[1]	39.53±7.36
d[1]	91.45±4.73
e[1]	78.36±7.36
f[1]	72.89±6.90
Palbociclib[2]	9.34±0.54
Vorinostat[1]	14.91±0.84

Results of the MTT assay on the MCF-7 cell line, 48h of incubation, % of cellular viability calculated based on the negative control. [1]Diluted in DMSO. [2]Diluted in HCl 0.1M.

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SEPTEMBER 23-27 2024
19BMOS
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Efficient *N*-arylation and *N*-alkylation of quinazolines using PEG-400 as green solvent

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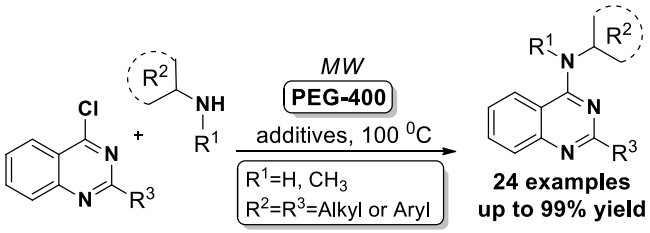
Keywords: *N-arylation, N-alkylation, PEG-400.*

ABSTRACT

Quinazolines represent a significant class of aromatic *N*-heterocycles.[1] Derivatives of 4-aminoquinazoline are particularly valuable due to their presence in numerous pharmaceuticals, including erlotinib, gefitinib, and prazosin, and their role as antagonists of human adenosine A3 receptors.[2-4] The extensive utilization of this structural motif in biologically active compounds underscores the necessity for developing selective protocols to access functionalized derivatives.[5] Thus, this study presents a green, cost-effective, and efficient method for *N*-arylation and *N*-alkylation employing PEG-400 in a microwave reactor (Scheme 1). This novel synthetic approach holds promise for future applications in multifunctional supramolecular nanosystems[6] and in the development of candidates for cancer therapies, exemplified by the successful synthesis of Verubulin and analogs in high yields.



Scheme 1. Protocol employed in microwave-assisted reaction.

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New series of Schiff bases for lanthanide luminescent sensitization

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Keywords: *Schiff base, lanthanide coordination compound, fluorescence.*

ABSTRACT

Design of luminescent coordination compounds based on lanthanide ions involves the synthesis of organic ligands for sensitization that improve energy absorption upon coordination with the metal center. Planar and rigid structures with high electronic π-delocalization are often selected for these applications.[1]
In this work, we present the synthesis of a new series of Schiff base ligands using appropriate hydrazides as precursors (***Figure 1***). These hydrazides are obtained from the reaction between carboxylic acids and hydrazine monohydrate, using 1,1'-carbonyldiimidazole (CDI) as a coupling agent.[2]
Differences in reactivity were observed among various hydrazides during the ligand formation stage. Computational calculations revealed that ligand **4.e** (***Figure 1***) could not be synthesized due to "peri" and "alpha" electronic effects, as well as intramolecular hydrogen bonding within the hydrazide structures. These factors have a significant influence on the nucleophilicity of the N-terminal of the hydrazides. Finally, we present the solid-state fluorescent properties of the synthesized ligands.

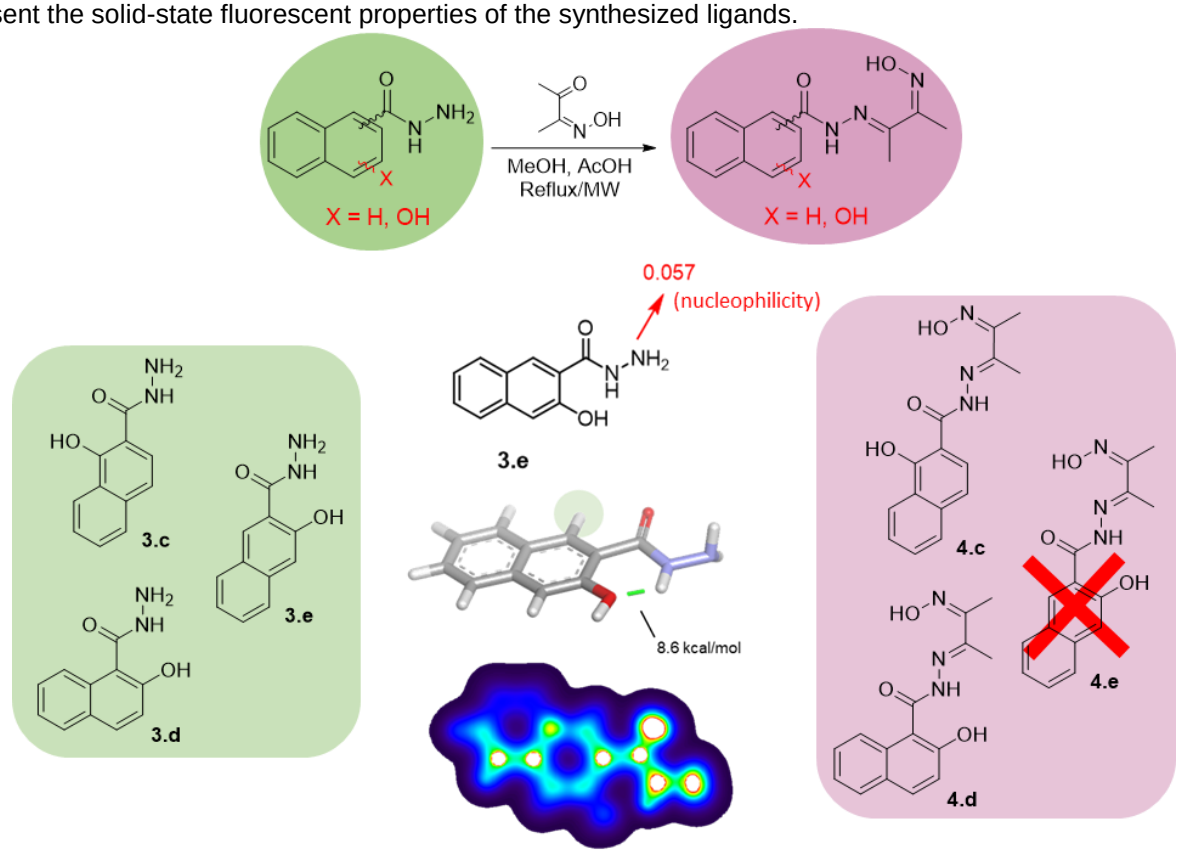

Figure 1: *Computational studies on the reactivity differences among various hydrazides.*

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Efficient synthesis of pharmaceutical relevant *N*-nitrosamines under flow reaction conditions

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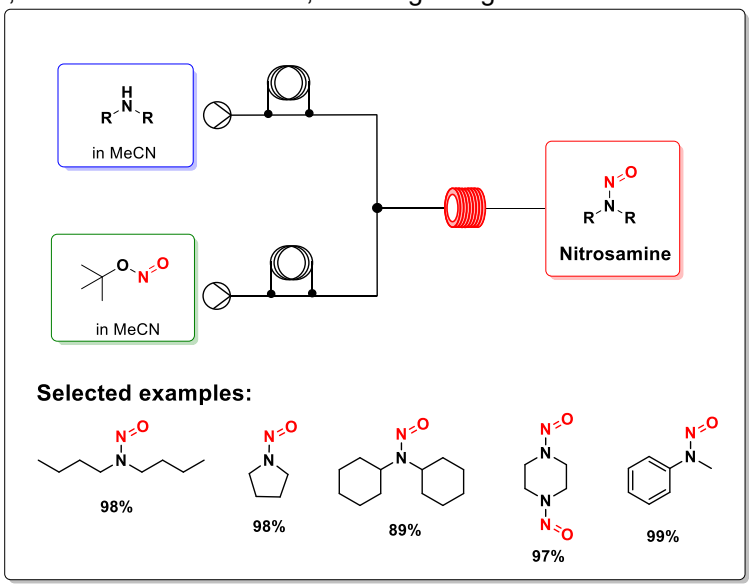
Keywords: Nitrosamines, tert-butyl nitrite, Continuous flow.

ABSTRACT

A detection of pharmaceutical impurities, such as nitrosamines, has become a significant concern in the industry since their presence was discovered in Sartan class medications around mid-2018. *N*-nitrosamines are nitroso compounds known for their carcinogenic potential in animals[1]. Traditionally, synthesizing these nitrosamines involves nitrous acid, generated in situ by reacting sodium nitrite with mineral acids[2]. In our study, we explored an alternative to this classic synthesis, using tert-butyl nitrite (TBN) as a nitrosating agent via continuous flow reactions (Scheme 1). TBN stands out for its competitive cost, good reactivity, and solubility in common synthetic solvents[3]. Additionally, its application in continuous flow processes is advantageous due to moderate volatility and the formation of tert-butanol as a benign by-product, facilitating its removal from the reaction medium[4]. This approach has demonstrated potential in synthesizing nitrosamine derivatives under solvent-free, metal-free, and acid-free conditions, ensuring straightforward isolation and high yields[5].



Scheme 1. Continuous flow reactions proposed in this work.

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Synthesis of new marinoquinoline derivatives with potential antimalarial activity

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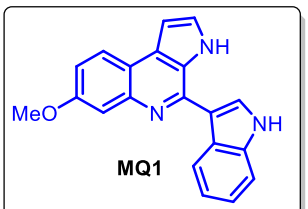
Keywords: *Malaria, Synthesis, Marinoquinolines.*

ABSTRACT

Malaria is a disease caused by species of the parasite *Plasmodium* spp,[1] which only in 2022 caused the deaths of 608,000 people. Currently, there are drugs available for the treatment of malaria, however, the parasites are gaining resistance to them, thus making the treatment ineffective.[2] Therefore, the development of new drugs capable of combating this disease is urgent. In this context of new drug discovery, a class of compounds called marinoquinolines (MQs) has been gaining prominence due to their inhibitory activities against *Plasmodium*.[3] Based on the structure of MQ1, previously synthesized by Professor Correia's group, it was decided to make new modifications to the indole portion of this substance, aiming to obtain more potent substances. Until now, 32 marinoquinolines have been synthesized from a synthetic route of 7 to 10 steps, of which 82% were active against *P. falciparum* 3D7, with IC_{50} values ranging from 320 nM to 5.9 μM.



MQ1

IC_{50} (*P. falciparum* 3D7) = 2.09 ± 0.09 μM

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Use of the Suzuki-Miyaura coupling reaction in the synthesis of chrysin biarylic derivatives for the investigation of their neuroprotective activities in glial cells

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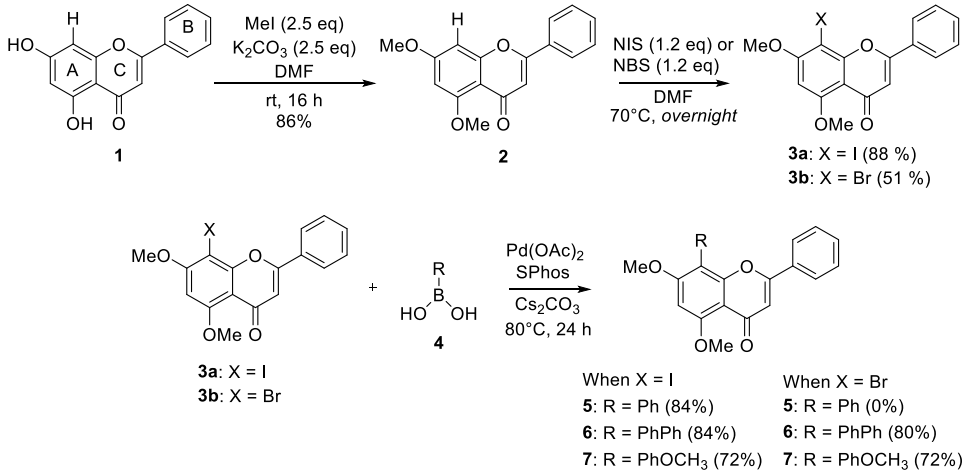
Keywords: *Chrysin derivatives, Suzuki-Miyaura coupling, Neuroprotective activity.*

ABSTRACT

Flavonoids make up a very interesting class of molecules present in nature. Its standard three-ring skeleton structure (A, B, and C, Scheme 1, compound **1**), with small variations in this structure, provide a pletora of biological and pharmacological activities such as antibacterial, antifungal, antiparasitic, anti-Alzheimer, antidepressant. Antidiabetic, antiobesity, anti-inflammatory, antioxidant, anticancer and cardioprotective activity.[1] Due this, some chrysin biarylic derivatives were synthesized by Suzuki-Miyaura cross-coupling reaction.[2,3] Therefore, the objective of this work is to make modifications to commercially available chrysin to synthesize biarylic compounds that could optimize their pharmacological properties. Coupling compounds were obtained in satisfactory yields (72 to 84%). The halogenation of compound **2** using NIS was obtained with higher yields when compared to NBS (88% and 51%, respectively). Among the coupling products, the yields of biarylic derivatives were similar when starting from **3a** or **3b**. The products obtained in the third stage will be investigated from a biological perspective regarding their neuroprotective activities in glial cells.



Scheme 1: Synthesis of chrysin biarylic derivatives.

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fapesb Fundação de Amparo à Pesquisa do Estado da Bahia
INCT ENERGIA & AMBIENTE
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Synthesis and antibiofilm and antibacterial activity evaluation of Tetrahydroindolone-Dihydropyrimidinone hybrids

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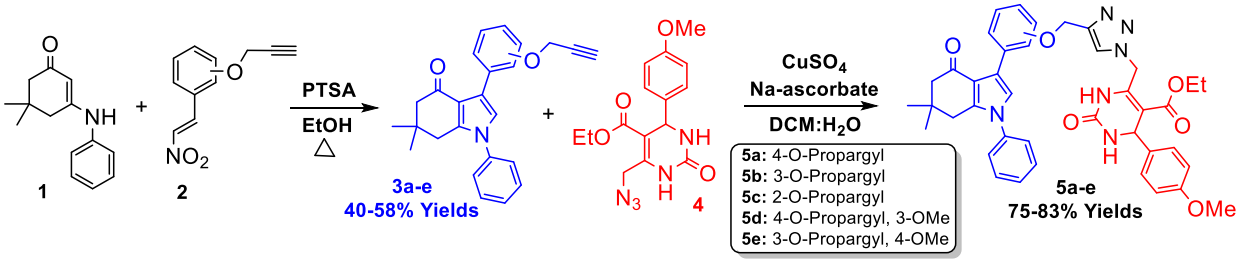
Keywords: *Hybridization, Dihydropyrimidinones, Antibiofilm*

ABSTRACT

Tetrahidroindolones are important scaffolds in Medicinal Chemistry such as SNX2112, a heat shock protein (Hsp90) inhibitor and anti-cancer HER kinase dependent.[1] Likewise, Dihydropyrimidinones are bioactive compounds including antibacterial and anti-cancer activities.[2] The hybridization of bioactive compounds can lead to discovery of more efficient drugs with fewer side effects.[3] Thus, Click CuAAC reaction of THI **3a-e** and azido-DHPM **4** afforded the hybrids *THI-DHPM* **5a-e**.



Scheme 1: General scheme for the synthesis of THI-DHPM hybrid compounds **5a-e**.

Biofilms are complex communities of microorganisms that adhere to surfaces and are embedded in a self-produced extracellular matrix that hinder the action of antibiotics. The antibiofilm activity of compounds **5a-e** at 100 µg/mL were evaluated against *Staphylococcus aureus* by crystal violet method.[4]

Table 1. Antibiofilm Activity of Hybrids THI-DHPM **5a-e** against *S. aureus.*

Entry	Compound	% of Biofilm Inhibition
1	**5a**	73
2	**5b**	78
3	**5c**	89
4	**5d**	31
5	**5e**	28
6	**Vancomycin**	72

The initial results have demonstrated the ability of **THI-DHPM** hybrids to inhibit the biofilm formation and bacterial growth. The bioactivity against *Pseudomonas aeruginosa* and the dose-response curves are under investigation as well as the toxicity in the *in vivo* model of *Caenorhabditis elegans*.

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Photoinduced Thiol-Ene “Click” Reaction

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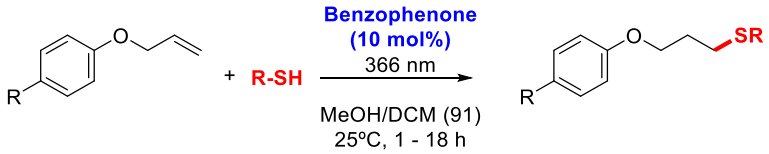
Keywords: *Thioalkylation, Photo Organocatalysis , Allyl ether.*

ABSTRACT

The hydrothiolation of alkenes known as the thio-ene click (TEC) reaction,[1] is a powerful tool for construction of C-S bonds in natural products, pharmaceuticals and organic materials.[2] A radical TEC reaction is reported for alkenes using benzophenone as an inexpensive photocatalyst at room temperature. Upon direct irradiation of benzophenone with light of 366 nm in the presence of the allyl ether and a series of alkyl and aryl thiols led to prepare a wide variety of thioethers in good to excellent yields. The photoreaction is depicted in Scheme 1.



Scheme 1.

Additional control experiments were further carried out to gain more insights into the reaction mechanism. Inhibition test with TEMPO clearly demonstrated a radical chain process during the formation of thioethers. Performing the photoreaction with deuterated solvents showed a HAT reaction from the solvent to the radical intermediate. Based on these experimental results and previous literature reports, a reaction mechanism was also proposed.

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Transition Metal-Free Hydroformylation Through A Combined Radical-Ionic Process

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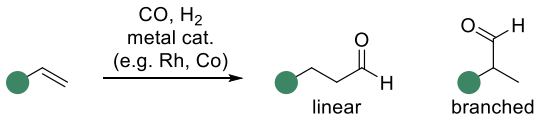
Keywords: *Hydroformylation, photocatalysis, organophosphorus chemistry*

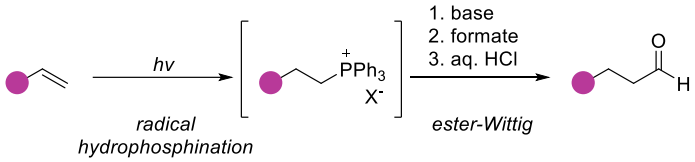
ABSTRACT

Hydroformylation represents one of the most widely applied examples of homogeneous catalysis in the chemical industry. Typically, it is performed with a transition metal catalyst (such as cobalt or rhodium) under high pressures of carbon monoxide and hydrogen (syngas) with an alkene, resulting in the formation of aldehydes. Despite its industrial importance, its application in academic research is limited as a result of the specialist equipment required to handle syngas at high pressure. Furthermore, the regioselectivity of addition can be difficult to control, with both linear and branched isomers being produced.[1] Our transition-metal free variant is based upon the combination of a photochemical method for the synthesis of phosphonium salts from alkenes followed by a Wittig reaction with a formate ester. This results in a simple and convenient one pot method for the synthesis of aldehydes from alkenes with exclusive linear selectivity. The work will describe the optimisation and scope of this process.

Classical hydroformylation procedure



This work: One-pot hydroformylation procedure



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SEPTEMBER 23-27 2024
19BMOS
BRAZILIAN MEETING ON ORGANIC SYNTHESIS
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Towards the synthetic optimization of (3aR,6aR)-6-((benzyloxy)methyl)-2,2-dimethyl-3a,6a-dihydro-4H-cyclopenta[d][1,3]dioxol-4-one

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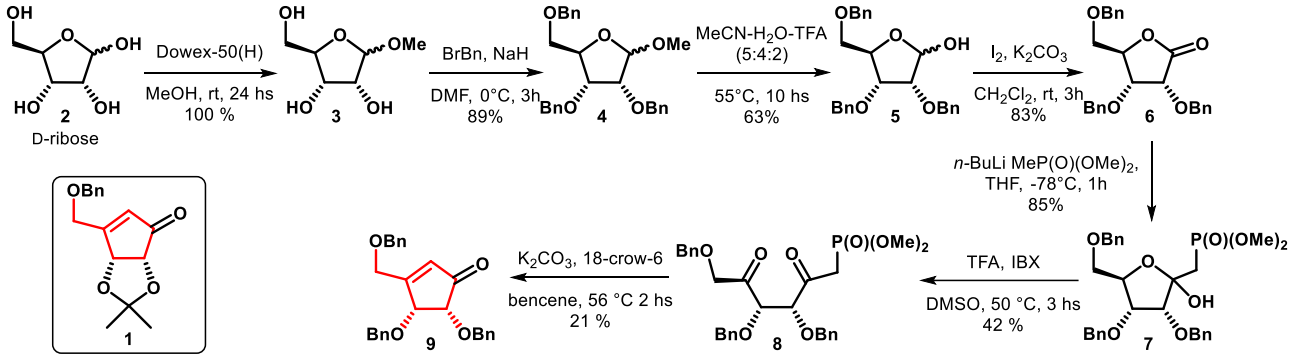
Keywords: *carbanucleosides, neplanocin C,* cyclopentenone.

ABSTRACT

Cyclopentenone 1 is a key intermediate that has been used in the synthesis of multitude carbocyclic nucleosides of interest[1]. Although there are several synthesis strategies[2,3,4], most of them present different difficulties. These include low yields, isomerization, irreproducibility, and the use of non-green reagents such as chromium trioxide. Therefore, our objective is to optimize the synthetic sequence of **1**, or a potential analogue that is suitably protected. A novel synthetic strategy is presented herein, based on D-ribose, a cheap and abundant natural product. The proposed synthetic route involves the preparation of analogue **9**, where the isopropylidene protecting group is replaced by benzyl groups. The synthetic route is developed in 7 reaction steps, avoiding the use of adverse reagents and yielding an overall yield of 3,5%.



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Sheila I. de Diego Saadia thanks UBA for the doctoral scholarship (Doctorate Program) and Marianne Bernhardt for the student scholarship. Sergio H. Szajnman and Juan B. Rodriguez are grateful to Universidad de Buenos Aires for Grant 20020220200020BA; to CONICET for Grant PIP 112-202001-01544CO and Agencia Nacional de Promoción Científica y Tecnológica for Grant PICT2021-I-A-00887.

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SEPTEMBER 23-27 2024
19BMOS
BRAZILIAN MEETING ON ORGANIC SYNTHESIS
BENTO GONÇALVES, RS - BRAZIL

Nb_2O_5/H_2O_2 as an efficient catalyst for primary alcohols oxidation under visible-light conditions

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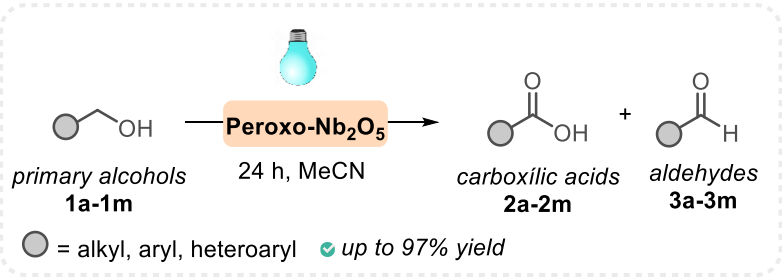
Keywords: *primary alcohols oxidation, visible-light, niobium pentoxide, hydrogen peroxide*

ABSTRACT

Oxidation reactions are extremely important in organic synthesis, since they are widely used in total syntheses of several bioactive compounds.[1] A example is Luzopeptin A, a drug with antibiotic and antitumor activities, whose total synthesis involves a selective oxidation process of an alcohol to a carboxylic acid. Furthermore, aldehydes/carboxylic acids are widely used in chemical, pharmaceutical and functional materials industries.[2] Aiming to promote the oxidation of alcohols, most of the synthetic methodologies in the literature involves drastic conditions (highly acidic media, temperatures and large amount of oxidants).[3] As alternative, the modification of Nb_2O_5 with peroxide groups results in photosensitive materials, when promoted to the excited state by the absorption of visible-light, injecting electrons into the semiconductor conduction band. Those electrons can reduce O_2 molecules, releasing superoxide ions, which afford the oxidation of organic matter.[4] We present here the use of modified Nb_2O_5 in the visible light-promoted oxidation of primary alcohols (Scheme 1).



Scheme 1. Oxidation of primary alcohols with Nb_2O_5/H_2O_2

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SEPTEMBER 23-27 2024
19BMOS
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Towards the Total Synthesis of Psilocybin/Psilocin: A Known Natural Psychoactive Compound with Prominent Therapeutic Properties

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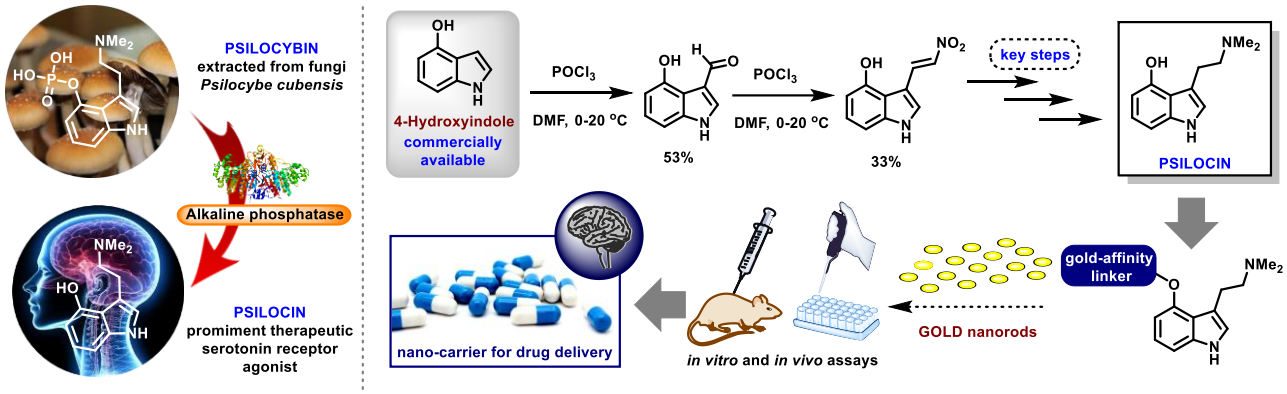
Keywords: *Total synthesis, psilocybin, medicinal chemistry.*

ABSTRACT

Nowadays, one in every eight people lives with a mental disorder.[1] However, easy access to effective treatment is not always available. Therefore, developing new alternatives for accessible treatment is in high demand. Psilocybin, a well-known psychoactive compound, can represent a viable option. It belongs to the hallucinogenic tryptamines/indolamines found in various mushroom species[2]. It has been gaining attention as a therapeutic agent.[3] Psilocybin is rapidly metabolized leading to its metabolite psilocin[4] which acts as a selective serotonin receptor agonist and is a classic hallucinogen.[5] It has shown promise in the treatment of alcoholism,[6] smoking,[7] depression,[8] obsessive-compulsive disorder[9], and anxiety.[8] The synthetic importance of psilocybin and psilocin is therefore clear. In this work we propose an optimized synthetic route for obtaining an unprecedented nano-carrier system for drug delivery using psilocin as the center bioactive unit, leading to a prominent new therapeutic methodology.



Scheme 1. Overview of the development of a new nano-carrier system for drug delivery using psilocin.

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SEPTEMBER 23-27 2024
19BMOS
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Selectivity in the Photo-Fries rearrangement reaction of Aryl Esters carried out in micro heterogeneous media

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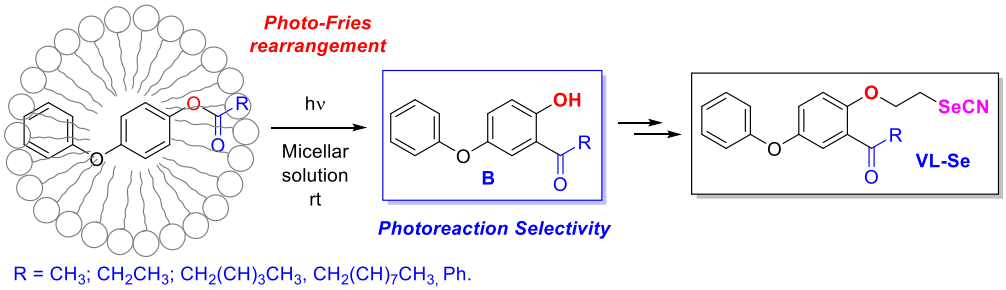
Keywords: *Photo-Fries rearrangement, micellar solutions, aryl esters.*

ABSTRACT

The Photo-Fries rearrangement reaction of aryl esters was discovered by Anderson and Rees[1] in 1960 and was found to proceed efficiently in homogeneous media providing the *ortho*-regioisomers and the phenols. However, a notable selectivity on the product distribution can be controlled if the photoreaction is carried out in micellar solution providing 2-hydroxyphenones **B** as the sole photoproduct in almost quantitative yields. Furthermore, this methodology can be useful as a key step of a synthetic approach in the preparation of **VL-Se**, which exhibits promising activity against *Trypanosoma cruzii*.[2]



R = CH_3; CH_2CH_3; $CH_2(CH)_3CH_3$, $CH_2(CH)_7CH_3$, Ph.

Upon direct irradiation of aryl esters in micellar solutions (CTAC, SDS and Brij-P35) with light of 254 nm led to prepare intermediates **B** in 85 – 98% yields with quantum yields of reaction (ϕ_R) up to 0.10. UV-visible absorption and NMR (DCS, NOESY and DOSY) spectroscopies were used to determine the location of the aryl esters within the hydrophobic core.

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SEPTEMBER 23-27 2024
19BMOS
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Aromatization of betanin promoted by trimethylsilyldiazomethane

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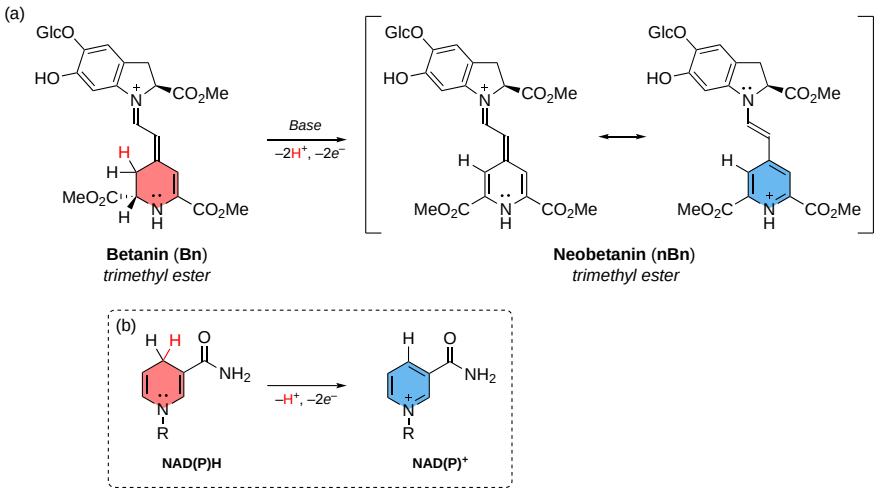
Keywords: *betanin, oxidation, aromatization, hydride transfer, esterification.*

ABSTRACT

Betanin (betanidin 5-*O*-glucoside, E162) is a natural pigment found in beetroots, used as a food dye.[1] In the late 1960s, Dreiding and coauthors used diazomethane to produce the methyl ester of betanin but obtained the methyl ester of neobetanin, its pyridinic analogue.[2] The oxidation mechanism was not further investigated, likely due to diazomethane's high toxicity and explosion hazards. We confirmed that oxidizing betanin with diazomethane produces di- and trimethylated neobetanin. We also show that trimethylsilyldiazomethane,[3] a safer methylating agent, esterifies and oxidizes betanin as effectively. Both methods indicate the $2H^+/2e^-$ oxidation and esterification by a color change from magenta to yellow. Purification via C18-reversed phase flash chromatography yielded a mixture of di- and tri-methylated neobetanin, up to 30%. The reaction likely proceeds with betanin methyl ester acting as a hydride shuttle, similar to biomolecules like NADH (Scheme 1).[4] This showcases a bio-based system for stabilizing betalain dyes as neobetalain derivatives.



Scheme 1. Oxidation of betanin and NAD(P)H. (a) For betanin, either CH_2N_2 or Me_3SiCHN_2 promote aromatization via $2H^+/2e^-$-oxidation. (b) Oxidation of nicotinamide adenine dinucleotide (phosphate) [NAD(P)]. In this case, $H^+/2e^-$ are usually abstracted as hydride by nicotinamide-dependent enzymes.

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SEPTEMBER 23-27 2024
19BMOS
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Synthesis of Selenium and Tellurium-Containing Sulfonamides Derived from Lupeol

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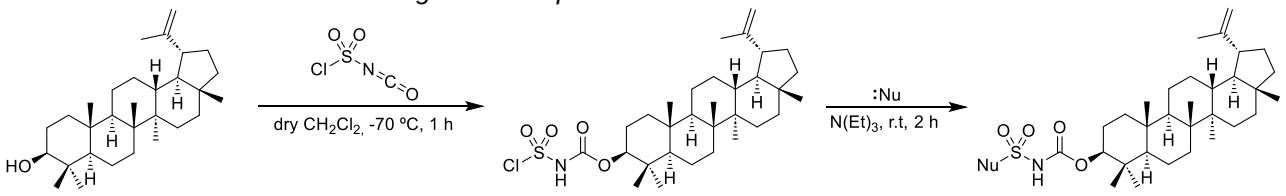
Keywords: *Lupeol, semi-synthesis, sulfonamide, selenium, tellurium*

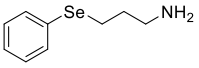
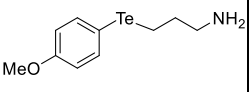
ABSTRACT

Natural products play an important role in drug discovery, however, practical applications have challenges such as low solubility in aqueous media, unstable structures, and high toxicity. The development of semisynthetic derivatives can help overcome these problems and improve the biological activities of a natural product[1]. Sulfonamides are known to have antimicrobial, anti-inflammatory, anti-diabetic and anti-cancer activities[2]. Organic compounds containing selenium and tellurium are reported to exhibit antimicrobial, anti-inflammatory, antidiabetic, antiparasitic and antitumor activities[3,4]. In this study, three sulfonamides were synthesized via a one-pot reaction between the natural triterpenoid lupeol (**1**) and chlorosulfonyl isocyanate (-70ºC, N_2 atmosphere, anhydrous medium), forming a carbamate (**2**), followed by the addition of a nucleophile (water (**3**), amino selenide (**4**), amino telluride (**5**)) in the presence of triethylamine. The final sulfonamides (**3-5**) were obtained with yields ranging from 41% to 99%. As perspectives, we plan to increase the compounds library and evaluate their biological activities.

Figure 1 - Preparation of sulfonamides 3-5



1 2 3-5

Product	Nu	Yield (%)
3	H_2O	98
4		99
5		41

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SEPTEMBER 23-27 2024
19BMOS
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Selenium-Functionalized Ionic Liquids: Synthesis and Biological Activity

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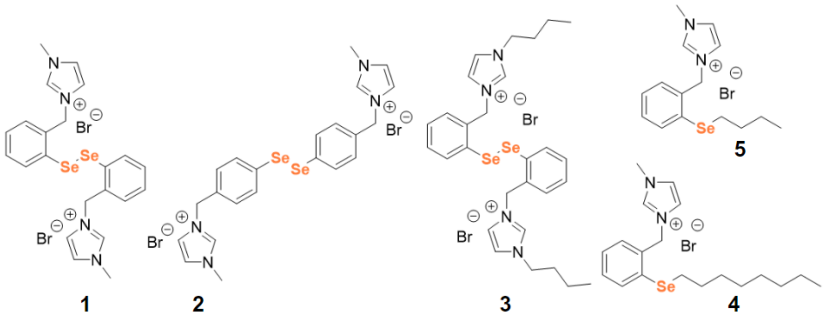
Keywords: *Ionic Liquids, Selenium, Biological activity*

ABSTRACT

The versatility of selenium-derived organic compounds has increasingly highlighted their chemical and biological relevance. By combining these with the unique properties of Ionic Liquids (ILs), this study focuses on synthesizing five selenium-imidazole functionalized ILs (Scheme 1), with two novel additions (4 and 5) to this class of compounds. Furthermore, these compounds exhibit great solubility in water, showcasing their versatility for bioavailability assays.

Thus, bioactivity experiments were conducted on Calu and Vero cells and demonstrated the efficacy of these ILs against the SARS-CoV-2 virus whilst still maintaining low cell toxicity, potentially underscoring their therapeutic nature. Cell toxicity induced by the compounds was also verified by the MTT assay, monitoring dehydrogenase activity, and trypan blue assay, both of which yielded favorable results.



Scheme 1. Ionic Liquids Synthesized

This research aims to contribute to the development of new antimicrobial and antiviral agents by exploring the unique properties of these selenium-derived Ionic Liquids.

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SEPTEMBER 23-27 2024
19BMOS
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Development of 3,5-*O*-di-*tert*-butylsilylene-D-galactofuranoside analogues for the synthesis of arabinogalactans from *M. tuberculosis*

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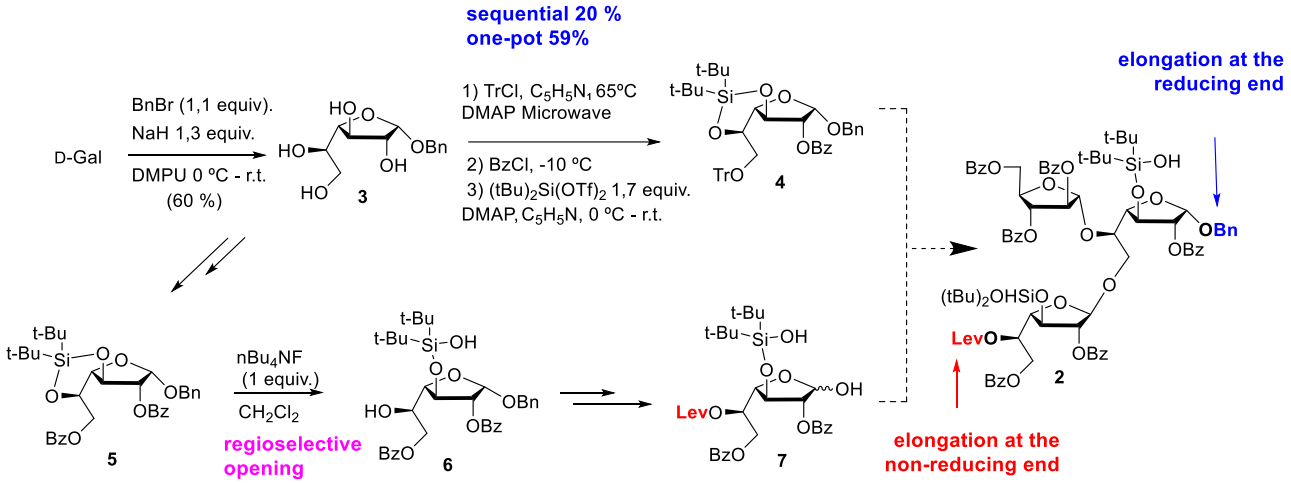
Keywords: Galactofuranose, glycosylation, *Mycobacterium tuberculosis*.

ABSTRACT

The development of synthetic methodologies for the construction of galactofuranose-containing oligosaccharides is crucial due to the presence of the xenobiotic Gal*f* unit in pathogenic bacteria. We have developed an effective method for the 5-OH regioselective opening of 3,5-*O*-di-*tert*-butylsilylene-D-galactofuranosides, further employed for the synthesis of derivatives of *Aspergillus fumigatus* galactofuran.[1] To explore the scope of this methodology, we focused on the synthesis of trisaccharide **2**, which has the skeleton of the branched trisaccharide [α-D-Ara*f*-(1-5)]-β-D-Gal*f*-(1-5)-D-Gal*f* (**1**) found in *Mycobacterium tuberculosis* arabinogalactan. The protective groups were chosen to enable the subsequent elongation of the trisaccharide **2** by coupling with other units at both reducing and non-reducing ends. Compound **4** (the precursor of the reducing end of **2**) was synthesized in three steps from **3** using a one-pot methodology. Compound **7** (the precursor of the non-reducing end of **2**) was synthesized from **3** by the regioselective opening methodology in very good yields. The synthesis of **4** and **7** proved to be effective.



ACKNOWLEDGEMENTS

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SEPTEMBER 23-27 2024
19BMOS
BRAZILIAN MEETING ON ORGANIC SYNTHESIS
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Synthesis of Selenium and Tellurium-Containing Sulfonamides Derived from Lupeol

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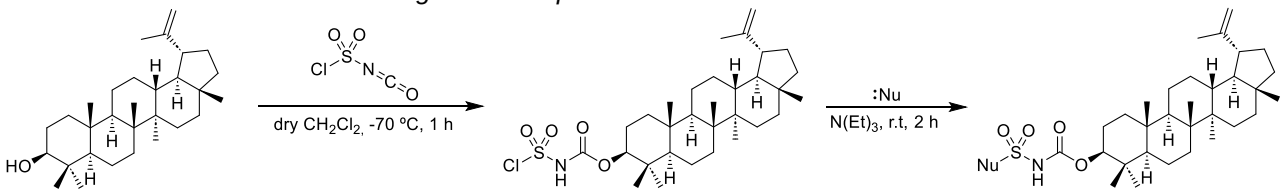
Keywords: *Lupeol, semi-synthesis, sulfonamide, selenium, tellurium*

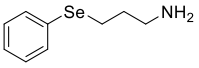
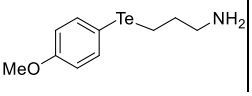
ABSTRACT

Natural products play an important role in drug discovery, however, practical applications have challenges such as low solubility in aqueous media, unstable structures, and high toxicity. The development of semisynthetic derivatives can help overcome these problems and improve the biological activities of a natural product[1]. Sulfonamides are known to have antimicrobial, anti-inflammatory, anti-diabetic and anti-cancer activities[2]. Organic compounds containing selenium and tellurium are reported to exhibit antimicrobial, anti-inflammatory, antidiabetic, antiparasitic and antitumor activities[3,4]. In this study, three sulfonamides were synthesized via a one-pot reaction between the natural triterpenoid lupeol (**1**) and chlorosulfonyl isocyanate (-70ºC, N_2 atmosphere, anhydrous medium), forming a carbamate (**2**), followed by the addition of a nucleophile (water (**3**), amino selenide (**4**), amino telluride (**5**)) in the presence of triethylamine. The final sulfonamides (**3-5**) were obtained with yields ranging from 41% to 99%. As perspectives, we plan to increase the compounds library and evaluate their biological activities.

Figure 1 - Preparation of sulfonamides 3-5



1 2 3-5

Product	Nu	Yield (%)
3	H_2O	98
4		99
5		41

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CNPq, CAPES, FAPEMIG, LAREMAR

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SEPTEMBER 23-27 2024
19BMOS
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Attempts to synthesize a benzofuran-3(2*H*)-one from eugenol, a key intermediate to potentially antimicrobial aurones

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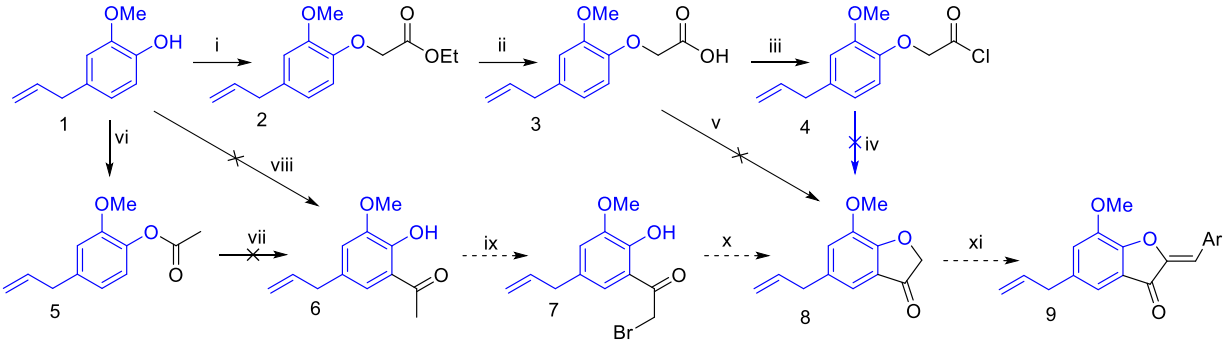
Keywords: *molecular hybridization, biological activity, phenylpropanoids.*

ABSTRACT

Aurones are natural bioactive compounds that can be used as starting materials to create compounds with therapeutic potential, often explored through hybridization to maximize their effectiveness[1]. Eugenol is an antimicrobial phenylpropanoid known for a long time[2]. Due to the urgent demand for improved medicines against trypanosomiasis and fungal diseases, we designed new molecular hybrids containing aurone and eugenol moieties. Given the documented antiparasitic and antimicrobial activities of aurones and eugenol derivatives, we predicted that fusion of these pharmacophores would produce compounds of significant biological relevance with the general structure represented as **9** in Scheme 1 (the Ar moiety is not yet to be disclosed since previous results on this are not yet published). We used eugenol (**1**) as a starting material, aiming to synthesize the key intermediate benzofuran-3(2*H*)-one (**8**). Then, based on a traditional methodology[3], **1** was converted to the acetic intermediate (**3**) in two steps and this was converted to the respective acyl chloride (**4**). The acid derivative **3** and its acyl chloride **4** were tentatively subjected to intramolecular aromatic acylation conditions based on the available reagents at that time (steps v and vi), but none of them led to the desirable product or even to a mixture of products accessible to separation. Alternatively, compound **1** was converted to the acetyl ester (**5**), which could in turn be converted to the ketone intermediate **6** by Fries rearrangement (step vii). In another attempt, we tried to obtain this ketone **6** directly from **1** (step viii). However, we obtained only untreatable mixtures with both approaches. Possibly, the allylic side chain interferes with the clean obtaining of the intended products, given its ability to react with electrophiles. In our searches in the literature, we did not find methodologies for direct aromatic acylation with substrates of this nature, so other approaches must be worked on.



i: Ethyl bromoacetate, K_2CO_3, DMF, 25 °C; ii: LiOH, THF, 40 °C; iii: $SOCl_2$, 70 °C; iv: $AlCl_3$, DCM, 0 °C to 25 °C; v: PPA, 80 °C or MSA, 80 °C or H_2SO_4, 0 °C to 25°C or PTSA, $CaCl_2$, MW; vi: Ac_2O, DCM, TEA, 25 °C; $AlCl_3$, NaCl, 110 °C or Zn, MW; viii: Ac_2O, $ZnCl_2$, 25 °C; ix: $CuBr_2$, EtOAc/DCM, reflux; x: TEA, ACN, reflux; xi: respective aromatic aldehydes under different conditions

Scheme 1: Synthesis route to new potentially bioactive aurones.

ACKNOWLEDGEMENTS

Thanks to FAPEMIG (APQ-00686-18; APQ-00352-18, APQ-00544-23, RED-00110-23 and APQ-01455-24).

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SEPTEMBER 23-27 2024
19BMOS
BRAZILIAN MEETING ON ORGANIC SYNTHESIS
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Telescopic one-pot synthesis of pyrido[2,3-*a*]phenazin-5-amines

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Keywords: *IBX oxidation, aza-heterocycles, quinoline.*

ABSTRACT

The synthetic routes to access pyridophenazines are scarce in literature.[1a-d] Besides, some routes require multi-steps to reagent preparation[1a-b] and have limited product scope.[1a-d] Due to their fluorescent properties, pyridophenazines can be employed to determine DNA by fluorescence titration[1c] and as ligands in the synthesis of photoluminescent Zn(II) and Cd(II) complexes.[1e] In this work, a telescopic one-pot approach to access pyrido[2,3-*a*]phenazin-5-amines (**4**) was developed from 8-hydroxiquinolines (**1**), by oxidation, subsequent Michael addition and *o*-phenylenediamine (**3**) condensation (Scheme 1). The synthetized pyrido[2,3-*a*]phenazin-5-amines showed fluorescent (Figure 1a), solvatochromic (Figure 1b) and metal-ligand behaviors.

Scheme 1. Telescopic synthesis of pyrido[2,3-*a*]phenazin-5-amines.

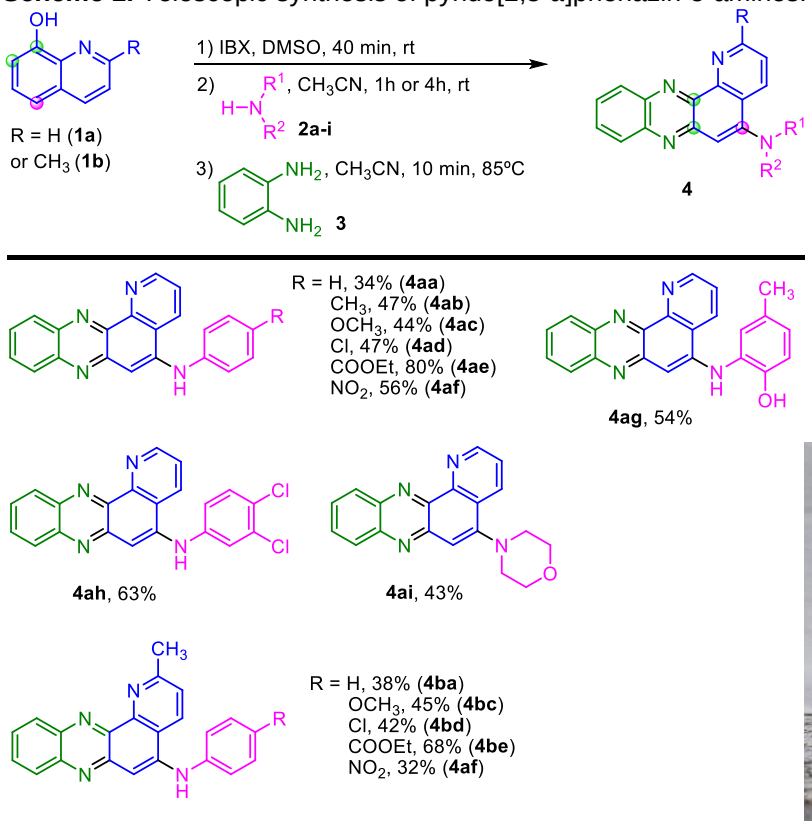

Figure 1a. Fluorescent behavior of **4ae** (5.10^{-4} mol/L).

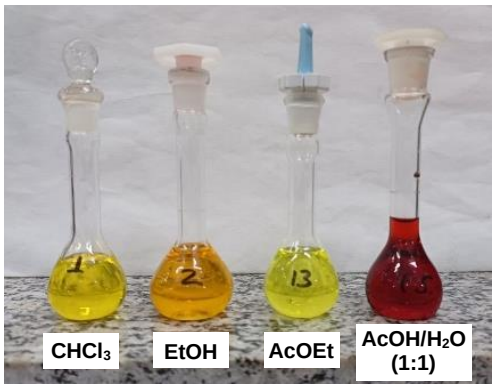

Figure 1b. Solvatochromic behavior of **4ae** (10^{-3} mol/L).

ACKNOWLEDGEMENTS

CAPES, FAPESB, INCT, CNPq

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SEPTEMBER 23-27 2024
19 BMOS
BRAZILIAN MEETING ON ORGANIC SYNTHESIS
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Silver(I)-catalyzed β-hydride migration from α-diazo esters: mild and stereoselective synthesis of (1*E*,3*E*)-dienes and mechanistic insights

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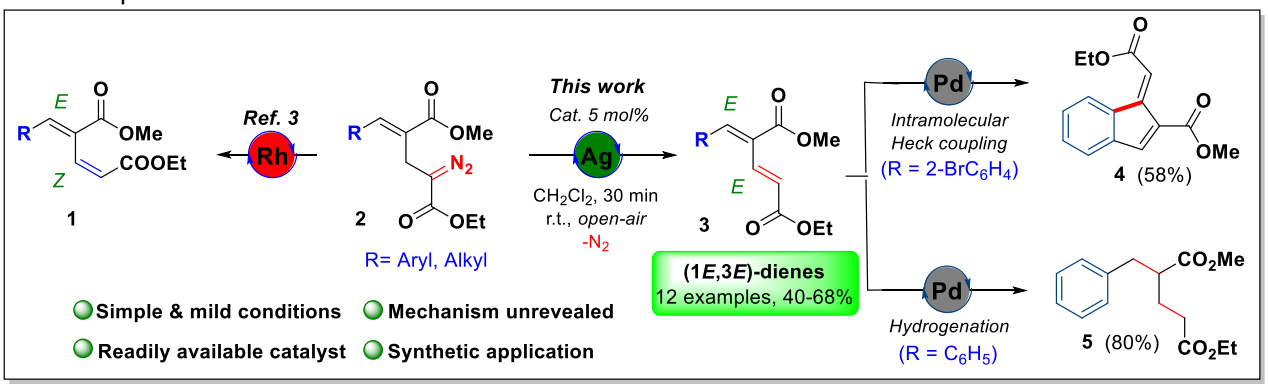
Keywords: *Diazo compounds, 1,3-Dienes, Computational methods*

ABSTRACT

The structural motif of 1,3-dienes is of considerable significance, as they are frequently encountered in a plethora of natural products and biologically active compounds.[1] Consequently, the control of diastereoselectivity in 1,3-dienes reactions has emerged as a crucial objective in the advancement of efficient synthetic methodologies, given the pivotal role of stereochemistry in the domains of drug discovery and total synthesis.[2] In a previous work from our group, conjugated 1,3-dienes of *E*,*Z* configuration (**1**) were diastereoselectively synthesized through the β-hydride migration of donor-acceptor diazo compounds **2** with rhodium(II) catalysts.[3] In the current investigation, the introduction of silver(I) triflate as the catalyst also induces the decomposition of the aforementioned diazo compounds **2**, although the resulting 1,3-dienes **3** possess *E*,*E* configuration (Scheme). The computational results indicated that the formation of dienes **3** is dependent on the formation of a C=C double bond with *E* geometry. A simplified model combined with microkinetic simulations[4] was employed to identify the key factors influencing this stereoselectivity, where the extrusion of molecular N_2 was found to be the rate determining step.[5] The synthetic versatility of (1*E*,3*E*)-diene **3** was evaluated with selected palladium-catalyzed post-functionalizations, resulting in the formation of novel compounds **4** and **5**.



Scheme. Silver-catalyzed diastereoselective synthesis of (1*E*,3*E*)-dienes **3** from donor-acceptor diazo compounds **2**.

ACKNOWLEDGEMENTS

CNPq, CAPES, FAPESC, INCT-Catálise

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SEPTEMBER 23-27 2024
19BMOS
BRAZILIAN MEETING ON ORGANIC SYNTHESIS
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Synthesis of enantioenriched helical complexes

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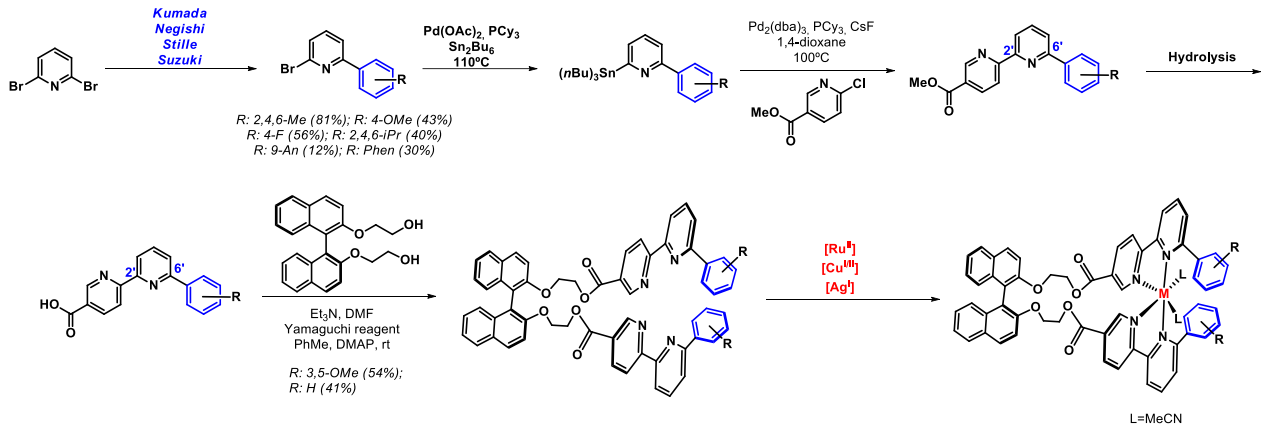
Keywords: *Chiral-at-metal complexes, Helical, Cross-coupling.*

ABSTRACT

Bipyridines and their derivatives are commonly used in the synthesis of metal complexes catalysts. This work focuses on the synthesis of their derivatives, by introducing chiral backbones linkers to yield enantioenriched helical complexes. The synthesis of the bipyridines moieties was achieved by cross-coupling reactions such as Negishi, Suzuki, Stille and Kumada as well deprotonative-metalation reactions. Finally, the diol linker backbone was attached by Yamaguchi reaction. These bisbypiridine ligands were applied in the synthesis of ruthenium, copper and silver complexes. Their use in catalytic reactions is ongoing.



ACKNOWLEDGEMENTS

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SEPTEMBER 23-27 2024
19BMOS
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Methodological Study for the Synthesis of Symmetric and Unsymmetrical Sulfides from Bunte Salts

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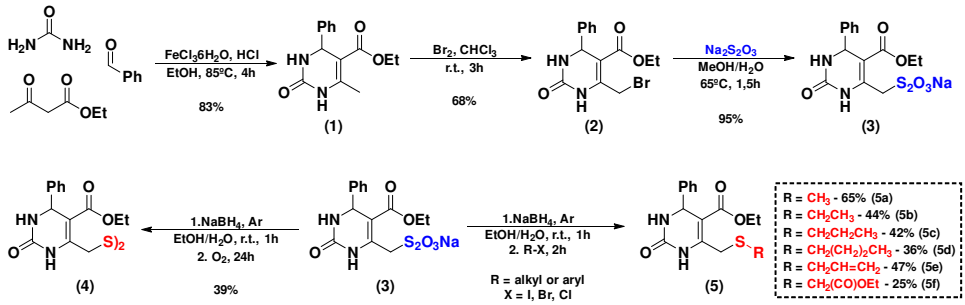
Keywords: *Bunte salts, Organochalcogen, Dihydropyrimidinone, Green chemistry.*

ABSTRACT

The search for sustainable methodologies in synthesizing sulfur-containing organic compounds remains crucial in the chemical industry [1] and various other fields. This study focuses on using Bunte salts as precursors for sulfur-containing derivatives, offering a viable alternative to traditional organometallic methods [2]. Our methodology involves the preparation of Bunte salts from halogenated dihydropyrimidinones in a straightforward procedure. The aim is to synthesize hybrid sulfides and dihydropyrimidinones, leveraging the biological properties of dihydropyrimidinones for potential therapeutic advancements. [3].

Figure 1 – Strategies on the Synthesis of Sulfides and Disulfides from Bunte Salts



During the optimization process, reducing agents, reagent stoichiometry, temperature, solvent, and extraction methods were optimized (Figure 1). All compounds were characterized using NMR and HRMS techniques. This approach circumvents the need for organometallic procedures, offering a promising alternative in the preparation of disulfides and sulfides, in aqueous media. Future research will involve other electrophiles, including Michael acceptors and epoxides, to further elucidate the scope and limitations of the procedures and to prepare a new class of derivatives for new biological prospections. Se-Bunte salts are also under investigation with similar approach, allowing to prepare selelnium-containing derivatives.

ACKNOWLEDGEMENTS

We thank CAPES, CNPq, and FAPESC for their financial support.

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SEPTEMBER 23-27 2024
19BMOS
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Telescoped CO_2-Mediated Amide Synthesis from Nitroarenes in a Continuous Flow Regime

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Keywords: *Amide Bond, Continuous Flow, Tube-in-tube*

ABSTRACT

The amide bond is one of the most important functional groups in organic molecules, it is ubiquitous in pharmaceuticals, natural products, and crucial for biomolecules[1,2]. Herein, we describe an efficient telescoped synthesis of functionalized amides utilizing CO_2 as a mediator under continuous flow conditions. It envisions a minimal interference protocol starting from cheap and available nitroarenes undergoing electrochemical transformation to yield iminophosphoranes. Such iminophosphoranes can be reacted with carbon dioxide without the need of activating species, such as DBU, in a pressurized tube-in-tube reactor, generating isocyanates *in-situ*, followed by trapping with a variety of carboxylic acids to yield substituted amides. The initial electrochemical step is performed with quantitative yield as established by Costa e Silva[3], and the product is used in the next step without purification. So far, optimized conditions of the amidation step have been nearly established with up to four variations of carboxylic acids tested with independent yields of up to 92%, for two steps (Fig. 1).

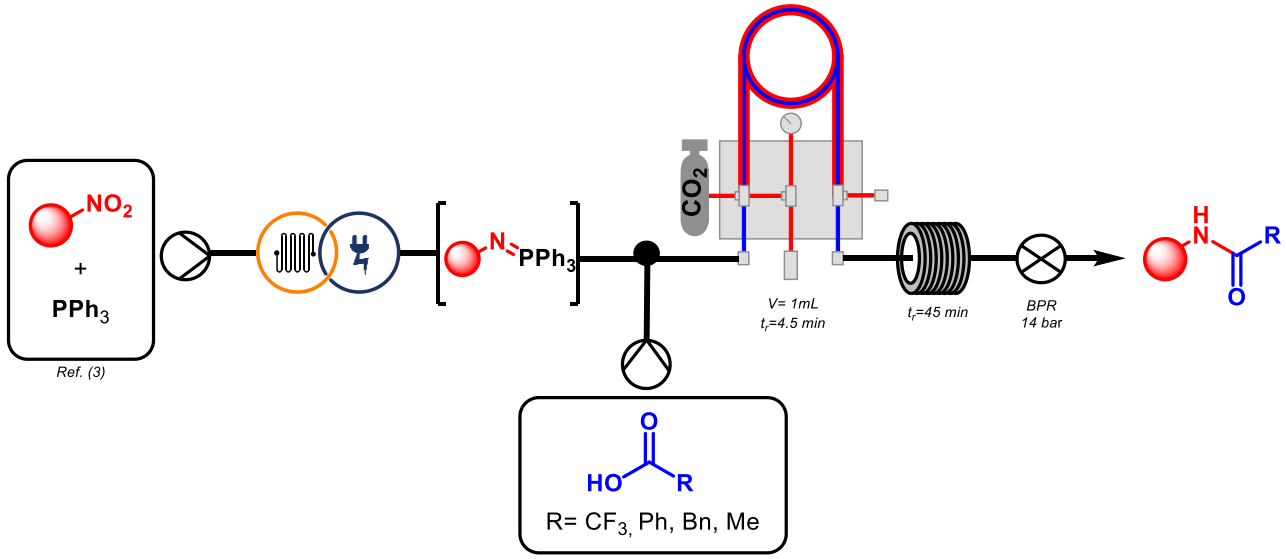

Figure 1. Telescoped CO_2-Mediated Amide Synthesis from Nitroarene in a Continuous Flow Regime.

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SEPTEMBER 23-27 2024
19BMOS
BRAZILIAN MEETING ON ORGANIC SYNTHESIS
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Enantioselective Heck-Matsuda Reaction Coupled to Organotin Transmetalations

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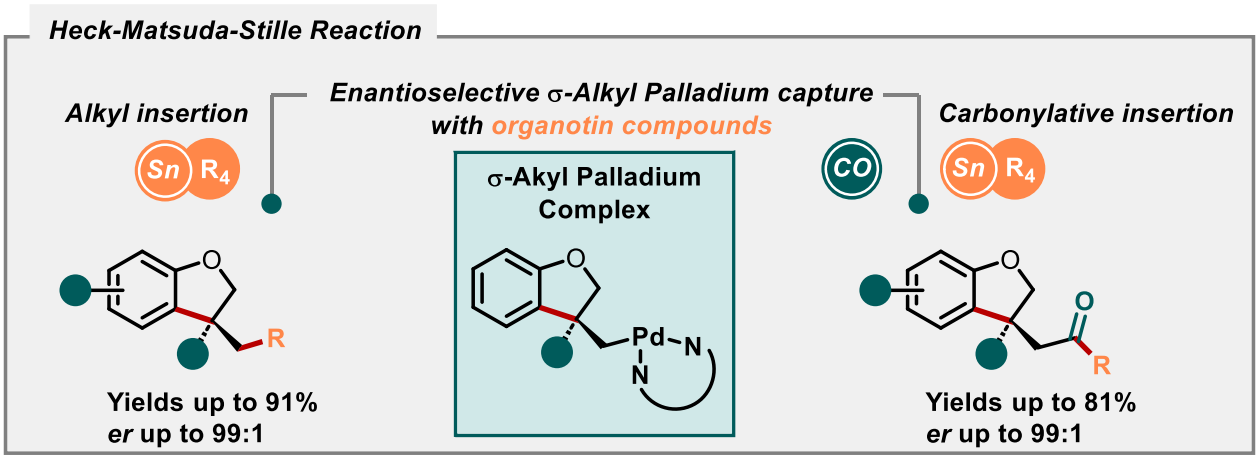
Keywords: *Pd-Catalysis, Enantioselective Synthesis, Heck-Matsuda and Stille Coupling.*

ABSTRACT

Enantioselective Heck-Matsuda Reaction is a powerful method for building high valued natural products and building blocks in organic synthesis.[1] The intramolecular version of this reaction is still underexplored and remains a challenge in the field with few examples of success in the literature.[2,3] In this work, an efficient asymmetric one-pot synthesis of 3,3-disubstituted-dihydrobenzofuran has been developed through a palladium-catalyzed Heck-Matsuda reaction, followed by subsequent carbonylation and/or organotin transmetalation employing chiral *N*,*N* ligands. The Heck-Matsuda-Stille reaction is performed under mild conditions from readily available starting materials and tolerates a wide range of functional groups. This methodology provides straightforward access to a diverse array of enantioenriched dihydrobenzofuran bearing either a carbonyl or a side alkyl chain adjacent to a quaternary stereogenic center in yields up to 81% and *er* up to 99:1.



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SEPTEMBER 23-27 2024
19BMOS
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Synthesis of a new series of 1,2,3-triazole-4-yl-phosphonates

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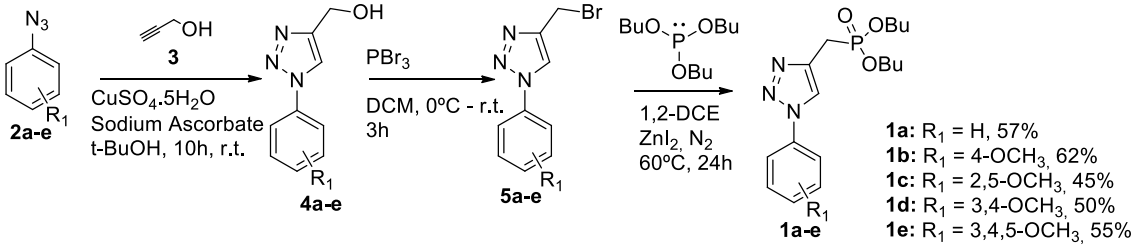
Keywords: *1,2,3-triazoles, phosphonates, click chemistry*

ABSTRACT

Triazoles are known for their diverse biological activities and wide applicability in medicinal chemistry[1], materials science[1], and chemical synthesis[2]. They often serve as pharmacophore groups due to their favorable chemical properties, which include hydrogen bonding capabilities, and potential for π-π stacking interactions with biological targets[3]. Similarly, the phosphonate group acts as a pharmacophore by providing key interactions that can enhance a drug's binding affinity, and overall efficacy[4]. The combination of these two functionalities in a single molecule – 1,2,3-triazole and phosphonate – opens up possibilities for the development of new pharmacologically active compounds. Future studies will focus on the detailed biological evaluation of the 1,2,3-triazole-4-yl-phosphonates **1a-e** (Scheme) in various disease models. The synthesis of **1a-e** initially involved the 1,3-dipolar cycloaddition reaction between azides **2a-e** and **3**, followed by bromination of **4a-e**. The nucleophilic substitution reaction to the saturated carbon of **5a-e** with tributyl phosphite provided the desired compounds **1a-e** in moderate yields.



Scheme. Preparation of phenyl-1,2,3-triazole phosphonates

ACKNOWLEDGEMENTS

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19BMOS
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Synthesis of new polyurethanes from biomass-derived diols

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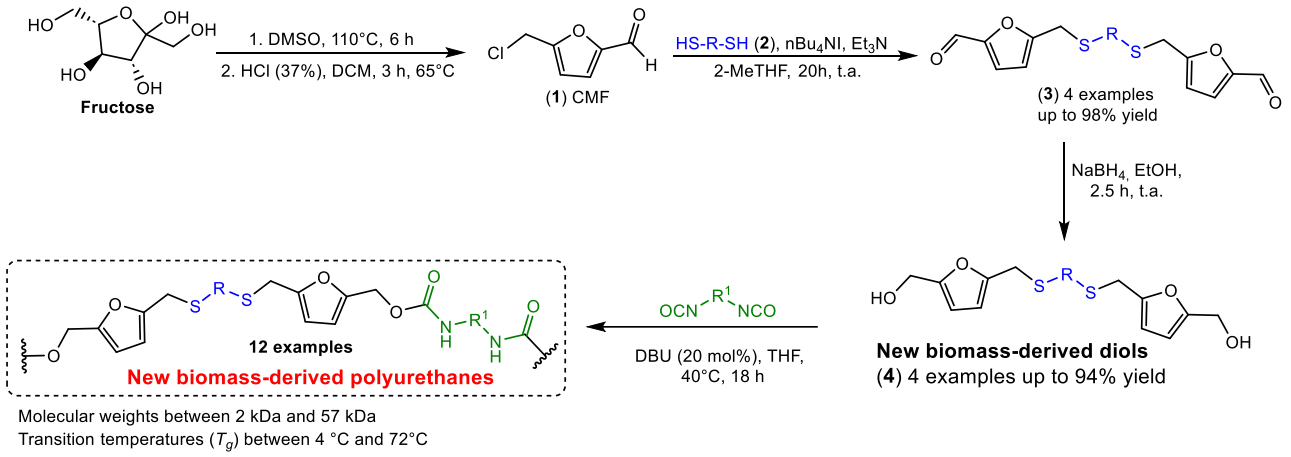
Keywords: *Polyurethanes, biomass-derived diols, 5-(chloromethyl)furfural, polyaddition reaction.*

ABSTRACT

Polyurethanes represent an interesting class of polymeric materials with extensive potential for various applications. They are industrially produced through the polyaddition reaction between diols and diisocyanates, primarily derived from petrochemical sources.[1,2] There has been a growing interest in developing new polymeric materials from biomass-derived molecular platforms, such as 5-(chloromethyl)furfural (CMF).[3,4] The work presented herein showcases the synthesis of new polyurethanes by the reaction between biomass-derived diols (**4**) and commercially available diisocyanates using an organic base as the catalyst (Scheme 1). Initially, we explored the synthesis of new dialdehydes (**3**) through the substitution reaction between CMF (**1**, obtained from fructose) and dithiols (**2**). Different reaction conditions were tested, resulting in the desired products (**3**) in moderate to excellent yields (up to 98%). These dialdehydes were then reduced using sodium borohydride to produce the corresponding diols, which were used to synthesize new biomass-derived polyurethanes.



Scheme 1. The synthetic pathway utilized to produce new polyurethanes derived from biomass.

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TiO_2-catalyzed direct diazenylation of active methylene compounds with diazonium salts

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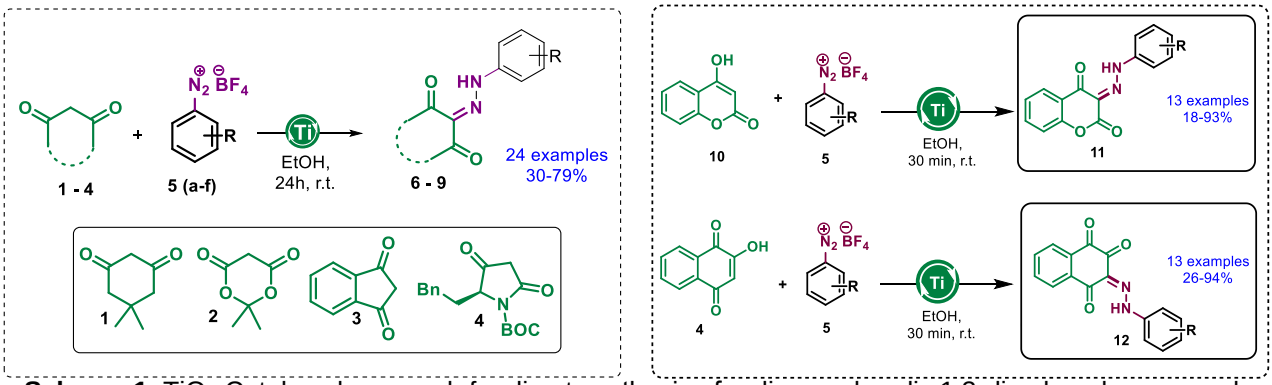
Keywords: *heterogeneous catalyst,* dicarbonyl compounds, diazenylation.

ABSTRACT

Azo compounds play a crucial role in medicinal chemistry, serving as fundamental building blocks for substances with diverse bioactivities.[1,2] Direct diazenylation via active methylene species emerges as an efficient strategy for incorporating the azo group into the structure of cyclic 1,3-dicarbonyl compounds (or in its enol form). Moreover, 1,3-carbonyl structures, such as coumarins and naphthoquinones are recognized pharmacophores of bioactive compounds, exhibiting remarkable antioxidant properties and actively participating in redox reactions.[3,4] These hallmarks make them highly valuable targets in pharmaceutical research focused on therapeutic development. Within this scope, his work reports a rapid, and scalable direct diazenylation of cyclic 1,3-dicarbonyl compounds, 4-hydroxycoumarin, and lawsone, employing an accessible and recyclable, heterogeneous catalyst (TiO_2) (Scheme 1). This transformation showed high compatibility with both electron-rich and electron-poor diazonium salts, and the corresponding products were isolated in good yields using eco-friendly solvents at room temperature.



Scheme 1. TiO_2-Catalyzed approach for direct synthesis of α-diazoaryl cyclic 1,3-dicarbonyl compounds.

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SEPTEMBER 23-27TH 2024
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Organocatalytic Mannich reaction as key step for the synthesis of a series of L-pentofuranose-mimetic iminosugars with potential anti-trypanosomal activity

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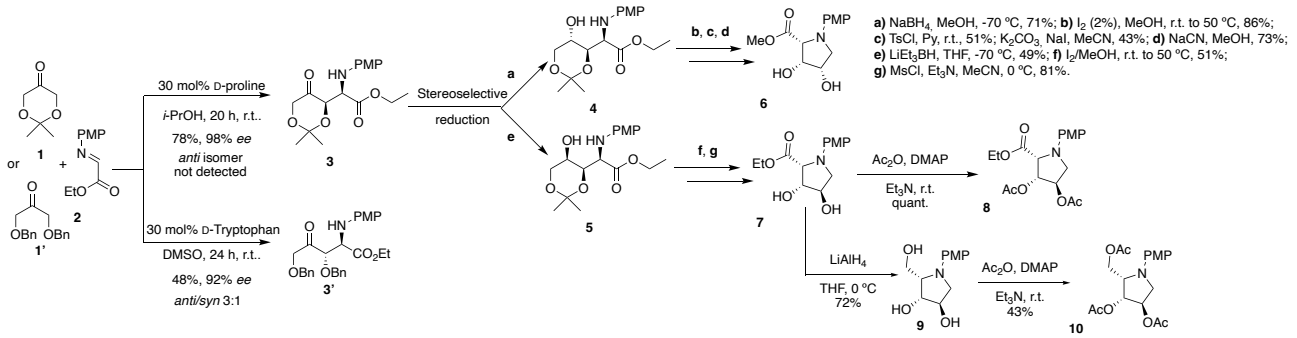
Keywords: *Glycomimetics, Iminosugars, Organocatalysis*

ABSTRACT

Iminosugars are natural glycomimetics whose structural similarity to carbohydrates turns them into potential competitive inhibitors of enzymes acting on sugar substrates. Particularly, their antiparasitic activity has been studied, among others.[1] We are then focused on use of an organocatalyzed Mannich reaction as key step for the synthesis of a series of L-pentofuranose-mimetic iminosugars, with potential anti-trypanosomal activity.[2]



The *syn* Mannich reaction giving (2*R*,3*R*)-stereochemistry in compound **3** was performed using D-proline as catalyst, while the *anti* isomer (2*S*,3*R*, **3'**) was achieved using a primary aminoacid such as D-tryptophan as catalyst. A series of 5 L-pentofuranose-mimetic iminosugars was then prepared in a stereoselective manner from compound **3**.

As part of our search of novel antiparasitic agents, a preliminary characterization against bloodstream *T. brucei brucei* was investigated for compounds **3**-**10**.[3] The screening was performed at 10 μM, and compound **6** showed an EC_{50} = 3.8 μM, emerging as new head-of-series, to be optimized.

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Support from CSIC-Udelar (Comisión Sectorial de Investigación Científica), ANII (Agencia Nacional de Investigación e Innovación), PEDECIBA (Programa de Desarrollo de las Ciencias Básicas) and FOCEM (MERCOSUR Structural Convergence Fund) are gratefully acknowledged.

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New Insights on the Reactivity and Selectivity of Nucleophilic Fluorination Mediated by Hydrogen Bonding Solvation

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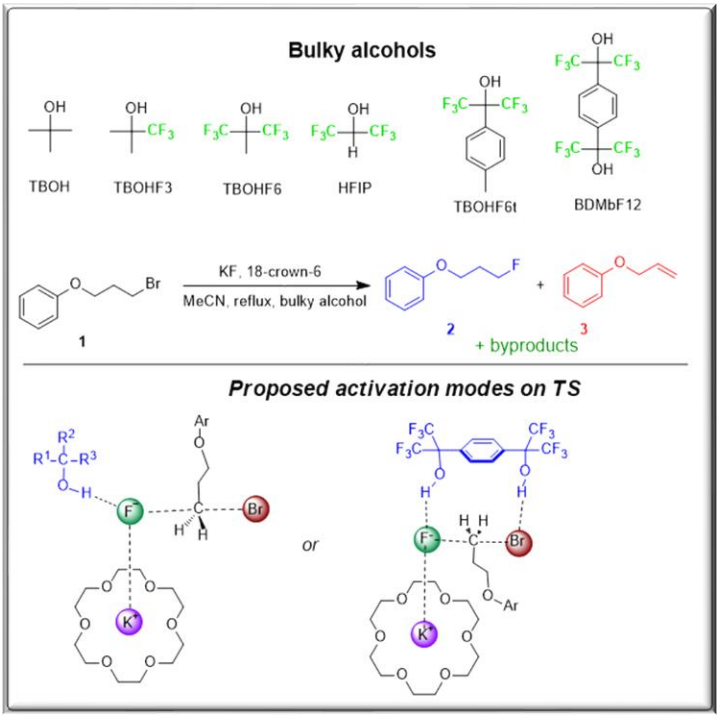
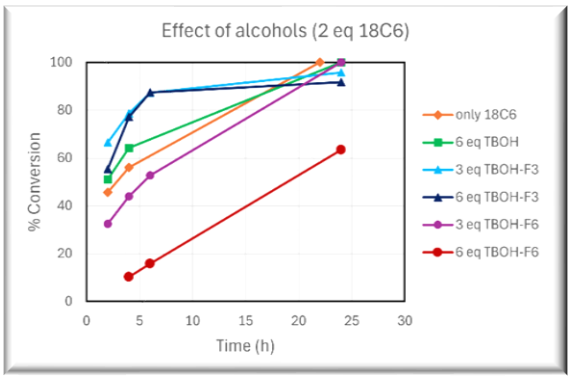
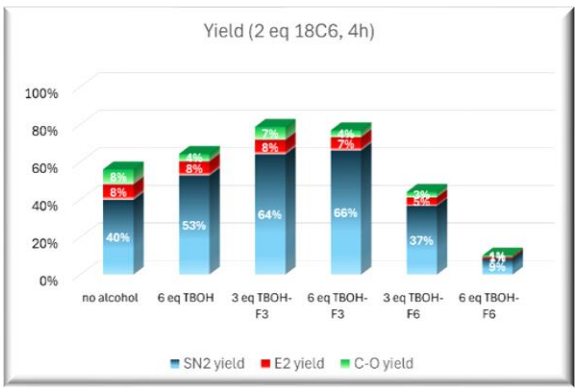
Keywords: *Nucleophilic fluorination, microsolvation, theoretical calculations.*

ABSTRACT

Fluorination reactions of alkyl bromides face the problem of high competition between S_N2 and E2 reactions.[1] KF salt, as a source of nucleophile fluoride, has limitations due to low solubility issues.[2] However, combining crown ethers with hydrogen-bonding donor species could enhance both reactivity and selectivities.[3-7] Herein, we reported the extensive experimental and theoretical investigations of the effects of stoichiometric amounts of diverse bulky alcohols, combined with 18-crown-6, for fluorination reactions of primary and secondary alkyl bromides. Raising the hydrogen-bonding strength of TBOH-F3 (6 eq) with fluoride ions and substrate **1**, led to good reactivity and chemoselectivity, with almost 80% conversion at 4h and 9:1 S_N2/E2 selectivity. Hexafluorinated alcohols also suppressed E2 reactions, however, the increase in acidity was a limiting factor due to the formation of nucleophilic alkoxides and the formation of ethers. For the TBOH-F6, the kinetics behavior has changed, leading to a slower reaction rate with high chemoselectivity.







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SEPTEMBER 23-27 2024
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New Aromatics from a Chitin-based Nitrogenated Furanic Platform

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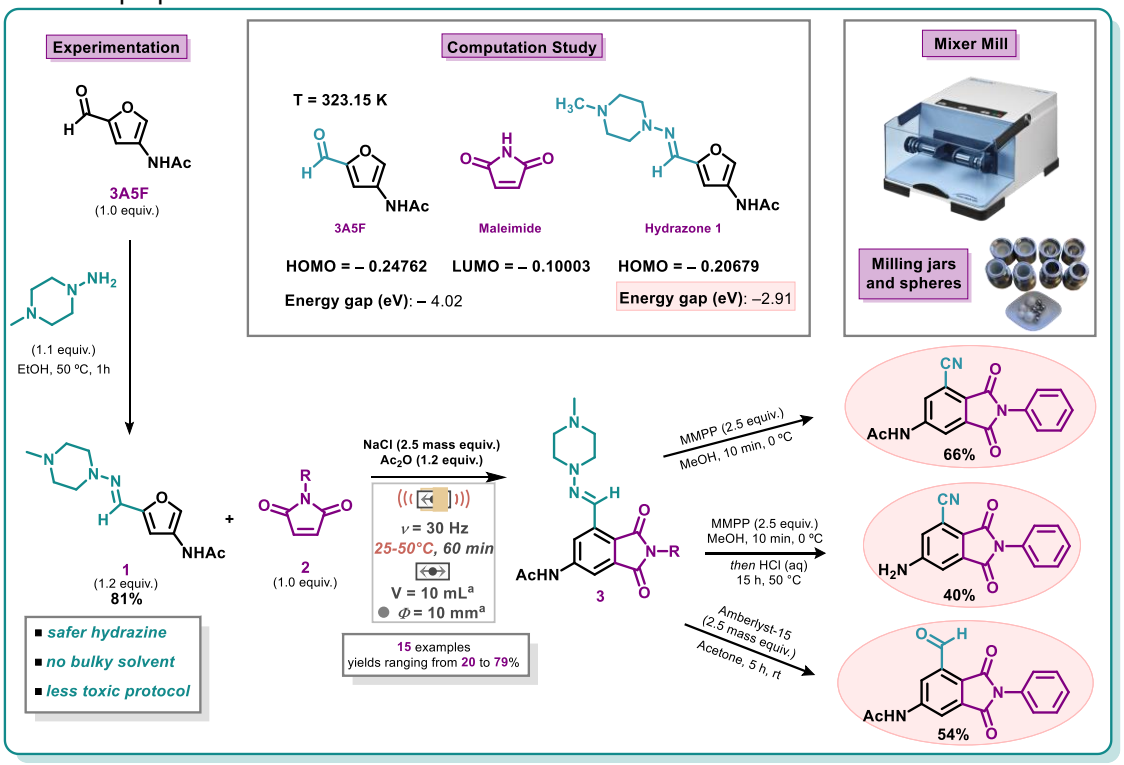
Keywords: *Chitin Biomass, Mechanochemistry, Green Chemistry.*

ABSTRACT

Chitin biomass is a rich renewable resource that widely exists in crustacean shells and arthropod exoskeleton, being the second most abundant natural polysaccharide after cellulose. Recently, the use of furans derived from chitin has become a promising source for nitrogen fixation in high added-value compounds. In this context, we explored the mechanochemical synthesis of aromatic compounds from renewable sources, in agreement with many of the principles of Green Chemistry. Herein, we address the challenge of using the chitin-derived furan 3-acetamido-5-furfural aldehyde (**3A5F**) to favour the formation of 4-acetylaminophthalimides, using the hydrazone approach. Theorical calculations confirmed that hydrazone (**1**) is more reactive than **3A5F** in the Diels-Alder reaction with maleimide as dienophile. Under optimized conditions, Diels-Alder reaction followed by spontaneous aromatization afforded 4-acetylaminophthalimides in up to 79% yield. Further derivatizations were also performed to showcase the synthetic potential of the new aromatics prepared.



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STD-NMR Applied to Study Intermolecular Organization of Polymers-Ionic Liquids Hydrogels

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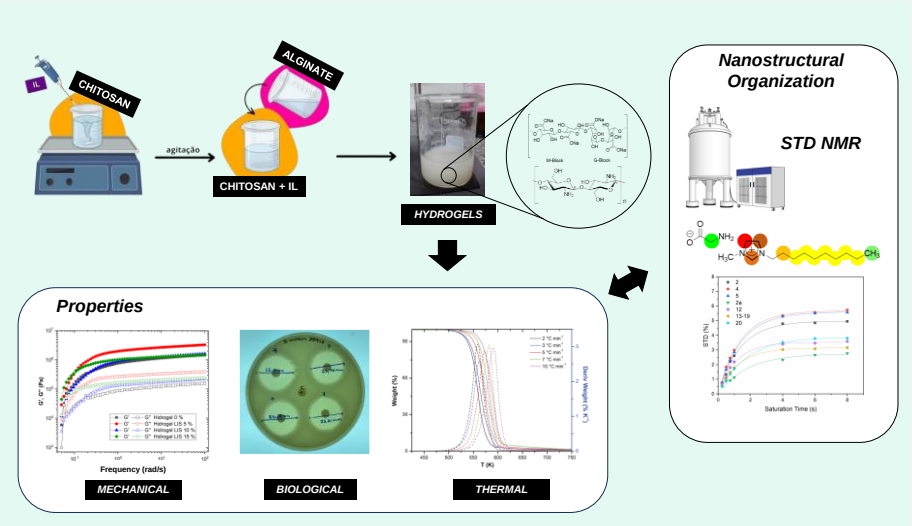
Keywords: *Ionic Liquids, hydrogels, STD-NMR, quitosan, alginate.*

ABSTRACT

The interaction between two natural polysaccharides, an anionic (sodium alginate) and a cationic (chitosan) one in the presence of ionic liquids in an aqueous medium, can result in the formation of promising hydrogels for applications such as cosmetics and in food industry. In this study, four ILs were synthesized and applied in the obtention of hydrogels derived from polyelectrolyte complexes[1,2]. The ILs are derived from imidazolium cation with an alkyl side chain and an organic anion – from amino acids (glycine and lysine) or essential oils (clove and cinnamon). The synthesis involved an S_N2 reaction of methylimidazole with the respective alkyl halide, followed by anion exchange (from halide to hydroxide) using resin and subsequent neutralization with acid of the anion of interest. The physicochemical properties of pure ILs and as additive of gels were evaluated. Structural characterization of hydrogels was conducted using Saturation Transference Difference-Nuclear Magnetic Resonance (STD-NMR). Thermal properties were assessed through Thermogravimetric Analysis (TGA) and Differential Scanning Calorimetry (DSC) to determine thermal behavior and stability. Mechanical properties were evaluated using oscillatory rheology.



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Synthesis of 1-D-Glucal Amides Derived from 1-Iodo-D-Glucal Through Carbonylative Cross-Coupling Reaction

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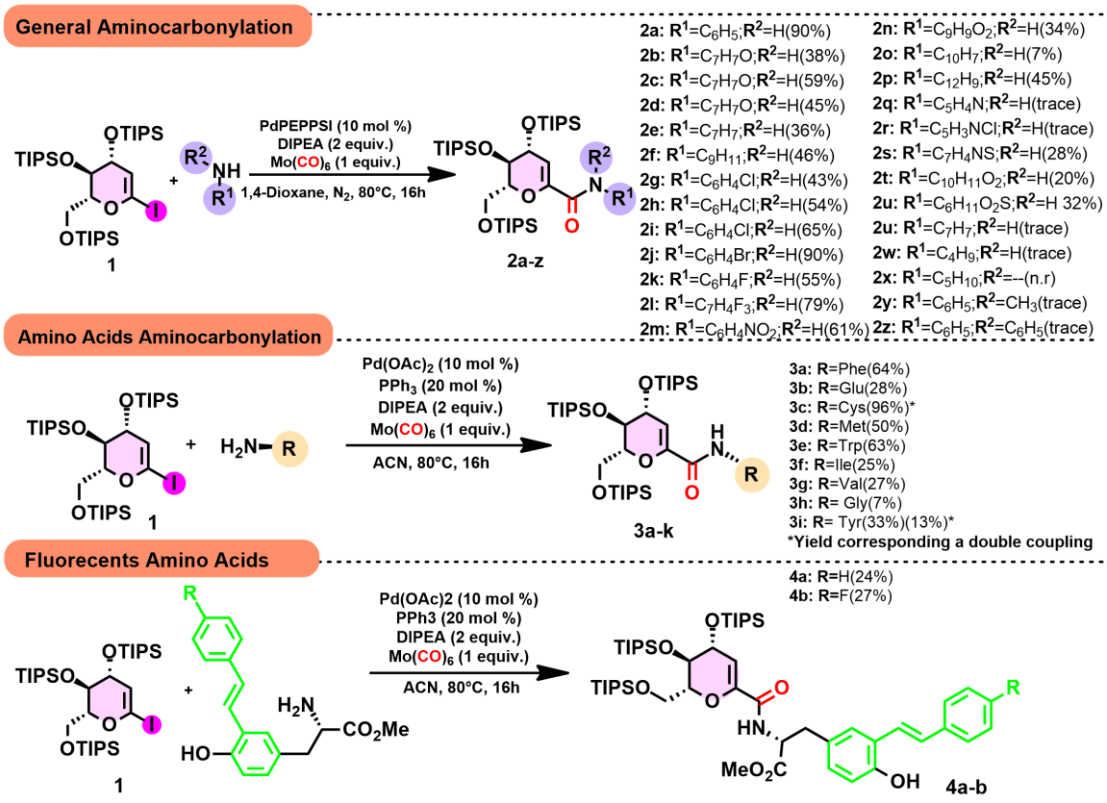
Keywords: *Carbonylative Coupling, 1-Iodoglucal, Amides.*

ABSTRACT

C-aryl/C-alkynyl glycosides and the amide functional group occur naturally or in synthetic products, often found in biologically active molecules.[1,2] Carbonylative cross-coupling reactions with carbon monoxide are significant methods for synthesizing carbonyl derivatives.[3] This project focuses on utilizing 1-D-iodoglucal in palladium-catalyzed carbonylative coupling reactions to produce new amidoglucals and glucal esters. We conducted optimization experiments to determine the best reaction conditions and explored the scope of the aminocarbonylation reaction, testing various aromatic and heteroaromatic compounds, primary and secondary amines, alkyl amines, and two amino acid esters. Additionally, we thoroughly optimized the aminocarbonylation process, particularly focusing on amino acids esters, including fluorescent derivatives derived from tyrosine. We initiated a substrate scope study and synthesized a series of new C-glycosyl amino acids.



Scheme 1: Reaction for synthesis of new 1-D-Glucal-Amides

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Synthesis of a series of Quinone-Fused Pyrrole Derivatives

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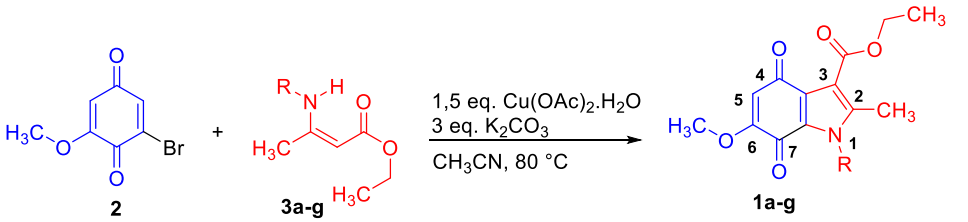
Keywords: *Quinone, Pyrrole, Cu-catalyzed synthesis*

ABSTRACT

Quinone derivatives are clinically known drugs for treating cancer. These compounds can exert their therapeutic effects due to their redox cycling, which reduces oxygen to reactive oxygen species (ROS), and their ability to act as electrophiles, forming covalent bonds with cellular nucleophiles.[1,2] Our research group has focused on the annulation of quinone with a pyrrole nucleus to develop novel antitumor compounds. Annulated compounds decrease the formation of semiquinones and reactive oxygen species, which are typically responsible for the cumulative cardiotoxicity side effects associated with various quinone derivatives.[2] This work describes the synthesis of a series of quinone-fused pyrrole derivatives **1a-g**, functionalized at the N-1, C-2, and C-3 positions of the heterocyclic ring, to evaluate their cytotoxic effects against several human tumor cell lines. The target compounds **1a-g** were synthesized via copper(II)-mediated annulation of bromobenzoquinone (**2**) with β-enamino esters (**3a-g**) (Scheme).[3]



1a: R = H, **75%**
1b: R = -CH_2CH_2OH, **67%**
1c: R = C_6H_5, **31%**
1d: R = 4-CH_3-C_6H_4, **50%**
1e: R = 4-OCH_3-C_6H_4, **40%**
1f: R = 4-Cl-C_6H_4, **37%**
1g: R = 4-F-C_6H_4, **38%**

Scheme: Preparation of quinone-fused pyrrole derivatives

ACKNOWLEDGEMENTS

CAPES, UFF, PPGQ-UFF, FAPERJ, PIBITI/CNPq.

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19BMOS
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Synthesis, optical emission, redox and thermal properties of 2,8-diaryl-imidazo[1,2-*a*][1,8]naphthyridines

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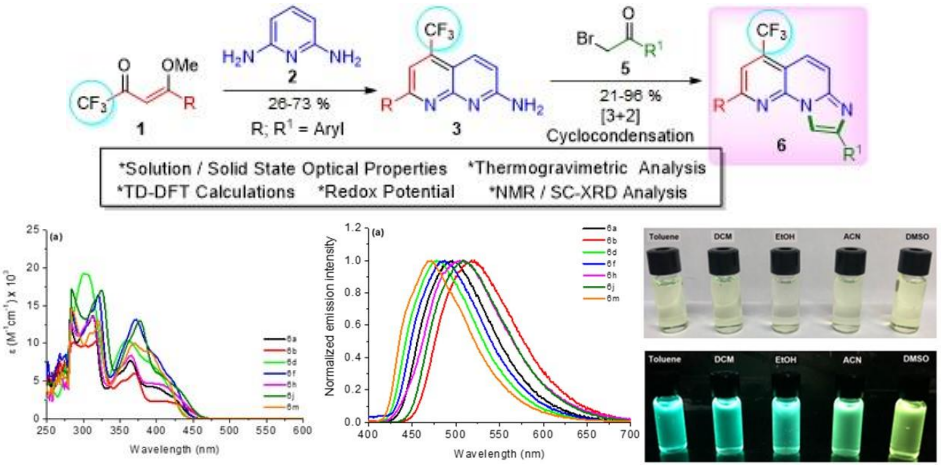
Keywords: *Imidazo[1,2-a][1,8]naphthyridines, Photophysics , [3+2] Cyclocondensation.*

ABSTRACT

The present work reports a study on the novel series of thirteen examples of 2,8-diaryl-4-(trifluoromethyl)imidazo[1,2-*a*][1,8]naphthyridines (**6**), in which 2,8-diaryl = C_6H_5, 4-BrC_6H_4, 4-$OMeC_6H_4$, 4-$CF_3C_6H_4$, and 2-naphthyl (Scheme 1) [1]. Series **6** was obtained by an intermolecular and regioselective [3+2] cyclocondensation reaction of a series of selected 7-aryl-2-amino-5-(trifluoromethyl)-[1,8]naphthyridines (**3**) with 1-aryl-2-bromo-ethanones (**5**) [2]. Aromatic amines **3** and bromo ethanones **5** were synthesized by previously reported methods, which reacted 2,6-diamino-pyridine (**2**) with 4-aryl-4-methoxy-1,1,1-trifluorobut-3-en-2-ones (**1**) to obtain **3** [3] and reactions of acetophenones **4** with elemental bromo to achieve **5** [4]. All new compounds **6** were fully characterized by ^{1}H, ^{13}C-, ^{19}F-NMR and IR spectroscopy, SC-XRD, and HRMS methods. The optical and electrochemical properties of heterocycles **6** were determined by UV-Vis, steady-state and time-resolved fluorescence emission (solution and solid state), TD-DFT calculations, and redox potential which showed a strong influence and dependence of the substitution position in the heterocyclic core. In addition, the TGA experiments showed good thermal stability for the new nitrogenated tricyclic system **6**.



Scheme 1. Synthesis and properties of 2,8-diaryl-4-(trifluoromethyl)imidazo[1,2-*a*][1,8]naphthyridines (**6**).

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The authors would like to thank the following entities: The coordination for improvement of higher education, Personnel-CAPES Finance Code 001) for the fellowship and the National Council for Scientific and Technological Development-CNPq: proc. No 305.379/2020-8 and 403.134/2021-8, and the Research Support Foundation of the State of Rio Grande do Sul-FAPERGS: proc. No. 17/2551-0002099-7 for financial support.

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19BMOS
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Synthesis and anti-tumoral activity of *N,N*-dipropargylamino-pyrimidines and bistriazole derivatives against C6 glioma cell line

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Keywords: *N,N-Dipropargylamino pyrimidines, Huisgen cycloaddition reaction, Anti-tumoral activity.*

ABSTRACT

An improvement in pharmacokinetic efficiency is observed when a bromine atom is inserted into analogues to development of new anti-tumor drugs [1]. Compounds containing pyrimidine and/or triazole nuclei have broad spectrum of pharmacological activities, including anticancer activity, just like molecules containing halogens in their structure [2]. In this work, dipropargylated and diallylated aminopyrimidines **3** and **5** were synthesized through a *N*,*N*-bimolecular nucleophilic substitution reaction from **1** with alkyl halides **2** and **4** [3]. The compounds **3** were subjected to a Huisgen dipolar [3+2] cycloaddition reaction to obtain the respective bistriazoles **7** [3]. The presence of the 4-bromophenyl substituent in **3** and **5** increased cytotoxicity activity against glioblastoma tumoral C6 cell line. Moreover, a simple structural comparison between the triazole core **7** and respective monoheterocyclic substrates **3** and **5** (Fig. 1) showed an increase of cytotoxicity activity (IC50) of the scaffolds of **7** in comparison to the precursors **3** and **5**.

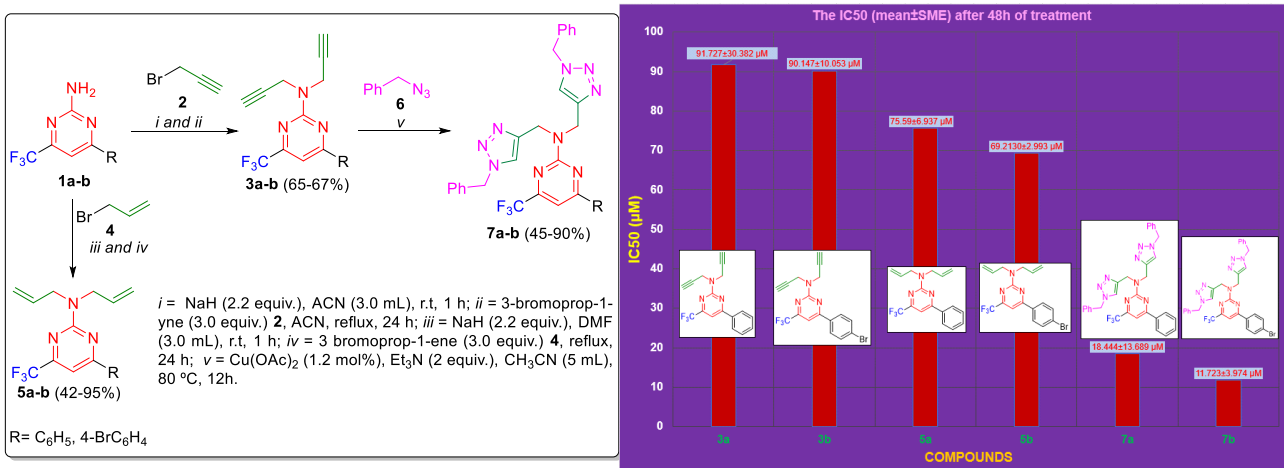

Figure 1. Synthesis and cytotoxicity for anti-tumoral glioma C6 cell line by MTT test of compds. **3**, **5**, **7**.

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The authors would like to thank the following entities: The Coordination for Improvement of Higher Education Personnel-CAPES (Finance Code 001) for the fellowships and the National Council for Scientific and Technological Development-CNPq: proc. No 305.379/2020-8 and 403.134/2021-8, and the Research Support Foundation of the State of Rio Grande do Sul–FAPERGS: proc. No. 17/2551-0002099-7 for financial support.

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19 BMOS
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Telescopic one-pot synthesis of chromene derivatives from lawsone, aldehydes and Meldrum's acid in water.

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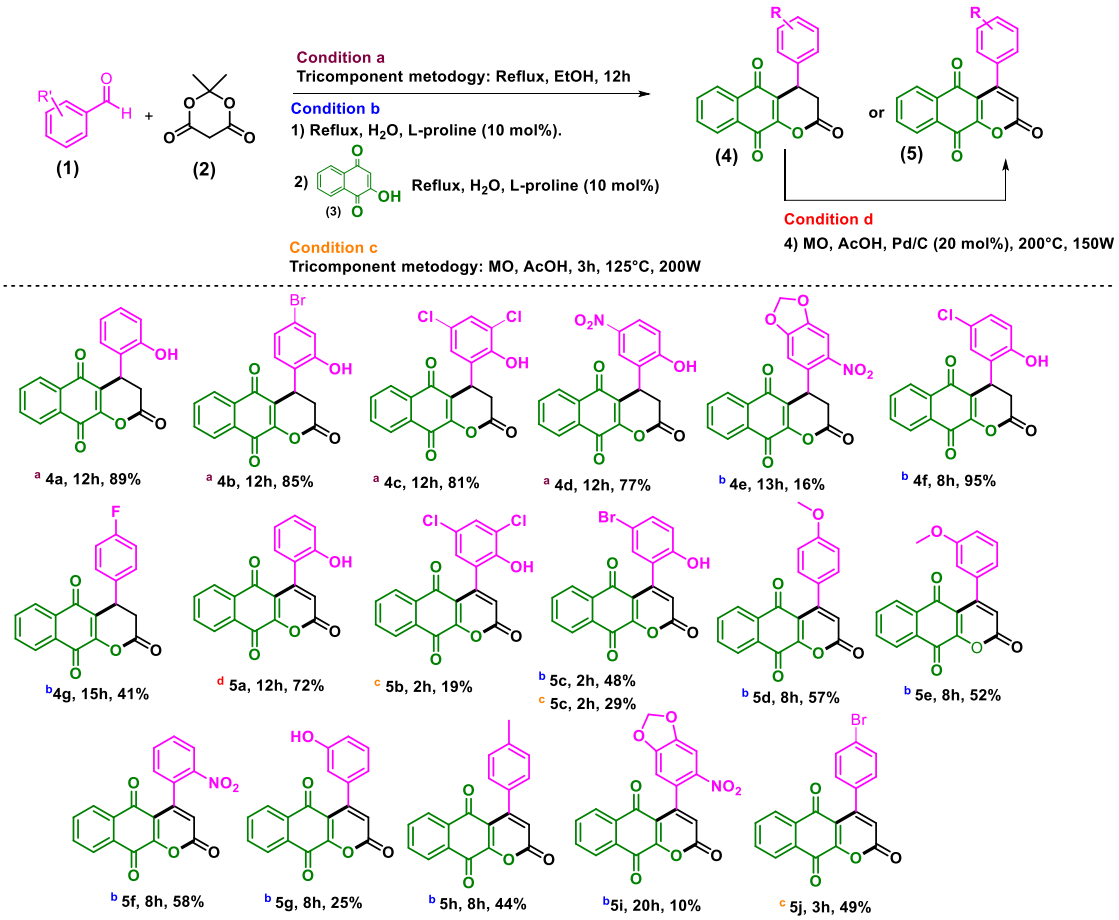
Keywords: *chromene derivatives, telescopic, one-pot.*

ABSTRACT

O-heterocycles as benzo[*g*]chromenes represent a broad spectrum of biological activities[1]. As a consequence, significant efforts have been made to develop new sustainable methods for constructing and modifying this crucial structure.[2] Here, we reported a new protocol of telescopic one-pot synthesis of chromene derivatives **4** and not previously described **5** from lawsone, aldehyde, and Meldrum's acid under different conditions **(Scheme 1)**. All products are solid compounds and were obtained with high purity and good yields.



Scheme 1: Synthesis of chromene derivatives **4** and **5** under different conditions.

ACKNOWLEDGEMENTS

FAPESB CAPES INCT CNPQ

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Palladium(II)-Catalyzed C–H Arylation of 1,4-Naphthoquinones, α-Tetralones and Benzophenones Derivatives

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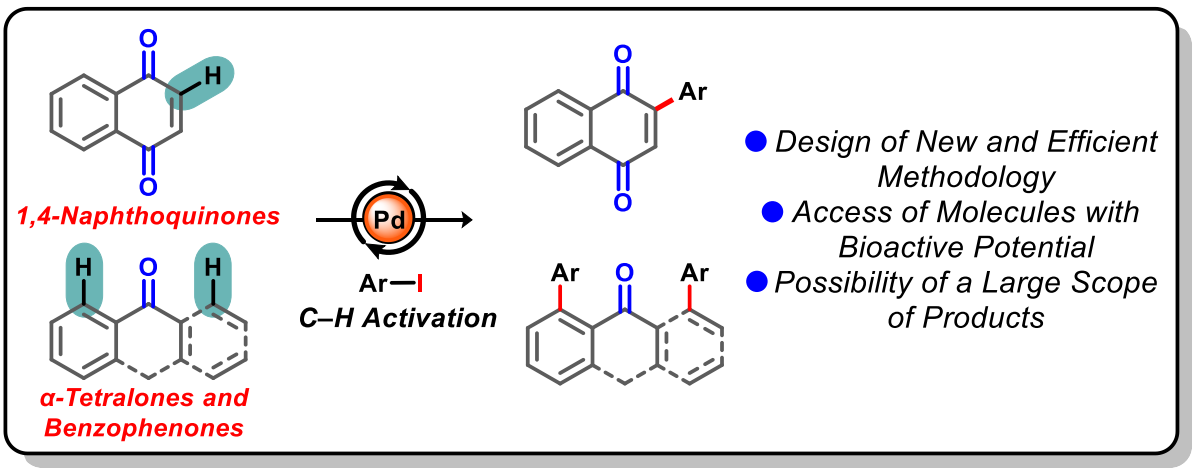
Keywords: *C-H activation, palladium(II), methodology*

ABSTRACT

The activation of C–H bonds for functionalizing organic molecules represents a contemporary platform in organic synthesis, demonstrating unparalleled efficiency in the late-stage functionalization of medicinal prototypes and marketed pharmaceuticals.[1] Consequently, new methodologies are constantly being developed to achieve highly potent synthetic techniques for forming new C–C or C–heteroatom bonds.[2] Transition metal catalysis (TM catalysis) is frequently employed to facilitate these transformations and has experienced exponential growth, enabling the late-stage introduction of desired substituents and the construction of complex molecular motifs.[3] In this work, we developed a methodology for the selective C–H activation of 1,4-naphthoquinones, α-tetralones and benzophenones using palladium(II) salt and various aryl iodides, yielding arylsubstituted derivatives. This approach not only provides a robust tool for synthesizing structurally diverse and complex compounds but also expands the scope of palladium(II)-catalyzed C–H activation, thereby opening new avenues for the development of derivatives with bioactive potential.



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Imidazo[1,2-*a*]pyridine-tetrazole hybrids: phytotoxic and photophysical properties

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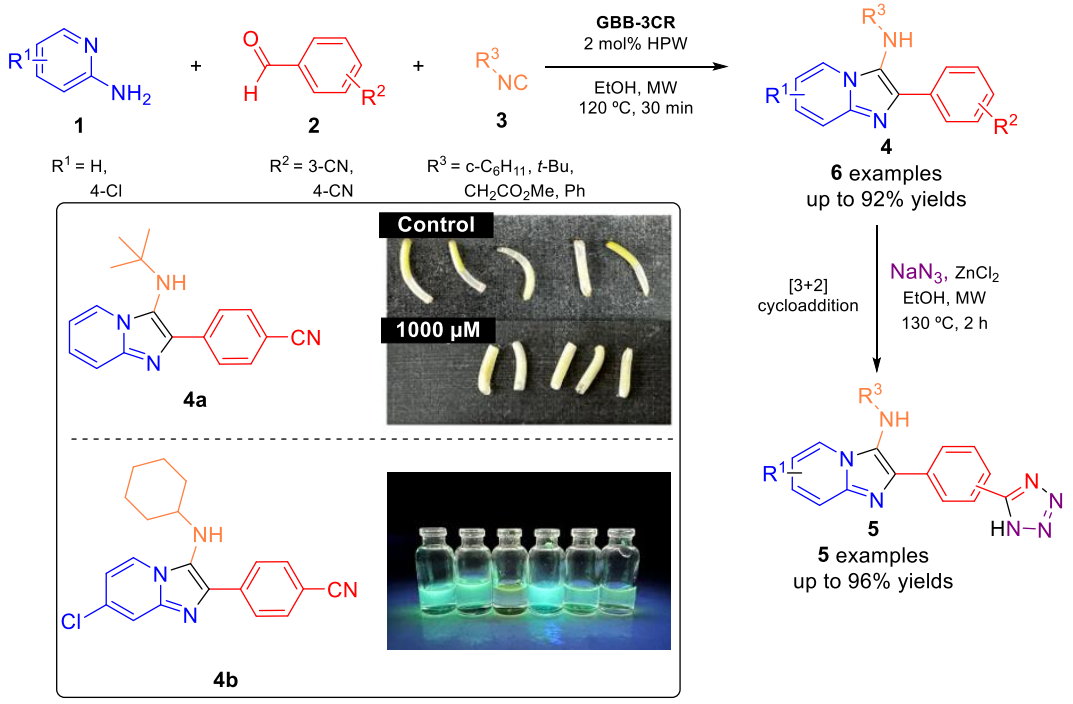
Keywords: *multicomponent reactions, GBB-3CR, imidazo[1,2-a]pyridine, tetrazoles, phytotoxicity.*

ABSTRACT

The synthesis of hybrids of imidazo[1,2-*a*]pyridine with substituted tetrazoles emerges as an interesting methodology as both are pharmacophoric groups of great commercial interest for the pharmaceutical industry.[1,2] In our synthetic route, imidazo[1,2-*a*]pyridines were initially synthesized via the phosphotungstic acid (HPW) catalysed Groebke-Blackburn-Bienaymé three-component reaction (GBB-3CR) using 2-aminopyridines, cyanobenzonitriles, and isocyanides, in ethanol under microwave heating.[3] Subsequently, the GBB-3CR adducts **4** were employed in [3+2] cycloaddition reactions with NaN_3 under a new approach using microwave heating and $ZnCl_2$ as catalyst to obtain the corresponding tetrazole hybrids. All synthesized compounds were screened in etiolated wheat coleoptile bioassays, as well as in seeds of *Lactuca sativa*, *Nasturtium officinale*, and *Solanum lycopersicum*, and some of them exhibited a good phytotoxic activity **(4a)**. Finally, photophysical properties of compounds **4** and **5** were studied along with computational calculations at B3LYP/6-31G(d,p) theory level. The theoretical values nicely agree with the experimental results **(4b)**.



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A green synthesis of 2,5-disubstituted thiophenes from terminal alkynes: a telescopic approach

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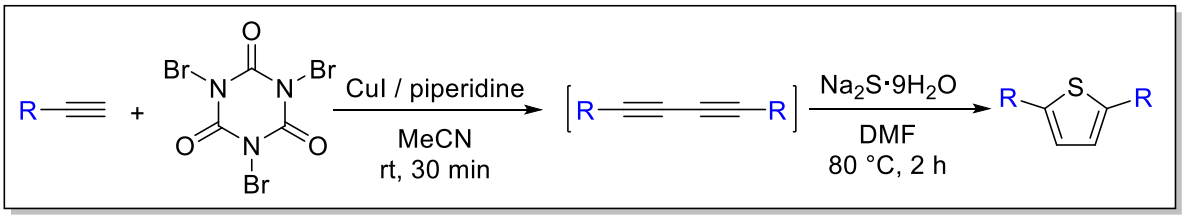
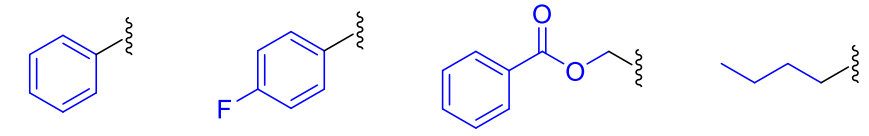
Keywords: *thiophenes, Glaser coupling, tribromoisocyanuric acid.*

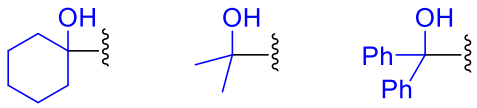
ABSTRACT

The present work focuses on the one-pot synthesis of 2,5-disubstituted thiophenes from terminal alkynes. The method uses a greener version of the Glaser coupling, utilizing copper(I) iodide, piperidine and tribromoisocyanuric acid (TBCA).[1] TBCA proved to be an excellent source of electrophilic bromine,[2] can also be used as an oxidant,[3] has a facile synthesis,[4] and a great atom economy. This reagent also allows the Glasser reaction to be conducted under mild conditions and no catalyst is needed.
The reaction then proceeds in a telescopic manner, without the isolation step of the recently formed 1,3-diynes, to the formation of the corresponding thiophene through heterocyclization using sodium sulfide in DMF at 80 °C for 2 h.
Therefore, the proposed method gives 2,5-disubstituted thiophenes in 70-95% yield, higher than the usual two-steps approach, with a range of terminal aliphatic or aromatic alkynes.





(95%, 81%*) (94%) (90%) (75%)



(71%, 66%*) (70%) (82%)

* Two steps reaction

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We thank CNPq and FAPERJ for the financial support.

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Rufinamide® Luminescent Hybrids: Design, synthesis and photophysical properties of news 3-(1-aryl-1*H*-1,2,3-triazol-4-yl)-1,1-difluoro-1*H*-1λ⁴,9λ⁴-pyrido[1,2-*c*][1,3,5,2]oxadiazaborinines

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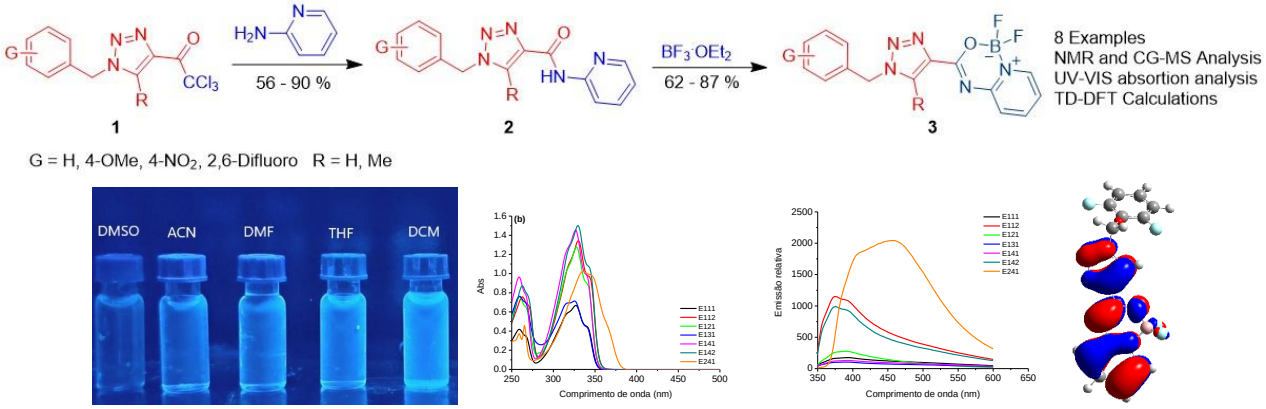
e-mail: helio.bonacorso@ufsm.br

Keywords: *Rufinamide, 1,3,5,2-Oxadiazaborinine, Fluorescence.*

ABSTRACT

Rufinamide is a drug that was granted orphan drug status for the adjunctive treatment of Lennox-Gastaut syndrome. Being a drug leader, analogues have been developed and studied to resolve achieve greater effectiveness [1], but its distribution and exact docking in the brain mass isn't yet known. So, an efficient fluorescent probe could help to solve it. Recently, 1,3,5,2-oxadiazaborinine dyes have been synthesized due to their photophysical properties, and their subsequent use as pigments, materials and in photodynamic therapy [2-3]. Backed up by literature [4] and in order to improve the photophysical behavior, a new series of amides of Rufinamide analogs (**2**) were synthesized by us from ketones (**1**) and hybridized to furnish the novel series of Rufinamide analogs linked to 1,3,5,2-oxadiazaborinines (**3**), (Scheme 1). Also, it was studied their molecular structure by NMR, SC-XRD, photophysics (UV-Vis) and computational TD-DFT calculations.



Scheme 1 - A summary of this study: Synthesis and photophysical properties of 3-(1-aryl-1*H*-1,2,3-triazol-4-yl)-1,1-difluoro-1*H*-1λ⁴,9λ⁴-pyrido[1,2-*c*][1,3,5,2]oxadiazaborinines (**3**).

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SEPTEMBER 23-27 2024
19BMOS
BRAZILIAN MEETING ON ORGANIC SYNTHESIS
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Radical C3-alkylation of coumarin via Pd-photocatalyzed Heck reactions

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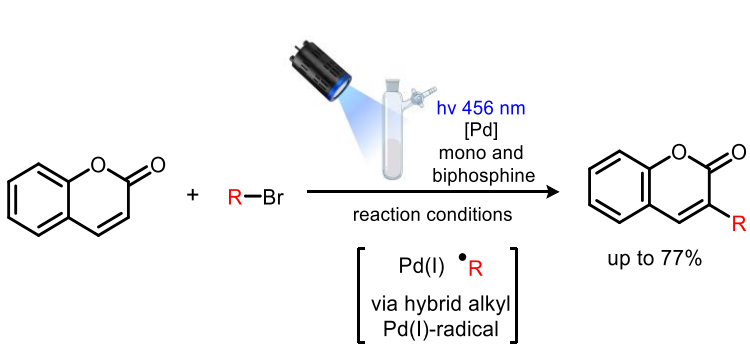
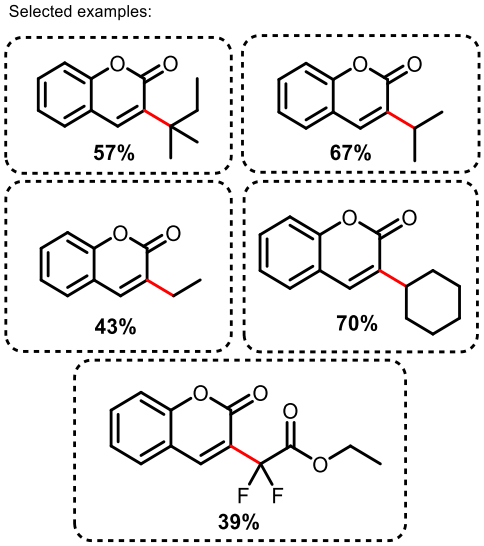
Keywords: *Transition Metal Catalysis, Photochemistry, Coumarin, Organic Synthesis.*

ABSTRACT

Coumarin derivatives, known for their important bioactivities, are frequently used in medicinal chemistry.[1] Functionalization at the C3 position of coumarins represents a valuable synthetic approach to modulate their biological properties. However, metal-catalyzed general methodologies for direct installation of alkyl groups in coumarins with high regioselectivity are still limited. Traditional methods based on cross-coupling reactions use excess oxidant and high temperatures,[2] which can often limit the scope of the reaction.

In this work, we achieved the C3-alkylation of coumarins through a palladium-photoredox Heck reaction using alkyl halides as radical precursors; an effective strategy to the formation of C–C bonds under mild conditions using visible light as energy source.[3] This transformation is catalyzed by a photoactive complex formed from a palladium source and the combination of mono- and biphosphines as ligands. Furthermore, primary, secondary, and tertiary alkyl bromides were successfully used as substrates, resulting in the formation of the desired products as a single regioisomer in up to 77% yield.





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Remote radical alkylation of silyl dienol ether by palladium-photoredox catalysis: a direct access to γ-alkylated α,β-unsaturated ketones

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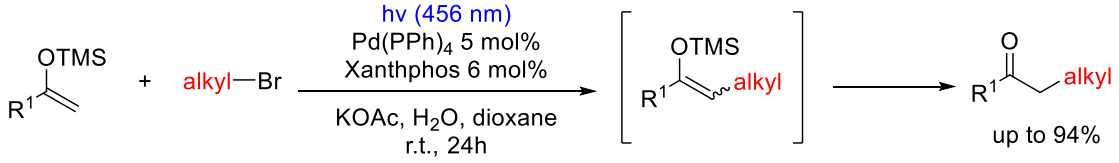
Keywords: *Transition Metal Catalysis, Photoredox Catalysis, Palladium Chemistry, Organic Sythesis*

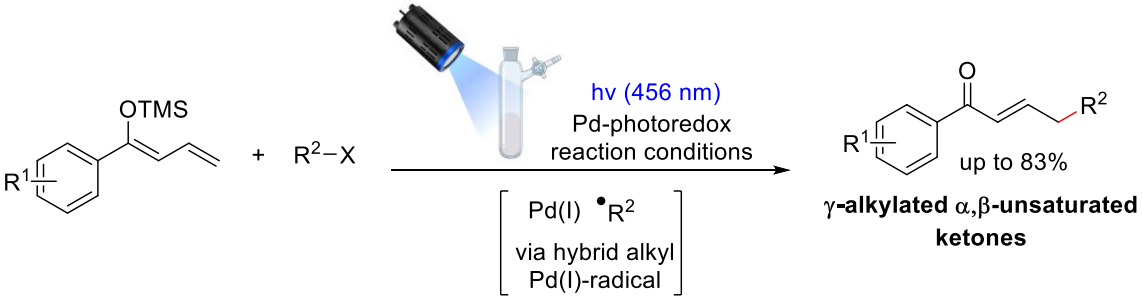
ABSTRACT

Transition metal-photoredox catalysis have become a growing research area in the past few years. The dual function of the catalyst plays an important role for the success of this type of synthetic approach: the metal complex acts as photoredox catalyst and maintains its classical activity in subsequent transformations to provide the desired product, without the need for an exogenous photosensitizer. In particular, for reactions catalyzed by palladium, this strategy makes it possible for transformations inaccessible to classical palladium ground state chemistry to be carried out from the excited state of the catalyst.[2] A representative example is the Heck reaction involving alkyl substrates, which is very challenging for classical Pd-catalyzed cross-coupling reactions, but is feasible by Pd-photoredox strategy.[3] Therefore, in this work, we present an initial study for vinylogous alkyl radical addition to silyl dienol ethers providing direct access to γ-alkylated α,β-unsaturated ketones in up to 83% yield under visible light Pd-photoredox reaction conditions.

Fu (2020)- Palladium-catalyzed α-alkylation of silyl enol ether



This work - Palladium-photoredox catalyzed γ-alkylation of silyl dienol ether



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SEPTEMBER 23-27TH 2024
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BRAZILIAN MEETING ON ORGANIC SYNTHESIS
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Synthesis and thermal and structural characterization of novel Ionic Liquids with imidazolium cations and carboxylate anions.

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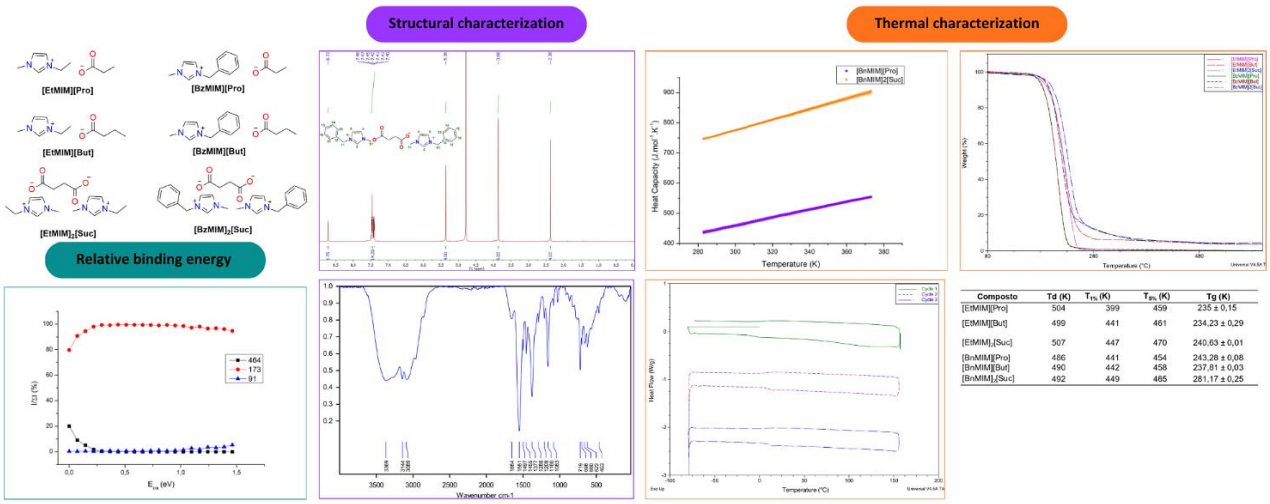
Keywords: *Ionic Liquids, synthesis, structural characterization, thermal analysis.*

ABSTRACT

In this study, six ionic liquids (ILs), three of which are novel, were synthesized using ethyl-methyl-imidazolium or benzyl-methyl-imidazolium cations and carboxylate anions derived from propionic, butyric, succinic, and glutaric acids. The physicochemical properties of these compounds were evaluated and compared to determine the effects of structural modifications on the cations and anions. The synthesis involved an SN2 reaction of methylimidazole with the respective alkyl halide, followed by anion exchange (from halide to hydroxide) using an anion exchange resin and subsequent neutralization with acid. Structural characterization was conducted using NMR, ESI-MS-MS, and IR spectroscopy. Thermal properties were assessed through Thermogravimetric Analysis (TGA) and Differential Scanning Calorimetry (DSC) to determine thermal stability and behavior, respectively. TGA revealed that structures with two carboxylates tend to decompose 5% and 10% at higher temperatures compared to analogous structures with a single carboxylate. No phase transitions were observed for any structures, indicating amorphous behavior within the studied temperature range (193 K to 433 K). Relative binding energy evaluation via ESI-MS-MS was assessed for $[BnMIM]_2[Suc]$. Specific heat capacity (Cp) measurements indicate that the presence of the second carboxylate group results in an increase in Cp compared to the analogous monocarboxylate, as expected due to the higher molecular mass of this structure. Additionally, qualitative and quantitative solubilities, bromide content, density, and the relative binding energies for the other compounds are being measured [1,2].



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SEPTEMBER 23-27 2024
19 BMOS
BRAZILIAN MEETING ON ORGANIC SYNTHESIS
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2-(((4-(Trifluoromethyl)quinolin-6-yl)amino)methyl)phenols: Synthesis and optical properties

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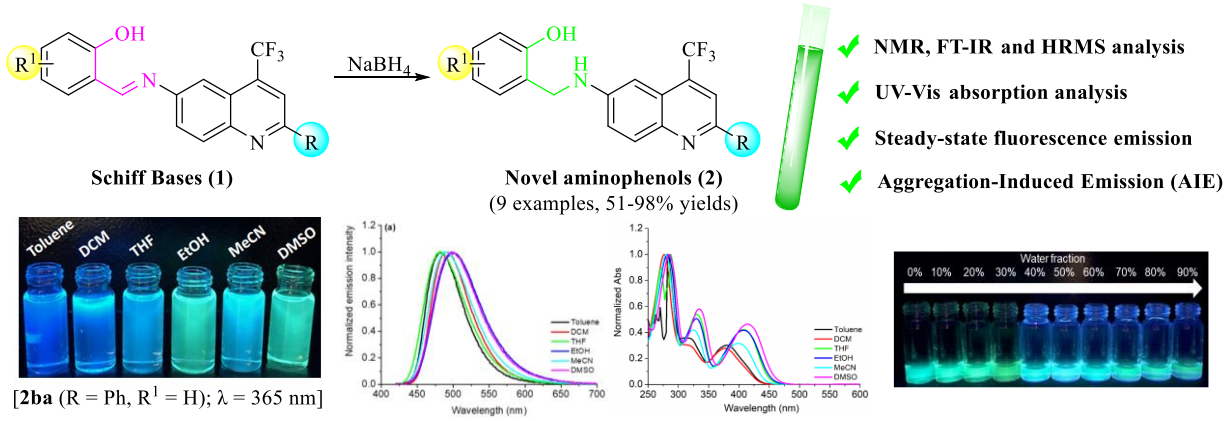
Keywords: *Aminophenols, quinolines, photoluminescence.*

ABSTRACT

Secondary amines are compounds of biological interest and have also been employed in the synthesis of products that are of interest in pharmaceutical and agricultural industries [1-4]. Although the secondary amines are well now for their biological interest, the synthesis of organic compounds that presents interesting photophysical characteristics have been drawing considerable attention in the last years. This highlights the significance of creating organic compounds possessing these photophysical properties, which have garnered significant attention and found extensive applications in the chemistry of materials [5]. In this regard, this study sought to evaluate the synthesis by a simple reduction method starting from Schiff bases (**1**) and using sodium borohydride as reduction reagent, to obtain a new series of 2-(((alkyl/aryl/heteroaryl)-4-(trifluoromethyl)quinolin-6-yl)amino)methyl)phenols (**2**). Subsequently, it was studied the UV-Vis absorption analysis and steady-state fluorescence emission properties, both in liquid and solid state for these hybrid system quinoline-phenol **2**, as depicted in Scheme 1 [6].



Scheme 1. A summary of this study: the synthesis and photophysical properties of 2-(((alkyl/aryl/heteroaryl)-4-(trifluoromethyl)quinolin-6-yl)amino)methyl)phenols (**2**).

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The authors would like to thank the following entities: The Coordination for Improvement of Higher Education Personnel-CAPES (Finance Code 001) for the fellowships and the National Council for Scientific and Technological Development-CNPq: proc. No 305.379/2020-8 and 403.134/2021-8, and the Research Support Foundation of the State of Rio Grande do Sul-FAPERGS: proc. No. 17/2551-0002099-7 for financial support.

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SEPTEMBER 23-27 2024
19BMOS
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Selective fluorination reactions in 5-aryl(heteroaryl)-7-(trifluormethyl)-2-methylpyrazole[1,5-*a*]pyrimidines

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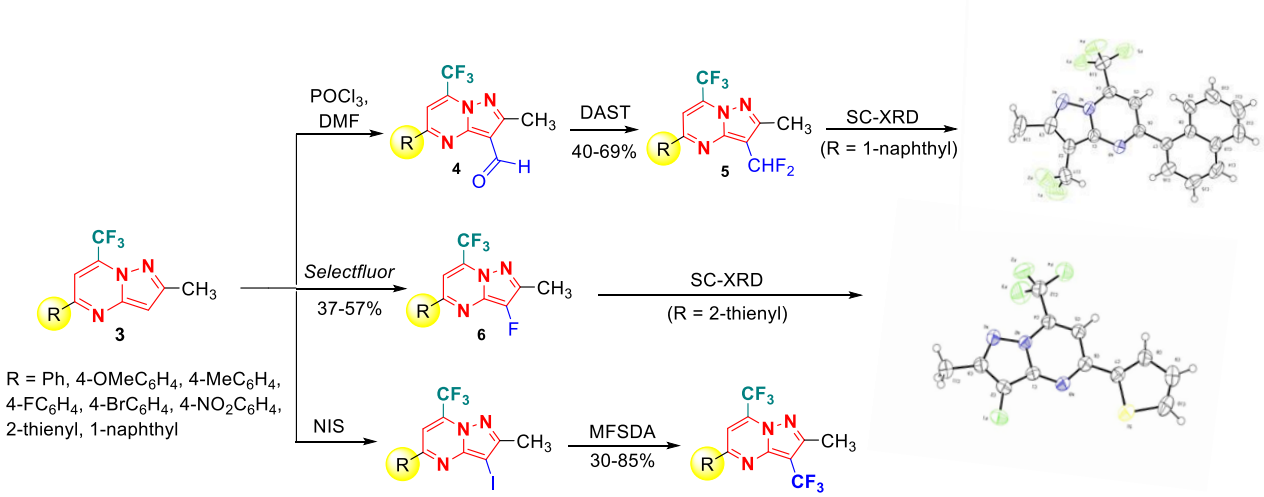
Keywords: *Fluorination reaction, Pyrazole[1,5-a]pyrimidines, DAST-MFSDA-Selectfluor*

ABSTRACT

The incorporation of fluorine atoms into organic molecules has garnered significant interest in synthetic and medicinal chemistry. Extensive research has demonstrated that fluorine atoms can modify crucial properties of organic compounds such as acidity and basicity. Moreover, they can impact absorption, transport, and interactions with drug receptors [1-3]. In this regard, this work presents the synthesis of a three new series of fluorinated pyrazole[1,5-*a*]pyrimidines (Scheme 1) obtained from three different synthetic routes that involves: (i) synthesis of 3-formylpyrazolo[1,5-*a*]pyrimidines (**4**) followed by a DAST-mediated nucleophilic difluorination for the synthesis of 5-aryl(heteroaryl)-3-difluormethyl-7-(trifluormethyl)-2-methylpyrazolo[1,5-*a*]pyrimidines (**5**); (ii) a regioselective electrophilic fluorination employing the fluorinating reagent Selectfluor for the synthesis of 5-aryl(heteroaryl)-3-(fluoro)-7-(trifluoromethyl)-2-methylpyrazolo[1,5-*a*]pyrimidines (**6**) and, (iii) a sequential reaction involving an iodination with N-bromo succinimide (NIS) followed by a trifluoromethylation using methyl fluorosulfonyldifluoroacetate (MFSDA)[4] to obtain 3,7-bis(trifluoromethyl)-pyrazolo[1,5-*a*]pyrimidine (**8**).



Scheme 1. A summary of this study: Synthetic routes for fluorinated pyrazolo[1,5-*a*]pyrimidines **5**, **6**, **8**.

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Exploring the reaction of sulfoxonium ylides with allylic carbocations

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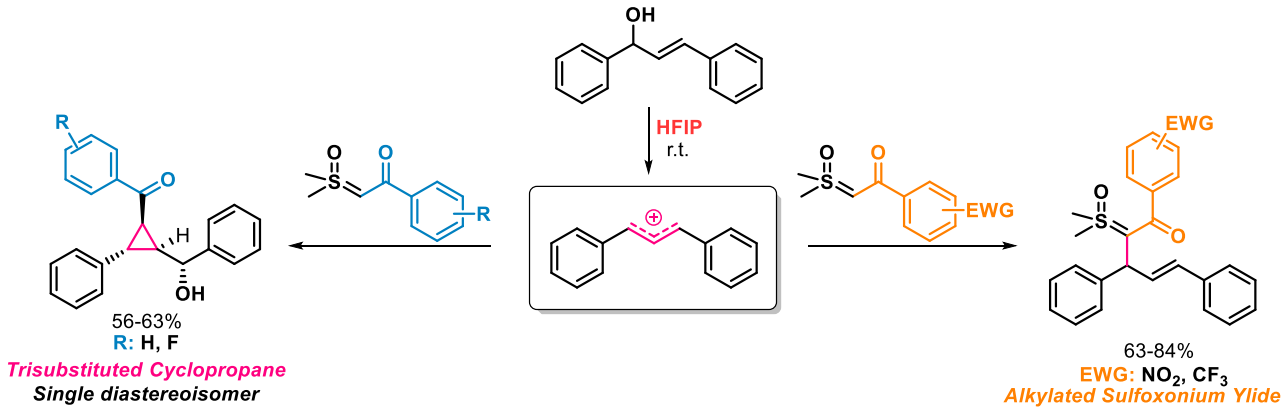
Keywords: *Sulfoxonium Ylides, Carbocation, Cyclopropane.*

ABSTRACT

Sulfoxonium ylides are valuable tools in the construction of complex molecules.[1] Despite their extensive applications,[2] the reaction of α-carbonyl sulfoxonium ylides with carbocations has been overlooked. Herein we described the reaction of sulfoxonium ylides with allylic carbocations. As a starting point for our studies, we evaluated the reaction of *trans*-1,3-Diphenyl-2-propen-1-ol with α-carbonyl sulfoxonium ylide, under various reaction conditions to promote the formation of the carbocation. We discovered that HFIP (hexafluoroisopropanol) effectively promotes the formation of the carbocation,[3] leading to the formation of two distinct product depending on the sulfoxonium ylide employed. When sulfoxonium ylides with strong electron-withdrawing groups were used, the addition of the sulfoxonium ylide to the carbocation was followed by a deprotonation step, resulting in the formation of an alkylated sulfoxonium ylide. Using other ylides, the addition was followed by a cyclization, leading to trisubstituted cyclopropane as the major product. With the optimal conditions, a scope was constructed.



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Design and Synthesis of 1,2-Naphthoquinone Derivatives

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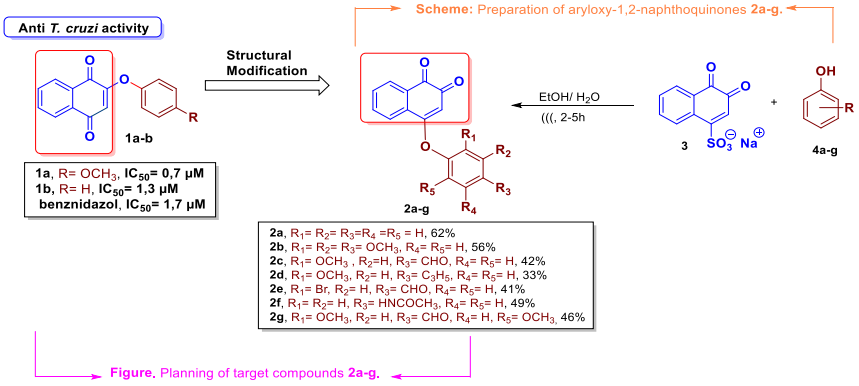
Keywords*: Trypanosoma cruzi, naphthoquinones, phenols.*

ABSTRACT

Chagas disease (CD), also known as American trypanosomiasis, is a serious parasitic infection caused by the protozoan parasite *Trypanosoma cruzi*.[1] Although benznidazole and nifurtimox are currently the standard treatments for Chagas disease, their limitations in terms of side effects and efficacy in the chronic phase highlight the urgent need for continued research and innovation in the field of CD treatment.[2, 3] Aryloxy-1,4-naphthoquinones **1a-b** (**Figure**) have been reported in the literature[4] as potential inhibitors of the protozoan *Trypanosoma cruzi*, presenting promising IC_{50} values. As part of our research program focused on the discovery of new inhibitors of *Trypanosoma cruzi*, we report the synthesis of several aryloxy-1,2-naphthoquinones **2a-g** via the nucleophilic substitution reaction of the sodium-4-sulfonate salt 1,2-naphthoquinone **3** with the corresponding phenols **4a-g** (**Scheme**). The **2a-g** series was strategically designed by replacing the 1,4-quinonoid core, present in the antiparasitic compounds **1a-b**,[4] with a 1,2-quinonoid ring (**Figure**).



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Synthesis, derivatization and radiolabeling of carbasugars for the detection of hidden infections

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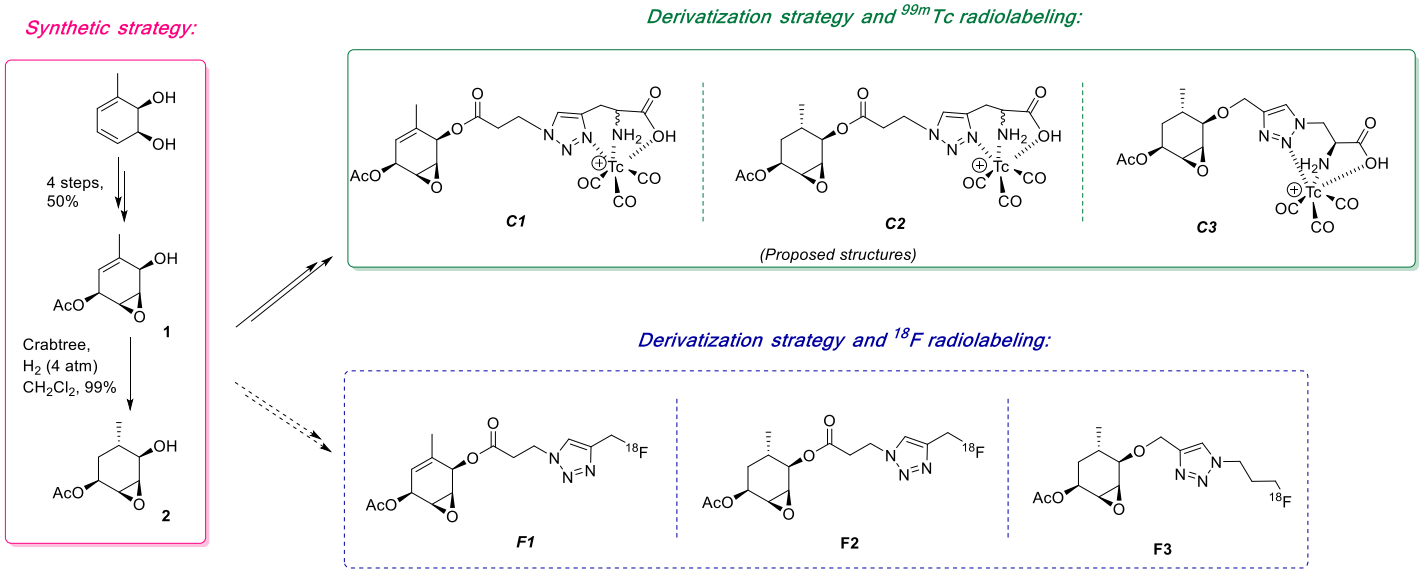
Keywords: *Ampelomins, Derivatization, Radiolabeling.*

ABSTRACT

Ampelomins represent a group of carbasugars with promising biological activity.(1) Our research group is dedicated to the synthesis,derivatization and radiolabeling of these compounds with ^{99m}Tc and ^{18}F for their potential use as diagnostic agents in detecting hidden infections through molecular imaging.The targeted ampelomins are synthesized from a common precursor **1** obtained from the toluene derived *cis*-cyclohexadienediol, resulting in an overall yield of 50% over 4 steps.(2) Building upon the successful acquisition and characterization of three ^{99m}Tc complexes in a previous stage,this study showcases the advancements achieved thus far in the derivatization and radiolabeling of **1** and its hydrogenated derivative **2** with ^{18}F.The derivatization approach involves incorporating a linker containing an azide group or a triple bond, followed by a Huisgen cycloaddition with propargylic alcohol or bromopropanazide. Subsequently, the alcohol or bromide is substituted with [^{18}F]F.So far, we have obtained the precursor of compound **F2** (8 steps, overall yield 25%) (Figure_1).



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Telescoped Continuous Flow Photochemical and Electrochemical Synthesis of Butyrolactones

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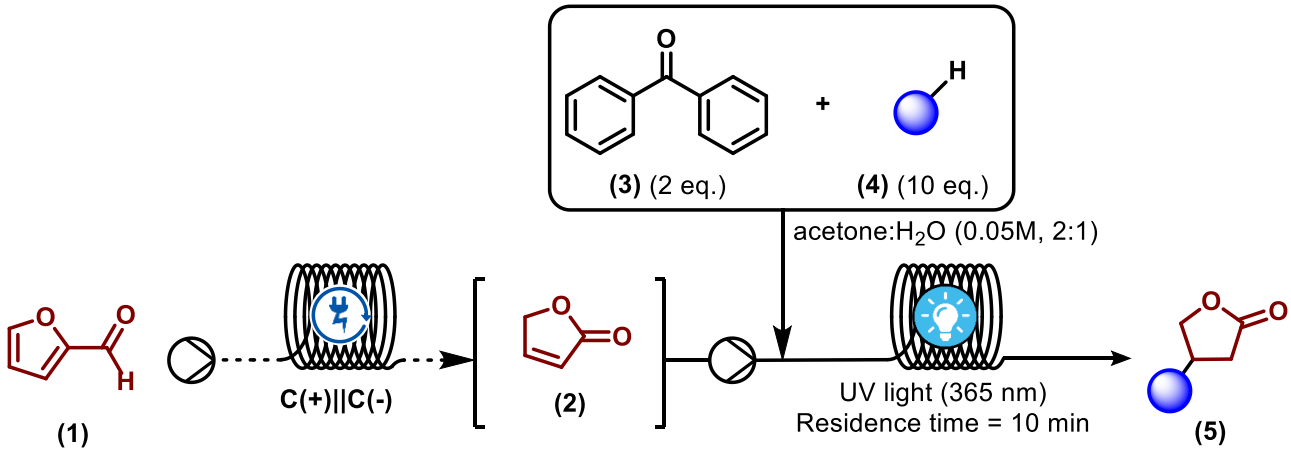
Keywords: *Photochemistry, Electrochemistry, Continuous Flow.*

ABSTRACT

The environmental impact resulting from the excessive use of fossil fuels has driven the advancement of more sustainable technologies and processes, in line with the recommendations of the United Nations (UN) as expressed in the Sustainable Development Goals (SDGs). Thus, there is a growing demand for innovative solutions that seek to valorize biomass and utilize sustainable energy sources such as light and electrical power. Herein, we describe the conversion of furfural (**1**), derived from the abundant biomass polymer hemicellulose, into bioactive butyrolactones (**5**) using integrated photochemical and electrochemical processes under continuous flow conditions. First, furfural is converted into (2H)-5-furanone (**2**) via anodic oxidation of water.[1,2] This is followed by a photochemical step, where the alkylation of (2H)-5-furanone (**2**) is mediated by benzophenone (**3**), enabling a hydrogen atom transfer (HAT) step on a selected H-donor group (**4**), resulting in the alkyl butyrolactone.[3] Under optimized conditions, (**5**) was obtained in 80% yield in the photochemical step using isopropanol as H-donor group (**4**).

The electrochemical step and the integration of the two steps in a telescoped process are now in progress and will be presented.



Scheme 1: Telescoped electrochemical and photochemical synthesis of alkyl butyrolactones (**5**).

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Synthesis of 2-phenyl-1H-benzo[d]imidazole-derived fluorescent G-quadruplexes ligands

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Keywords: *fluorescence, benzimidazole, ligands.*

ABSTRACT

This work presents the unprecedented results of the synthesis, structural characterization and determination of the photophysical properties of a series of 1-ethyl-2-aryl-1H-benzo[d]imidazoles iodide salts with potential application as fluorescent ligands for G-quadruplexes. The products were obtained by a condensation reaction of benzene-1,2-diamine with substituted benzaldehydes (**1a-e**) and two subsequent alkylations, obtaining the compounds (**3a-e, 4a**). The synthetic route and the yield of products **3a-e** and **4a** are shown in **Scheme 1**. The UV-vis emission properties were investigated, all compounds absorbed in the ultraviolet region presenting fluorescence. Thermal stability was evaluated by thermogravimetric analysis and the results are shown in **Table 1**. The chemical structure of the compounds was determined by ^{1}H, ^{13}C NMR and two-dimensional experiments: COSY, HSQC, HMBC.

Scheme 1. Synthesis of salts derived from 1-ethyl-2-phenyl-1H-benzo[d]imidazole.

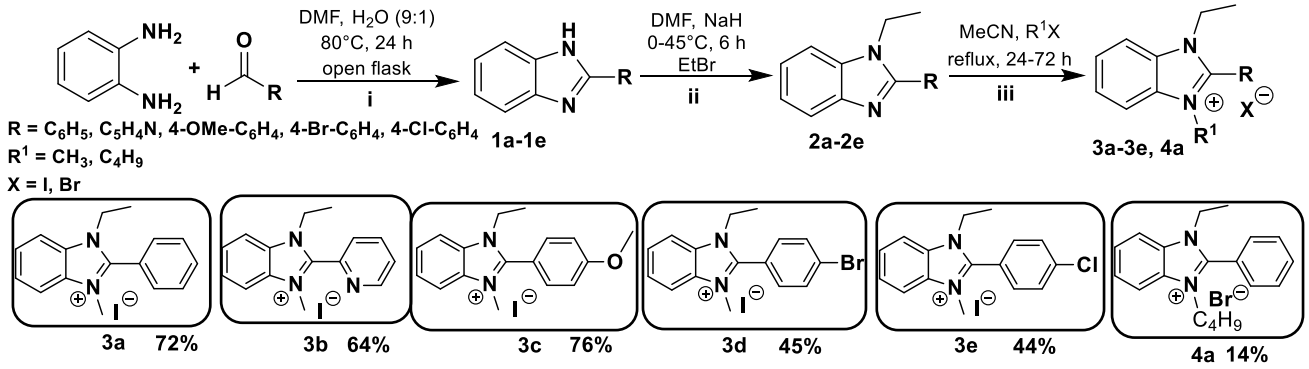

Table 1. Decomposition temperature (T_d) and melting point (T_m) of compounds **3a-e** and **4a**.

Compound	T_d[a] (°C)	T_m[b] (°C)	Compound	T_d[a] (°C)	T_m[b] (°C)
3a	261	198	3d	270	160
3b	233	150	3e	266	244
3c	273	171	4a	243	248

[a]Decomposition temperature. [b]Melting temperature.

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Metal-free Synthesis of Isoquinoline Derivatives Via Intramolecular Cyclization Through C-C(sp) Bond Activation

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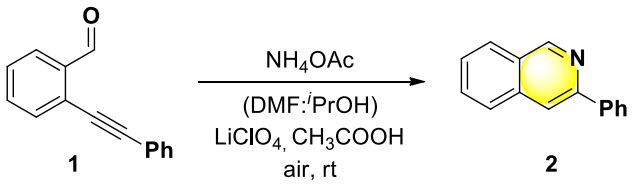
Keywords: *Isoquinoline, Cyclization, Heterocycles.*

ABSTRACT

Isoquinoline derivatives exhibit remarkable biological activities, including antitumor, anti-inflammatory, and analgesic effects [1]. Metal catalysts such as Rh(III), Pt(0), Ag(I), Cu(I), and Au(I) have been successfully employed for the intramolecular cyclization of these substrates [2]. This project seeks to develop a metal-free methodology for the synthesis of isoquinoline derivatives via oxidative cyclization under less demanding conditions compared to those reported in the literature (Scheme 1).

Scheme 1. Synthesis of Isoquinoline Derivatives.



Previous results demonstrated conversions ranging from 40% to 97%, as determined by GC-MS analysis. The reaction conditions were optimized using a mixture of *N*,*N*'-dimethylformamide (DMF) and isopropyl alcohol (iPrOH) as the solvent, with acetic acid as an additive. The reactions proceeded at room temperature with ammonium acetate as the amine source and lithium perchlorate as oxidant (Table 1). This approach offers advantages in selectively obtaining product **2** with high conversion rates, while also presenting itself as an environmentally friendly method.

Table 1. Optimization of Reaction Conditions.[a]

Entry	Derivation from standard conditions	Yield (%)[b]
1	Acetonitrile	40
2	No DMF at 60 °C	60
3	No DMF	60
4	NaOH instead of NH_4OAc	20
5	At 60 °C	97
6	None	97

[a]Reaction conditions: 2-(phenylethynyl)-benzaldehyde (0.25 mmol), NH_4OAc (1 equiv.), lithium perchlorate (1 equiv.), DMF:iPrOH (2ml:2ml) and AcOH (1 equiv.) at room temperature for 1 hour. [b] Yield determined by GC-MS analyses.

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Oxazoline-based dyes for fluorescent enantioselective differentiation of carbohydrates in solution

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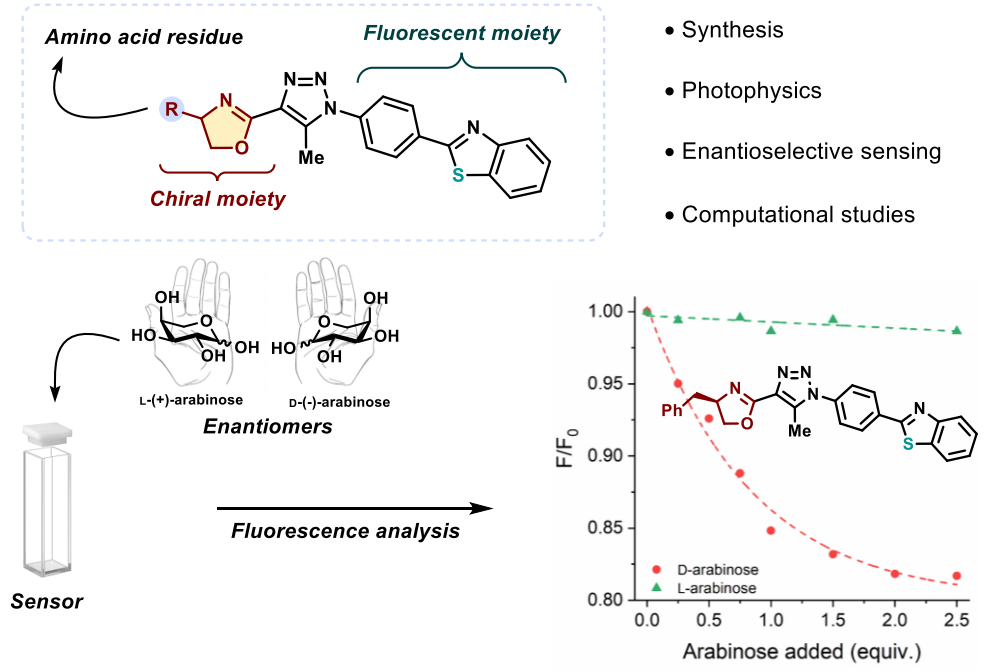
Keywords: *Chiral sensing, fluorescence spectroscopy, oxazoline*

ABSTRACT

Understanding the interaction of small molecule with chiral biomolecules is key to study the mechanism of action of drugs in biological systems. As such, it is worth highlighting the enantiomeric differentiation of carbohydrate enantiomers in solution, applying a simple steady-state fluorescence emission spectroscopy. Herein, we present the synthesis of chiral 2-oxazolines derived from amino acids-based *N*-(2-hydroxyethyl) amides, containing a fluorophoric benzothiazole core. A series of six 2-oxazolines were synthetized in good yields and their photophysical properties were evaluated by UV-Vis absorption and fluorescence emission spectroscopies. Thereafter, these dyes were studied as optical sensors for the enantioselective differentiation of two carbohydrate enantiomers pairs in solution. Theoretical calculations have been performed to better understand the observed interaction dye-analyte. Results indicate that dye-bearing D-phenylalanine residue stands out exhibiting calculated enantioselectivity values higher than previously reported.[1] It is noteworthy that the obtained response is mainly due to weak interaction forces, such as hydrogen bonds.



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Au nanoparticles decorated with derivatized thiols: synthesis, characterization and applications

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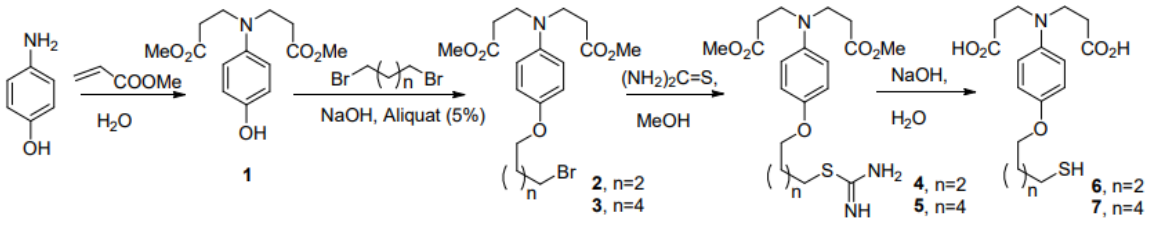
Keywords: *nanotechnology, ligands, metal ions*

ABSTRACT

The study of gold nanoparticles (AuNPs) is of interest in the nanotechnology field due to their physicochemical properties. [1]
Two organic ligands were synthesized, with a terminal thiol capable of binding to AuNPs, a chromophore group and an aminodicarboxylate group (derived from aminodipropionic acid) with a known capacity to bind metal ions. The incidence in the colloidal system of the chain length linking the chromophore group and the thiol was studied.
The synthesis began with an *aza*-Michael addition to afford iminodiester (**1**), ***Scheme 1***.



***Scheme 1*:** Synthesis of ligands

The alkylaryl ethers (**2**)-(**3**) were obtained through Williamson´s synthesis. The substitution of bromine with thiourea and its subsequent hydrolysis gave the products (**6**)-(**7**). [2]
AuNPs were prepared according to a previous work, [3] and then decorated with the ligands.
The system is chemically stable under the tested pH and ionic strength conditions, enabling metal ion binding and potential use as sensors.

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DIRECT SELENIZATION OF THE C(sp^2)-H BOND OF QUINOLINE VIA ELECTROSYNTHESIS

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Keywords: *Electrosynthesis, quinoline, selenium.*

ABSTRACT

Quinoline-derived compounds are well-known for their diverse biological activities, acting as pharmacological agents with antibacterial, antiviral, anti-inflammatory, and antioxidant properties[1]. The increasing number of publications on electrochemical synthesis highlights the importance of research focused on synthesizing compounds using this environmentally friendly methodology, offering a more sustainable alternative compared to traditional methods[2]. This work describes the electrosynthesis of quinoline-derived organoselenium compounds, aiming to explore their potential biological activity. Initial studies directly employing quinoline yielded unsatisfactory results due to its low reactivity. Therefore, experiments were conducted using quinoline *N*-oxide and diphenyl diselenide as a selenium source. This approach resulted in conversions ranging from 69% to 98%, as determined by ^{1}H-NMR analysis across various reaction times (Table 1). The optimized reaction conditions include a reaction temperature of 70 °C, $TBABF_4$ as the supporting electrolyte, acetonitrile as the solvent, platinum electrodes for both the cathode and anode, and a current application of 24 mA.

Figure 1 – Reaction scheme

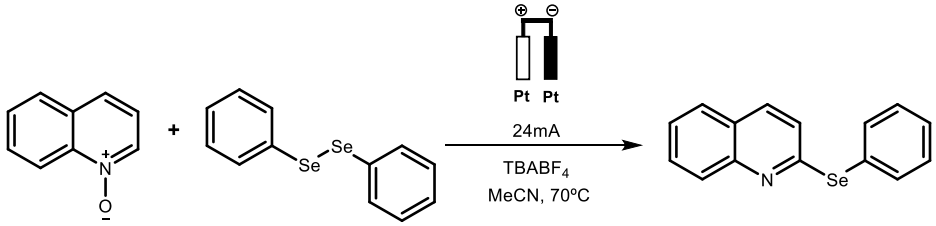

Table 1 – Conversion to product analyzed by ^{1}H-NMR

Time	Conversion (%)
6 hours	69%
8 hours	98%
11 hours	98%
24 hours	96%

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CMU/UDESC, FAPESC, CNPq

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Eletrochemical Diselenation of BODIPY Fluorophores for Bioimaging Applications and Sensitization of $^1O_2$

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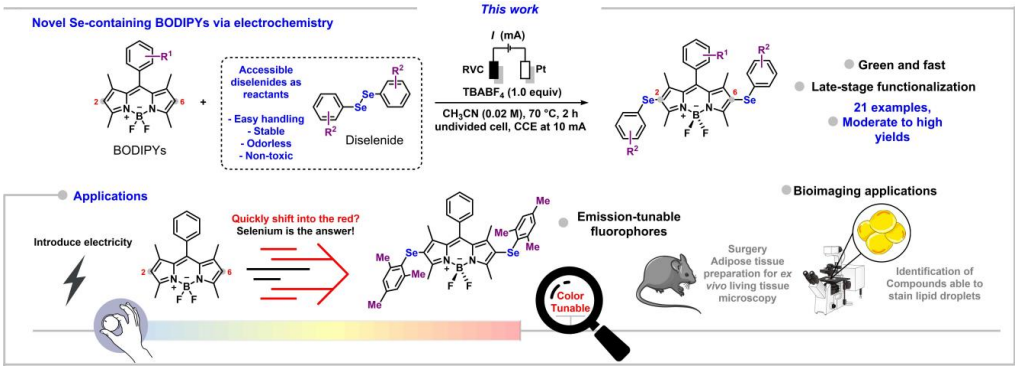
Keywords: *electrochemistry, BODIPY, synthesis, selenium, fluorescence*

ABSTRACT

In this study, we discuss the development of a new efficient method with a scope-extensive approach for the late-stage electrochemical diselenation of BODIPYs. The photophysical studies of the selenium-compounds reveal red-shifted absorption – corroborated by TD-DFT and DLPNO-STEOM-CCSD computations – and color-tunable emission with large Stokes shifts when compared to their precursors. The effect of the heavy atoms of Se facilitate the intersystem crossing that generates triplet states that sensitize 1O2 and display phosphorescence in PMMA films at RT and in a frozen glass matrix at 77 K. Importantly, the seleniumcontaining BODIPYs demonstrate the ability to selectively stain lipid droplets, exhibiting distinct fluorescence in both green and red channels. This work demonstrates the potential of electrochemistry as an efficient method for synthesizing unique emission-tunable fluorophores with broad-ranging applications in bioimaging and related fields.



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SEPTEMBER 23-27 2024
19BMOS
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Electrochemical Halogenation of Naphthoquinones: A Modular and Sustainable Strategy towards Trypanocidal Compounds

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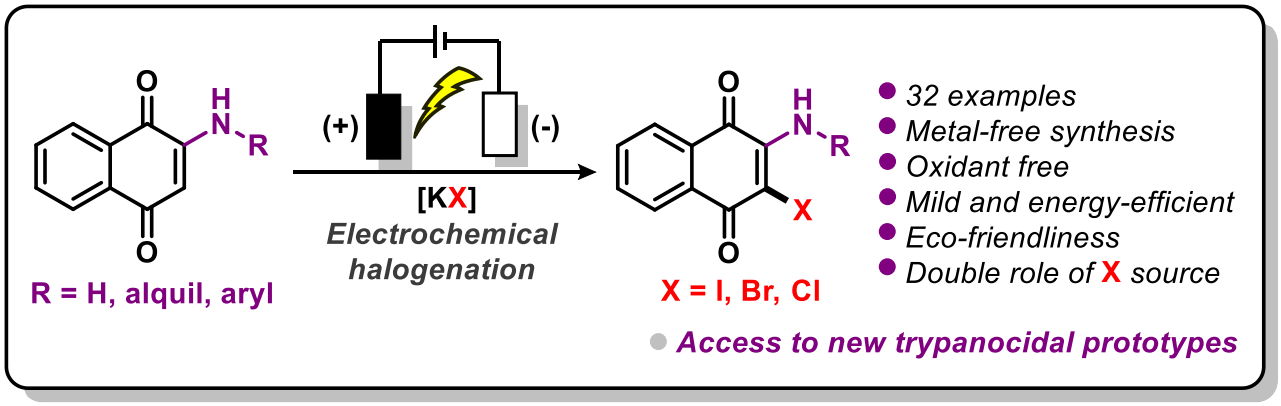
Keywords: *Electrochemistry, Halogenation, Quinones, Chagas Disease, Medicinal Chemistry*

ABSTRACT

Quinones are a class of privileged scaffolds, widely found in nature. Historically, these molecules have been used since antiquity as dyes and in popular medicine. Among quinoidal compounds, 1,4-naphthoquinones stand out due to their immense potential as pharmacological prototypes.[1] In recent years, several 1,4-naphthoquinones containing amino and/or halogenated moieties have been identified as potent anti-infective agents, showing potential in combating *T. cruzi*, the causative agent of Chagas' disease.[2] Electrochemistry has emerged as a powerful strategy for the structural modification of molecules, particularly through the insertion of halogens by electrochemical halogenation methods.[3] This research aims to develop an environmentally friendly electrochemical halogenation of 2-amino-1,4-naphthoquinones. This new methodology works in the absence of oxidants, featuring a dual role of the employed salt, acting both as halogen source and electrolyte, resulting in 32 amino-halogenated derivatives with good yields under mild conditions. This novel approach provides access to new potent trypanocidal prototypes.



Scheme 1. Electrochemical halogenation of 2-amino-1,4-naphthoquinones.

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SEPTEMBER 23-27 2024
19BMOS
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Generation and Capture of Naphthoquinonynes: A New Frontier in the Development of Trypanocidal Quinones via Aryne Chemistry

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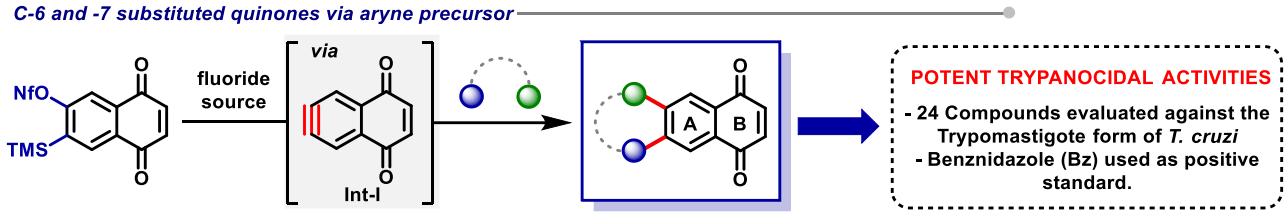
Keywords: *Aryne chemistry, Trypanocidal activity, naphthoquinones*

ABSTRACT

Chagas disease, caused by the parasite *Trypanosoma cruzi*, presents significant challenges in treatment, particularly due to the limitations of the currently available drugs, benznidazole (BZ) and nifurtimox (NFX).[1] Quinones are involved in key biochemical processes and have numerous pharmacological applications, including remarkable trypanocidal activity.[2-7]Studies made by our research group have demonstrated that A-ring functionalization of naphthoquinones can (i) improve trypanocidal activity and (ii) provide compounds with lower cytotoxicity.[2-7] Recently, we have described methods for the generation and *in situ* capture of naphthoquinonynes, and this enables polyfunctionalizations at the C-5, -6 and -7 positions.[8] The current study investigated the use of amines and pyridine-*N*-oxides as reaction partners to achieve regioselective functionalization of A-ring naphthoquinones. This approach led to the discovery of 14 new compounds that demonstrated higher activity compared to benznidazole, in which two of these newly identified compounds exhibited approximately 10-fold greater activity than BZ.



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SEPTEMBER 23-27 2024
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Ruthenium-Catalyzed C–H Alkenylation of Quinones to Introduce SuFEx Functionalization: A Potential Building Block for Bioactivity Valorization

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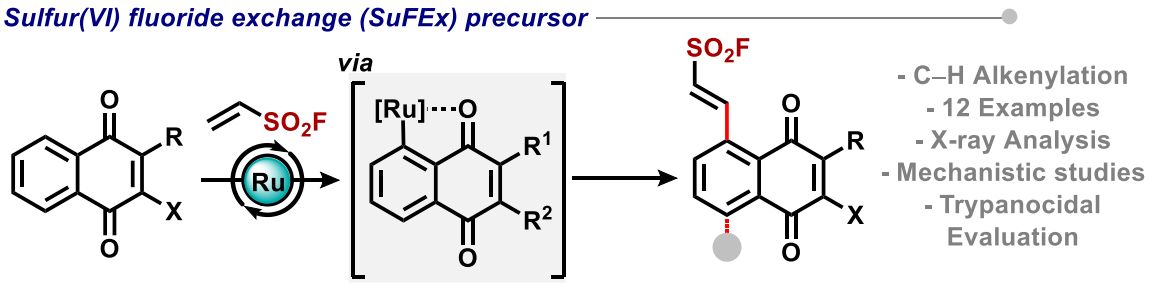
Keywords: *SuFEx, C–H activation, catalysis, naphthoquinones*

ABSTRACT

The development of organic molecule synthesis with potential biological activities is a continually evolving field of chemistry. The use of C–H activation techniques mediated by transition metal catalysis has introduced new methods for modifying previously unreactive molecular sites,[1] enabling the construction of a wide variety of compounds.[2] Another significant advancement is the development of click reactions,[3] inspired by nature's efficient heteroatom linkage mechanisms. A recent example is the sulfur(VI) fluoride exchange (SuFEx),[4] which provides a methodology for creating molecular connections related to sulfur(VI) reactivity. In this work, 1,4-naphthoquinoidal/SuFEx hybrids were synthesized through Ru-catalyzed C–H alkenylation of 1,4-naphthoquinones, achieving moderate to good yields. These molecules were tested for their trypanocidal activity, yielding promising results. Mechanistic investigations supported understanding the alkenylation mechanism. This study is the first report of quinoidal derivatives containing the SuFEx component, allowing future derivatizations to obtain a large and diverse library of compounds.



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SEPTEMBER 23-27 2024
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Multicomponent reactions in the synthesis of phenytoin derivatives for formation of products with potential anticonvulsant activity

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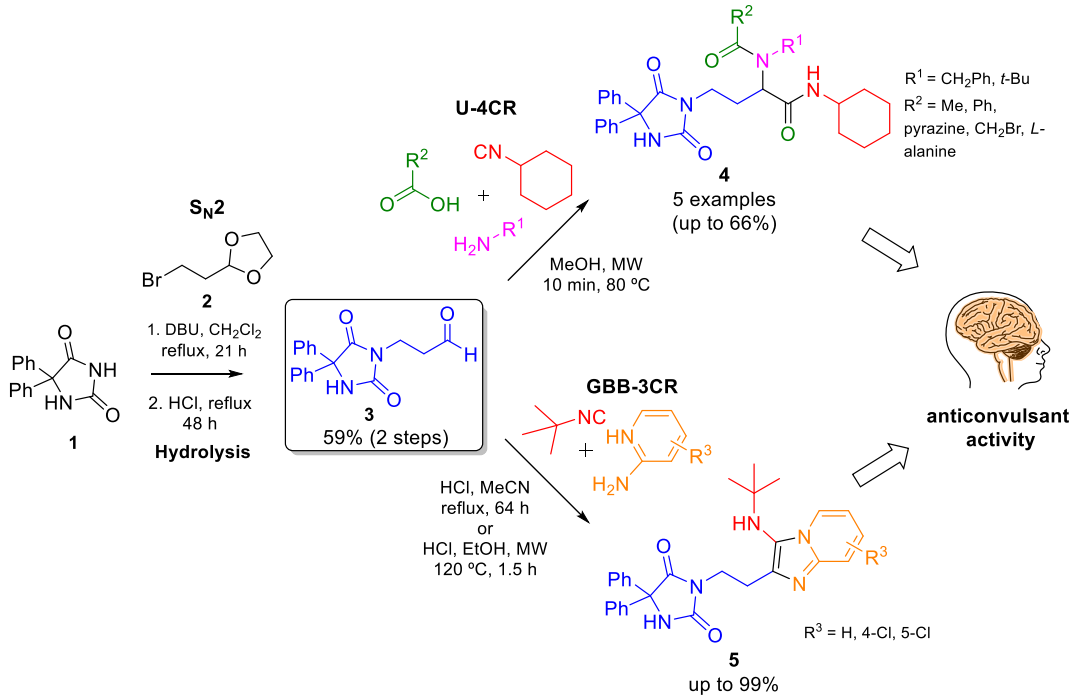
Keywords: *phenytoin, GBB-3CR, Ugi-4CR*

ABSTRACT

Epilepsy is a common neurological disorder that affects people of all ages.[1] Approximately 95% of antiepileptic drugs were approved before 1985 and control seizures in 60-70% of patients.[2] Therefore, the search for safer and more effective drugs is essential in the field of Medicinal Chemistry.[3] Phenytoin is used in the treatment of epilepsy, one of the most widely used anticonvulsants globally and is on the WHO's List of Essential Medicines.[4,5] This study focused on the structural conversion of phenytoin into an aldehyde derivative (**3**) from which new compounds with potential anticonvulsant activity were obtained through Ugi-4CR and GBB-3CR multicomponent reactions. Initially, the synthesis of aldehyde **3** was performed via *N*-alkylation, followed by acetal hydrolysis. This intermediate was then employed in the Ugi reaction with different carboxylic acids, amines, and isocyanides in MeOH under microwave heating, yielding analogs **4** in good yields. The use of aminopyridine derivatives provided GBB adducts **5** in high yields (up to 99%) under HCl catalysis. In both approaches, novel compounds with potential antiepileptic activity (yet to be tested) were synthesized.



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SEPTEMBER 23-27 2024
19BMOS
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Design and Synthesis of a New Series of Pyrido[3,4-*b*]carbazole Derivatives

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Keywords*: 5,8-dihydroisoquinoline, pyrido[3,4-b]carbazole, antitumor.*

ABSTRACT

Cervical cancer is considered the second most common malignant tumor in women globally, following breast cancer.[1] It is closely associated with infection by the Human Papillomavirus, which primarily infects squamous epithelial cells, leading to significant lesions and the potential development of malignancy.[2] Calothrixin B (**1**), an alkaloid isolated from the cyanobacterium *Calothrix*[1], is known for its potent inhibitory effect on cervical carcinoma cell line, with IC_{50} value observed at nanomolar concentration.[3,4,5] Based on the molecular hybridization technique, pyrido[3,4-*b*]carbazoles **3a-h** (Figure) were designed to combine structural features of the following compounds: Calothrixin B (**1**) and 7-fluorophenylamino-5,8-dioxo-5,8-dihydroisoquinoline (**2**), a quinone that exhibits cytotoxic activity against MRC-5, AGS, J82 and SK-MES-1 cells[6]. The synthesis of target compounds **3a-h** involved the palladium-catalyzed cross-coupling reaction of 7-arylamino-5,8-dioxo-5,8-dihydroisoquinoline-4-carboxylates **4a-h** (Scheme). Aromatic amines **5a–h** were transformed into the corresponding compounds **4a–h** by ultrasound-accelerated Michael addition to the electrophilic quinone, compound **6**, under cerium catalysis[7].

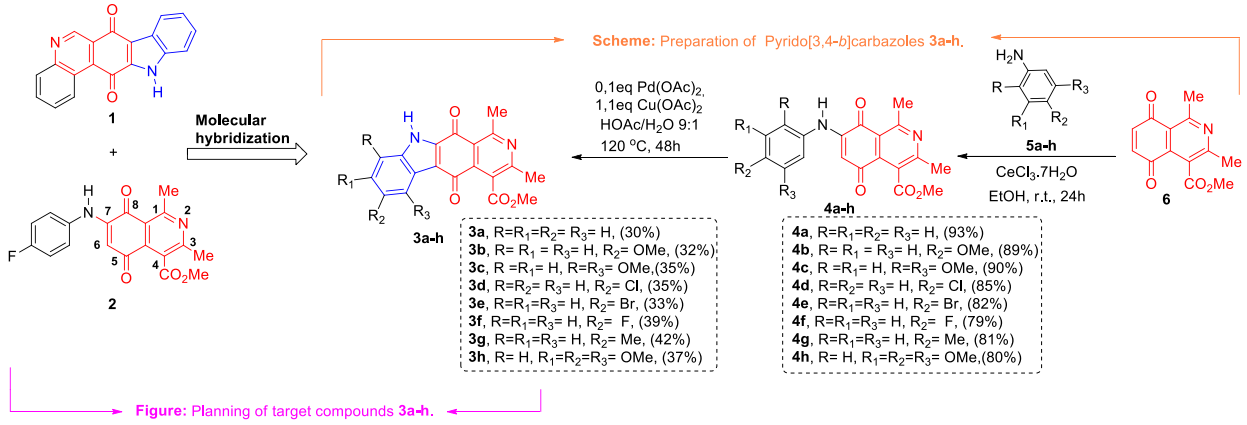

Figure: Planning of target compounds **3a-h.**

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SEPTEMBER 23-27 2024
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Synthesis and optimization of MMV1788223 as new anti-Malarial agent

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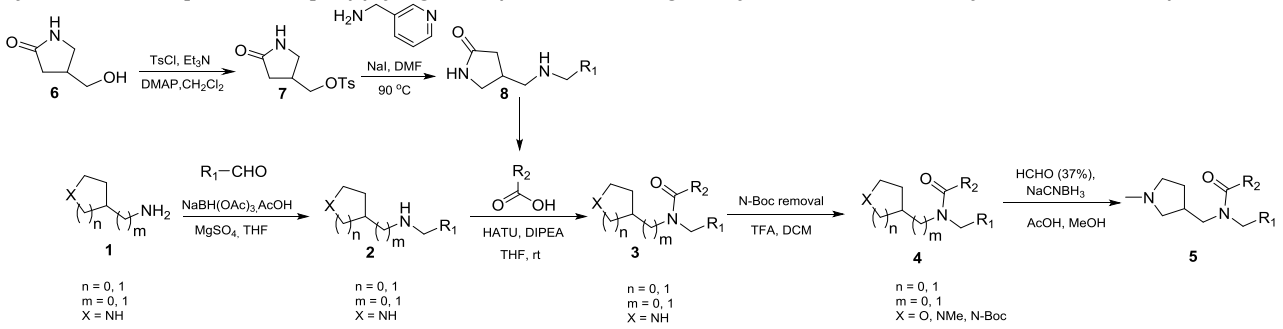
Keywords: *Medicinal Chemistry, Malaria, Drug Discovery.*

ABSTRACT

Medicines for Malaria Venture (MMV) has been committed to reduce the burden of malaria in endemic countries since 1999, by promoting and supporting drug discovery projects focused on the discovery of clinical candidates for malaria treatment and prophylaxis[1]. In line with this goal, UNICAMP team, USP team, and MMV work in collaboration to discover novel clinical candidates to treat Malaria. Malaria is a disease with prevalence in low-income countries, disproportionately affecting children and pregnant women[2]. The ideal candidate for treatment must have low predicted dose, long duration and low resistance risk, combined with acceptable DMPK properties. An efficient and low-cost synthesis is desirable, to guarantee an accessible treatment for every patient[3]. **MMV1788223** was identified in an MMV screen as a Hit Compound, with interesting activity (Pf IC_{50} = 1.39 µM) and a good ADME profile, as an attractive candidate to be optimized for potency and to minimize hERG risk. To prepare the **MMV1788223** and a series of derivatives, we developed an 8-step synthetic route [Scheme 1], applying 3-steps in a convergent synthesis to efficiently obtain the compounds.



Scheme 1. Synthetic approach to obtain compound **MMV1788223** and its derivatives.

30 compounds were obtained to elucidate SAR in this series. The most promising compound of the series showed low hERG risk and an improved potency to 0.22 µM. Despite the promising activity of the series, screening of representative analogs against the Swiss Tropical and Public Health Institute (STPH) resistant panel, highlighted the presence of cross resistance (XR) against *Pf*k1 and *Pf*Dd2 strains**.** Unfortunately, XR is an eliminatory parameter for further investigation of the series by MMV. The work done on this series reinforces the importance of screening confirmed active compounds against resistant strains of *P. falciparum* at an early stage of the drug discovery process.

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SEPTEMBER 23-27 2024
19BMOS
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Electrosynthesis of Benzofurans and Benzofuranols derivatives using sacrificial silver electrode

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Keywords: *Organic Electrosynthesis, Sacrificial Electrodes, Heterocyclic Chemistry.*

ABSTRACT

Molecules containing oxygenated heterocycles are recognized for their significant biological activities. Benzofurans, in particular, are notable for their presence in compounds with antidepressant, anti-inflammatory, and antitumor activities. Additionally, (*Z*)-2,3-Dihydrobenzofuran-3-ol derivatives are crucial intermediates for the synthesis of aurones, which display a wide range of biological activities.[1,2]

The application of electrosynthetic protocols in organic synthesis allows for more selective reactions, improved atom economy, and a reduction in reaction steps, while also employing less hazardous reagents.[3] Electrosynthesis enable redox transformations, allowing the formation of carbon-carbon (C-C) and carbon-heteroatom (C-heteroatom) bonds through the direct use of electric current to drive chemical reactions.[4] Considering this, we developed an electrosynthetic procedure for the synthesis of oxygenated heterocycles 2-phenylbenzofuran **2** and (*Z*)-2,3-dihydro-1-benzofuran-3-ol **4** derivatives. This method achieved good yields using a silver sacrificial electrode in short reaction times, as illustrated in Figure 1. The reaction mechanism is still under investigation, and further studies, including DFT calculations, will be performed.

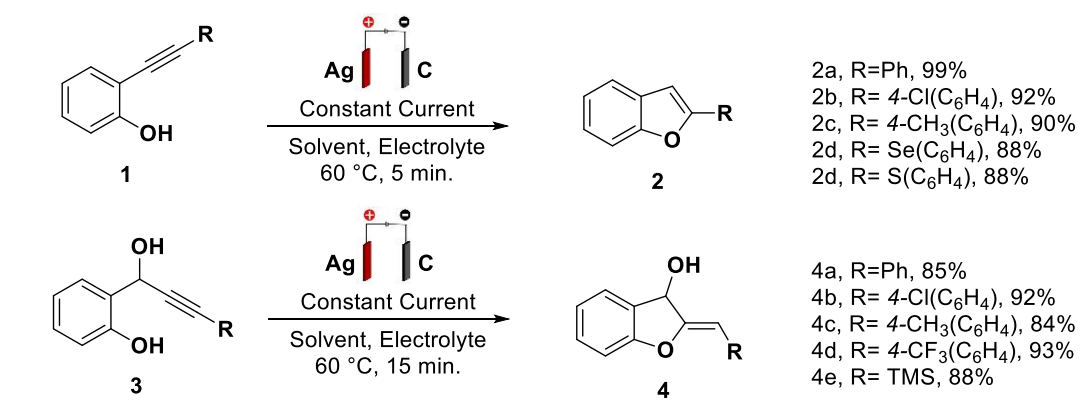

Figure 1. Electrosynthesis of Benzofurans and Benzofuranols derivatives.

ACKNOWLEDGEMENTS

The authors would like to acknowledge INCT Catálise/FAPESC, FAPESP, CNPq and CAPES for their financial support.

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SEPTEMBER 23-27 2024
19BMOS
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Reactivity study of isopiperitenol and *p*-mentha-2,8-dien-1-ol for the synthesis of cannabidiol and cannabidiolic acid methyl esther

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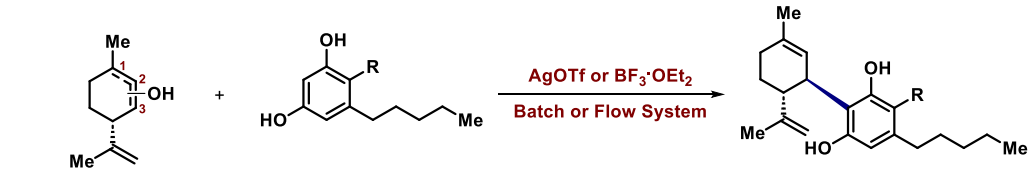
Keywords: *Phytocannabinoids, Friedel-Crafts reaction, batch and flow systems.*

ABSTRACT

Cannabidiol (**1**) is a phytocannabinoid with notorious pharmaceutical applications associated with its antiepileptic,[1] anxiolytic-like,[2] and chemoprotective properties.[3] Hence, synthetic approaches targeting cannabidiol and other cannabinoids are encouraged. We highlight the Eschenmoser approach, which is based on a Friedel-Crafts reaction between an allylic alcohol, such as isopiperitenol (**2**) or *p*-mentha-2,8-dien-1-ol (**3**), and an olivetolic compound (**4** or **5**) in the presence of a Lewis acid.[4] However, the difference in reactivity between alcohols **2** and **3** has never been investigated since the establishment of this strategy. Therefore, this study compares the reactivity of allylic alcohols **2** and **3** with compounds **4** and **5**, using AgOTf and $BF_3{\cdot}OEt_2$ as Lewis acids, affording cannabidiol (**1**) or cannabidiolic acid methyl esther (**6**) in batch and flow systems. Reactions were monitored by HPLC-PDA. Our data showed that isopiperitenol (**2**) has higher reactivity than *p*-mentha-2,8-dien-1-ol (**3**). DFT calculations are being performed to complement the data obtained.



2: double bond between C_1 and C_2, C_3 = -OH;
3: C_1 = -OH, double bond between C_2 and C_3.

4 (R = H)
5 (R = CO_2Me)

1 (R = H)
6 (R = CO_2Me)

- ✓ 16 experiments - 8 in batch, 8 in flow;
- ✓ Higher reactivity of **2** compared to **3**;
- ✓ Higher conversion with **4** compared to **5**;
- ✓ Higher selectivity with **5** compared to **4**;
- ✓ Higher conversion and selectivity in flow compared to batch.

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SEPTEMBER 23-27 2024
19BMOS
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Exploring the Antidepressant Potential of Dihydropyrimidin-2-thiones with Sertraline-like Substitution Patterns

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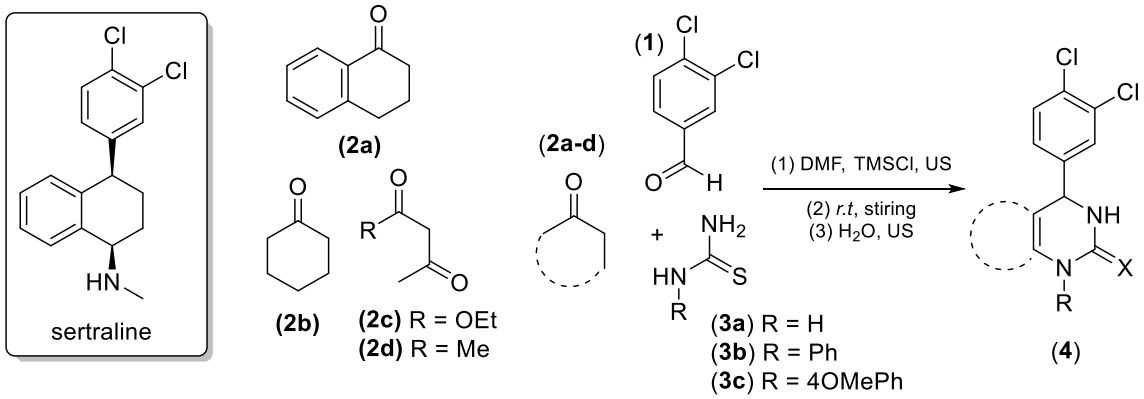
Keywords: *Biginelli reaction; antidepressant effect; sertraline; dihydropyrimidin-2-thiones*

ABSTRACT

Dihydropyrimidin-2-thiones (DHPMs) are heterocyclic compounds widely investigated as privileged scaffolds capable of interacting with various biological targets. Although antiproliferative, antimicrobial, and antioxidant activities are the most studied roles for this class of compounds, their neuropharmacological activity has been poorly investigated[1]. Due to this aspect and the structural similarity between the antidepressant drug sertraline and DHPMs, we synthesized DHPMs featuring a 3,4-diCl-Ph moiety, as found in sertraline. The optimized reaction conditions involved using trimethylsilyl chloride as a promoter agent in *N,N*-dimethylformamide, utilizing ultrasound at room temperature. The DHPMs were obtained with a moderate yield and purified by ethanol or acetonitrile recrystallization. The compounds developed in this study will be evaluated for their antidepressant effects on planarians (*Girardia tigrina*), an alternative animal model that possesses many of the neurotransmitters found in vertebrates[2]. This is the first report to explore the similarity between the DHPM scaffold and the antidepressant sertraline.



Scheme 1. Synthesis of DHPMs with sertraline-like substitution patterns.US: ultrasound.

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We are grateful to CNPq and FAPERGS call 07/2021 process n. 21/2551-0002121-7; call 07/2022 processes n. 23/2551-0000114-4 and 23/2551-0001944-2; call universal/2023 process n. 409009/2023-7 and call 14/2022 process n. 23/2551-0000919-6 for the financial support.

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SEPTEMBER 23-27 2024
19BMOS
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Batch and Continuous Flow Total Synthesis of Cannabidiol

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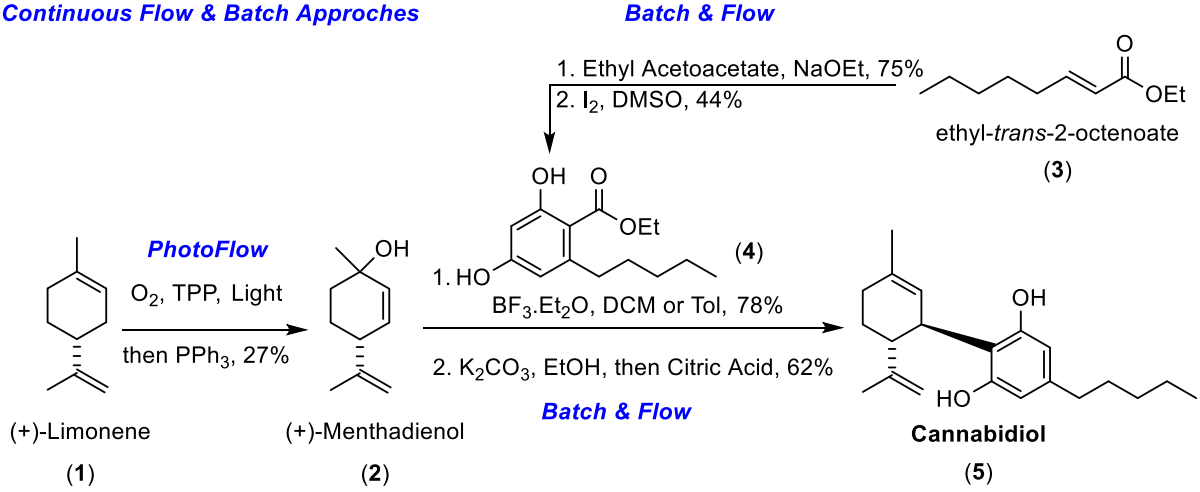
Keywords: *Cannabidiol, Continuous flow, Total Synthesis*

ABSTRACT

We present a comprehensive total synthesis of cannabidiol (**5**)[1,2] that integrates both batch and continuous flow conditions.[3,4] Our approach aims to streamline the synthesis of olivetolic acid derivatives and utilize an enantiomerically pure monoterpene moiety (*p*-mentha-2,8-dien-1-ol (**2**)), obtained from naturally occurring (*R*)-(+)-limonene (**1**) by photocatalysis. Key reactions include the synthesis of olivetolic ester (**4**) from ethyl-*trans*-2-octenoate (**3**) reacting with the enolate of ethyl acetoacetate followed by aromatization, and a Friedel-Crafts alkylation with **2** and decarboxylation. These reactions are successfully adapted to continuous flow, thus resulting in improved yields and selectivities. This study[5] not only offers a scalable and efficient route for cannabidiol synthesis but also contributes to the synthetic approaches to access cannabinoids with potential applications in medicinal and industrial contexts.



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The authors thank the São Paulo Research Foundation FAPESP (grant 2013/07276-1, 2020/06874-6, 2023/04020-8 and F.C.B. fellowship 2021/06110-9), CNPq (K.T.O. research fellowship 303333/2022-7), FUNDECT (grant 204/2022), FAPERJ and CAPES Financial Code 001.

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SEPTEMBER 23-27 2024
19BMOS
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Synthesis of the Pheromone of *Duponchelia fovealis* Zeller, 1847 (Lepidoptera, Crambidae) for Pest Control in Strawberry Crops

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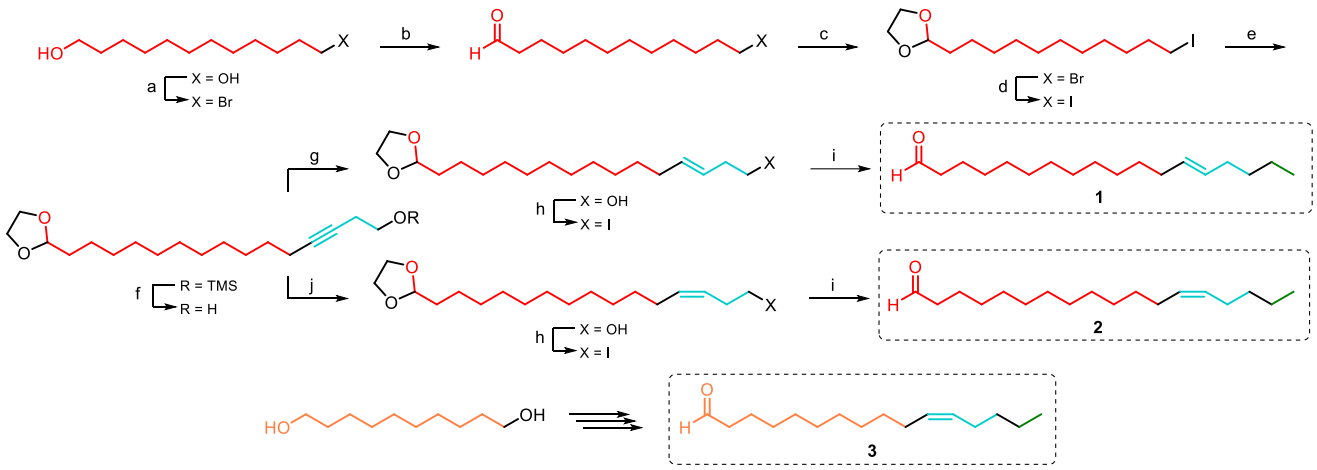
Keywords: *Alkene synthesis, C≡C stereoselective reduction, Pest management, Semiochemicals.*

ABSTRACT

Strawberry (*Fragaria × ananassa*) production has increased in Brazil, but the *Duponchelia fovealis* has been a key pest of the crop, causing losses in yield and even plant death. Mouár et. al. (2018) identified the pheromone used by this pest females as the aldehydes: (*E*)-octadec-13-enal (**1**), (*Z*)-octadec-13-enal (**2**), and (*Z*)-hexadec-11-enal (**3**) in a 10:1:0.1 ratio. In this context, our objective was to synthesize pheromones **1**-**3** for application in pest control. In the synthesis shown below, a substitution reaction with alkynyl anion was a key step leading to a triple bond intermediate. This compound can be stereoselectively reduced to the *E* isomer in the synthesis of compound **1** and to the *Z* isomer for the synthesis of compound **2**. Pheromone component **3** was synthesized in a similar way. The compounds were used in field tests and around thirteen males were collected in traps for 28 days.



Reagents and conditions: (a) HBr, toluene, reflux (*Dean Stark*), 10h; (b) TEMPO, NaOCl, KBr, CH_2Cl_2, buffer pH 8,6, 0 °C, 1 h; (c) Ethylene Glycol, toluene, reflux (*Dean Stark*), 4h; (d) KI, acetone, reflux, 4h; (e) 3-((trimethylsilyl)oxy)prop-1-yn-1-yl lithium, TMEDA, THF, reflux, overnight; (f) TBAF, THF, r.t., 2h; (g) $LiAlH_4$, diglyme, reflux, overnight; (h) I_2, PPh_3, imidazole, CH_2Cl_2, r.t., 4 h; (i) MeOH/H_2O, *p*TSA, r.t., 2h; (j) H_2 (5 psi), Pd/C, quinoline, hexane, 2h.

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SEPTEMBER 23-27 2024
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Exploring the reactivity of glycals in photocatalytic reactions

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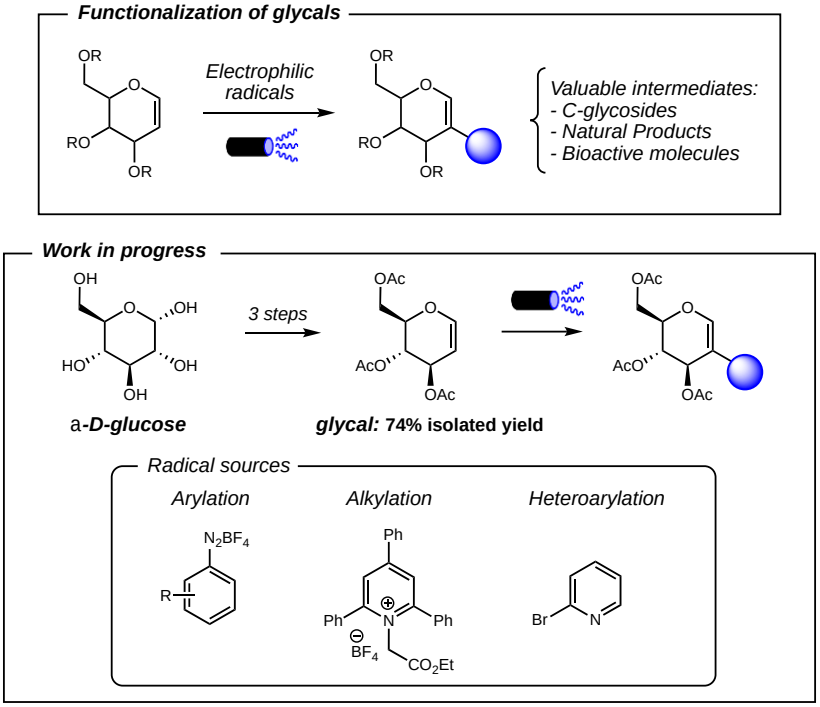
Keywords: *C-glycoside, Glycal, Photocatalysis.*

ABSTRACT

Functionalization of unsaturated monosaccharides is a powerful strategy to synthesize a variety of glycoside derivatives, such as sugar mimics, and enantiomerically pure molecules. In this context, catalytic radical transformations not only offer new avenues for the synthesis of new complex carbohydrates but also overcome the limitations of classical protocols.[1,2] In this study, we are exploring the reactivity of glycals using different photocatalytic approaches for the synthesis of *C*-glycosides.



Scheme 1. Functionalization of glycals via photocatalysis

Our initial efforts focused on synthesizing the protected glycal from D-glucose, achieving a 74% overall yield through a sequence of peracetylation of glucose, bromination, and elimination bromine reactions. We then investigated the C(2)-arylation by reacting the glycal with aryldiazonium salts under blue LED irradiation under different reaction conditions.[3] However, in most cases we observed diazonium salt degradation and partial recovery of the starting material. Since aryl radicals are not highly electrophilic, we decided to explore alternative partners for this reaction, such as Katrisky salt and bromopyridine.[4,5] Further studies aimed at synthesizing alkylated and heteroarylated C-glycosides are currently underway.

ACKNOWLEDGEMENTS

The authors thank CAPES, CNPq and FAPERJ for financial support.

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SEPTEMBER 23-27 2024
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Silver-Catalyzed Intramolecular Cyclization of Guanidine Motifs onto Alkynes

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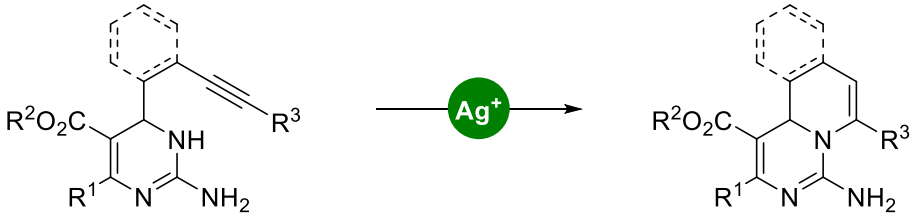
Keywords: *Catalysis, Intramolecular Cyclization, Guanidine Derivatives.*

ABSTRACT

Organic compounds containing guanidine groups in their structures have received significant attention from the scientific community, possibly most likely due to their numerous potential biological applications.[1] In this regard, we became interested in developing an intramolecular cyclization strategy promoted by a metal catalyst aiming at the preparation of polycyclic guanidine derivatives,[2] and a silver salt was found to be a convenient choice as a promoter of this transformation.



Studies involving the scope of this transformation, key aspects of reaction mechanism and potential biological activities of these compounds are being currently investigated.

ACKNOWLEDGEMENTS

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SEPTEMBER 23-27 2024
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Scaling up the Synthesis of *p*-mentha-2,8-dien-1-ol Under Continuous Photoflow Conditions

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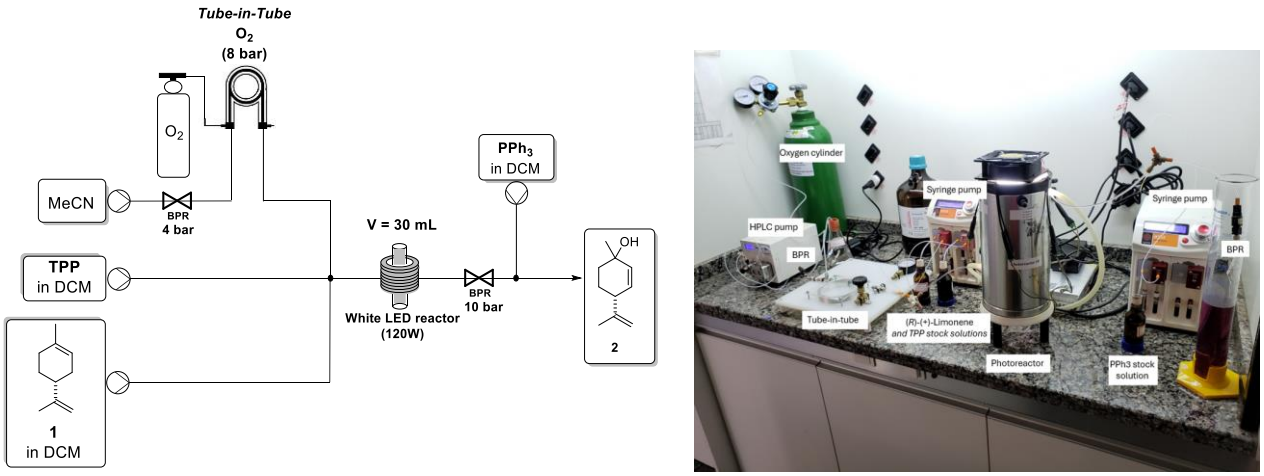
Keywords: *Organic synthesis, continuous flow, photocatalysis*

ABSTRACT

We present the scale-up of the synthesis of *p*-mentha-2,8-dien-1-ol (**2**), a key intermediate for synthesizing cannabidiol and its derivatives.[1,2] Our methodology is based on the continuous flow photooxidation of (*R*)-(+)-limonene (**1**) to their hydroperoxide intermediates, followed by the *in-situ* reduction to the corresponding alcohols (Scheme 1). The setup consists of the saturation of acetonitrile with O_2 *via* a tube-in-tube reactor (8 bar) followed by the encounter of a stream of (*R*)-(+)-limonene (**1**) and another of *meso*-tetraphenylporphyrin in DCM. After mixing, the solution was irradiated by 120 W white LEDs in a 30 mL PFA photoreactor. Upon exiting the photoreactor, the resultant mixture was quenched with a stream of triphenylphosphine. The protocol was optimized to a 6-minute residence time with a maximum productivity of 6.5 g/day. A scale-up experiment was performed, processing 37.5 mmol of (*R*)-(+)-limonene (**1**) over 6 hours, resulting in 1.5 g of product.



Scheme 1: Scale-up protocol for *p*-mentha-2,8-dien-1-ol synthesis under continuous-flow conditions.[3]

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Synthesis of a BODIPY-dihydropyrimidinone derivative

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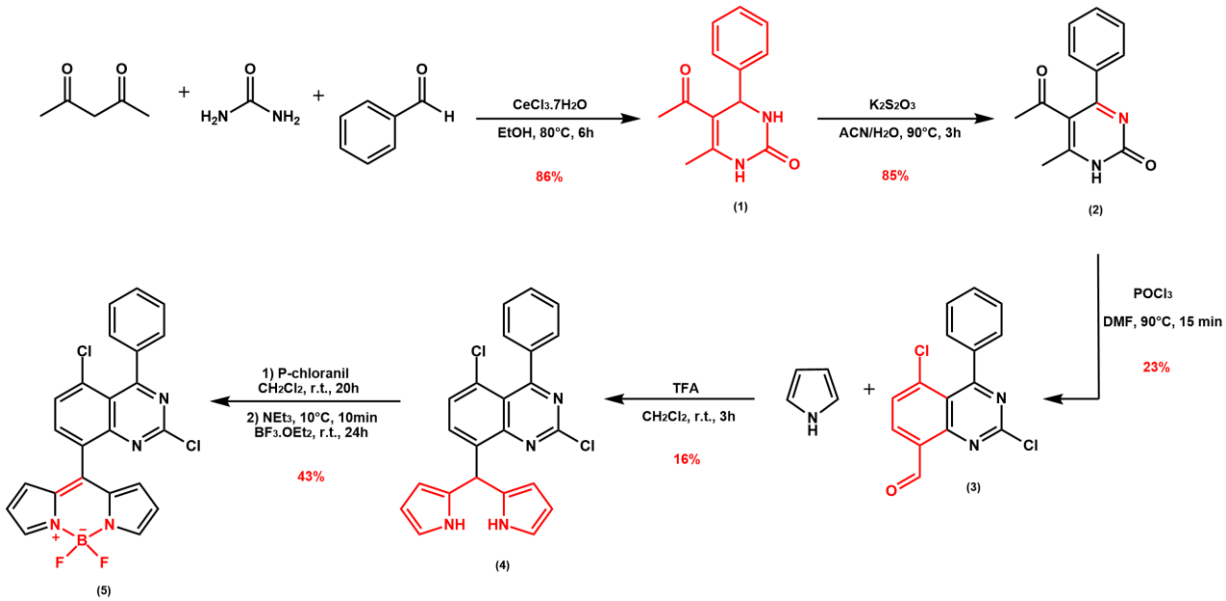
Keywords: *Fluorescence; BODIPY; dihydropyrimidinone.*

ABSTRACT

Fluorescent probes may be used for sensing organic substances or metal ions, emitting fluorescence signals for their detection [1]. Due to their advantages such as high sensitivity, selectivity, fast response time, and minimal invasiveness in biological systems, these probes have been studied for various applications [2]. Parallel to studies on fluorophores, dihydropyrimidinones (DHPM), have been extensively investigated due to their biologically active properties, structural similarity to natural products and nucleic acids, and wide variety of interactions with biomolecules [3]. The main objective of this work is the synthesis of hybrid fluorophores containing the BODIPY core and the DHPM residue for subsequent study of their photophysical properties. DHPM were chosen as the key components to explore their influence on the photophysical properties of the BODIPY core. The scarcity of information in the literature involving fluorescent probes containing these two classes of molecules, as well as their well-known biological properties, motivated the study, development, and synthesis of the new fluorophores. These compounds were synthesized according to sequence presented route and characterized through 1D and 2D NMR spectroscopy. To evaluate the photophysical properties of the compounds, ultraviolet-visible (UV-Vis) and fluorescence spectroscopic methods will be employed.

Figure 1 – General strategy on the synthesis of BODIPY-DHPM derivative



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We thank CAPES, CNPq, and FAPESC for their financial support.

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SEPTEMBER 23-27 2024
19BMOS
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Telescoped Synthesis of *N*-Substituted 8*H*-Indeno[1,2-*d*]thiazol-2-amine Promoted by Tribromoisocyanuric Acid

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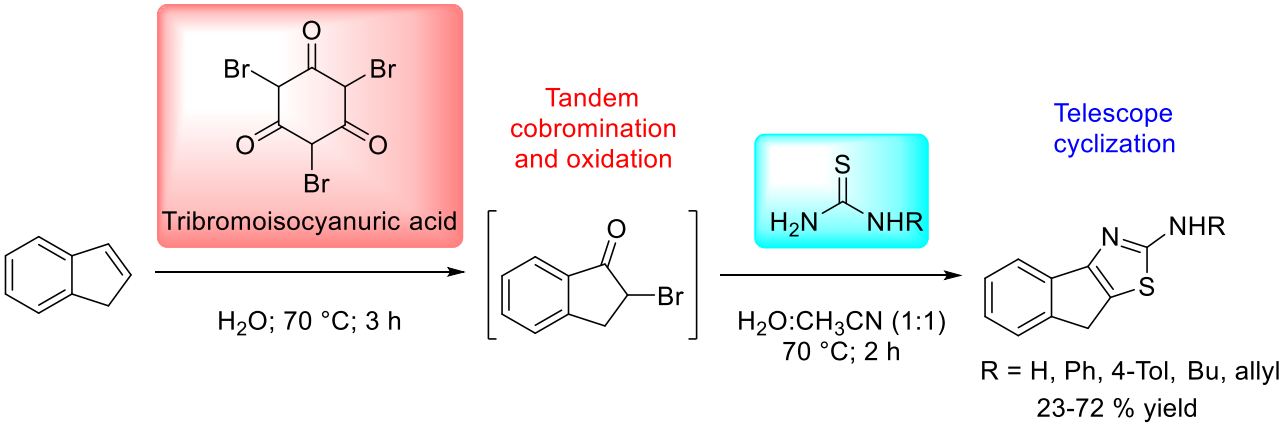
Keywords: *Oxidation, 2-Aminothiazole; Cyclization*

ABSTRACT

2-Aminothiazole compounds are notoriously important due to its applications in medicinal chemistry and photochemistry. Among the framework diversification employed, ring fused thiazoles, particularly indeno fused, demonstrated beneficial gain on biological properties such as tumor growth inhibition[1] and as adenosine receptor ligand.[2]

8*H*-Indeno[1,2-*d*]thiazol-2-amine derivatives are usually synthesized *via* Hantzch reaction of *α*-haloindanone with mono-substituted thioureas. To avoid manipulation of the hazardous *α*-haloketone, commonly it is generated *in situ* by reacting indene or 1-indanone with *N*-haloimides.[3,4] Among the *N*-haloimides, trihaloisocyanuric acids present higher atom economy and are comparatively an ease of access reagent.

In this work we explore tribromoisocyanuric acid for the tandem halogenation/oxidation reaction with indene thus forming 2-bromoindanone which enabled us to telescope synthesize 2-aminothiazoles directly by the addition of the selected thioureas.



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SEPTEMBER 23-27 2024
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Linear Free Energy Relationships of Organocatalyzed Asymmetric Michael Additions

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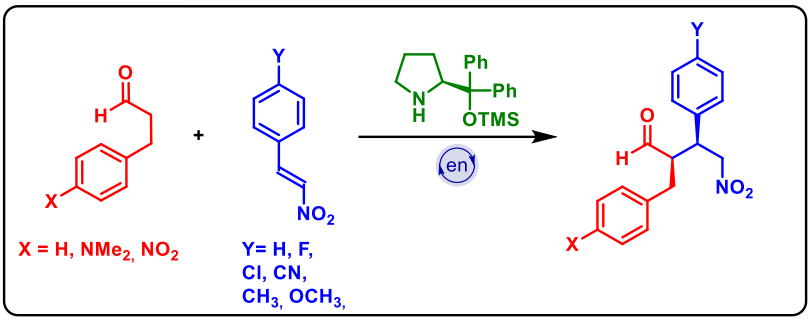
Keywords: Michael addition, Nitroolefins, LFER..

ABSTRACT

The enantioselective Michael addition between aldehydes and nitroolefins mediated by *in situ* generated enamines was the first asymmetric C–C bond formation using diarylprolinil silyl ether catalysts. Originally described by Hayashi and co-workers in 2005,[1] studies of the mechanism of this reaction were performed by several groups[2-6]

This transformation was shown to be a multistep process that involves intermediates such as aminocyclobutanes[2] and dihydrooxazine *N*-oxides.[3] These could either be productive reactive intermediates (on-cycle species) that lead to the observed product or resting states (off-cycle species).[7]

For this reaction, the rate determining step and the stereodetermining step seem to not coincide.[2] This leaves an open question about the influence of Linear Free Energy Relationships (LFER)[8] on the selectivity and the reactivity of the system. In order to answer this fundamental question, we undertook kinetic experiments to obtain the appropriate Hammett plots for *para*-substituted nitrostyrenes and hydrocinnamaldehydes.



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SEPTEMBER 23-27 2024
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An Expedient Synthesis of tetra-*ortho*-fluoro-azobenzenes *via* Nucleophilic Aromatic Substitutions (S_NAr)

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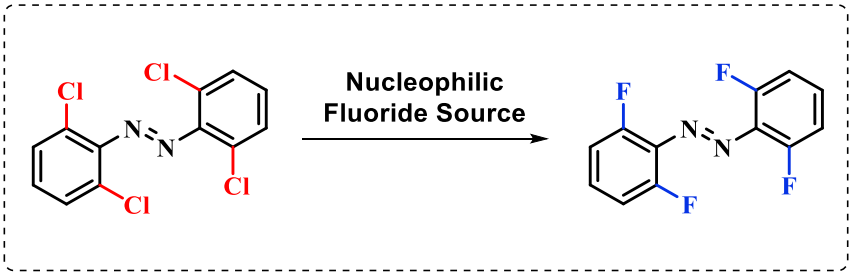
Keywords: *Photoswitch, Fluoride alcohol adducts, S_NAr.*

ABSTRACT

The *E* to *Z* photoisomerization of azobenzenes have shown great applicability for the generation of photoswitches, which can be used to prepare chemical probes controlled by light used to study a plethora of biological systems[1].The introduction of four halogens in the positions *ortho* to the azo group allows for the both a red-shift of the $\lambda_{E\rightarrow Z}$ as well as a longer half-life for the Z isomer [2]. In 2016, Trauner and coworkers[3] perfomed the synthesis of tetra-*ortho*-chlorinated azobenzenes using directed C-H activation *via* palladium catalysis. In 2021, Sanford and coworkers[4] used hydrophobic alcohol adducts of fluorides as a source of fluoride anion for S_NAr reactions, allowing for mild reaction conditions that do not require the use anhydrous solvents and reagents. This work uses fluoride-hydrophobic alcohol adducts in S_NAr reactions for the interconversion of tetra-*ortho*-chloro-azobenzenes into their tetra-fluoro counterparts. This methodology allows for a straightforward synthesis of tetra-*ortho*-fluoro-azobenzenes.



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SEPTEMBER 23-27 2024
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Visible Light-Mediated Diastereoselective Synthesis of Novel *C*-Glycopeptides

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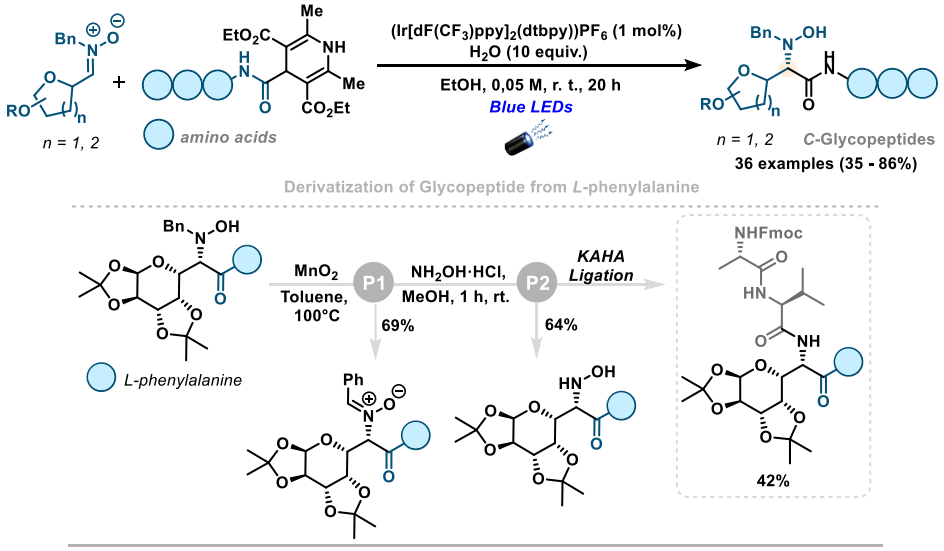
Keywords: *C-Glycopeptides, photocatalysis, diastereoselective synthesis, glycosyl nitrones.*

ABSTRACT

The incorporation of carbohydrates into peptides can significantly enhance their pharmacological properties, including metabolic stability, target selectivity, and membrane permeability.[1] Despite some advances, synthetic methods for *C*-glycosylation of peptides and amino acids continue to present a significant challenge, with most methods relying on multistep preparations, harsh conditions, and a lack of stereocontrol.[2] To tackle this challenge, we decided to investigate the synergy between a range of glycosyl nitrones and the 4-amido 1,4-dihydropyridine (1,4-DHPs) derived from amino acids and peptides – two highly versatile synthons – employing a photocatalytic radical addition approach. Therefore, we have developed a mild and operationally simple photocatalytic protocol for synthesizing novel glycopeptides. This protocol demonstrates good stereoselectivity and performs well across a wide variety of substrates, including modified glycosides and peptides. Additionally, the resulting products possess a versatile hydroxylamine group that can be further modified, serving as a bioconjugation handle for additional applications.



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SEPTEMBER 23-27 2024
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Novel D-π-A Iminocoumarin-Based Molecules: Synthesis, Photophysical Properties, and Preliminary Evaluation as Photosensitizers for DSSCs

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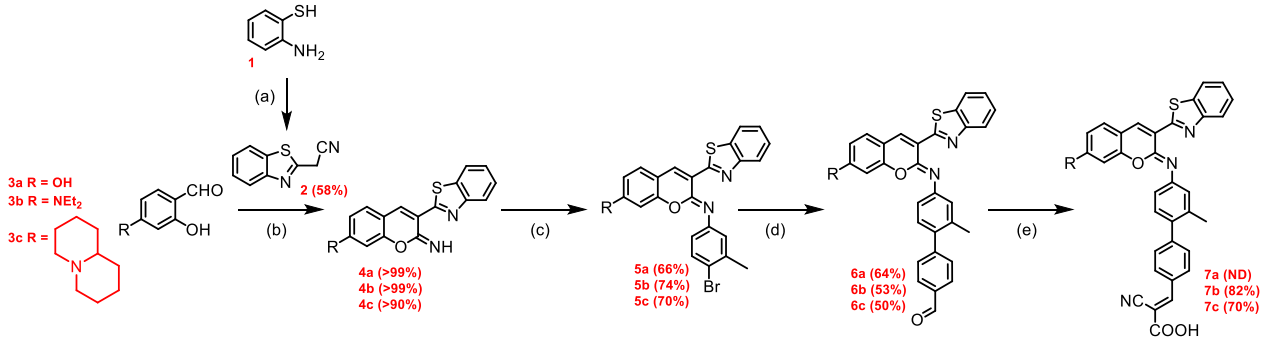
Keywords: *Coumarins, Dye-Sensitized Solar Cells, benzothiazoles.*

ABSTRACT

In recent years, coumarin derivatives have generated significant interest in their applications in dye-sensitized solar cells (DSSCs) due to the ease of modifying their photophysical properties by introducing substituents/groups. Thus, the present work reports the synthesis of iminocoumarin benzothiazole hybrids to investigate their potential applications as sensitizers in DSSCs (Scheme 1). Initially, 2-aminothiophenol (**1**) underwent a cyclization reaction with malonitrile in ethanol and acetic acid, yielding benzothiazole **2**. Subsequently, **2** underwent a Knoevenagel condensation reaction with hydroxybenzaldehyde (**3**) in the presence of piperidine and ethanol, resulting in iminocoumarins **4**. The reaction of **4** with 4-bromo-3-methylaniline produced the desired intermediates, 2-phenyliminocoumarins **5**. These intermediates underwent a Suzuki coupling reaction with 4-formylphenylboronic acid to form **6**. Finally, the condensation reaction between **6** and cyanoacetic acid, led to photosensitizers **7** in good yields (70-82%). The structures of the synthesized target compounds were characterized by FTIR, ^{1}H-NMR, HRMS, and UV-Vis spectra. Therefore, preliminary results show that the target compounds can be considered precursors for the design of coumarin-based D-π-A molecules and can be used in further studies.



Scheme 1. Synthesis of iminocoumarin-benzothiazole hybrids. Reagents and solvents: a) malonitrile, EtOH, AcOH; b) EtOH, piperidine; c) 4-bromo-3-methylaniline, AcOH; d) 4-formylphenylboronic acid, K_2CO_3(aq), THF, $Pd(PPh_3)_4$; e) $NCCH_2COOH$, piperidine, ACN.

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Asymmetric Synthesis of 1,4-Oxachalcogenanes and 1,4-Azochalcogenanes

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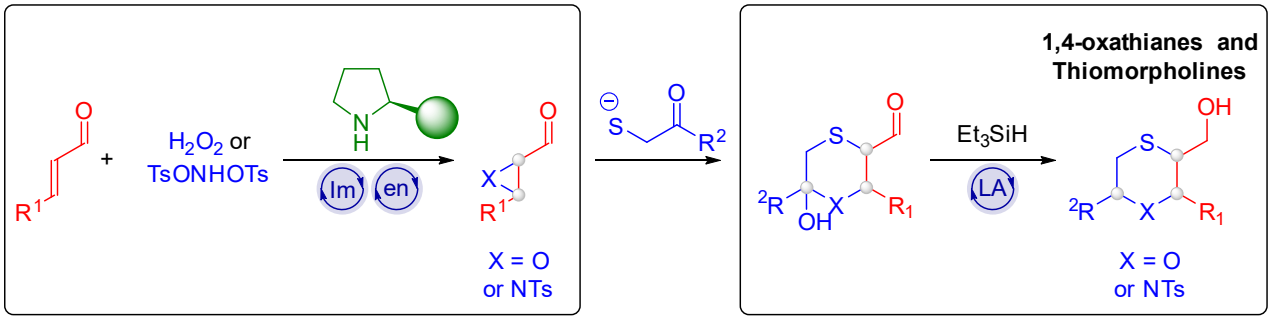
Keywords: *Catalysis, stereoselective synthesis, 1,4-oxachalcogenane*

ABSTRACT

Morpholine is a heterocyclic compound present in a wide range of commercial drugs as well as drug candidates. Its prominent in medicinal chemistry due to it's great pharmacological potential, as well synthetic feasibility.[1] 1,4-Oxathianes and thiomorpholines have the potential to serve as bioisosteres for 1,4-dioxanes and morpholines,[2] allowing them to imitate their pharmacological effects while potentially presenting improved or altered biological activity. This attribute renders them advantageous in drug discovery programs, facilitating the generation of analogs of current medications with potential enhancements of effectiveness and bioavailability. We were able to synthetize 1,4-oxathianes and thiomorpholines enantioselectively via organocatalysis. By reacting chiral *α*,*β*-epoxy **1**[3] or *α*,*β*-*N*-Tosyl-aziridine aldehydes **2**[4] with *in situ* generated *α*-keto thiolates **3**,[5] a ring opening driven by ring-strain followed by a hemiacetalization/hemiamination afforded the key heterocyclic aldehyde **4**. Reduction with a mild reducing agent in the presence of Lewis acids afforded de desired 1,4-Oxathianes and thiomorpholines.



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Synthesis of 9,10-bis(organochalcogenyl)phenanthrenes by cyclization of (biphenyl-2-alkyne)chalcogenides

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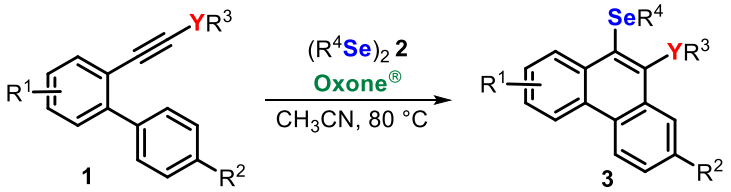
Keywords: *Chalcogenphenanthrenes, Green chemistry, Oxone, Selenium*

ABSTRACT

A fairly large number of phenanthrenes are found in nature and most of them have important applications in medicinal chemistry.[1] In the other hand, studies on the synthesis of organochalcogen compounds, especially those with at least one sulfur, selenium or tellurium atom in their structure, have been intensively explored in organic chemistry.[2] This fact occurs due to the promising properties that these molecules present, such as intermediates in organic synthesis, catalysts and, mainly, due to their pharmacological activities.[3]

In this way, a protocol was developed for the synthesis of 9,10-bis(organochalcogenyl)phenanthrenes through a radical cyclization of (biphenyl-2-alkyne)chalcogenides in the presence of diorganyl diselenides, Oxone® as a green oxidizing agent, and acetonitrile at 80 °C. This study exhibits high regioselectivity, is operationally simple and scalable, allowing the synthesis of 16 compounds in yields of up to 97% and in short reaction times (1-4 h).[4]



R^1 = H, 4,5-$(CH_3O)_2$, 5-F; R^2 = H, CH_3, Cl, F

R^3 = alkyl, aryl; R^4 = alkyl, aryl, heteroaryl; Y = Se, S

- regioselective
- green oxidizing agent
- metal-free
- short reaction times: 1-4 h

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SEPTEMBER 23-27 2024
19BMOS
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Photocatalysis as a tool for the development of certified reference materials: a case study in university technology transfer

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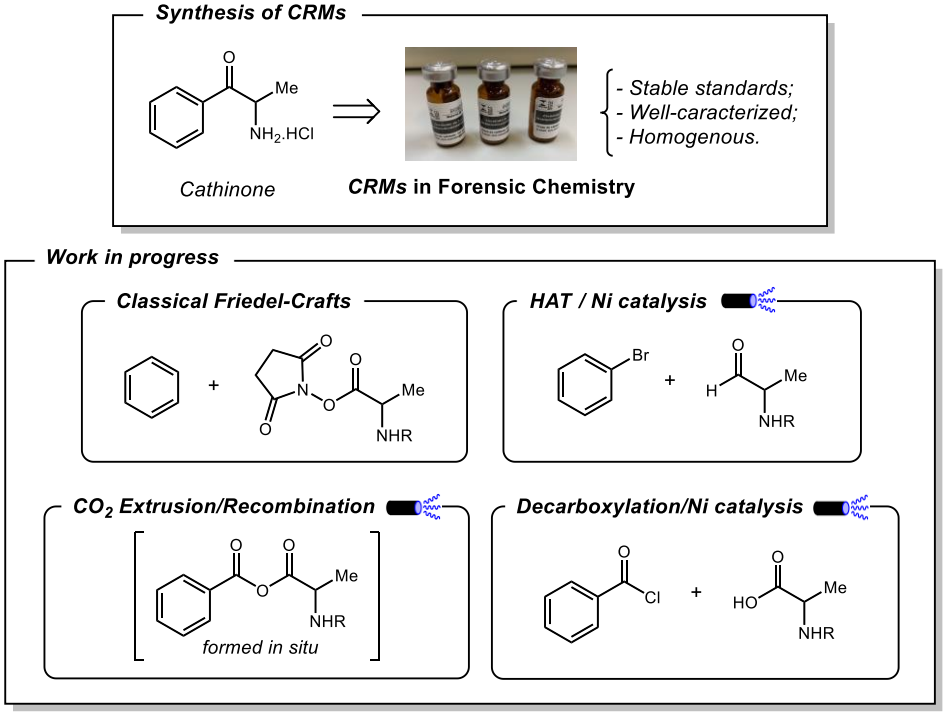
Keywords: *Photocatalysis, Certified Reference Materials, Amphetamines*

ABSTRACT

Certified Reference Materials (CRMs) are well-characterized, stable and homogeneous standards used in forensic analyses to ensure accuracy, traceability and consistency in measurements and identifications.[1] The national production of CRMs is crucial for reducing import costs, ensuring availability and adapting materials to local needs. In this study, we are investigating photocatalytic strategies for the synthesis of cathinones, amphetamine derivatives which are currently not produced in Brazil, aiming to establish a straightforward method for their production and certification for forensic chemistry applications.



Scheme 1. Photocatalytic strategies for synthesis of cathinone CRM

Our initial efforts to obtain these derivatives involved a Friedel-Crafts reaction as a key step, using toxic benzene, which furnished the product with low yield. In contrast, the photocatalytic coupling of readily available and inexpensive protected alanine or its aldehyde offers a more straightforward approach. Preliminary results using metallaphotoredox catalysis have been promising. Further studies to explore CO_2 extrusion and coupling via nickel-photoredox catalysis with acyl chlorides are under investigation.[2-6]

ACKNOWLEDGEMENTS

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High-throughput screening of new Iron catalysts for Enantioselective Reductions by Online ESI-MS

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Keywords: High-throughput screening, *Iron-catalyst, Mass Spectrometry, Imine reduction.*

ABSTRACT

Assisted by high-throughput Electrospray Ionization Mass Spectrometry (ESI-MS/MS) screening, we developed chiral Fe-thiosquaramide catalysts (Fe-TSQ) **4** for the enantioselective imine reduction of dihydro-β-carboline (DHBC) to chiral tetrahydro-β-carbolines (**2**-THBCs). Chiral aryl and alkyl **2** were isolated in excellent yields and enantioselectivities up to 98 and ee 99%, respectively, employing 5-15 mol% of Fe-TSQ as catalyst.[1-2] ESI-MS is an important technique for mechanistic studies of chemical reactions in solution covering homogeneously catalyzed reactions.[3] Online high-throughput screening by ESI-MS gave a very clean spectrum displaying two Fe-containing cationic species, which spread the development of catalysts **4** (Figure 1A). When $NaCNBH_3$ was employed as source of hydride, species **6** was observed that explained why imines **1** were not concomitantly reduced by free borohydride in a non Fe-catalytic manner, which would afford (+/-)-**2** and decreasing %ee, but in fact **6** might be acting as a hydride source for formation of active Fe-complex intermediate **5**.[4]

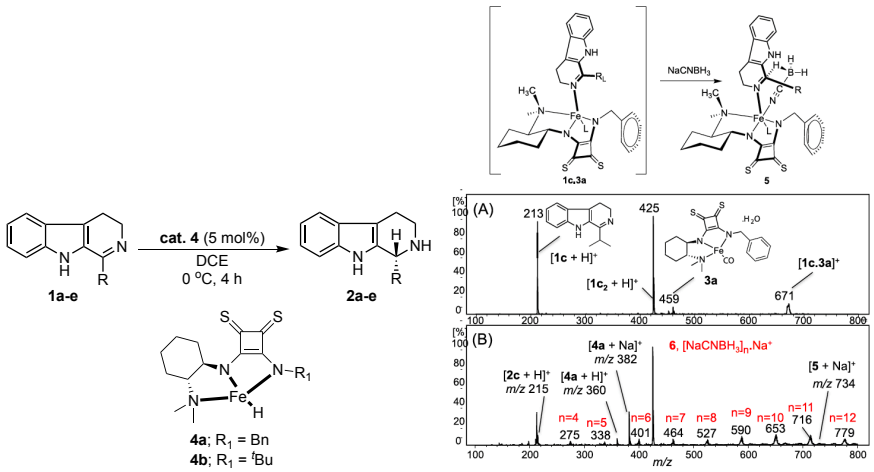

Figure 1. Proposed mechanism based on high-throughput ESI-MS monitoring of the reaction of **1c** and **3a** with $NaCNBH_3$ in DCE. (A) First, a complex between **3a** and **1c** was observed. (B) By adding $NaCNBH_3$, **5** was intercepted and **1c** reduced to **2c** after 3−30 min.

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SEPTEMBER 23-27 2024
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Electrosynthesis of Benzothiazole Derivatives Using Sacrificial Electrodes

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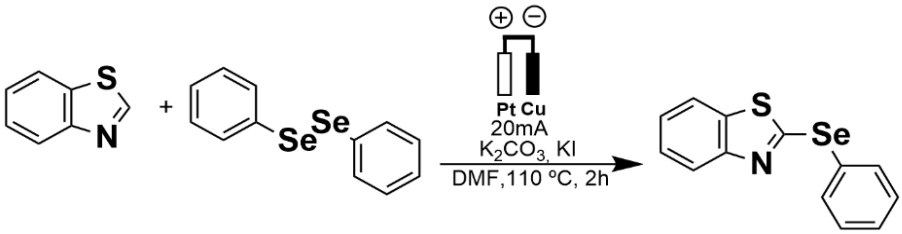
Keywords: *Benzothiazole, Electrosynthesis, Sacrificial Electrodes.*

ABSTRACT

Benzothiazole derivatives have demonstrated remarkable biological activities, including anticancer, antimicrobial, and neuroprotective properties[1]. Electrosynthesis has proven to be an environmentally friendly and efficient approach for the chalcogenation of organic molecules[2].This project aims to develop an electrochemical methodology for the synthesis of benzothiazole derivatives (Scheme 1).

Scheme 1. Synthesis of Benzothiazole Derivatives using sacrificial electrodes.



Previous results indicated conversion yields ranging from 3% to 81%, as determined by NMR analysis. Reaction conditions were optimized (Table 1).

Table 1. Optimization of Reaction Conditions.

Entry	Solvent	Base (mmol)	Catalyst	Electrode	T (ºC)	t (h)	Yield (%)[a]
1	ACN	-	-	Pt:Pt	r.t	12	-
2	DMF	-	-	Pt:Pt	120	2	-
3	DMF	K_2CO_3 (0.75)	-	Pt:Cu	60	2	3%
4	DMF	K_2CO_3 (0.75)	-	Pt:Cu	120	2	41%
5	DMF	K_2CO_3 (0.75)	-	Pt:Cu	110	2	81%[b]

[a]Conversion by H NMR. [b]Reaction conditions: The base was added on the reaction when the temperature system was around 65ºC.

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Chiral Monothiosquaramides as Efficient Catalysts for the Enantioselective Imine Reduction of Dihydro-β-carbolines

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Keywords: *Monothiosquaramides, Tetrahydro-β-carbolines, Stereoselectivity, Imine reduction.*

ABSTRACT

The search for new sustainable chiral organometallic complexes by substituting expensive and toxic metals with non-toxic and cost-effective metals with higher catalytic efficiency is a good concept from both environmental and commercial. Thus, we developed various chiral monothiosquaramide[1] catalysts **4-6** (Pd- or Fe-MTSQs) for the enantioselective reduction of dihydro-β-carboline imines (DHBCs), as shown in Figure 1.[2-4] Optimized reaction conditions revealed selectivities ranging from 90%-98% ee, and good yields. The substituents at the 1-position of THBC played a critical role in obtaining stereoselectivities and their configurations (*R* or *S*, Figure 1) when Pd-MTSQs were employed. Alkyl groups at the 1-position of chiral **2a-c** were isolated with excellent enantioselectivities (90%-98% ee), and it was confirmed that their major isomer had a *R* configuration, using 5 mol% of catalysts. Surprisingly, *S* configuration was observed in the case of aryl groups at the 1-position of **1d,e**, yielding (*S*)-aryl-**2d,e** with 95%-96% ee.[5]

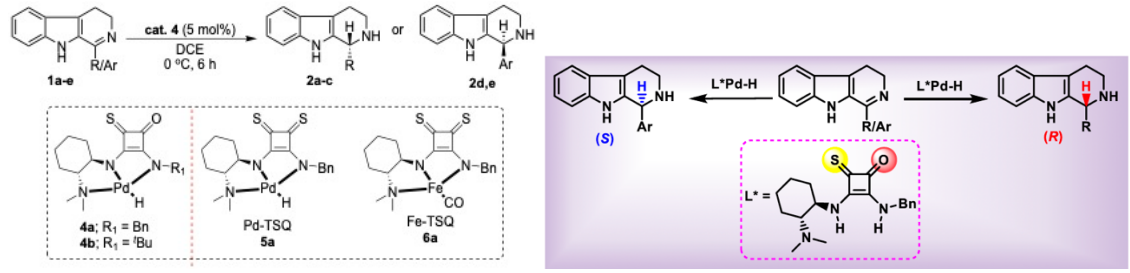

Figure 1: Pd- and Fe-monothiosquaramides catalyzed enantioselective imine reduction of imines.

ACKNOWLEDGEMENTS

L.S.S. and F.M.N. are grateful to FONDECYT-ANID Projects #1220618 and #1210576, respectively. F.A.A.R. is thankful for an ANID doctoral grant (#21221447).

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ANO-catalyzed multicomponent synthesis of 3-alkyl-*N*-substituted pyrroles

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Keywords: *Multicomponent reaction, Paal-Knorr synthesis, Ammonium niobium oxalate*

ABSTRACT

The use of green chemistry principles is a powerful tool on the development of more sustainable protocols in organic synthesis along with making chemical processes cleaner. Whitin this context, multicomponent reactions (MCR) and the use of environmentally friendly catalysts stands out. MCR involves procedures in which three or more reactants are added to a single flask and react with each other to form a single product. MCRs are attractive from an environmental point of view, as they especially cover principles #2 and #8 of green chemistry, atom economy and reduction in the formation of derivatives.[1] Furthermore, ammonium niobium oxalate (ANO) is a stable, cheap, easy-to-handle and highly versatile catalyst to promote organic transformations,[2] even more if it can act in a heterogeneous way, being recovered and reused. Therefore, the union of MCR with ANO catalysis proved to be efficient to synthesize 3-alkyl-*N*-substituted pyrroles through an eco-friendly methodology, with excellent performance.

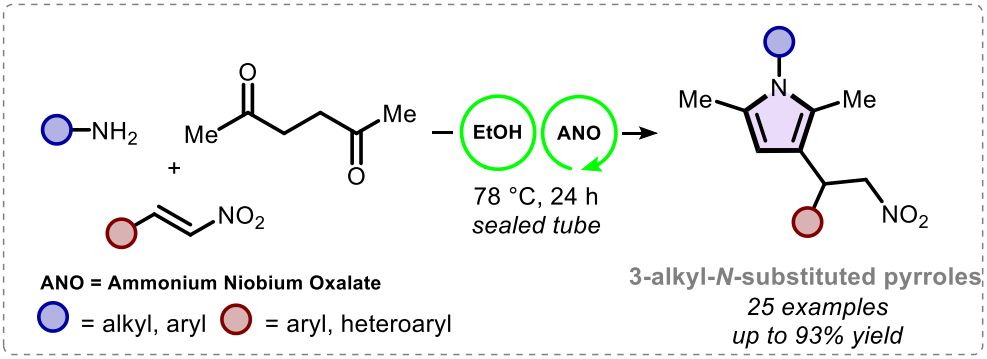

Figure 1. ANO-catalyzed multicomponent synthesis of 3-alkyl-*N*-substituted pyrroles.

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We thank for the financial support and scholarships from the Brazilian agencies CNPq, FAPERGS, CAPES and FINEP.

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Reductive Amination Reactions under Electrosynthesis Conditions

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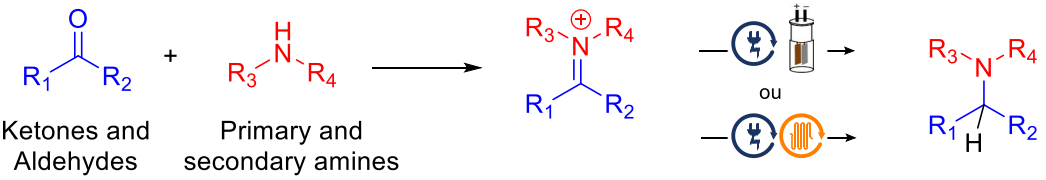
Keywords: *Reductive Amination, Electrosynthesis, APIs.*

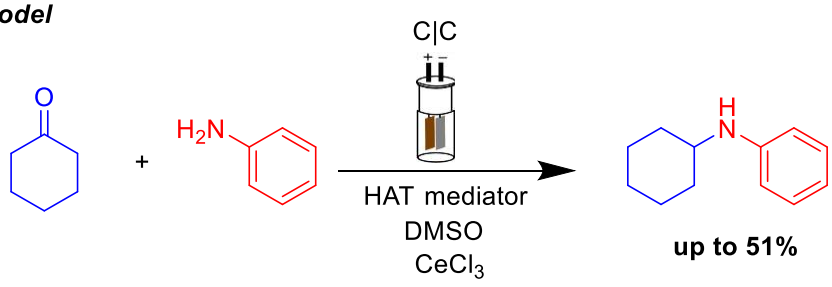
ABSTRACT

We present the investigation of the reductive amination of aldehydes and ketones with primary and secondary amines, focusing on the *in-situ* generation of the iminium ion (or imine) and its electrochemical reduction. Given the limited precedents for this reaction under electrochemical conditions with respect to conditions,[1] our methodology involves the screening of various electrodes, including graphite carbon, glassy carbon, magnesium, platinum, and copper. Additionally, we aim to determine the optimal solvents, electrolytes, and concentration conditions to enhance efficiencies in batch cells, which will later be applied to continuous flow electrochemical reactors. By optimizing these parameters, we seek to develop a robust and efficient protocol for reductive aminations under electrochemical conditions, and then transposing this methodology for valuable API synthesis.[2] So far, we have investigated the reaction between cyclohexanone and aniline, thus achieving the corresponding secondary amine in up to 51% yield.

Methodology



Reaction Model



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Visible Light and Triselenium Dicyanide (TSD): New Horizons in the Selenocyanation of Enamino Compounds

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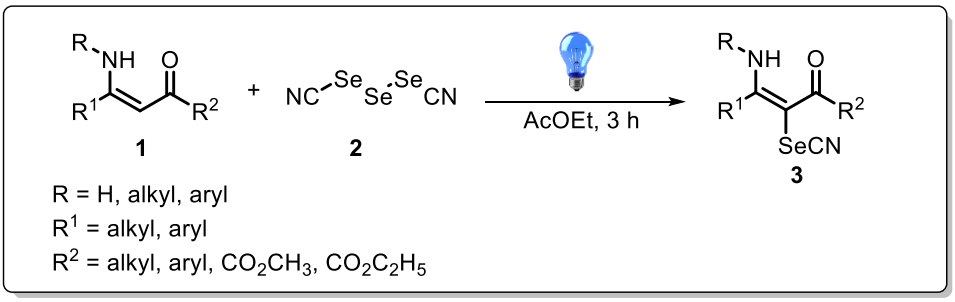
Keywords: *visible light, organochalcogen, selenocyanate*

ABSTRACT

Enaminones or enamino esters, containing an amino group linked by a carbon-carbon double bond to a carbonyl or ester, are valuable synthons due to their amphiphilic nature.[1] Visible light photocatalysis has revolutionized synthetic transformations by offering environmentally friendly and manageable processes that align with green chemistry principles. This technique facilitates the chemical transformation of enaminones, enabling efficient production of organic compounds and the construction of Se-based structures. The chemistry of organoselenium compounds has advanced significantly, particularly due to their notable biological activities. Organoselenium derivatives, especially selenocyanate compounds, are key intermediates in organic synthesis due to selenium's unique reactivity. Potassium selenocyanate (KSeCN) is commonly used but presents operational challenges due to its sensitivity to humidity and tendency to decompose. Alternatively, triselenium dicyanide (TSD) serves as an electrophilic and radical selenocyanate source, providing smoother access than KSeCN and facilitating the conversion of intermediates into selenium-containing systems via C≡N bond. From a pharmaceutical standpoint, enamino selenocyanate compounds hold promise as bioactive compounds through molecular hybridization, though they remain largely unexplored. The advancements in visible light photocatalysis and organoselenium chemistry pave the way for innovative and sustainable approaches in organic synthesis.[2] In this way, we developed a novel method for the synthesis of enamino compounds containing a selenocyanates moiety by reacting triselenium dicyanide (TSD) and enaminone/enaminoesters under blue light irradiation. The reactions are triggered by the formation of Se-centered radical species, followed by the addition enamino π-bond.



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Visible light-promoted synthesis of 3-selanylthiochromenones

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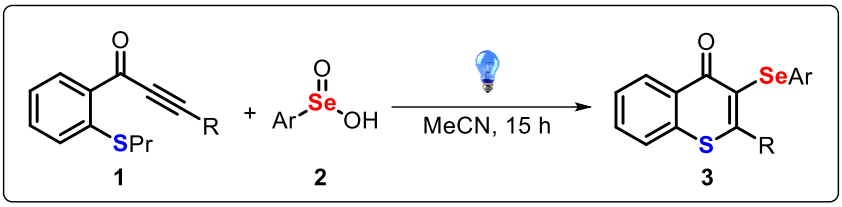
Keywords: *visible light, organochalcogen, EDA-complex.*

ABSTRACT

Principle #6 of Green Chemistry underscores the necessity of energy-efficient designs in chemical processes to reduce economic and environmental impacts. To achieve this, the chemical industry must explore alternative, efficient energy sources and develop synthetic procedures operable at room temperature and pressure.[1] Technologies like electromagnetic irradiation (microwave, UV, visible light), sonochemistry, and mechanochemistry have been crucial over the past decades, facilitating valuable chemical transformations. Visible light photocatalysis has seen a significant surge since the early 21st century. Advances in this area have sparked interest in transformations through direct excitation of substrate-derived species or transition metal complexes by visible light, without photosensitizers, greatly impacting organic synthesis by providing innovative solutions and new reactivity forms.[2]

Thiochromenones, important in natural products, drug candidates, and biologically active molecules, belong to the flavones family and feature a benzo-fused thiopyranone core.[3] Meanwhile, the critical roles of selenoenzymes like glutathione peroxidase (GPx) and thioredoxin reductase (TrxR) in protecting against reactive oxygen species (ROS) have spurred interest in organoselenium compounds. This interest has led to the discovery of selenium-containing and selenium-functionalized heterocycles with potent activity against various pathologies, making them promising candidates for new bioactive compounds. Among organoselenium reagents, benzeneseleninic acid (BSA) derivatives stand out due to their stability, lack of odor, and ease of handling, offering a sophisticated alternative for producing Se(II)-containing products from Se(IV)-based electrophilic species.[4]

A visible light-mediated protocol was developed for the construction of 3-selanyllthiochromenones by a radical annulation of ortho-thioaryl ynones. The reaction is triggered by a sulfur-centered radical, which is formed through the light excitation of an intramolecular electron donor-acceptor complex (EDA-complex). The reactions were conducted under open-air conditions, not requiring metal catalysts, oxidant species, or heating, making this a mild and environmentally friendly approach to access valuable compounds.



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This study was financed in part by the Coordenacão de Aperfeiçoamento de Pessoal de Nível Superior – Brasil (CAPES), CNPq, FAPEGS, and FINEP are acknowledged for financial support.

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A French Connection in Organic Synthesis

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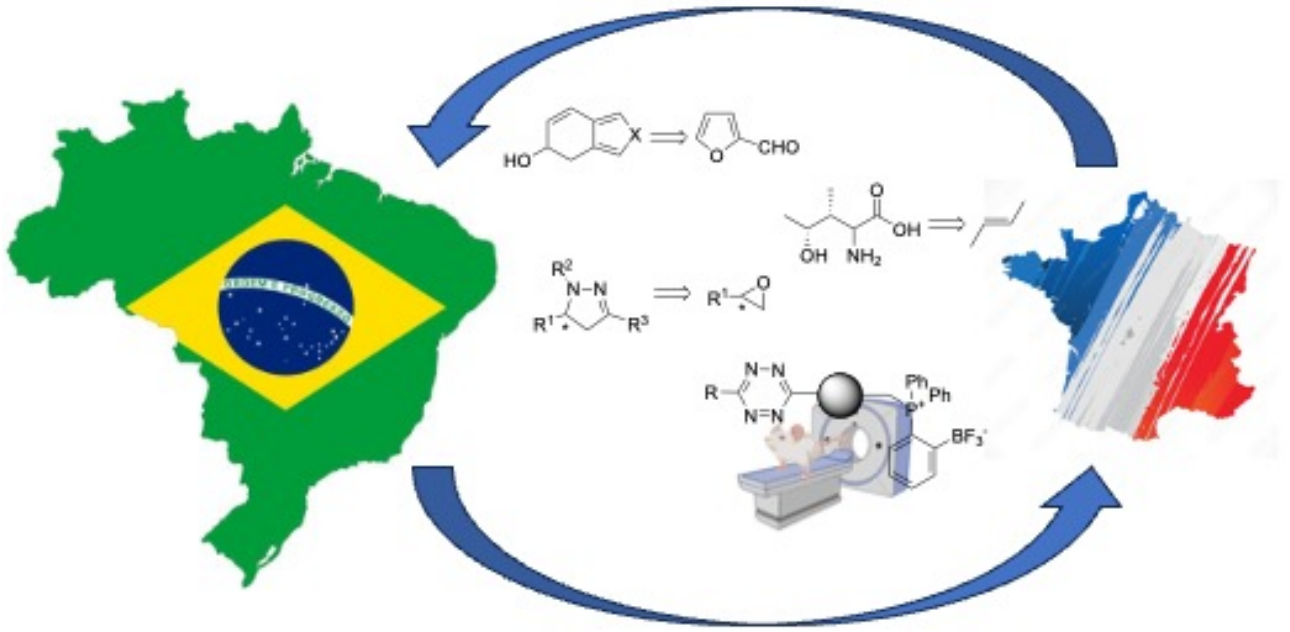
Keywords: *Organic Synthesis, stereoselective synthesis, Medicinal Chemistry.*

ABSTRACT

For years now, we have promoted research exchanges to promote bilateral training and enhanced research experience in the field of organic synthesis with perspectives on biological and health related applications.
Through this presentation we will highlight various research projects that have been conducted by young Brazilian researchers in our group. This includes heterocycles rearrangements, asymmetric synthesis of biologically relevant compounds, as well as on going green approaches to polyfunctional starting materials and development of molecular tools for in vivo imaging by Positron Emission Tomography.
We will also illustrate the potential for further developments at binational levels.



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SEPTEMBER 23-27 2024
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BENTO GONÇALVES, RS - BRAZIL

Synthesis and biological prospecting of 4-quinolone-3-acylhydrazone derivatives as potential anti-HIV-1 candidates

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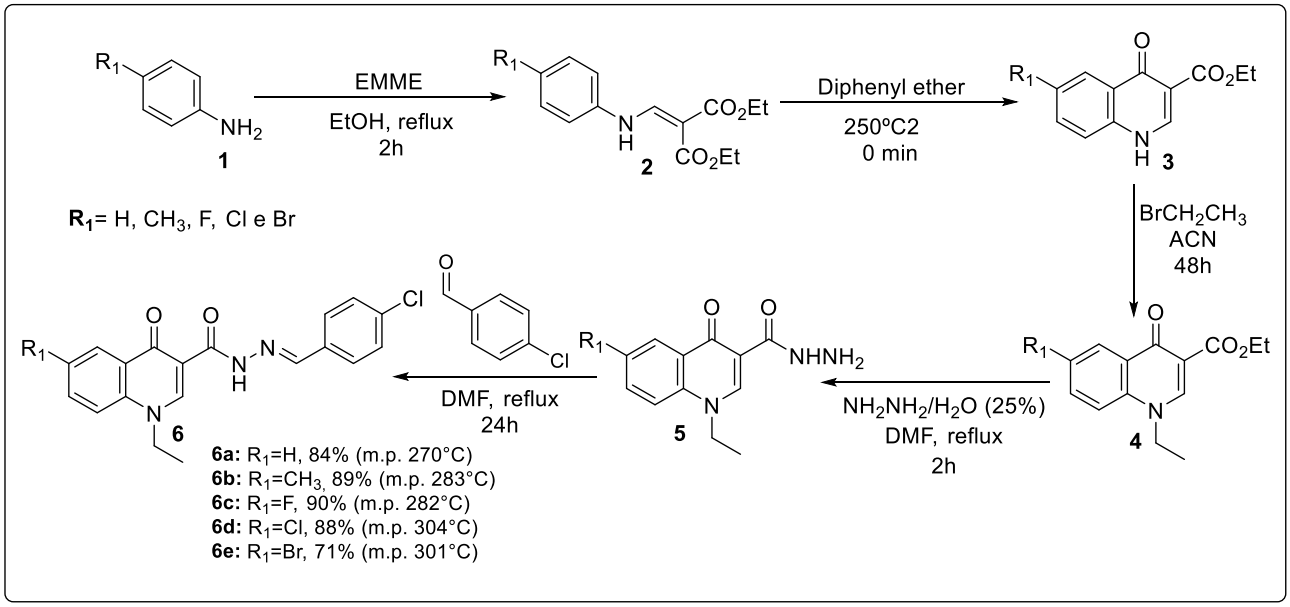
Keywords*: 4-quinolone; acylhydrazone; HIV-1; Antiviral*.

ABSTRACT

The development of resistance to Human Immunodeficiency Virus (HIV) reverse transcriptase inhibitors necessitates ongoing research and innovation in antiretroviral therapy.[1,2] Many substances containing the 4-quinolone nucleus have clinical applications as antibacterials, as well as other so-called non-classical activities, such as antiviral properties, with Elvitegravir being an example.[3] In this study, derivatives 4-quinolone-3-acylhydrazones were synthesized and are being evaluated against HIV-1 virus. Initially, substituted anilines (**1a-e**) were subjected to a condensation reaction with diethyl ethoxymethylenemalonate (EMME), followed by thermal cyclization yielding 4-quinolones (**3a-e**). These compounds were then alkylated with bromoethane leading to compounds **4a-e**. Subsequently, these substances were reacted with hydrazine monohydrate to obtain hydrazides **5a-e**. These derivatives, in turn, were reacted with p-chlorobenzaldehyde under acid catalysis, producing **6a-e** (Scheme 1), with yields ranging from 18% to 44%. The structures of these substances were confirmed by spectroscopic data and are currently undergoing biological evaluation.



Scheme 1: Synthetic route for obtaining compounds **6a-e**.

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CNPq, PPGQ-UFF, PROAP-UFF, CAPES, FAPERJ

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Photochemically-promoted C-H insertions of N-heterocycles with aryldiazoacetates

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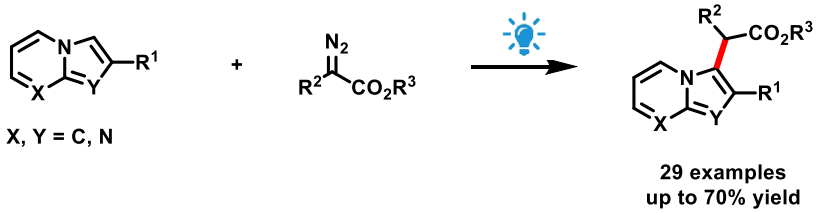
Keywords: *Diazo compounds, Blue Light, C-H insertions.*

ABSTRACT

Electro-rich nitrogen-containing heterocycles play a crucial role in organic and biological chemistry due to their presence in various natural products and synthetically useful building blocks.[1]
In this context, we developed a functionalization strategy for the formal C-H insertion of such heterocycles into aryldiazoacetates via a visible light-mediated process, which involves the generation of free carbenes as key reactive intermediates.[2,3]



In this work, 29 examples were prepared in synthetically useful yields (up to 70%), thus illustrating this new reactivity found for a number of electron-rich *aza*-heterocycles.

ACKNOWLEDGMENTS

We are grateful to Fapesp for a PhD fellowship to RMSS (22/12360-0) and a Research Grant to IDJ (22/01104-3).

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[3] For a selection of recent reviews, see: a) Zhang, Z.; Gevorgyan, V.; *Chem. Rev.*, **2024**, *124*, 7214. b) Gallo, R. D. C.; Cariello, G.; Goulart, T. A. C.; Jurberg, I. D.; *Chem. Commun.*, **2023**, *59*, 7346. c) Yang, Z.; Stivanin, M. L.; Jurberg, I. D.; Koenigs, R. M.; *Chem. Soc. Rev.*, **2020**, *49*, 6833.

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Synthesis of new analogs of an anti-malarial agent in a hit-to-lead phase

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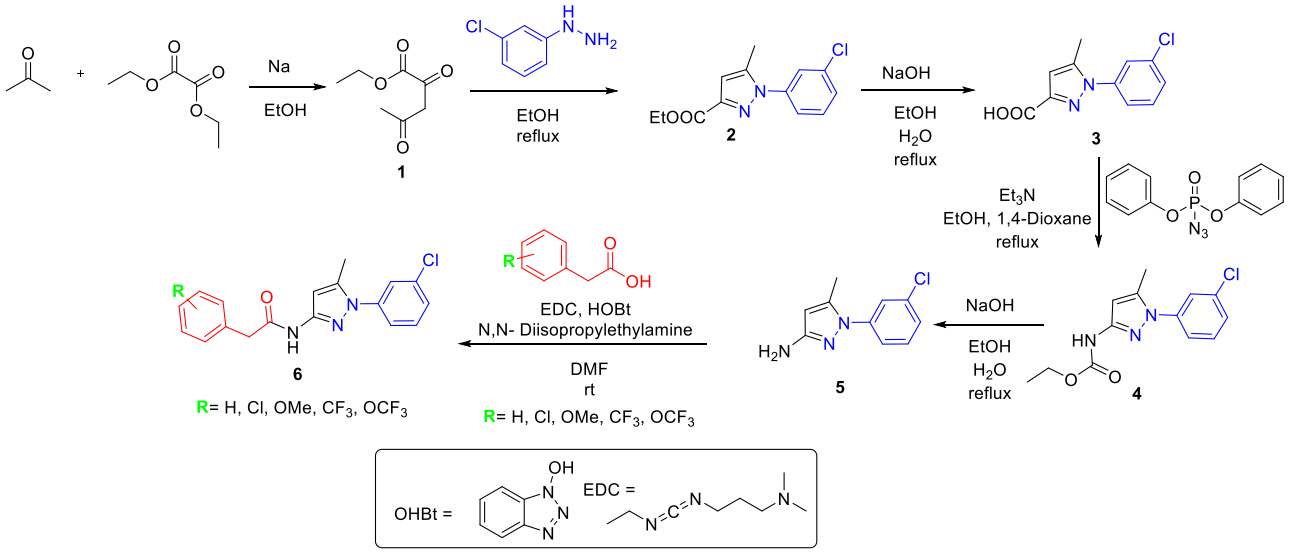
Keywords: *Medicinal chemistry, hit-to-lead, anti-malarial agent.*

ABSTRACT

Malaria remains a significant global health challenge, necessitating the continuous development of new therapeutic agents[1,2]. In this study, we report the design, synthesis, and preliminary biological evaluation of novel analogs of anti-malarial agents during the hit-to-lead phase of a drug discovery program led by Medicines for Malaria Venture (MMV) in collaboration with UNICAMP and USP teams (MINDI Consortium). Our research focused on the structural modifications of compound **6**, generated as a Hit compound by an MMV screening for phenotypic blood stage. The most potent derivatives of the series were synthesized using a general protocol of 6-step synthetic route as shown in Scheme 1. *In vitro* anti-malarial activity was assessed against *Plasmodium falciparum* strain to build the SAR study. It was possible to improve the anti-malarial activity reaching IC_{50}=200 nM. However, the analogs exhibited metabolic instability, which was a restriction to move forward the series to lead optimization phase.



Scheme 1. Synthetic route used to obtain compound **6** and its derivatives.

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Enantioselective Synthesis of Pyrroloindolines Bearing Heteroaromatic Side-Chains

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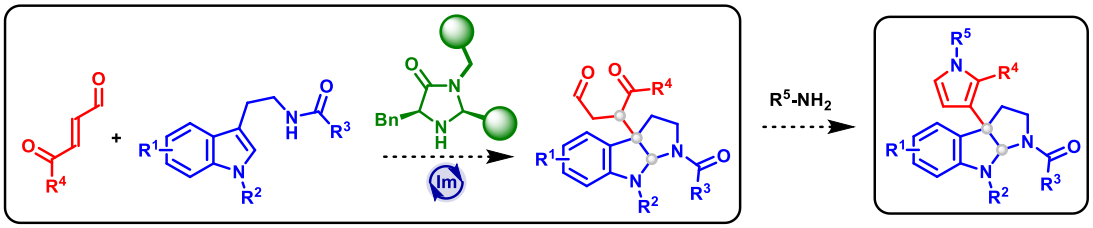
Keywords*: Imidazolidinone, γ-keto-α,β-unsaturated aldehydes, Tryptamines.*

ABSTRACT

Pyrroloindoline is a tricyclic benzofused heterocyclic system found in several bioactive compounds with pharmaceutical potential.[1] Natural and synthetic compounds bearing pyrroloindolines in their structure were found to have antitumor and antibacterial activity.[2] Given the growing impact of neurodegenerative diseases, pyrroloindolines acting as cholinesterase inhibitors were investigated for the treatment of Alzheimer's disease.[3]

In 2004, MacMillan and co-workers described the enantioselective synthesis of pyrroloindolines from unsaturated aldehydes and tryptamines. In his work, MacMillan reacted *α,β*-unsaturated aldehydes and *N*-carbamoyl-tryptamines using enantioselective iminium-ion catalysis.[4]

In this work, pyrroloindolines bearing heteroaromatic side-chains are prepared using chiral iminium ions formed *in situ* from *γ*-keto-*α,β*-unsaturated aldehydes. The initially formed 1,4-dicarbonyl compounds are then subjected to different Paal-Knorr reactions. The loss of the stereocenter initially formed *β* to the aldehyde moiety means that the enantioselectivity of the final product is dependent on the diastereoselectivity of the first step.



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Tunable Divergent Reactivity of Aziridinium Ylides in the Synthesis of Complex Piperidines and Azetidines

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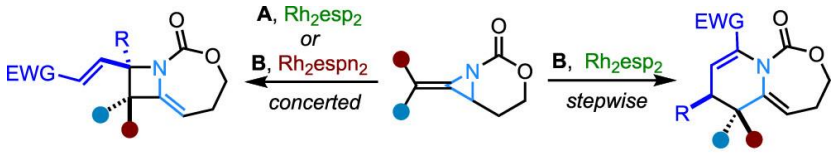
Keywords: aziridinium ylide, tunability, selectivity control

ABSTRACT

Nitrogenated heterocycles comprise the cores of several synthetically useful compounds, including pharmaceuticals, bioactive natural products, agrochemicals, and other drug-like molecules[1–4]. Currently, 84% of structurally unique and approved drugs contain at least one nitrogen atom, being 59% of then nitrogen-bearing heterocycles. The widespread interest in methods to increase the fraction of sp^3 carbon atoms (Fsp^3)[5] of drug-like scaffolds in a stereocontrolled manner, while enabling explorations of unusual amine chemical space, inspired our efforts to tune the reactivity of aziridinium ylides. A sequential nitrene–carbene transfer of simple allenes leads to divergent product outcomes depending on the nature of the carbene precursor, furnishing products of different ring sizes. Both products, four-membered heterocyclic azetidines, and the six-membered dehydropiperidine, are scaffolds of interest in medicinal chemistry[4]. In addition, the catalyst control over the ring size via proposed hydrogen-bonding interactions between the catalyst and substrate was explored. Computational studies were employed to gain insight into the major features of substrates and catalysts that influence the tunable reactivity of aziridinium ylide intermediates formed in this chemistry.



- both reagent and catalyst control of ring expansion
- flexible post-functionalizations
- DFT studies to elucidate pathways
- potential to telescope nitrene/carbene transfer

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19 BMOS
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Photocatalytic strategies for the synthesis of *C*-nucleoside analogues

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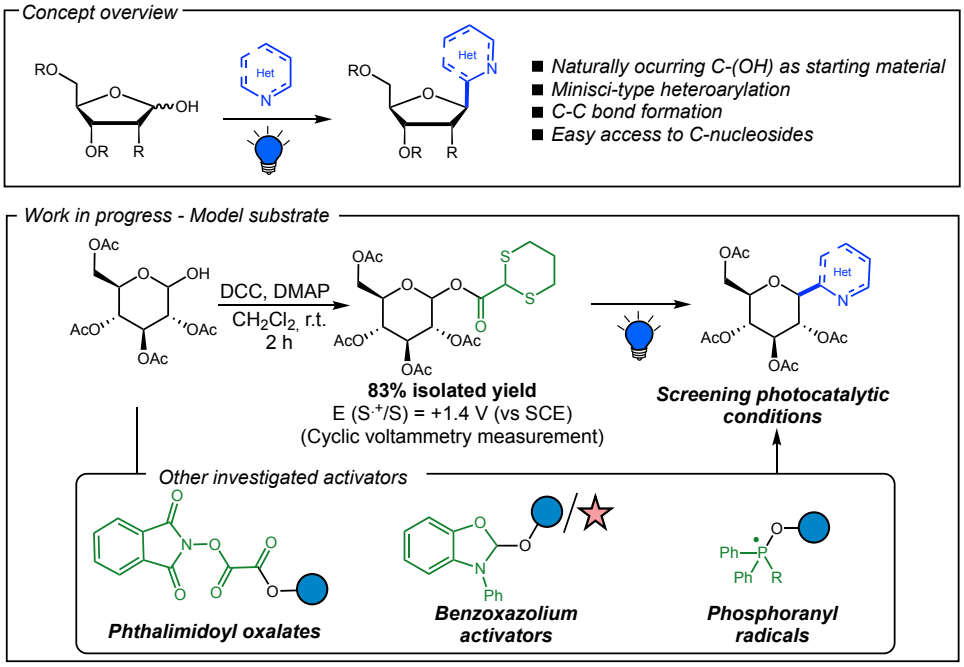
Keywords: *C-O Functionalization, C-Nucleosides, Photocatalysis.*

ABSTRACT

Nucleosides and nucleotides are biological molecules involved in critical processes like genetic information storage and transmission. Many nucleoside analogues are important bioactive compounds used in medicine and agroindustry.[(1,2)] *C*-nucleosides hold significant potential for developing new molecules and studying biological processes. However, their synthesis is usually time-consuming, involving multiple derivatization steps.[(3)] Therefore, new methods to directly functionalize naturally-occurring C-(OH) bonds in glycosides are highly sought, and photocatalysis emerges as a powerful paradigm-changing tool for synthetic carbohydrate chemistry.



Scheme 1: General concept overview and work progress.

In this work, we explore photocatalytic strategies for deoxygenative arylation of C-O bonds in glycosides, aiming to efficiently synthesize valuable *C*-nucleoside analogues *via* Minisci-type substitution. Voltammetry studies of dithiane-activated glucose revealed an intriguing irreversible oxidation at +1.4V. Despite testing several photocatalysts, none have proven effective in promoting this oxidation thus far. As we evaluate stronger oxidants, we are also testing other promising C-O photo-activators with glucose and ribose derivatives, envisioning their carbon-centered anomeric radicals.

ACKNOWLEDGEMENTS

The authors thank CAPES, FAPERJ and CNPq for financial support.

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SEPTEMBER 23-27 2024
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Solvent-Controlled Selective Synthesis of 1,4-Benzodithiins and 1,4-Benzodithiafulvenes *via* Cyclization and Ring Contraction

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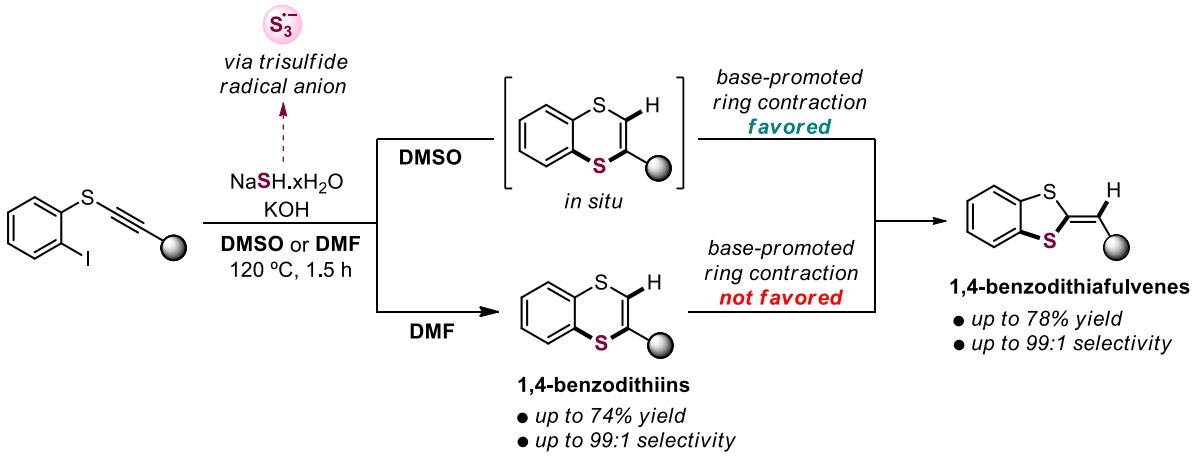
Keywords: *Cyclization, 1,4-dithiins, dithiafulvenes.*

ABSTRACT

1,4-Dithiins are a class of non-aromatic, sulfur-rich heterocycles with promising applications in materials sciences due to their non-planar structure and reversible one- and two-electron oxidations.[1] In contrast, dithiafulvene (DTF) derivatives exhibit remarkable electron-donating properties and have been used as valuable molecular building blocks for the preparation of π-extended tetrathiafulvalene vinylogues (TTFV).[2] In this study, we present a solvent-controlled selective synthesis of 1,4-benzodithiins and 1,4-benzodithiafulvenes through the addition of NaHS to 2-iodoaryl thioalkynes in DMF and DMSO, respectively. These reactions rapidly form a 6-membered ring (1,4-benzodithiin) in both solvents. However, in DMSO, a base-promoted ring contraction occurs, leading to the highly selective formation of a 5-membered ring (1,4-benzodithiafulvene). The reaction scope is currently under investigation, and so far, more than 15 examples of these 6- and 5-membered heterocycles have been selectively obtained with yields of up to 78% and selectivity ratios of up to 99:1.



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Selenoesters acting as benzoyl donors on lipase-catalyzed reactions

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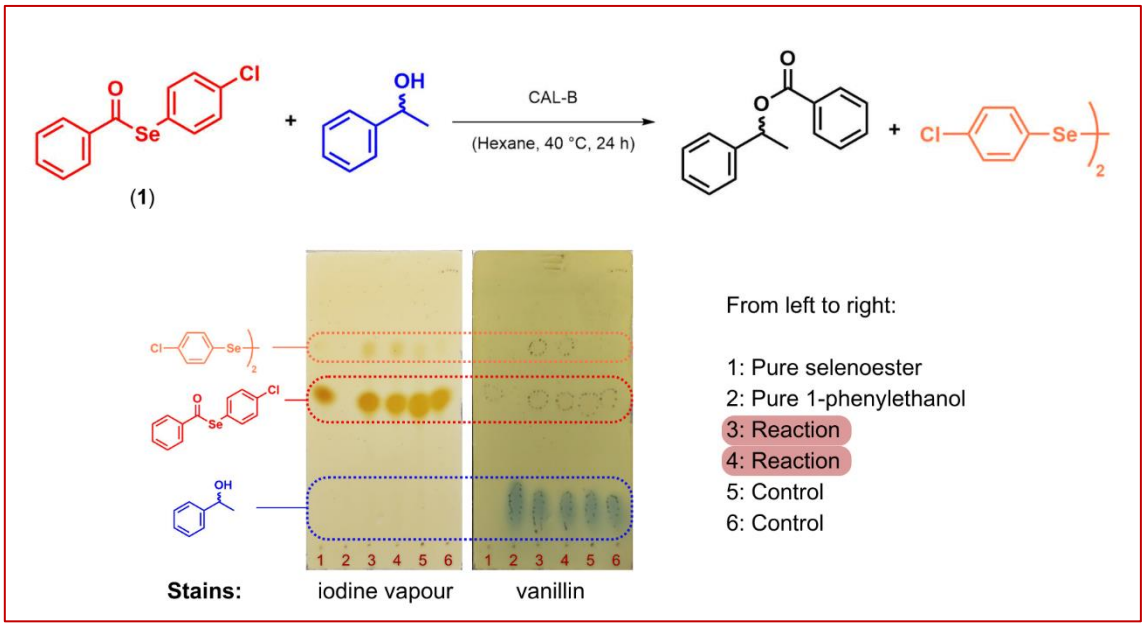
Keywords: Selenoesters, Lipases, Benzoyl donor

ABSTRACT

Organoselenium compounds have been described in the literature for their most diverse potentials, including biological activity, and as key intermediates in organic and inorganic synthesis[1-4]. Initially used in limited research, after the 1970s, biological and chemical studies involving the chalcogen Selenium[1,4] have grown exponentially. The selenoesters, a subclass of organoselenium compounds, are examples of broadly applied Se-containing molecules mainly used as acyl donors in organic synthesis[3].
Recently, selenoesters were applied successfully as acyl donors in lipase-catalyzed reactions[3]. Hence, we decided to evaluate the selenoesters' potential as benzoyl donors. Therefore, Se-(4-chlorophenyl) benzoate (**1**) was used as substrate in the EKR reaction carried out using the lipase CAL-B; 1-phenylethanol as nucleophile in hexane as solvent under 40 °C in batch mode. A control reaction was also carried out for analysis and comparison. After 24 h, the occurrence of reaction was observed only on the flask with CAL-B.



Scheme 1. Selenoester **1** used as benzoyl donor in lipase-catalyzed enzymatic kinetic resolution

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Iodine-catalyzed synthesis of pyrido/benzo[*b*][1,4]selenazines

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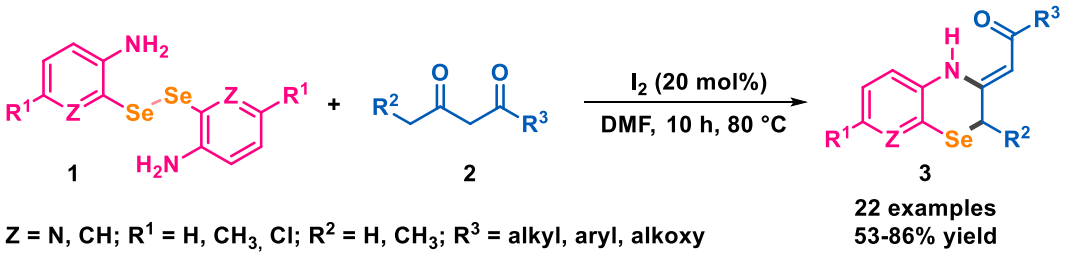
Keywords: *Iodine, β-dicarbonyl compounds, 1,4-selenazines.*

ABSTRACT

The synthesis of selenium-functionalized heterocycles is of growing interest due to their widespread applications as synthetic intermediates, optoelectronic devices, and pharmacologically active compounds.[1] Among them, benzo[1,4]selenazines, bearing a selenium and a nitrogen atom organized in a six-membered ring fused to a benzene unit, found synthetically usefulness in the preparation of functional organic materials,[2] and in medicinal chemistry as multi-targeting drug to treat Alzheimer's disease and microbial infections.[3]

This work describes the selective synthesis of pyrido/benzo-fused 1,4-selenazines through the reaction of bis(3-amino-2-pyridyl) or bis(2-aminophenyl) diselenides **1** with various *β*-dicarbonyl compounds **2**. When molecular I_2 was used as catalyst, a series of pyrido/benzo[*b*][1,4]selenazines **3** bearing an exocyclic *α*,*β*-unsaturated system with *Z* configuration were obtained (Scheme 1). The versatility of the protocol was demonstrated not only by the access to a variety of 1,4-selenazine derivatives, but also by the structural diversity in the 1,3-dicarbonyl precursors, incorporating multifunctionalities in the synthesized heterocycles.



Scheme 1. Synthesis of pyrido/benzo[1,4]selenazines.

ACKNOWLEDGEMENTS

The authors thank FAPERGS (ARD 23/2551-0000800-9) and CNPq. This study was financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brazil (CAPES) - Finance Code 001. RFS also thanks CNPq for the fellowship received.

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SEPTEMBER 23-27 2024
19BMOS
BRAZILIAN MEETING ON ORGANIC SYNTHESIS
BENTO GONÇALVES, RS - BRAZIL

Mechanochemical synthesis of aromatics from biomass derived terpenes

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Keywords: *Terpenes, aromatization, mechanochemistry.*

ABSTRACT

Over the past few decades, Green Chemistry has attracted attention of academia and industry due to safer activities towards humans and environment[1]. In this scenario, mechanochemistry has emerged as an enabling technology, matching high synergy with some principles of Green Chemistry, *e.g.* efficiency and sustainability [2]. Our research group has interest in the valorization of terpenes derived from biomass to synthesize phthalimides using RETSCH mixer mill MM 400. We commenced our study performing the Diels–Alder reaction between isoprene **(1)** and maleimides **(2)**. Afterwards, the adduct **(3)** undergoes aromatization in the presence of iodine and base, yielding phthalimides with yields around to 72% in solution and 89% in mechanochemistry conditions **(4)**.

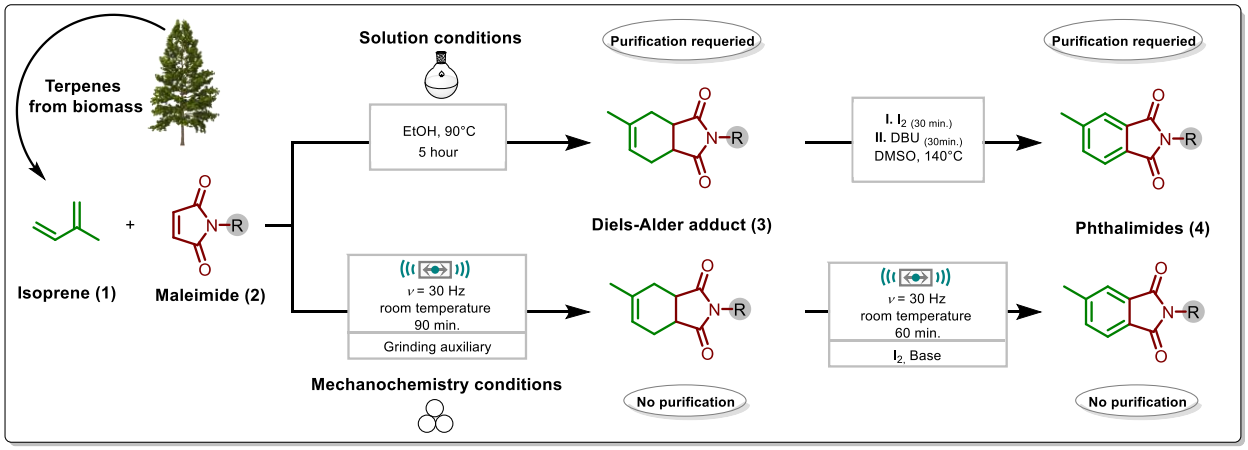

Figure 1. Conditions Diels-Alder and Aromatization Reaction

Compared to solution-based protocol, similar results are obtained in some advantages, like granting time saving, no use of bulk solvent use and no need of further purification according to Table 1.

Table 1. Conditions Aromatization Reaction

Solution conditions

Base	Time (min.)	Temperature (°C)	Solvent	Concentration (M)	Conversion (%)[1]	Yield (%)[1]
TMG	60	140	DMSO	0,1	100	48
DBU	60	140	DMSO	0,1	79	72

Mechanochemistry conditions

Base	Time (min.)	Temperature (°C)	Gringind Auxiliary	Jug* | Sphere*	Conversion (%)[1]	Yield (%)[1]
TMG	60	r.t	NaCl (2.5 mass eq.)	25 mL | 15mm	100	89
DBU	90	r.t	NaCl (2.5 mass eq.)	25 mL | 15mm	73	45

[1] Determined by NMR; *Stainless steel materials.

ACKNOWLEDGEMENTS

We are grateful to FAPESP for the financial support for this work (grant 2021/06661-5), FAEPEX, CAPES, the Brazilian National Council for Scientific and Technological Development – CNPq (JCP, 308540/2021-2) and the Institute of Chemistry of the State University of Campinas.

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SEPTEMBER 23-27 2024
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Small molecule drugs: Synthesis of SePh-benzocaine

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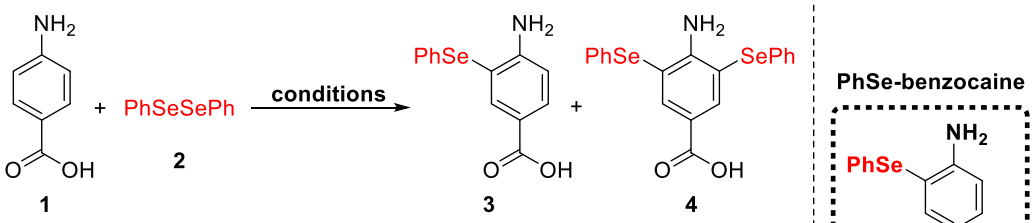
Keywords: *Selenium, organic synthesis, benzocaine*

ABSTRACT

Compounds containing selenium are increasingly notable due to their potential applications in biochemistry, organic synthesis, and materials science.[1] They stand out in medicinal chemistry for their promising pharmacological properties, such as anti-inflammatory, anticancer, and antidepressant effects.[2] In this sense, benzocaine is a significant compound in the field of medicine due to its wide range of applications as a local anesthetic. Its ability to block nerve signals makes it essential for procedures requiring temporary numbing of specific areas.[3] In this sense, and in line with our objective of synthesizing small drugs containing selenium atoms in their structure, we describe in this work our efforts in the synthesis of selenylated benzocaine derivatives (SePh-benzocaine).



conditions:
i) **1** (0.5 mmol), **2** (0.25 mmol), I_2 (20 mol%), DMSO, 110 °C
ii) **1** (0.5 mmol), **2** (0.5 mmol), I_2 (20 mol%), DMSO, 110 °C
iii) **1** (0.5 mmol), **2** (0.25 mmol), TCCA (0.18 mmol), EtOH, 25 °C
iv) **1** (0.5 mmol), **2** (0.5 mmol), TCCA (0.36 mmol), EtOH, 25 °C
v) **1** (0.5 mmol), **2** (0.25 mmol), TCCA (0.18 mmol), EtOH, 0 °C

Scheme 1

To achieve our objective, a series of reaction conditions were tested between acid 4-aminobenzoic acid **1** and diphenyl diselenide **2** (Scheme 1). Under all tested conditions (i-v), a mixture of mono- **(3)** and bis-selenylation **(4)** products was obtained, with higher proportions of bis-selenylation products **(4)**. We are still in the process of optimizing the reaction conditions to selectively obtain the mono- and bis-selenated products. Once the selectivity control of the reaction is achieved, an esterification reaction of the products will be carried out to synthesize PhSe-benzocaine.

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SEPTEMBER 23-27 2024
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Synthesis of 4-quinolone-α-aminophosphonate derivatives with antiviral profile

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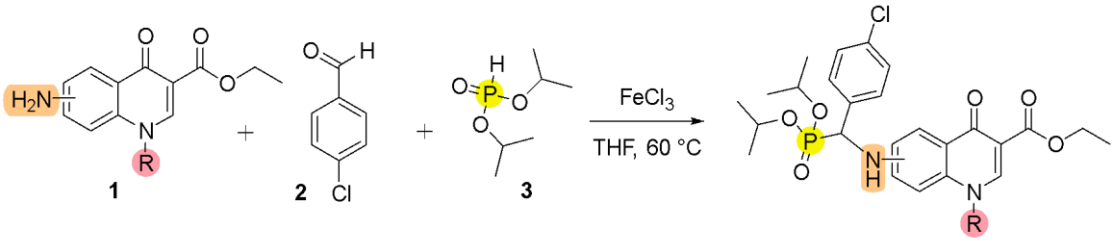
Keywords: *quinolones, phosphonates, α-aminophosphonates.*

ABSTRACT

α-Aminophosphonates, natural analogues of amino acids, constitute an important class of compounds with diverse biological activities such as antiviral.[1,2] Recent studies indicates that incorporating heterocyclic moieties into α-aminophosphonates significantly enhances their biological activity.[3] As an notable class of heterocycles, 4-quinolone derivatives are associated with various bioactivities and can be synthesized by different synthetic methods, allowing the design and preparation of compound libraries with different structural variations designed to modulate their pharmacological effects.[4] Conjugating these fragments with known bioactive structural scaffolds, might, therefore, lead to more effective agents. Thus, this work aims to synthesize new 4-quinolone-α-aminophosphonate derivatives (**4**) in order to obtain substances with enhanced antiviral profiles. The proposed compounds were synthesized using the Kabachnik-Fields reaction, which involves the condensation of an amino-4-quinolone (**1**), chlorobenzaldehyde (**2**) and diisopropyl phosphite (**3**) in the presence of a Lewis acid catalyst. The resulting products had their structures confirmed by spectroscopic analysis methods.



4a. 6-NH-CH(C_6H_4Cl)$C_6H_{14}O_3P$; R = Et
b. 7-NH-CH(C_6H_4Cl)$C_6H_{14}O_3P$; R = Et
b. 6-NH-CH(C_6H_4Cl)$C_6H_{14}O_3P$; R = Bz
b. 7-NH-CH(C_6H_4Cl)$C_6H_{14}O_3P$; R = Bz

Scheme 1 - Synthetic route to obtain 4-quinolone-α-aminophosphonate derivatives (**4**).

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Ru(II)-Catalyzed Asymmetric Transfer Hydrogenation of Aryl(1-aryl-1*H*-1,2,3-triazol-4-yl)methanones: A Novel Strategy for Developing CFTR traffic Correctors

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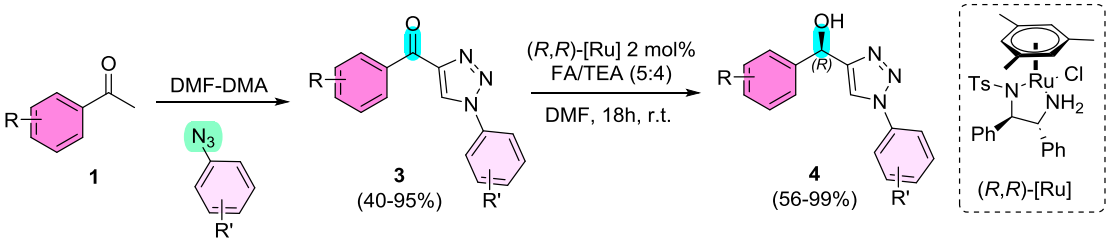
Keywords: *Catalysis, enantioselective synthesis, 4-acyl-1,2,3-triazoles.*

ABSTRACT

The aryl(1-aryl-1*H*-1,2,3-triazol-4-yl)methanols (**4**) have emerged as promising correctors of the misfolding of F508del-CFTR protein, the main mutation of cystic fibrosis.[1] Among the evaluated compounds, the racemic compound (*rac*)-**4b** exhibited the lowest EC_{50} value (1.70 µM). Subsequent evaluation of the enantiomers (*R*)- and (S)-**4b** revealed inactivity for one of them. To address this, a direct and practical method for the enantioselective synthesis of **4** was developed based on the Ru(II)-catalyzed the asymmetric transfer hydrogenation (ATH) of **3** (**Scheme 1**). [2] After optimization of the reaction conditions, ten substrates underwent ATH using 2 mol% of (*R*,*R*)-[Ru]. The conversion and observed enantiomeric excess (ee) were strongly influenced by substituent effects, with electron-donating or weakly donating groups in the ortho position to the carbonyl resulting in the highest ee (**Scheme 1**).



4a R= 2-Br; R'= 4-Br (92% conv., 80% ee)
4b R= 4-Br; R'= 4-Br (99% conv., 52% ee)
4c R= 4-Br; R'= 4-SCH_3 (56% conv., 36% ee)
4d R= 4-Br; R'= 4-CO_2H (*ND*)
4e R= 2-OMe; R'= 4-Br (77% conv., 82% ee)
4f R= 2,4-OMe; R'= 4-Br (58% conv., 80% ee)
4g R= 2-OH,4-OMe; R'= 4-Br (99% conv., 76% ee)
4h R= 2,4-OH; R'= 4-Br (94% conv., 78% ee)
4i R= 3,4,5-OMe; R'= 4-Br (96% conv., 50% ee)
4j R= 4-NO_2; R'= 4-Br (99% conv., 3% ee)

Scheme 1: Enantioselective synthesis of aryl(1-aryl-1*H*-1,2,3-triazol-4-yl)methanols

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SEPTEMBER 23-27 2024
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BRAZILIAN MEETING ON ORGANIC SYNTHESIS
BENTO GONÇALVES, RS - BRAZIL

Tribromoisocyanuric acid-mediated telescopic synthesis of selenazoles

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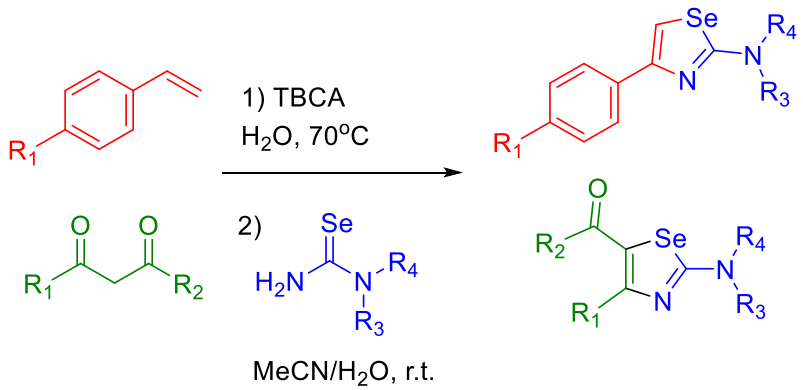
Keywords: selenazoles; tribromoisocyanuric acid; telescopic synthesis.

ABSTRACT

The telescopic approach in organic synthesis stands out for minimizing the production of chemical waste, reducing operational costs, and avoiding contact with toxic and/or unstable intermediates.[1] Selenazoles constitute a class of compounds of great medicinal and agriculture interest.[2,3] Traditionally, they are prepared via Hanztsch synthesis, however, this methodology has some disadvantages, such as the use of toxic and difficult-to-access reagents. Furthermore, more easily manipulated sources of electrophilic bromenium ions are being investigated. In this context, the option arises of using tribromoisocyanuric acid (TBCA) to carry out diverse halogenation reactions.[4] This work studies the telescopic synthesis of 2-amino-selenazoles mediated by TBCA. The results demonstrated that TBCA can be used in the preparation of 2-amino-selenazoles, highlighting the scope of the method. Moreover, the method could be used in the synthesis of 2-amino-selenazoles from not only styrene derivatives (57 – 65%), but also β-dicarbonyl compounds (25 – 68%), with a wide range of substitutions.



R_1 = H, CH_3, CF_3, Br, C_6H_5
R_2 = H, CH_3, C_6H_5
R_3 = H, CH_3
R_4 = H, CH_3

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SEPTEMBER 23-27 2024
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Synthesis and biological prospection of new derivatives 4-quinolone-3-hydroxamic acids with potential activity anti-HSV

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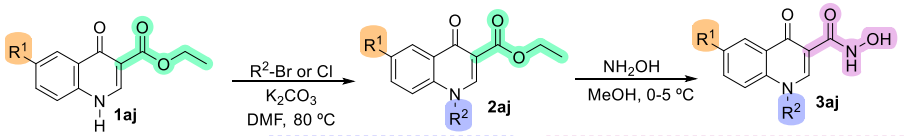
Keywords: *synthesis, methodological optimization, hydroxamic acids.*

ABSTRACT

4-quinolones are studied for their broad biological spectrum[1]. In this context Elvitegravir exemplifies a 4-quinolone used in clinical HIV treatment. Hydroxamic acids (HA) are studied as antiviral agents due to their coordination properties[2,3]. Thus, this study aim is to modify the 4-quinolone nucleus by introducing the HA group, resulting in derivatives **3aj** evaluated for their anti-HSV activity. The synthesis initially involved an alkylation reaction of 4-quinolones **1aj** followed by a S_N2 reaction with different alkylation reagents. The HA **3aj** were obtained through nucleophilic displacement on **2aj** previously synthesized, using hydroxylamine solution (NH_2OH) as the nucleophile, prepared *in situ* by treating $NH_2OH.HCl$ with KOH using methanol as solvent (Scheme 1). The synthesis was realized after methodological optimization and the newly **3aj** synthesized were structurally characterized (IR, MS, ^1H,^{13}C NMR and m.p.), yielding 18-67%. Ultimately the HA were subjected to anti-HSV activity tests, showing significant results with inhibition 60% to 100%.



2a: R^1:Cl; R^2: pr - 91% - 127 °C
b R^1:Br; R^2: pr - 89% - 140 °C
c R^1:F; R^2: pr - 80% - 132 °C
d R^1:Cl; R^2: pe - 87% - 103 °C
e R^1:CH_3; R^2: pe - 87% - 95 °C
f R^1:Cl; R^2: bn - 88% - 185 °C
g R^1:Br; R^2: bn - 87% - 165 °C
h R^1:F; R^2: bn - 88% - 210 °C
i R^1:H; R^2: bn - 80% - 121 °C
j R^1:I; R^2: bn - 79% - 129 °C

3a: R^1:Cl; R^2:pr - 63% - 201 °C (inhib 72%)
b R^1:Br; R^2:pr - 45% - 193-195 °C (inhib 81%)
c R^1:F; R^2:pr - 67% - 212 °C (inhib 60%)
d R^1:Cl; R^2:pe - 42% - 223-225 °C (inhib 61%)
e R^1:CH_3; R^2:pe - 51% - 220-222 °C (inhib 85%)
f R^1:Cl; R^2:bn - 42% - 223-225 °C (inhib100%)
g R^1:Br; R^2:bn - 44% - 214-215 °C (inhib 100%)
h R^1:F; R^2:bn - 18% - 224-226 °C (inhib 96%)
i R^1:H; R^2:bn - 54% - 202-203 °C (inhib 95%)
j R^1:I; R^2:bn - 32% - 196-198 °C (inhib 72%)

Scheme 1. Synthesis methodology for obtaining HA **3aj**.

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SEPTEMBER 23-27 2024
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Difluoro-triazaborinines containing benzo-fused imidazo-, oxazolo-, and thiazolo-pyrimido fragment as new luminescent frameworks

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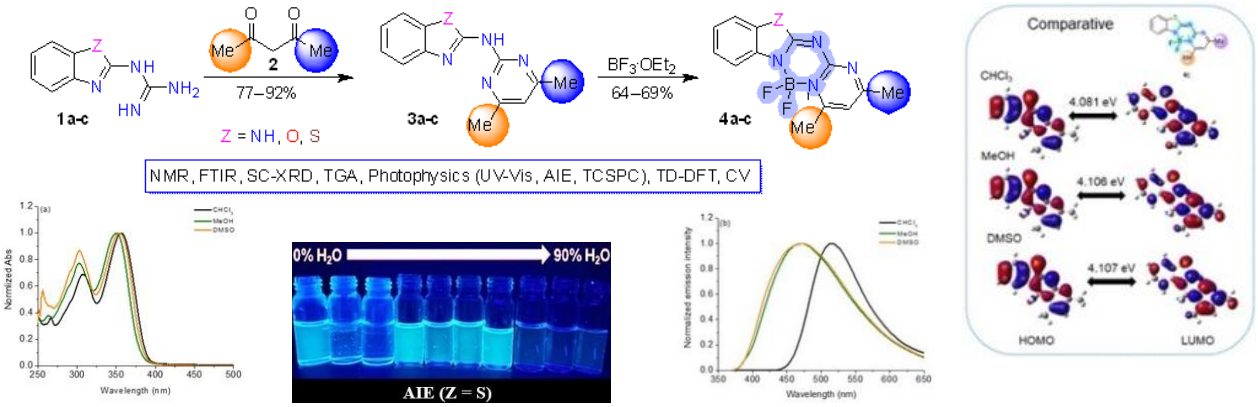
Keywords: *Triazaborinines; Photophysical; Fluorescence.*

ABSTRACT

In the present work the results of an efficient method for synthesizing three novel tetra–coordinated BF_2 complexes, specifically namely, 6,6-difluoro-2,4-dimethyl-6*H*-5λ⁴,6λ⁴-benzo[4,5]imidazo(oxazolo/thiazolo)[3,2-*c*]pyrimido[2,1-*f*][1,3,5,2]triazaborinines (**4**) is reported by us. The compounds **4** were synthesized via the reaction of selected *N*-(4,6-dimethylpyrimidin-2-yl)-benzo[*d*]imidazo(oxazolo/thiazolo)-2-amines (**3**) with $BF_3{\cdot}OEt_2$, employing Et_3N as a base[1,2]. Compounds **3** were previously obtained from the reaction of aminoguanidines (**1**) with pentane-2,4-dione (**2**). Optimized yields up 64% were achieved when the reactions were conducted in anhydrous $CHCl_3$ at room temperature for 24 hours. The structural characterization of BF_2 complexes **4** was elucidated through a combination of multinuclear NMR, FTIR, SC-XRD, and HRMS techniques. Compounds **4** demonstrated thermal stability up to 150 °C. The spectroscopic properties (in both solution and solid states) and the electrochemical properties of the synthesized derivatives were thoroughly investigated using UV–Vis spectroscopy, steady-state, time-resolved fluorescence emission, TD-DFT calculations, and redox potential measurements. The results of this study highlighted a dependence of the compounds' properties on the heteroatom (N, O, S) present within the heterocyclic scaffolds (Scheme 1).



Scheme 1. A summary of this study: Synthesis and protophysical properties of 6,6-difluoro-2,4-dimethyl-6*H*-5λ⁴,6λ⁴-benzo[4,5]imidazo(oxazolo/thiazolo)[3,2-*c*] pyrimido[2,1*f*][1,3,5,2]triazaborinines **4**.

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SEPTEMBER 23-27 2024
19BMOS
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Dynamic kinetic resolution of benzylic amines with palladium supported on dolomite and ionic liquids with microwave heating. A new approach.

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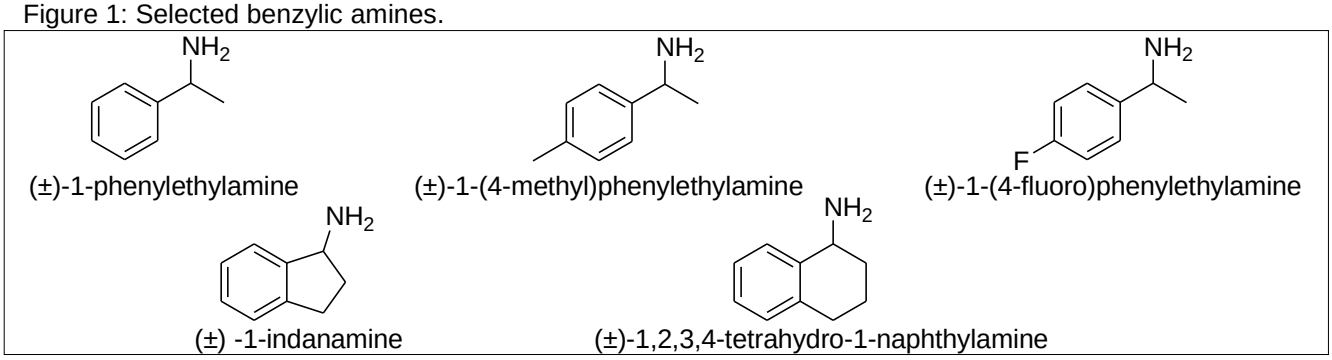
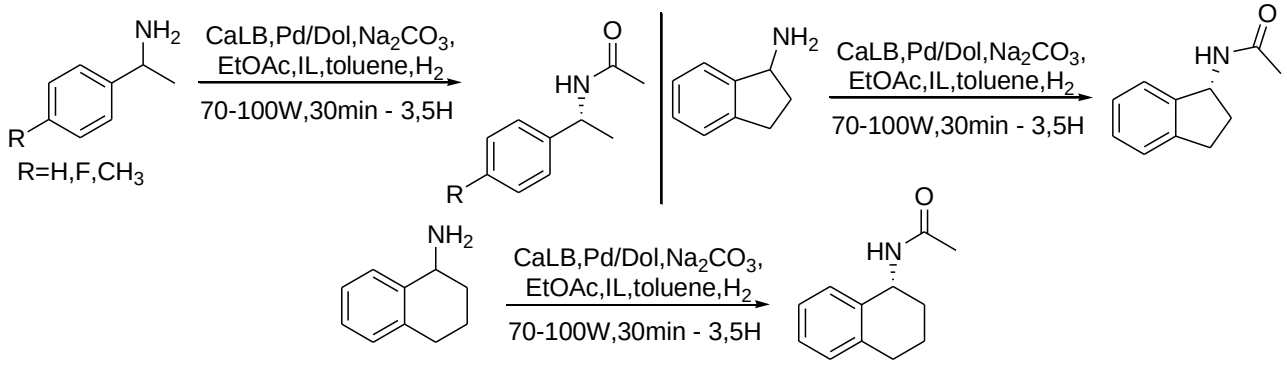
Keywords: *Dynamic kinetic resolution, Microwave, ionic liquid.*

ABSTRACT

Chiral amines are important building blocks for organic synthesis because they are present in a wide number of drugs and compounds with remarkable biological activity[1]. Dynamic kinetic resolution (DKR) constitutes an efficient method to prepare amines in enantiomerically pure form, which can provides 100% theoretical yield of a single enantiomer[1]. Ionic liquids (ILs) are stable, non-volatile and low toxic[2]. ILs were chosen because they stabilize palladium nanoparticles, thus improving their catalytic activity[2]. Microwave irradiation improves Pd catalyst performance by rapidly heating the reaction mixture by directly exciting the molecules, accelerating the catalytic reactions[1].

Figure 1: Selected benzylic amines.





Scheme 1: General procedure for DKR.

The conversion value of DKRs were between 60-100%, and yields ranged from 53-93%. These conditions can still be optimized. Futhermore, it was possible to reduce the reaction time from 24 h to up to 30 minutes. The results obtained demonstrated the efficiency of the Pd/Dol catalyst.

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We thank to Unifesp, Capes and Fapesp for financial support and scholarschips.

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SEPTEMBER 23-27 2024
19 BMOS
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Telluride-Based Pillar[5]arene: A Potent and Recyclable Catalyst for Alkylation Reactions in Water

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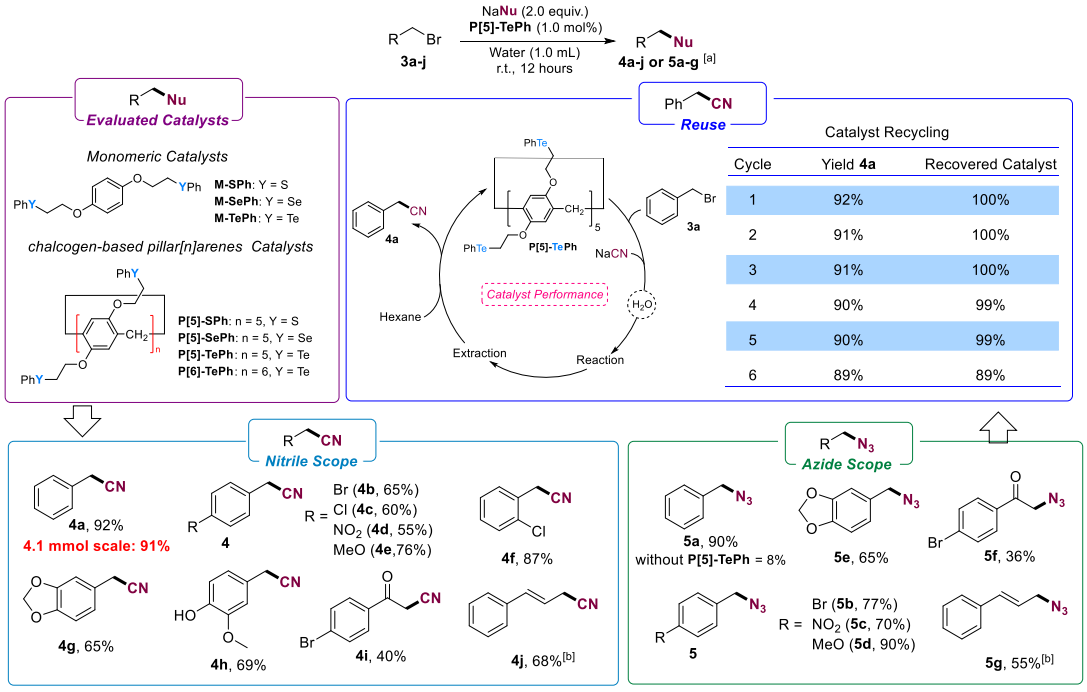
Keywords: *Organic catalysis, Organochalcogen, Supramolecular Catalysis.*

ABSTRACT

Pillar[*n*]arenes are a new generation of supramolecular macrocyclic hosts that can form inclusion complexes with small molecules through various interactions like dipole-dipole, hydrogen bonding, and π-π stacking.[1] Due to their short discovery time, the chemistry involving these macrocycles is still little explored, especially as catalysts, despite their ability to catalyze efficiently Heck and Suzuki coupling reactions.[2] In this way, we report the synthesis of chalcogen-based pillar[5]arenes, including new sulfide- and telluride-based pillar[*n*]arenes, and their catalytic activity in promoting alkylation of nucleophiles in aqueous solutions. The optimized protocol showed that using 1 mol% of **P[5]-TePh** is enough to convert benzyl bromide into nitriles or azides employing a variety of substrates containing both EWG/EDG groups and alfa-carbonyl moieties (Scheme 1). We also observed that the yield of the conversion of benzyl bromide to **3a** was not affected on a larger scale. Additionally, for our delight, the catalyst could be reused for 5 cycles with excellent recovery and no reduction in the yield of **4a** formation.



[a] *Isolated yield.* [b] *Cinnamyl chloride was used as substrate.*

Scheme 1.

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We thank the CNPq, CAPES, FAPERJ, FAPEMIG and INCT-Catalysis for the financial support.

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SEPTEMBER 23-27 2024
19BMOS
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Synthesis of [1,2,3]triazolo[1,5-*a*]quinolines promoted by organocatalyst and base

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Keywords: *Organocatalysis, 1,2,3-triazole, quinoline.*

ABSTRACT

Here, we present a one-pot sequential method for the synthesis of fused [1,2,3]triazolo[1,5-*a*]quinolines through successive cyclization and condensation. In this synthetic strategy, the intermolecular [3+2]-cycloaddition occurs between 1,3-dicarbonyl compounds and *o*-carbonyl-substituted phenylazide compounds, for the formation of the 1,2,3-triazole intermediates. Subsequently, an intramolecular condensation reaction generates the fused quinoline ring by the new *C*−*C* bond formation.

β-keto esters and 1,3-diketones were efficiently reacted in the presence of 20 mol% of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as catalyst in DMSO at 120 °C for 24 h, obtaining the target products (27 examples) generally in good yields (5-92%). Posteriorly, we adapted the protocol to synthesize secondary and tertiary [1,2,3]triazolo[1,5-*a*]quinoline 3-carboxamides in good yields (48-96 %) applying *β*-keto amides as starting material through a two-step synthetic strategy. The first step uses organocatalysis (10 mol% of diethylamine or DBU), while the second step uses inorganic base (1.2 or 0.1 equiv. of KOH) in short time of reaction (Figure 1).

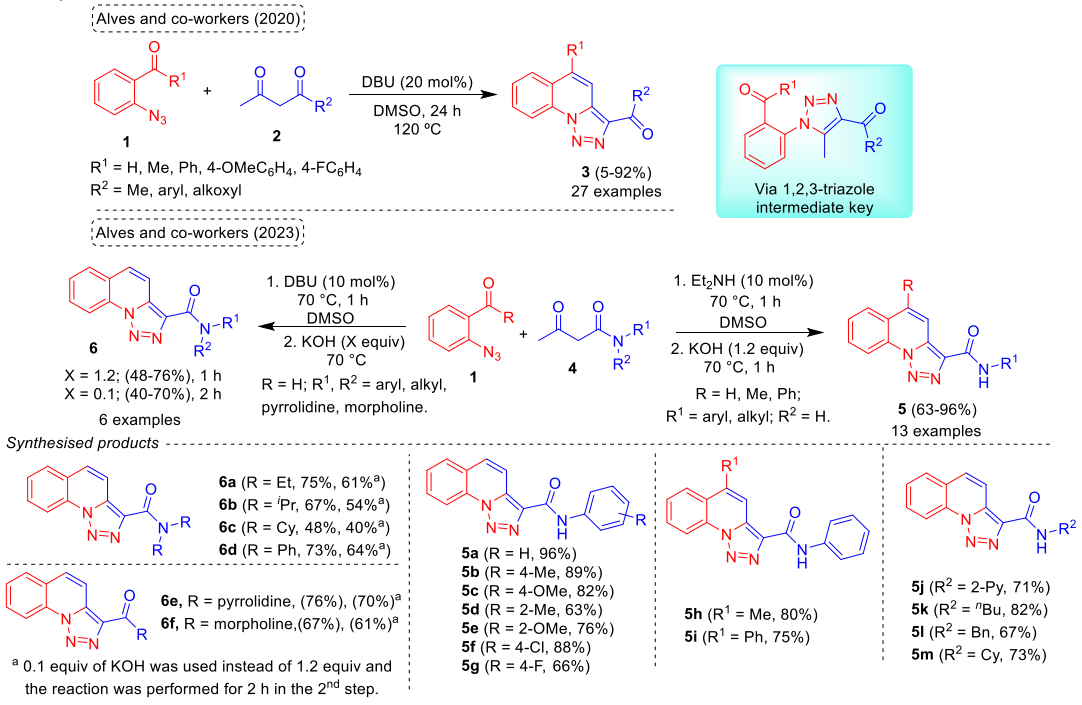

Figure 1

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The authors are grateful for the financial support and scholarships from the Brazilian agencies CNPq (Grants 409782/2018-1 and 308015/2019-3) and FAPERGS (PRONEM 16/2551-0000240-1). CNPq is also acknowledged for the fellowship for D.A.. This study was partially financed by CAPES-Finance Code 001.

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SEPTEMBER 23-27 2024
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Visible-Light-Mediated Cyclization of 1,3-Diones and Chalcogenoalkynes: A New Regioselective Method for Polysubstituted Chalcogenofurans

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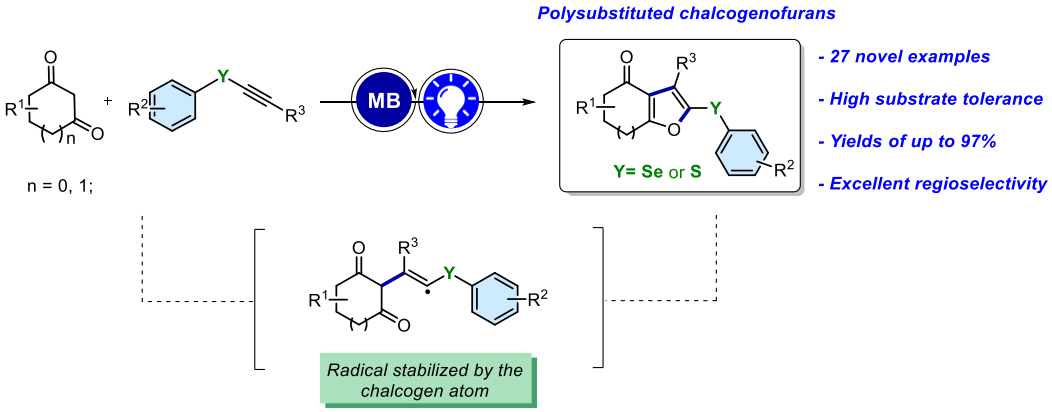
Keywords: *Photoredox catalysis, Polysubstituted Chalcogenofurans, Regioselectivity.*

ABSTRACT

The use of visible light as a mediator in chemical reactions represents a significant advance in energy efficiency.[1] This technique facilitates the activation of various substrates and the formation of new bonds under mild conditions, enabling the synthesis of valuable molecules.[2] Our research focuses on the synthesis of polysubstituted chalcogenofurans, which show considerable potential for diverse applications. The synthetic approach involves an oxidative cycloaddition reaction between 1,3-diones and chalcogenoalkynes. Blue LEDs served as the light source, methylene blue as the photocatalyst, and $(NH_4)_2S_2O_8$ as the oxidizing agent, all at room temperature for six hours. This method demonstrated remarkable versatility, applicable to various chalcogenoalkynes and 1,3-diones, yielding 27 chalcogenofurans with yields ranging from 67% to 97% and exhibiting excellent regioselectivity. Mechanistic studies revealed that a radical forms at the α-dicarbonyl carbon of the 1,3-dione, which then reacts with the chalcogenoalkyne to produce an olefinic intermediate stabilized by the adjacent chalcogen atom.



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SEPTEMBER 23-27 2024
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CuAAC reaction promoted the synthesis of promising selenyl-dihydropyrimidinones (DHPMs)

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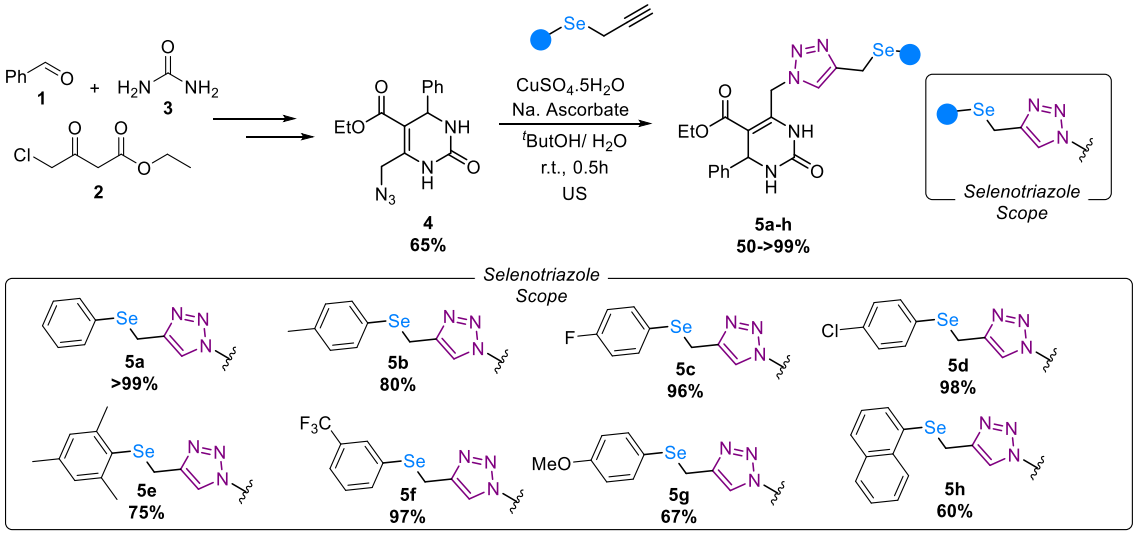
Keywords: *Selenium, heterocycles, 1,2,3-triazoles.*

ABSTRACT

Recent research has focused on molecular hybridization as a tool in the rational design of innovative drug candidate prototypes.[1,2] In particular, CuAAC reaction has been employed as one of the key strategies for this approach.[3,4] Within this scope, the combination of organochalcogens, 1,2,3-triazole and the dihydropyrimidinone (DHPM) nuclei is particularly promising.[5-8] In this context, we report the results of the design, synthesis of the molecular hybrids, uniting these three interesting synthetic frameworks in the same molecule, using CuAAC reaction as a synthetic approach. As a starting point, we used DHPM-azide **4**, previously synthesized *via* Biginelli reaction, and the selenoalkyne as model compounds. The optimized methodology was 0.2 mmol alkyne, 0.4 mmol azide and 10 mol% $CuSO_4.5H_2O$ under ultrasound irradiation. The scope of the reaction was explored with additional selenoalkynes, obtaining a series of 8 novel DHPM's-selenotriazoles derivatives **5a-h** in good to excellent yields (60->99%) (**Scheme 1**).



Scheme 1.

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We thank the UFF, PPGQ-UFF and CAPES, CNPq, FAPERJ for the financial support.

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SEPTEMBER 23-27 2024
19BMOS
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Synthesis of *N*-aryl Azacoumestanes with potential antileishmanial and antibreast cancer activity

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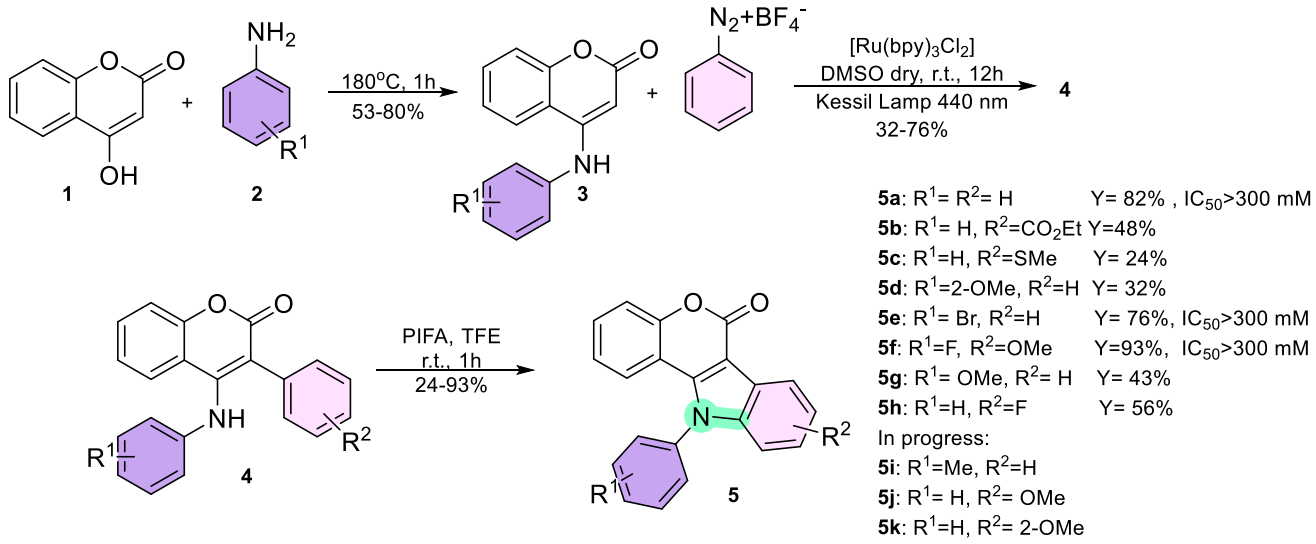
Keywords: *Photoredox catalysis, Hypervalent iodine*

ABSTRACT

Coumarins are an important class of benzopyrones found predominantly in plants known for their notable biological activities.[1] Functionalization at positions C-3 and C-4 is prone to transform this natural product in azacoumestanes **5**. The compound **5** could be synthesized via oxidative amination of **4**, which is derived from the amination of **1** followed by the photoredox arylation of **3** (**Scheme 1**). Previously, we showed that **4c,e,f** exhibited IC_{50} values comparable to miltefosine (an orally available drug for treatment) against the amastigote form of *Leishmania amazonensis*, with a selective index greater than 62.[2] The aim of this work is to synthesize novel *N*-aryl-azacoumestanes **5** through the formation of C-N bound using bis-trifluoroacetoxy iodobenzene (PIFA) and investigate the influence of conformational rigidity on the biological activity against leishmaniasis and breast cancer.



5a: R^1= R^2= H Y= 82% , IC_{50}>300 mM
5b: R^1= H, R^2=CO_2Et Y=48%
5c: R^1=H, R^2=SMe Y= 24%
5d: R^1=2-OMe, R^2=H Y= 32%
5e: R^1= Br, R^2=H Y= 76%, IC_{50}>300 mM
5f: R^1=F, R^2=OMe Y=93%, IC_{50}>300 mM
5g: R^1= OMe, R^2= H Y= 43%
5h: R^1=H, R^2=F Y= 56%
In progress:
5i: R^1=Me, R^2=H
5j: R^1= H, R^2= OMe
5k: R^1=H, R^2= 2-OMe

4a: R^1= R^2= H, Y= 32% , IC_{50}> 300 mM (*L. am. promastigote*), CC_{50} > 200 (*MCF-7* and *MDA-MD-231*)
4c: R^1=H, R^2=SMe, Y= 59 %, IC_{50}= 5.96 mM, SI= 18.6 (*L. am. promastigote*), CC_{50} > 200 (*MCF-7* and *MDA-MD-231*)
4e: R^1=Br, R^2= H, Y= 56% , IC_{50}= 9.05 mM, SI= 24.4 (*L. am. promastigote*), CC_{50} > 200 (*MCF-7* and *MDA-MD-231*)
4f: R^1=F, R^2= OMe, Y= 52% , IC_{50}= 5.65 mM, SI= 62.2 (*L. am. promastigote*), CC_{50} > 200 (*MCF-7* and *MDA-MD-231*)

Scheme 1: Synthetic Route of *N*-aryl-azacoumestanes and their biological activity against Leishmaniasis and breast cancer.

The compounds **5a**,**e,f**, were tested against promastigote form of *leishmaniasis amazonesis* demonstrating to be inactive, unlike the 3-aryl-4-*N*-aryl-coumarin **4** intermediates, confirming the importance of conformational rigidity for biological activity. On the other hand, for breast anticancer activity (*MCF-7* and *MDA-MD-231* cells), no significant changes were observed.

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SEPTEMBER 23-27 2024
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Potential Bioactive *N*-Heterocyclic/Spirocyclic Sulfonamides Building Blocks

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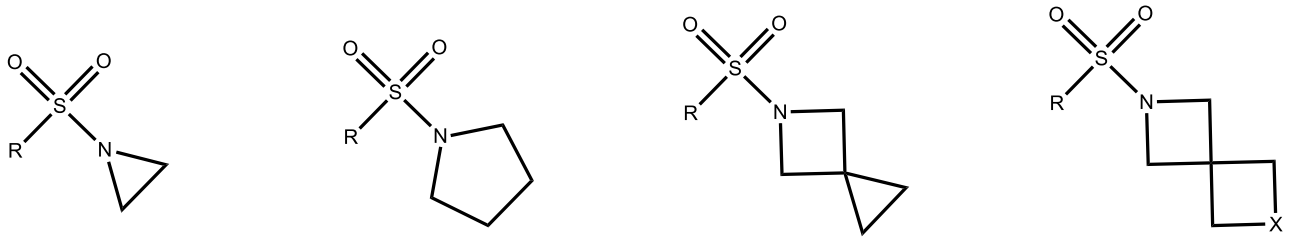
Keywords: *Sulfonamide,N-heterocyclic amines, Spirocyclic amines*

ABSTRACT

The suggestion by Lovering that compounds with higher fraction of sp^3 (Fsp^3= number of sp^3 hybridized carbon/ total hydrocarbon count) have a higher probability to transition from discovery, through clinical trial to drugs[1], has resulted in increased exploration of the vast chemical space[2] for saturated scaffolds. Particular attention has been given to quaternary carbon in small molecules which give them conformational restriction and structural complexity that are shown to impart increased potency, selectivity and metabolic stability.[3] As sulfonamides are a privileged structural class, widely represented in bioactive compounds,[4,5] we decided to synthesize aromatics and aliphatic sulfonamides presenting cyclic and spyrocyclic amines in its structures (Scheme I). These building blocks will be appended to chalcones scaffold and their biological activity will be evaluated.



R= $BrCH_2Ph$-, $BrCH_2$-

X= CH_2, NAr, NR, S, SO_2

Scheme I Sulfonamides from cyclic/spirocyclic amines

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SEPTEMBER 23-27 2024
19BMOS
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Sustainable chemical synthesis of high added-value aromatic compounds through the photochemical valorization of lignin

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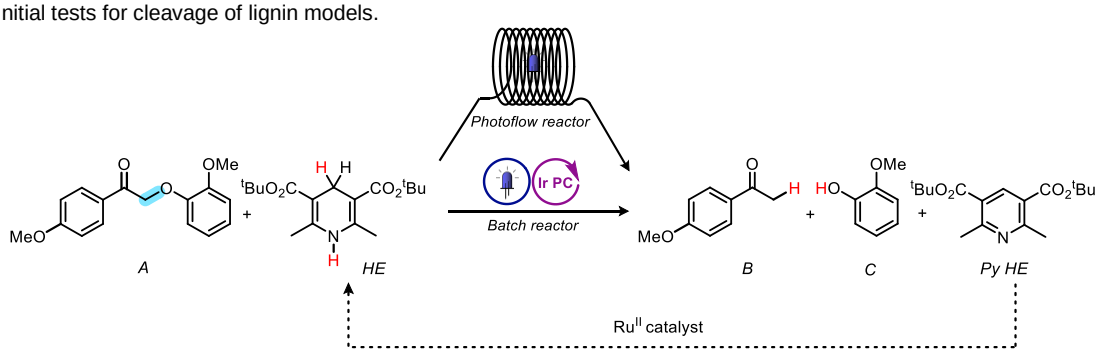
Keywords: *Photocatalysis, Biomass valorization, Green Chemistry.*

ABSTRACT

Lignin is nature's most abundant source of aromatic compounds and constitutes an attractive renewable resource to produce aromatic commodity chemicals.[1] Bearing this in mind, we propose the conversion of lignin into aromatic platform chemicals through the development of a continuous flow photocatalytic methodology for the reductive cleavage of lignin models using Hantzsch esters (HE) as a source of hydrogen.[2] In this strategy, HE is oxidized leading to the formation of the respective pyridine coproduct, which could be recycled back to the HE through catalytic hydrogenation using Ruthenium(II) catalysts.[3] In batch reactions, lignin model A was cleaved with HE in the presence of Iridium photocatalysts, providing products B and C in 84% yield at room temperature in 5 hours. Under continuous flow conditions, products B and C were obtained in 75% and 70% yield, respectively, in just 15 minutes. Following the optimization of reaction conditions, we plan to evaluate more complex lignin models and lignin itself.

Table 1. Initial tests for cleavage of lignin models.



Entry	Catalyst (loading)	Time	Condition	Conversion (%)	Yield B/C (%)
1	$[Ir(ppy)_2(dtbbpy)]PF_6$ (0.3%)	5 h	Batch	100	84/84
2	$[Ru(bpy)_3]Cl_2$ (0.5%)	4 h	Batch	40	29/24
3	$[Ru(bpy)_3]Cl_2$ (0.5%)	20 h	Batch	40	40/36
4	Eosin Y (1%)	20 h	Batch	82	*traces*
5	Rhodamine G (1%)	20 h	Batch	75	5/2
6	Fluorescein (1%)	20 h	Batch	0	*no reaction*
7	$[Ir(ppy)_2(dtbbpy)]PF_6$ (0.5%)	15 min	Flow	95	**75/70**
8	$[Ir(ppy)_2(dtbbpy)]PF_6$ (0.5%)	10 min	Flow	86	57/51

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The authors gratefully acknowledge financial support from the São Paulo Research Foundation – FAPESP (PDB, 2023/01232-4; MSF, 2022/15574-1; JCP, 2021/06661-5) and the Brazilian National Council for Scientific and Technological Development – CNPq (JCP, 308540/2021-2).

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Biaryl-4-hidroxi-1,2,3-triazoles as a platform for new fluorene-triazole hybrids

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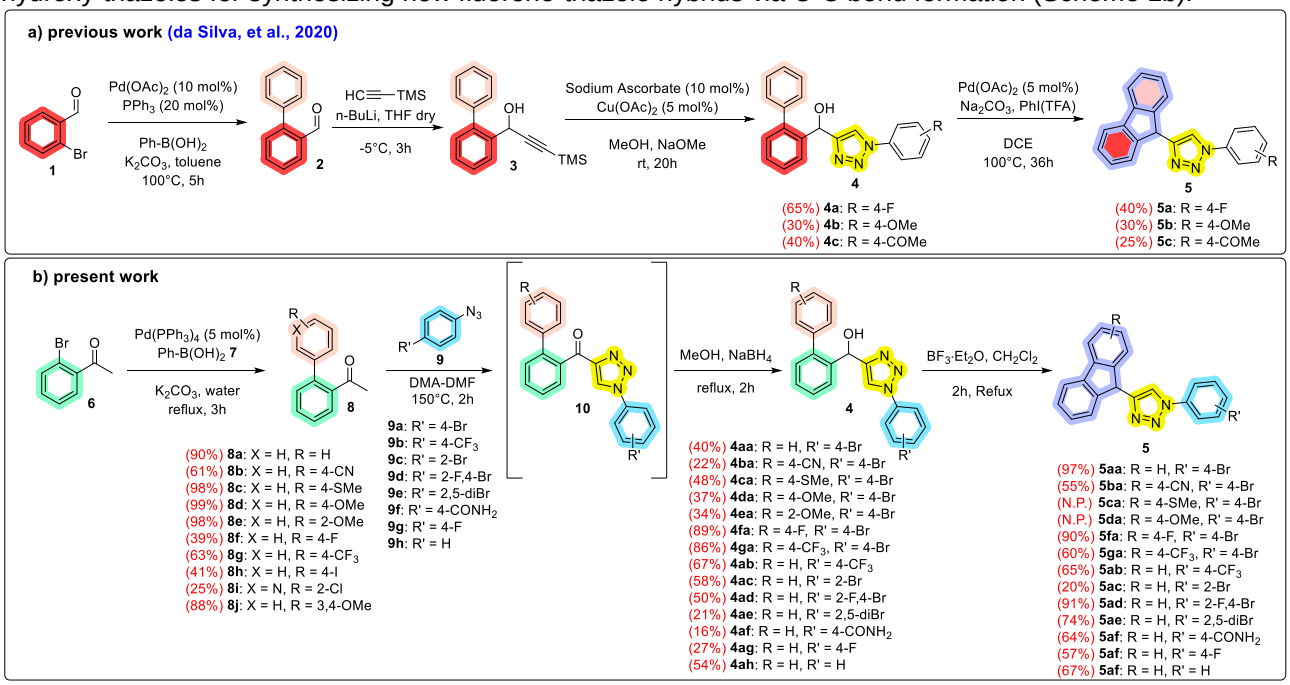
Keywords: *1,2,3-triazoles, Flurenes, Molecular Hybridization, 9H-fluorene-1,2,3-triazoles.*

ABSTRACT

Fluorenes are important scaffolds often targeted in medicinal chemistry[1,2]. In 2019, our research group reported the activity of three fluorene-triazole (**5**) against *Leishmania amazonensis*, obtained through a Friedel-Crafts alkylation of biaryl-4-hydroxy-1,2,3-triazoles (**4**), obtained via CuAAC (Scheme 1a)[2]. Since 4-acyl-1,2,3-triazoles (**10**) are readily available, we aim to leverage our expertise[3] in the biaryl system to obtain biaryl-hydroxy-triazoles for synthesizing new fluorene-triazole hybrids via C-C bond formation (Scheme 1b).



Scheme 1 – Overview of the synthesis of 9*H*-fluorene-1,2,3-triazoles

Biaryl acetophenones (**8**) were synthesized via a Suzuki reaction between acetophenone (**6**) and boronic acids (**7**) using, after optimizations, K_2CO_3, water and $Pd(PPh_3)_4$, achieving yields of up to 99%. Biaryl hydroxy-triazoles (**4**) were obtained in a tandem reaction between biaryl acetophenone (**8**), aryl azide (**9**), and DMA-DMF, followed by carbonyl reduction using $NaBH_4$, achieving yields from 16 to 89%. For the C-C bond formation, a Friedel-Crafts alkylation methodology was employed using BF_3. Eleven fluorene-triazole hybrids were obtained in yields of up to 97%.

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Dual-Catalysis Approach to Stereoselective [2 + 2] Cycloaddition of Erlenmeyer-Plöchl Azlactones

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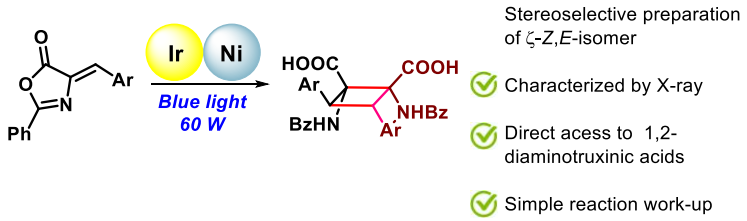
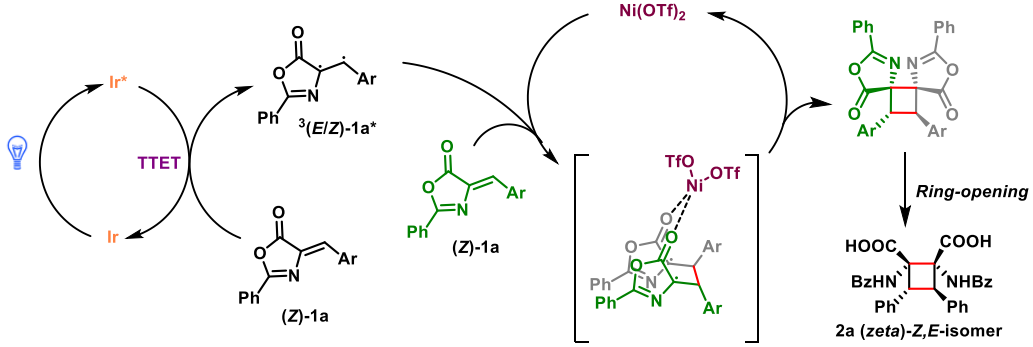
Keywords: *Photocatalysis, Dual-catalysis, Azlactone, Cycloaddition, Cyclobutane.*

ABSTRACT

Visible-light-driven dual catalysis was employed to stereoselective produce densely substituted cyclobutanes from Erlenmeyer-Plöchl azlactones. The single-step preparation of non-natural amino acid dimers containing the cyclobutane moiety was achieved through a synergy between iridium photocatalysis and catalytic nickel(II) triflate as a Lewis acid. The desired 1,2-(*zeta*)-*Z*,*E*-isomers were isolated in good yields and with high regio- and diastereoselectivity (in all cases, >19:1 d.r.). To the best of our knowledge, this is the first report of direct access to truxinic acid analogues using azlactones.



EPR studies supports proposing an Energy Transfer mechanism. Also, the measurements suggest that the combination of Ir and Ni increases the EPR signal compared to non-irradiated sample. DFT calculations showing that nickel triflate stabilizes the 1,4-biradical intermediate, leading to the zeta isomer.



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Synthesis and Neuroprotective Potential of Carvacrol-Derived Selenides-1,2,3-Triazoles for Alzheimer's Disease

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Keywords: *Acetylcholinesterase, organochalcogen, natural product.*

ABSTRACT

Natural products inspire synthetic chemists, and modifying these compounds can lead to promising new structures. In this context, theoretical tools optimize and guide the synthesis of these compounds [1-2]. Thus, our research focused on carvacrol, known for its neuroprotective properties, and organochalcogen derivatives that also exhibit a range of biological activities [3]. In this work, we designed structural modifications in carvacrol to potentiate its neuroprotective effects, particularly for Alzheimer's disease. First, azides (**2a-i**) were synthesized from chlorides (**1a-i**) by reacting sodium azide (NaN_3) with acetonitrile (CH_3CN) and 18-crown-6 as a catalyst, produced an 87-92% yield. Finally, we obtained nine new carvacrol-derived selenides-1,2,3-triazoles (**4a-i**) via click chemistry with yields ranging from 44% to 63%. Figure 1 shows the synthetic routes and docking molecular of compound **4e**, revealing interactions with residues Trp286 and Tyr341, suggesting potential as a therapeutic for Alzheimer's.

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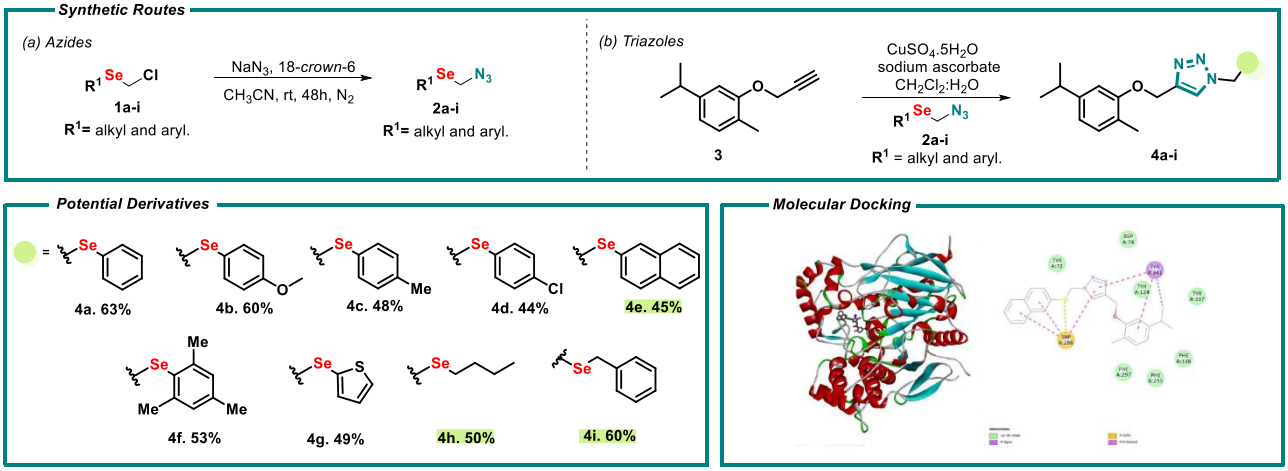

Figure 1. Synthetic routes for obtaining carvacrol derivatives and docking molecular of compound **4e**.

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PPGQ-UFF, CAPES, FAPERJ and CNPq.

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Synthesis of 4-arylchalcogenyl-1*H*-pyrazoles catalyzed by copper

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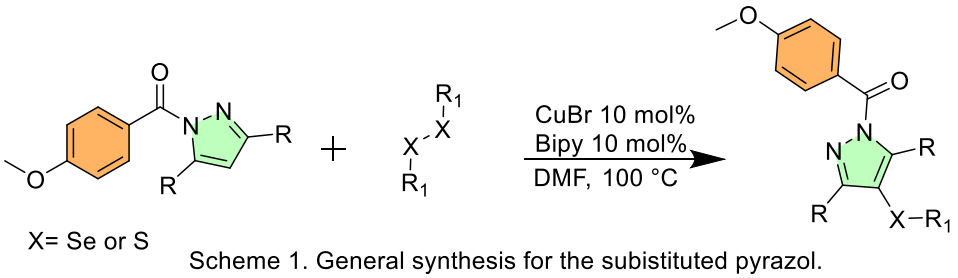
Keywords: *Pyrazoles, Organochalcogen compounds, Copper catalysis.*

ABSTRACT

Pyrazoles represent a significant class of biologically active nitrogen compounds, showing various properties. Regardless of the number of methods for synthesizing them, looking for other mild and accessible pathways to obtain these molecules is still of interest to synthetic organic chemists. Furthermore, organoselenium and organosulfur compounds are interesting molecules also due to their biological properties and selective reactions.[1] Despite that, overcoming some limitations for the formation of C-Se bonds that require harsh reaction conditions has been our focus, using copper as an efficient catalytic system.[2] Thereby functionalizing the pyrazole nuclei with organochalcogens compounds is still an expanding area of study, obtaining new selenium/sulfur-containing pyrazoles potentially applicable for biological studies. This allowed the synthesis of 8 novel derivatives, with yields ranging from 40% to 95% (Figure 1). In addition, some work is still underway to synthesize novel compounds using different substituents in the pyrazole and organochalcogen compounds.



Scheme 1. General synthesis for the subistituted pyrazol.

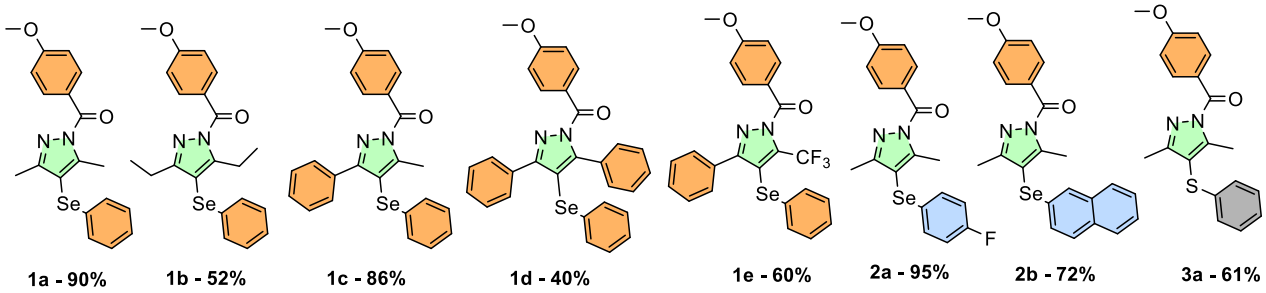


Figure 1. Obtained compounds through the synthesis.

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This study was financed by the Conselho Nacional de Pesquisa e Desenvolvimento (CNPq), Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), Fundação de Amparo à Pesquisa do Estado do Rio Grande do Sul (FAPERGS) e Financiadora de Estudos e Projetos (FINEP).

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19 BMOS
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Synthesis and Characterization of Highly Efficient Anticorrosive Organoselenium Derivatives Containing 1H-Tetrazole Nucleus

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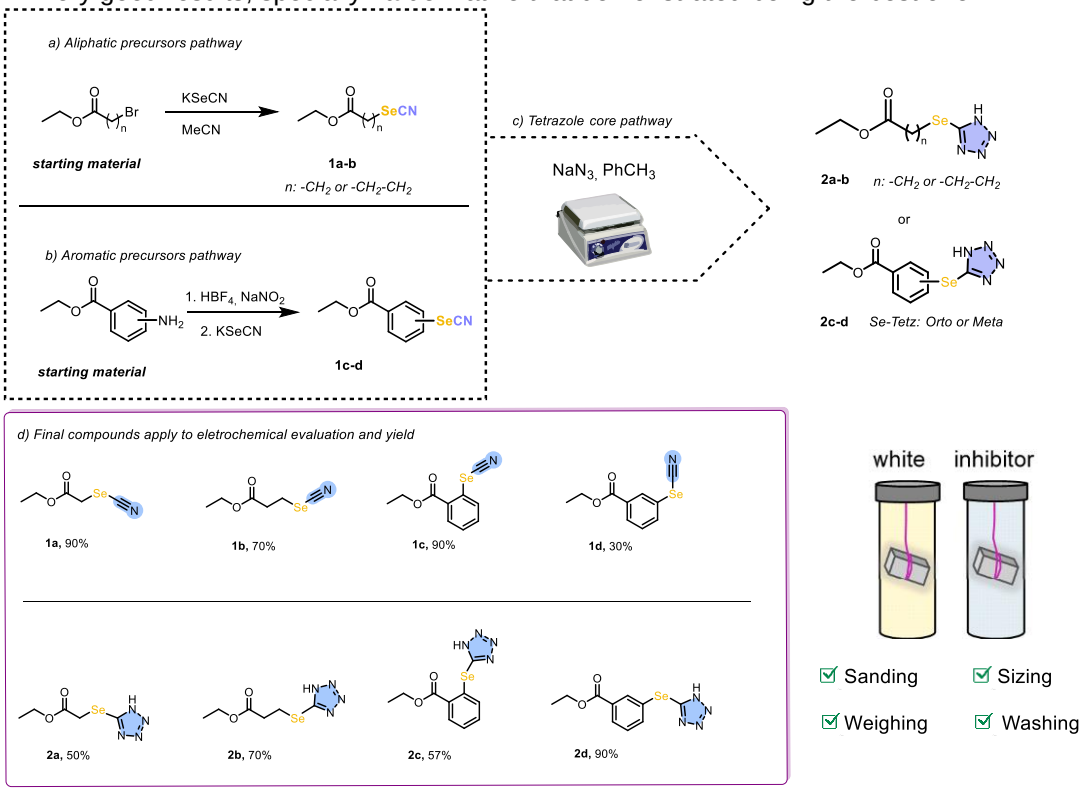
Keywords: *Anticorrosive, Selenium, Tetrazole.*

ABSTRACT

Corrosion is the spontaneous degradation of metallic materials due to environmental interaction. One main protection method for metal alloys is using organic corrosion inhibitors[1]. Compounds with heteroatoms (N, O, S) and π electrons enhance adsorbent properties on metal surfaces by donating electron pairs to empty d orbitals, forming protective layers[1]. Also, organoselenium[2] compounds are promising anticorrosives due to their strong bond formation with metals.ref Thus, this work aims to synthesize and evaluate organoselenium 1H-tetrazole derivatives to evaluate the anticorrosive effects The precursors **1a-d** (SeCN) were synthesized by combining the portion "SeCN" to the aliphatic (Scheme 1a) and aromatic (Scheme 1b) classes. The protocol used was based in two different methods: an SN2 reaction with bromides for aliphatic compounds and diazonium salt formation for aromatic compounds. The tetrazole[3] nucleus formation (Scheme 1c) was consistent for all SeCN precursors. By this way was possible to achieve **4** SeCN molecules and **4** tetrazole derivatives in excellent yields ranging from 30 to 90%. All these molecules were evaluated as anticorrosive and shown very good results, specially **2a** derivative that demonstrated being the best one.



Scheme 1. A) Aliphatic precursors pathway B) Aromatic precursors pathway C) Tetrazole core pathway D) Final compounds

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SEPTEMBER 23-27 2024
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Electrosynthesis of 2,3,5-trisubstituted selenium-chalcogenophenes from (*Z*)-chalcogenenynes and diselenides

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Keywords: *Organic electrosynthesis, selenophene, thiophene.*

ABSTRACT

The chemistry of heterocyclic compounds is constantly progressing with regard to the efficient development of methodologies for the construction of these important building blocks for academic and industrial applications. It is worth noting that the chemistry of Thio- and Seleno-heterocycles has the most diverse applications in synthesis, materials science and medicinal chemistry. Therefore, as part of the continuous effort of our research group to develop more efficient methods for the synthesis of calcogeno-heterocyclic compounds, herein we reported a new methodology to acess selenophene **3** and thiophene **4** derivatives using constant current, undivided cell using (Z)-chalcogenenyne **1a** and diorganoyl diselenides **2a** as starting material in this transformation (Figure 1). This electrochemical chalcogeno-ciclization of chalcogenoenynes involves a simple protocol, open-air, room temperature, short reaction times. The scope demonstrated good functional group tolerance and good to high yields. This approach represents an important contribution to the synthetic and medicinal chemistry and for the current C–Se/S chemistry.

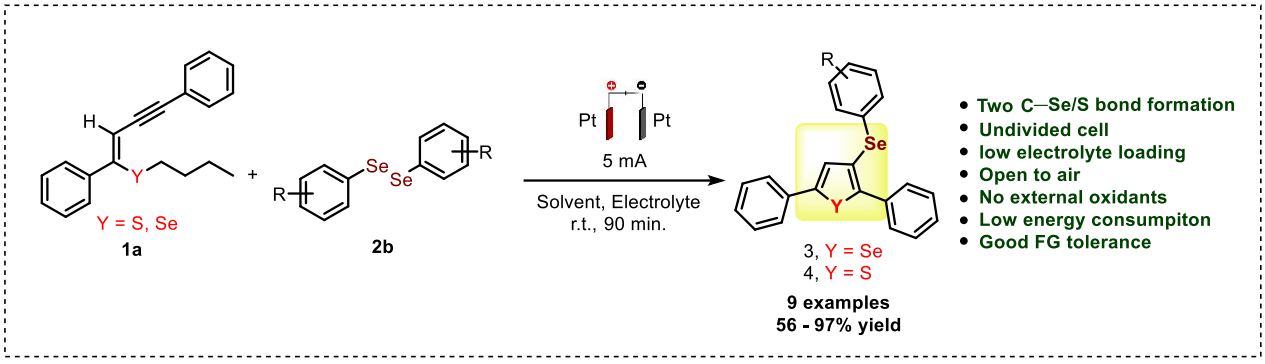

Figure 1. Electrosynthesis of trisubstituted chalcogenophenes from diselenides and Z-Chalcogenenynes

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The authors would like to acknowledge INCT Catálise/FAPESC, CNPq and CAPES for their financial support.

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Electrochemical Synthesis of *E*-Vinyl Chalcogen Halides

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Keywords: *Electrochemistry, Vinyl halides, Chalcogens.*

ABSTRACT

Tetrasubstituted alkenes are key intermediates in synthesis and also important biologically active compounds, however, their preparation as single isomers is challenging. The introduction of two selectively transformable moieties onto an internal alkyne enables the synthesis of these alkenes through successive cross-coupling reactions.[1–3] Herein, we describe a regio and stereoselective electrosynthesis of vinyl chalcogen halides *via* the anodic oxidation of diphenyl dichalcogenide **(1)** in the presence of alkynes **(2)** and mineral acids **(3)**. The target compounds **(4)** were obtained in yields up to 94% with *E/Z* ratios >95:5 as single regioisomers in most cases.

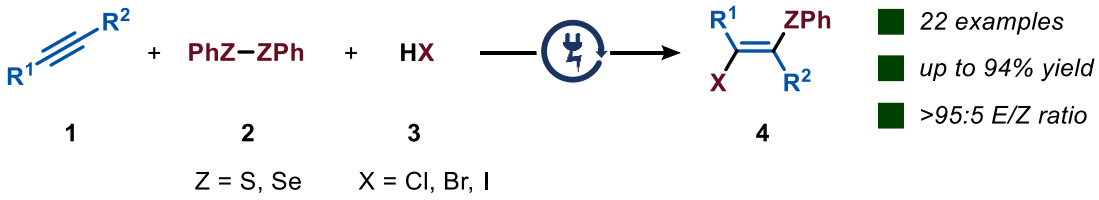

Figure 1: Electrochemical Synthesis of *E*-Vinyl Chalcogen Halides.

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4-acyl-1,2,3-triazoles as a platform to synthesize fused quinolone-triazole hybrids through oxidative C−H Amination

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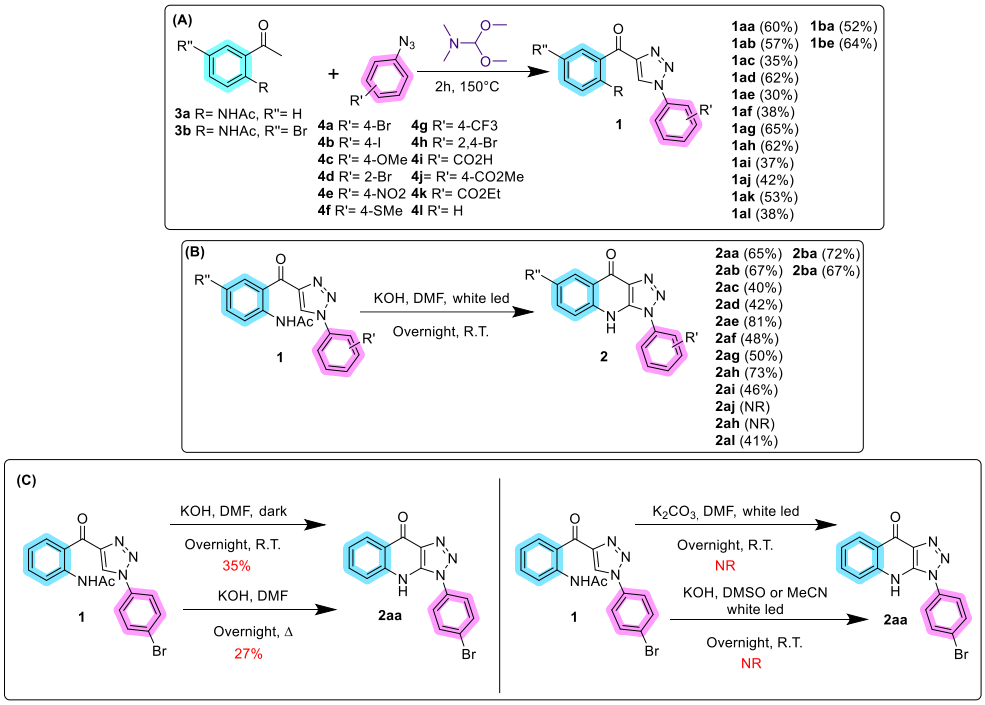
Keywords: *4-Acyl-1,2,3-Triazoles, Quinolene, fused quinolone-triazole, Oxidative C−H Amination*

ABSTRACT

Quinolones are essential in medicinal chemistry, present in many drugs.[1] Combining these structures with triazoles offers a promising blend of simplicity and effectiveness. Our research developed straightforward methods to synthesize 4-acyl-1,2,3-triazole derivatives (**1**).[2] Building on this, we explored cyclization methodologies to form C-N bonds, aiming for new fused quinolone-triazole hybrids (**2**) (Scheme 1a). Triazoles were synthesized in one step without solvents or metals by reacting acetophenone and aryl azide in DMA-DMF (Scheme 1b). After optimizing the conditions, compound **3** was obtained through Base-Mediated Intramolecular Oxidative C−H Amination using triazole **1aa**, KOH, and visible light, yielding **2a** in 65%. Various substitutions yielded 12 new compounds with yields up to 81%. Despite some limitations, control reactions were conducted to understand the pathway, resulting in an innovative methodology, the first report of this reaction in triazoles, allowing for the synthesis of new fused quinolone-triazole hybrids with good yields. good yields.



Scheme 1: (a) Solvent and metal-free synthesis of 4-acyl-1,2,3-triazoles; (b) Base-Mediated Intramolecular oxidative C−H Amination to obtain fused quinolone-triazoles; (c) control experiments.

ACKNOWLEDGEMENTS

The authors would like to thank CAPES, CNPq and FAPERJ for the financial support. Also, we link to thank PUC-Rio and CALPH for the structure that made the work possible.

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Continuous flow enatioselective synthesis of α-amino acid derivatives through asymmetric photoredox catalysis

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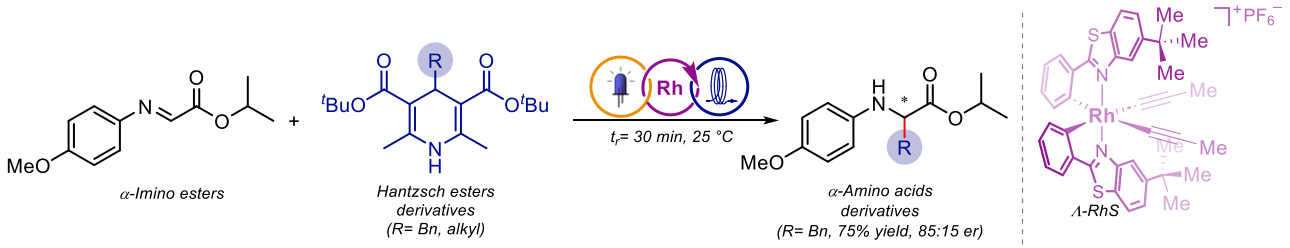
Keywords: *Enantioselective synthesis, photoredox catalysis, continuous flow chemistry, amino acids.*

ABSTRACT

Enantiomerically enriched α-amino acids and their derivatives are important building blocks, widely used in the pharmaceutical industry, drug research, and materials science.[1] Thus, straightforward and versatile methods for their synthesis are highly desirable. Herein, we reported a photochemical enantioselective addition of alkyl radicals to α-imino esters mediated by a chiral-at-metal Rhodium catalyst[2,3] under continuous flow conditions. Our approach enabled fast and direct access to enantioenriched derivatives of both natural and unnatural α-amino acids, achieving yields of up to 75% and enantiomeric ratios of up to 85:15.



Scheme. Enantioselective photoredox catalysis in a continuous flow system for the synthesis of α-amino acid derivatives.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge financial support from the São Paulo Research Foundation – FAPESP (Grant N.: MSF, 2022/15574-1; RCS, 2023/07466-7; KTO, 2023/04020-8; JCP, 2021/06661-5), the Brazilian National Council for Scientific and Technological Development – CNPq (JCP, 308540/2021-2), and the Coordination for the Improvement of Higher Education Personnel – CAPES

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Synthesis of 4-(Phenylchalcogenyl)tetrazolo[1,5-*a*]quinolines: A Novel Bicyclization Approach

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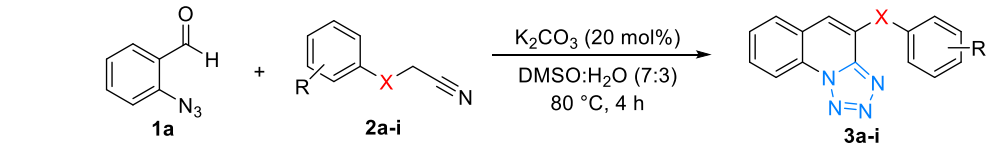
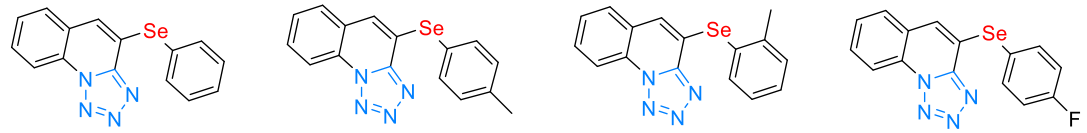
Keywords: *organochalcogen; tetrazoloquinolines; cyclization; heterocycles.*

ABSTRACT

Tetrazoles are a kind of azaheterocycles characterized by a five-membered ring containing four nitrogen atoms and one carbon atom. Quinoline, on the other hand, consists of a benzene ring fused to a pyridine ring. The combination of these two structures leads to tetrazoloquinolines, molecules that have garnered significant attention due to their biological activities and synthetic utility. Incorporating an organochalcogen group into the tetrazoloquinoline nucleus becomes noteworthy. Selenium and sulfur play crucial roles in metabolic pathways, and interest in the chemistry and pharmacology of these compounds has intensified over the years. Herein we describe a satisfactory and environmentally friendly strategy to prepare 4-(arylselanyl) and 4-(arylthio)tetrazoloquinolines with good to excellent yields.

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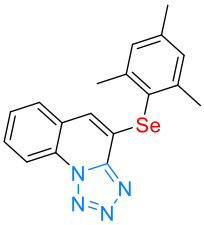
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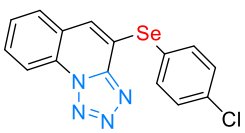
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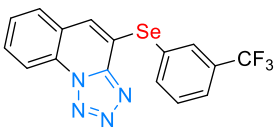
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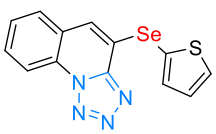
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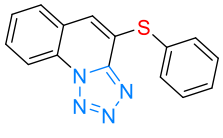
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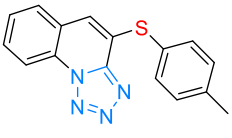
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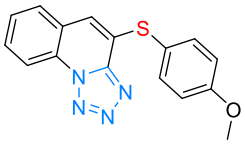
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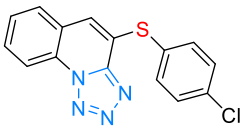
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Convergent synthesis of 2-iminothiazoles containing α-diazo carbonyl groups from 4-haloacetoacetates and thioureas

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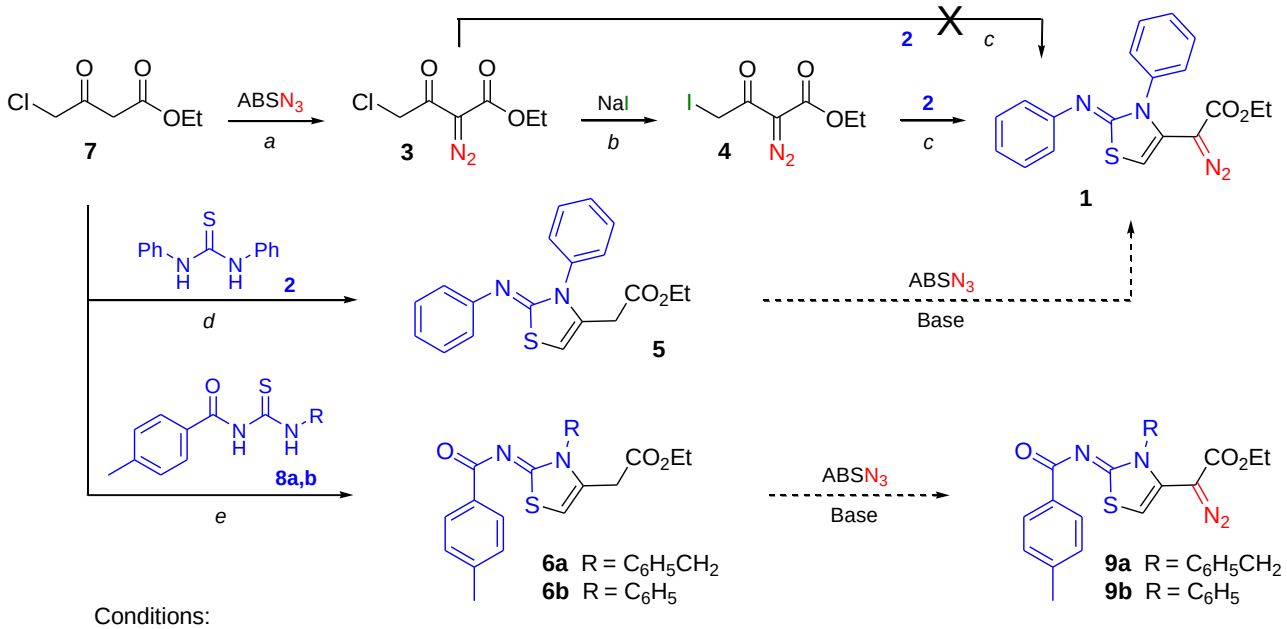
Keywords: *α-Diazo esters, Thioureas, Thiazoles*

ABSTRACT

2-Aminothiazoles are known for their diverse biological activities,[1] while α-diazo carbonyl compounds are valued as versatile building blocks.[2] However, research on the synthesis and reactivity of thiazoles containing α-diazo carbonyl groups remains limited.[3] This study presents the successful synthesis of α-diazothiazolyl ester **1** from *N,N'*-diphenylthiourea (**2**) and functionalized α-diazo esters **3** or **4**, as well as the synthesis of 2-iminothiazole-4-acetates **5** and **6** as substrates for the diazo transfer reaction (Scheme). Initially, the synthesis involved the reaction between *N,N*-diphenylthiourea (**2**) and γ-chloro-α-diazo-β-keto ester **3**, which was readily obtained from ethyl 4-chloroacetoacetate (**7**) through a method developed by us[4] (Scheme 1). However, the expected product **1** was not obtained. Therefore, the chlorine atom in **3** was first replaced with iodine to give the γ-iodo-α-diazo-β-keto ester **4**, which reacted with thiourea **2** to provide 2-iminothiazole **1** with 22% yield. In parallel, 2-iminothiazoles **5** and **6a,b** were synthesized from chloroacetoacetate **7** and the corresponding thioureas **2** and **8** in ethanol under reflux. These molecules are suitable precursors of α-diazothiazolyl esters **1** and **9a,b** through the base-catalyzed diazo transfer reaction, which is currently under investigation.



Conditions:
a: *t*-BuNH$_2$, THF, 3 h, r.t.; *b:* THF, 1 h, r.t.; *c:* THF, 48 h, r.t.; *d:* EtOH, 1 h, reflux; *e:* EtOH, 8 h, reflux.

Scheme. Synthesis of α-diazothiazolyl ester **1** and suitable thiazole precursors for the diazo transfer reaction.

ACKNOWLEDGEMENTS

CNPq, CAPES, FAPESC, INCT-Catálise

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Synthesis, *in vitro* and *in vivo* antitumoral effect against oral squamous cell carcinoma of new dithioethers based on catalyst-free Michael addition of thiols to α-xyloidone

Thaís B. Santos[1*], Sara T. B. Leal[1], Rafaella M. de A. C. Ribeiro[1], Alex de S. C. L. Canuto[2], Bruno K. Robbs[2], Vitor F. Ferreira[3] and David R. da Rocha[1]

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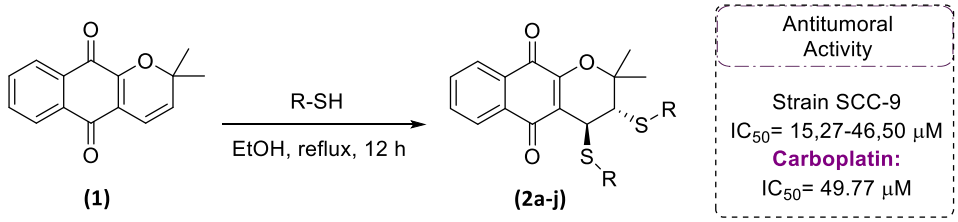
Keywords: *Cancer, catalyst-free synthesis, pyranonaphthoquinones, thia-Michael addition*

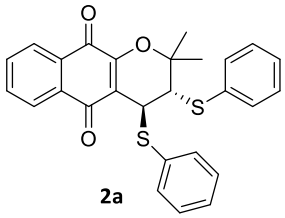
ABSTRACT

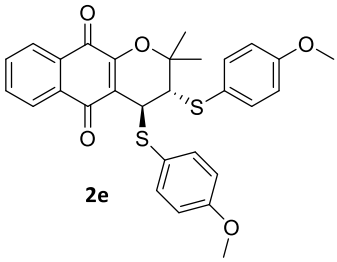
The Michael addition of thiols to α-xyloidone **(1)** led to the formation of ten dithioethers **(2a-j)** with yields between 36-73%. An initial screening against human tongue squamous cell carcinoma (SCC-9) showed an IC_{50} range between 15.27 and 46.50 μM (reference: carboplatin, IC_{50}= 49.77 μM). Dithioethers **2a** and **2e**, qualified in initial tests after evaluation in three different oral squamous cell carcinoma strains, were able to inhibit SCC-9 cell migration by 71.7 and 45.3%, respectively. **2a** showed a promise candidate for antimigratory agent, indicating a lower risk of metastatic cancer. In hemolysis assays, **2a** presented a rate of 1.06%, lower than carboplatin (1.34%). The mechanism of action of these dithioethers showed an induction of cell death by apoptosis and significant formation of reactive oxygen species. The relevant results show the potential of this molecules, obtained in this work in a single step from α-xyloidone for the first time in the literature.[1,2]



2a: R= Ph, 60 %; **2b:** R= 2-MePh, 53 %; **2c:** R= 3-MePh, 40 %; **2d:** R= 4-MePh; 60 %; **2e:** R= 4-OMePh, 61 %; **2f:** R= 4-FPh, 37 %; **2g:** R= 4-SMePh, 73 %;**2h:** R= 4-ClPh, 36 %; **2i:** R= 4-OHPh, 64 %; **2j:** R= 2-Naph, 67 %

Selected Derivatives





- qualified to in vivo assays
- **2a:** promise candidate for antimigratory agent
- lower hemolysis rate
- mechanism of action: cell death by apoptosis
- relevant ROS formation

ACKNOWLEDGEMENTS

FAPERJ, CAPES, CNPq

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Theoretical and Experimental approach to visible light-catalysed 6π-photoelectrocyclization

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1) Department of Fundamental Chemistry, University of São Paulo, USP, 05508-900
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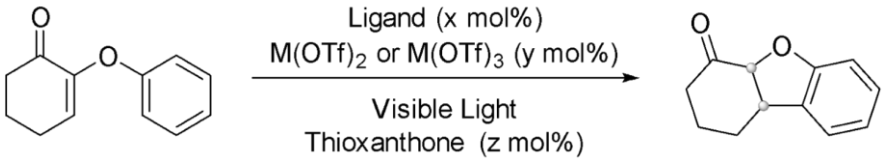
Keywords: *Asymmetric Synthesis, Photocatalysis, DFT*

ABSTRACT

Photocatalyzed reactions are an excellent technique to generate chiral compounds. Combined with Lewis acids, these processes can be visible light driven. This work aims to investigate the effects operating on a recently published 6π catalyzed electrocyclization [1] and explore catalysts that promote efficient visible light driven combining computational and experimental techniques.

Quiral ligands based on bisoxasoline, PyBox and N-Oxide structures coordinating with a metal entity were used to induce enantioselectivity in the studied reaction based on chiral complexation with the substrate. To achieve the triplet state, a photosensitizer is necessary. Efficient iridium photosensitizers are expensive and not commonly accessible. Instead, thioxanthone-based photosensitizers were utilized.

High level DFT calculations shows that neutral structures are more stable. Subsequent TDDFT calculations will examine its absortion and overlap with emission spectra photosensitizer. To prevent background reacitons, the complex that results in the strongest bathocromic shift is desired.



$M(OTf)_n$ = $Mg(OTf)_2$, $Ca(OTf)_2$, $Zn(OTf)_2$ or $Sc(OTf)_3$

ACKNOWLEDGEMENTS

The authors acknowledge the STI-USP, CNPq, CAPES and the São Paulo Research Foundation (FAPESP).

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Efficient Synthesis and *Iodine*-Functionalization of Pyrazoles using KIO_3/PhSeSePh System

João Pedro Senna S. C. Thomaz [1*], Thiago J. Peglow[1], Patrick C. Nobre[1] and Vanessa Nascimento[1]
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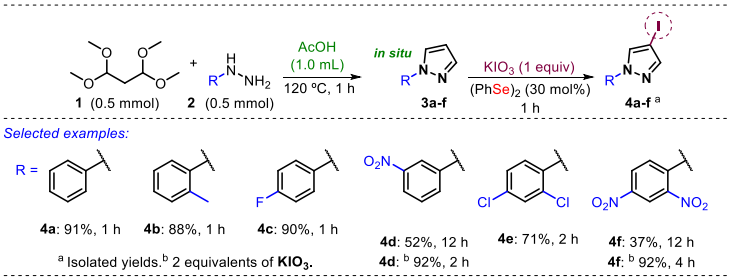
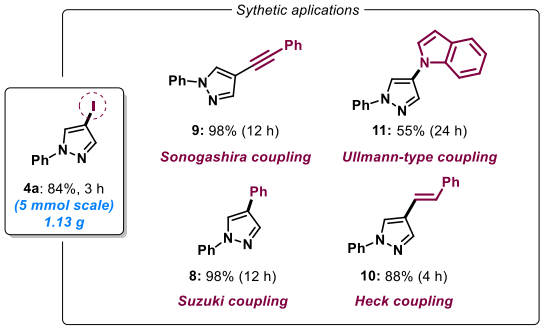
Keywords: *Heterocycles, selenium, iodination.*

ABSTRACT

Pyrazoles are five-membered heterocyclic compounds, containing two adjacent nitrogen atoms, found in a range of compounds with biological properties.[1] Currently, several pharmaceutical products on the market, incorporate pyrazole in their fundamental structure.[2] Furthermore, some derivatives demonstrate important photophysical properties, including very selective fluorescence sensors and high Stokes' shifts.[3] In this context, the 4-iodopyrazoles derivatives stands out in this class because they are important synthetic tools for various cross-coupling reactions. In particular, this becomes interesting since additional functionalization allowing access to more complex and valuable systems.[4] This led to a significant research field whose goal for new synthetic or functionalization routes for these promising structures.[5] In this way, we developed an easy one-pot synthesis of 4-iodopyrazoles using 1,1,3,3-tetramethoxypropane **1** and arylhydrazines **2**, followed by the utilization of a novel iodination system under acidic conditions (Scheme 1). Besides, large-scale product **4a** was used for synthetic applications, obtaining the cross-coupling products in good yields (Scheme 2).



Scheme 1. Scope investigation of 4-iodo-1-aryl-1*H*-pyrazoles **4a-f**. [a-b]



Scheme 2. Synthetic applications for compound **4a**.

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BMOS, UFF, FAPERJ, CAPES, CNPq, INCT-Catalysis.

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Ru(II)-Catalyzed Asymmetric Transfer Hydrogenation of α-Alkyl-β-Ketoaldehydes via Dynamic Kinetic Resolution

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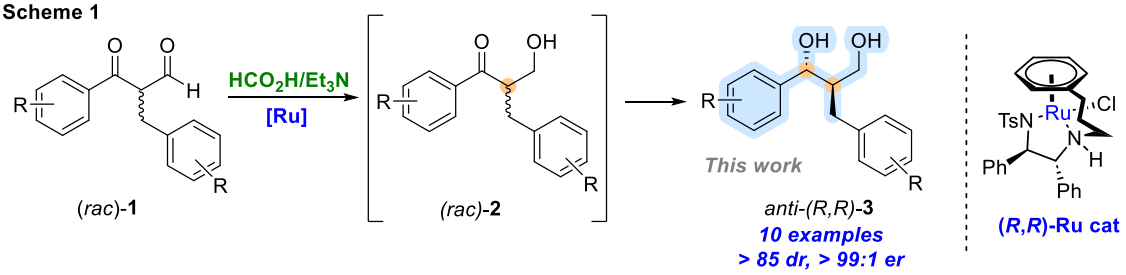
Keywords: *2-alkyl-1-phenylpropane-1,3-diols; ATH-DKR; Noyori-Ikariya catalysts; ruthenium; reduction; asymmetric catalysis; contiguous stereocenters; hydrogen bonding, oxetanes*

ABSTRACT

The 2-alkyl-1-phenylpropane-1,3-diols are structural motifs containing two adjacent stereocenters that are prevalent in various natural products. Notable examples include the lignans (-)-podophyllotoxin and (-)-sesaminone, as well as the flavonoid (+)-homoferrugenone [1–3]. The transition metal (TM)-catalyzed asymmetric hydrogenation (AH) of α-alkyl-β-ketoesters stands out as a straightforward approach to access these key intermediates. This method allows for the creation of two contiguous stereocenters in one single step through a dynamic kinetic resolution (DKR) [4–6]. However, the α-alkyl-β-ketoesters pose challenges in TM-AH-DKR reactions when compared to cyclic β-ketoesters or acyclic α-heteroatom-substituted β-ketoesters.

In this work, the (*R*,*R*)-Teth-TsDPEN-Ru(II) complex promoted the one-pot double C=O reduction of α-alkyl-β-ketoaldehydes through asymmetric transfer hydrogenation/dynamic kinetic resolution (ATH-DKR) under mild conditions. In this process, ten *anti*-2-benzyl-1-phenylpropane-1,3-diols (85:15 to 92:8 dr) were obtained in good yields (41-87%) and excellent enantioselectivities (>99% ee for all compounds) (Scheme 1).

Scheme 1



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SEPTEMBER 23-27 2024
19BMOS
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Exploring the reactivity of unsaturated organoboron compounds in cycloadditions and related reactions

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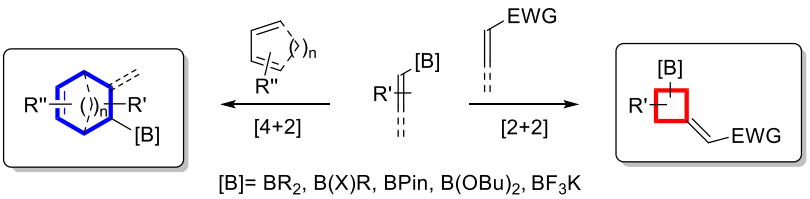
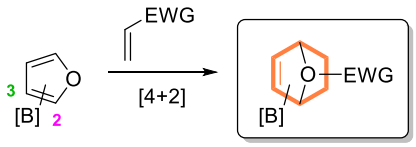
Keywords: *Organoboron compounds, cycloaddition reactions, rational design.*

ABSTRACT

Organoboron compounds show remarkable reactivity and selectivity and have been successfully used in diverse reactions in organic synthesis. We have contributed to the study and the development of cycloadditions and related reactions of unsaturated organoboron compounds. In particular, we have investigated and rationally designed varied Diels-Alder reactions of boron-substituted dienophiles[1] and dienes.[2] For example, we have studied the Diels-Alder reactions of dialkyl- and alkylhalovinylboranes, and alkenyl- and allenylboronates, including asymmetric and organocatalytic variants. In addition, we have explored the Diels-Alder reactions of boron-substituted furans, showing that trifluoroborates exhibit exceptional reactivity and selectivity. More recently, we have examined the thermal [2+2] cycloadditions of alkenyl- and allenylboronates. To demonstrate their synthetic potential and also to access structurally diverse molecules, the cycloadducts have been submitted to a range of useful chemical transformations. Theoretical calculations have been performed to shed light into the reaction mechanisms and to aid the further development of new reactions. In this talk, our latest results in this area will be presented.



[B]= BR_2, B(X)R, BPin, $B(OBu)_2$, BF_3K



[B] = BF_3K, BF_3TBA, BMIDA, BPin, $B(OH)_2$

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Synthesis of *N*-Heterocyclic functionalized arylselanyl benzenes

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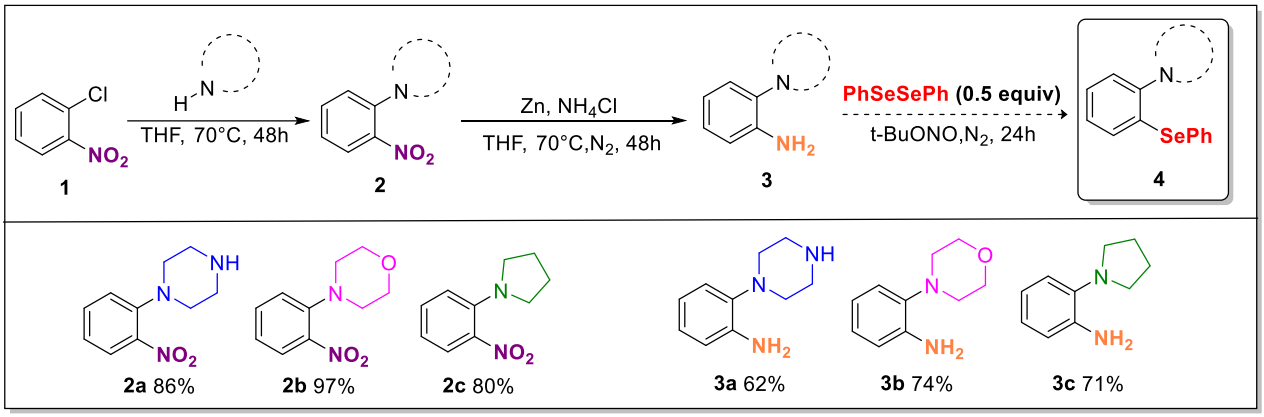
Keywords: *synthesis, N-heterocycles, selenium.*

ABSTRACT

N-Heterocyclic compounds are crucial in medicinal chemistry due to their unique chemical properties and biological activities. These compounds are integral to many drugs across various therapeutic classes, including antibiotics, anticancer agents, and antivirals, making them essential in the development of new treatments for a wide range of medical conditions.[1] Selenium-containing organic compounds are of significant importance due to their applications in organic synthesis, diverse biological activities, and potential therapeutic uses. These compounds exhibit antioxidant, anticancer, antiviral, and anti-inflammatory properties, making them valuable in the development of treatments for various diseases.[2] Thus, the search for molecules that combine these two types of structural units has become attractive and has been explored by our research group in recent years.[3] Thus, in this work, we describe our efforts to synthesize *N*-Heterocyclic functionalized arylselanyl benzenes **4**, aiming to apply the obtained products in the field of pharmacology (Scheme 1).



Scheme 1

We start our work with the synthesis of nitro compounds **2** through substitution reactions of 2-chloronitrobenzene with *N*-heterocycles, such as piperazine, morpholine, and pyrrolidine. The products were obtained in good yields and were subjected to reduction reactions to the respective anilines **3**, using a mixture of Zn and NH_4Cl. All the products were obtained in good yields and their structures were confirmed by NMR analyses. The transformation of the respective anilines **3** into *N*-Heterocyclic functionalized arylselanyl benzenes **4** is currently under development (Scheme 1).

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Synthesis new hypervalent heterocyclic Tellurium compound containing Te-N bond

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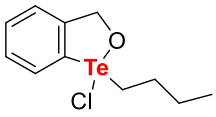
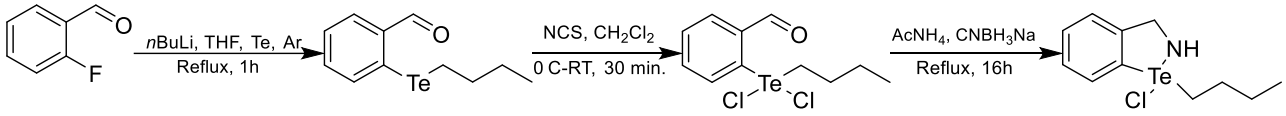
Keywords: *Organotellurium, hypervalent compounds, N-heterocycles.*

ABSTRACT

Tellurium compounds are good antioxidants, anti-inflammatory, immuno-modulating with potential antitumor activity[1], and hypervalent ones are known to be powerful cathepsin inhibitors[2]. Organotellurane **1**, for example, has shown good *in vitro* activity toward *L. amazonensis*[3] (IC_{50} = 5,7 μM, SI = 6), which is attributed to cathepsins inhibition. Herein, a method for synthesizing the nitrogenated analog of **1** is described. So, BuTe- moiety was inserted in 2-fluorobenzaldehyde followed by the tellurium oxidation in **2, in** 70% isolated yield, by sulfuryl chloride. Finally, reductive amination of **3**, in 50% isolated yield, led to the desired cyclic tellurane **4** in 5% isolated yield.



1



2 (70%) **3** (50%) **4** (5%)

Figure 1 – Synthetic route for compound 4.

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Direct amination of selenium containing α-cyanohydrin acetates

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Keywords: *α-Aminonitriles, selenium-containing compounds, direct amination.*

ABSTRACT

α-Aminonitriles are present in a huge variety of bioactive compounds and are versatile building block in organic synthesis. Several catalyzed methodologies, including the Strecker reaction, α-cyanation of amines, and direct amination are described in literature.[1,2] Among them, direct amination remains relatively underexplored. Selenium containing compounds also exhibits diverse biological activity, such as antitumoral, antimicrobial and antioxidant.[3] Herein, the synthesis of novel α-aminonitriles selenides via non-catalyzed direct amination of cyanohydrin acetate (**1**) was achieved by mixing in an amine, in a solventless reaction. (Figure 1). α-Aminonitriles selenides **3a-f** were obtain without the necessity of extraction, and isolated in 33-69% yield.

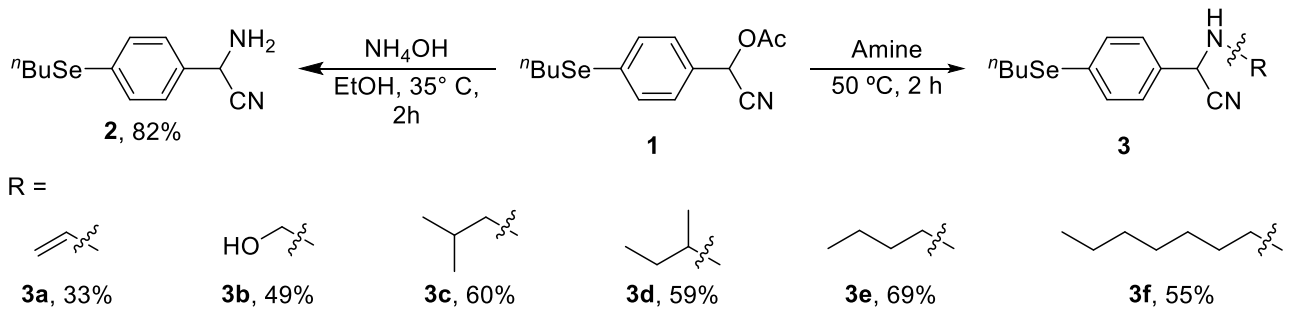

Figure 1 – Synthetic route for α-aminonitriles selenides.

This methodology leads to a simple and efficient synthesis of α-aminonitriles, with relatively good yields.

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Developing a sustainable approach for the synthesis of Phosphorus-containing amino acids

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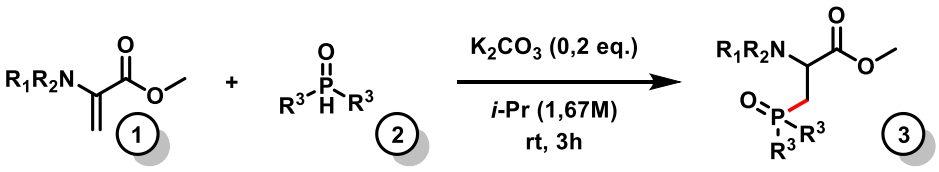
Keywords: *Phospha-Michael addition, stereoselective synthesis, amino acid functionalization.*

ABSTRACT

Amino carboxylic-phosphonic acids are prevalent in both natural products and synthetic bioactive molecules.[1] In this context, the artificial synthesis of non-hydrolyzable *C*-phosphorylated amino acids presents a significant area of research. The synthesis and utilization of α-amino acids bearing a phosphorus moiety have seen a resurgence of interest since the discovery of (*L*)-phosphinothricin in 1970. Notably, phosphorus-containing amino acids present a rich structural diversity, with functionalities that mimic carboxylates, thus serving as biologically active scaffolds.[2] Moreover, obtaining chiral products is crucial to the fine chemical industry, encouraging the development of asymmetric methodologies. This project focuses on the addition of derivatives of diphenylphosphine oxide and of phosphonates to dehydroalanine, yielding a range of phosphorus-containing amino acids under mild, base-catalyzed conditions with remarkable yields reaching up to 99%. An enantiomeric (using catalyst) and a diastereoisomeric (using chiral substrate) version of this reaction is currently under development.



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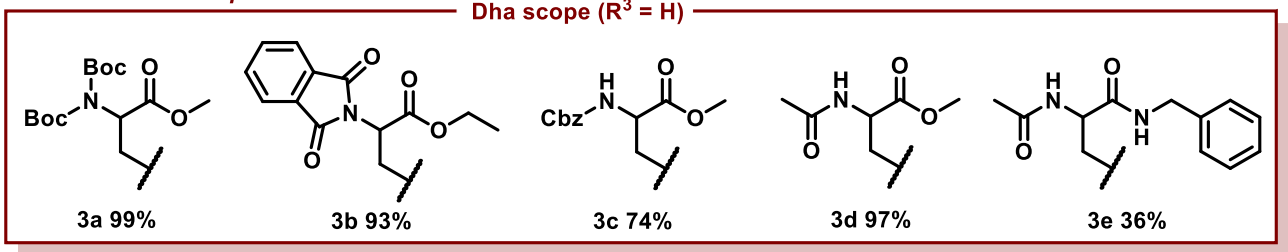

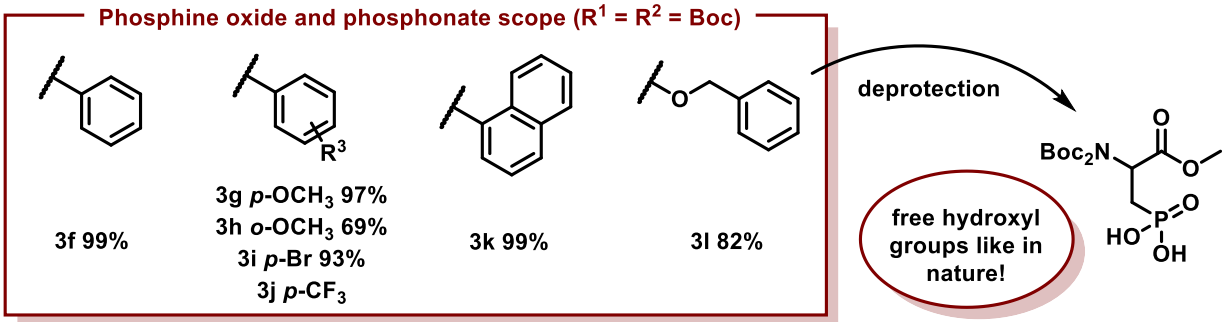

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PEC-NH_2 as a novel organocatalyst for the synthesis of 2-arylselanyl-1,3-diketones

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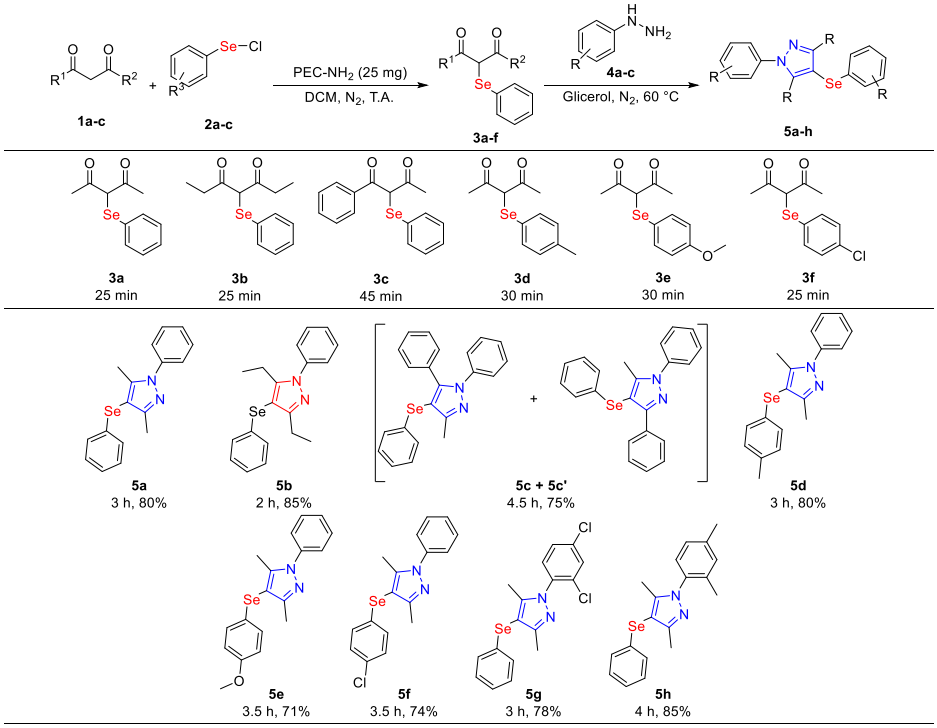
Keywords: *Organocatalysis, pectin, arylselanyl-diketones, pyrazoles.*

ABSTRACT

Organocatalysis is often ranked as one of the greenest catalysis strategies mainly due to its advantages over conventional metal catalysis, in which noble and potentially toxic metals are employed. Pectin (Pec) is a natural linear polysaccharide built up of α-(1→4)-*D*-galacturonic acid units in which some of the carboxyl groups are esterified with methanol or/and acetyl groups at the O-2 or/and O-3 positions. To the best of our knowledge, the use of Pec in organocatalysis was not reported, likely due to its low reactivity. but the highly functionalized backbone of Pec (–OH and –COOH groups, mostly) offers possibilities to increase its reactivity through derivatization. To verify this hypothesis, we synthesized a Pec-derivative functionalized with amino groups (PEC-NH_2) and investigated its ability to catalyze the synthesis of 2-arylselanyl-1,3-diketones. 1,3-Dicarbonyl compounds are attractive key intermediates in the synthesis of important compounds such as pyrazoles, benzodiazepines, isoxazoles, and pyrroles, for example. Herein we investigate the organocatalytic activity of PEC-NH_2 in the synthesis of 2-arylselanyl-1,3-diketones, which can be applied for the direct synthesis of chalcogen-pyrazoles.



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Potassium Persulfate Promoted the One-Pot *Seleno*-Functionalization of Pyrazoles under Acidic Conditions

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Keywords: *Selenium, heterocycles, C-H activation.*

ABSTRACT

In modern organic chemistry, the focus on environmental sustainability and efficiency is paramount. The "one-pot" reaction, is favored for its practicality as it reduces the need for multiple purification steps, thus aligning with sustainable practices.[1] In this sense, methods for obtaining *N*-heterocycles through one-pot procedures have emerged as an eco-friendly alternative in the preparation of added-value molecules, such as that containing pyrazoles core.[2] This *N*-heterocycles stands out as they are present in various drugs like Celecoxib and Crizotinib,[3] and agrochemicals such as Fluazolate and Fipronil.[4] Another hot scaffold, organoselenium compounds, has shown significant biological and redox-modulating properties, particularly in medicinal contexts.[5] Herein, we report a practical approach for the selective and one-pot synthesis of 4-selanylpyrazoles **5** or 4,5-bis(selanyl)pyrazole **6**. For this, it was used 1,1,3,3-tetramethoxypropane **1** (1 equiv) and aryl hydrazines **2** (1 equiv) in acetic acid at 120 °C for obtaining *in situ* the precursors 1-aryl-1*H*-pyrazoles **3**. Next, the selective selenylation reaction of the pyrazole intermediate **3** is promoted by diorganyl diselenides **4** and potassium persulfate (Figure 1). The products were proposed based on the ^{1}H NMR of precursor **3a** (Figure 2).[3a]

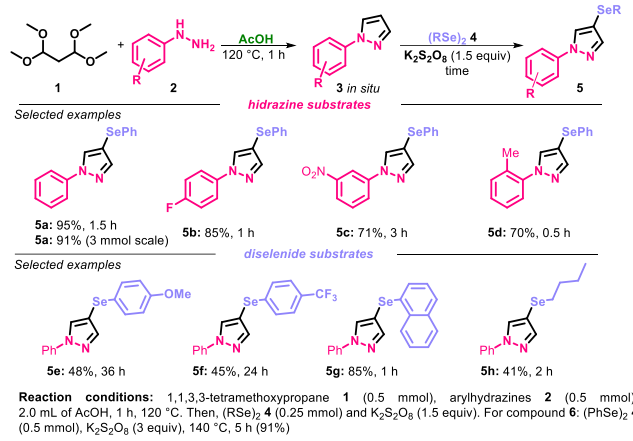

Figure 1. Selected scope of 1-aryl-4-(organylselanyl)-1*H*-pyrazoles **5a**-**h**.

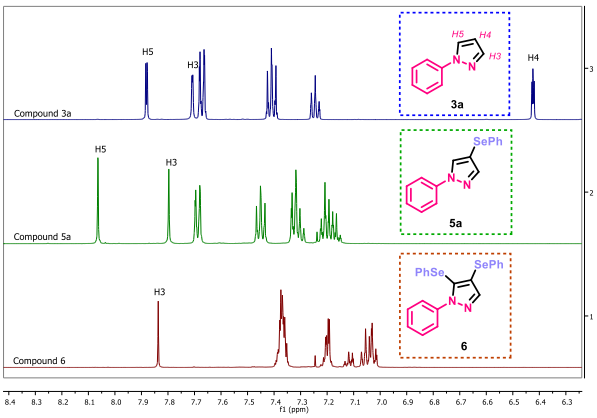

Figure 2. ^{1}H NMR experiments.

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Biocatalytic oxidation of glycerol carbonate promoted by laccase-mediator system

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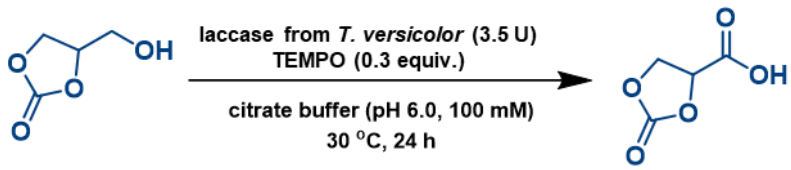
Keywords: *Biocatalysis, laccase, oxidation.*

ABSTRACT

Glycerol carbonate has been recognized as an important compound due to its eco-friendly nature, versatility in chemical synthesis, and wide-ranging industrial applications. Derived from glycerol, it serves as a precursor for polymers and pharmaceuticals, enhancing the performance and sustainability of materials and drugs.[1,2] Additionally, the oxidation of glycerol carbonate using biocatalysis represents a sustainable approach, further expanding its utility and contributing to developing an environmentally friendly chemical process. Therefore, we present the main results for the biocatalytic approach based on the laccase-mediator system to obtain the 2-oxo-1,3-dioxolane-4-carboxylic acid from glycerol carbonate. The combination of *Trametes versicolor* laccase and TEMPO was identified as an optimal oxidation system, using citrate buffer as the reaction medium. The glycerol carbonate oxidation process achieved a conversion rate of 98.9% at 30°C after 24 hours, with 99% selectivity for the intended product.



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BAICALEIN DERIVATIVES AS PROMISSING ANTICANCER AGENTS

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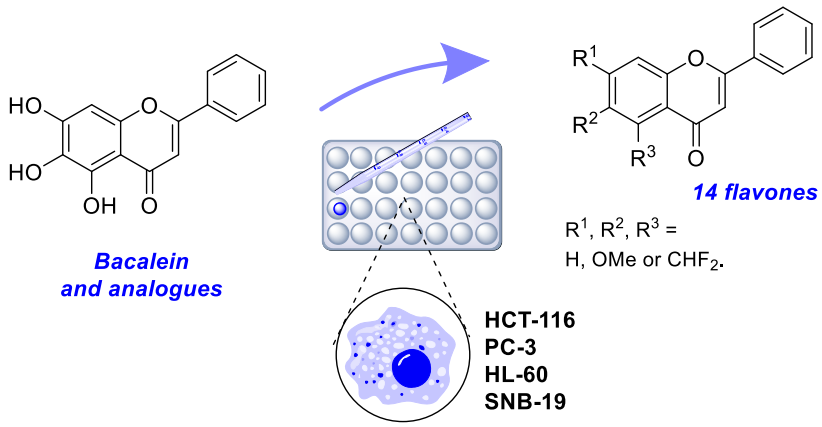
Keywords: *medicinal chemistry, anticancer, baicalein derivatives*

ABSTRACT

Baicalein is a natural flavone from *Scutellaria baicalensis* that exhibits antiproliferative activity in the micromolar range against human colon adenocarcinoma cell lines (SW480, HT-29, DLD-1)[1,2]. Thus, baicalein presents a promising scaffold for the design of new flavones with different substitution patterns for the evaluation of anticancer activity and structure-activity relationship (SAR) studies. The method consisted of modifications of baicalein and its analogues in different methoxylated and difluoromethylated patterns in the flavone A ring[3,4]. Fourteen baicalein derivatives were synthesized with yields ranging from 40 to 99%. These compounds will be evaluated for potential anticancer activity in HCT-116, PC-3, HL-60 and SNB-19 cell lines and investigation of the mechanism of action and SAR studies.



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Orange Peel Ashes as Catalyst for Glycerol Carbonate Synthesis

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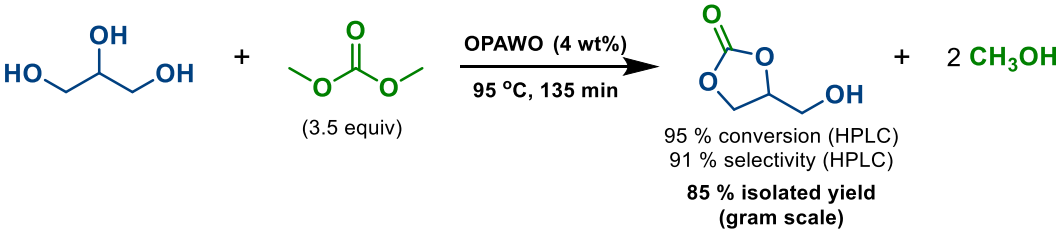
Keywords: *glycerol, biomass, catalysis.*

ABSTRACT

Glycerol carbonate (GC) is a versatile glycerol derivative[1] used as solvent, an ingredient in surface cleaners, dyes, plastics, cosmetic formulations, and an intermediate in polymer syntheses.[2] The transesterification reaction of dimethyl carbonate with glycerol catalyzed by basic metallic oxides is generally the most affordable approach to preparing GC. Biomass ashes are a rich source of alkaline metallic oxides,[4] thus a potential catalyst for GC synthesis. In this context, Brazil is the largest orange producer in the world,[3] resulting in large amounts of residual orange peels. Herein, we present a synthetic protocol using K_2O and CaO-rich orange peel ashes obtained after essential oil extraction, calcination at 650 °C, for 5 h, and designated as Orange Peel Ashes Without Oil (OPAWO). A Design of Experiments (DoE) with three-level and four-factor was employed to identify the optimal reaction conditions, which were determined to be a 1:3.5 ratio of glycerol and dimethyl carbonate, 4 wt% of catalyst at 95°C for 135 minutes. Under these conditions, GC was prepared with 85 % isolated yield.



Scheme 1. Synthesis of Glycerol Carbonate using Orange Peel Ashes Without Oil as catalyst.

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Design, synthesis and biological activity of menadione-1,2,3-triazole chalcogenides

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Keywords: selenium; menadione; organochalcogens.

ABSTRACT

Menadione and organochalcogen compounds are valued by chemists for their biological properties and versatility in organic synthesis.[1,2] Our study aimed to design a combination of these scaffolds into a unique structure to achieve molecules with relevant biological profile. Calcogenonaphthoquinone-1,2,3-triazole were synthesized via a *"click"* reaction between azide **1** derived from menadione and alkyne **2,** containing chalcogen atoms (Se and S), catalyzed by Cu(I).[3] The method proved to be effective in the presence of electron-withdrawing and electron-donating groups linked to the aromatic rings of chalcogenides. Furthermore, it was also possible to evaluate different substituents in the R_1 portion of the menadione. Through this protocol it was possible to obtain 16 new molecules with moderate to good yields (34-93%) in short reaction times. The compounds exhibited promising activity against *Mtb* H37Rv, especially compounds **3a**, **3c**, **3g**, and **3h**, with MIC values < 7.37 µM.

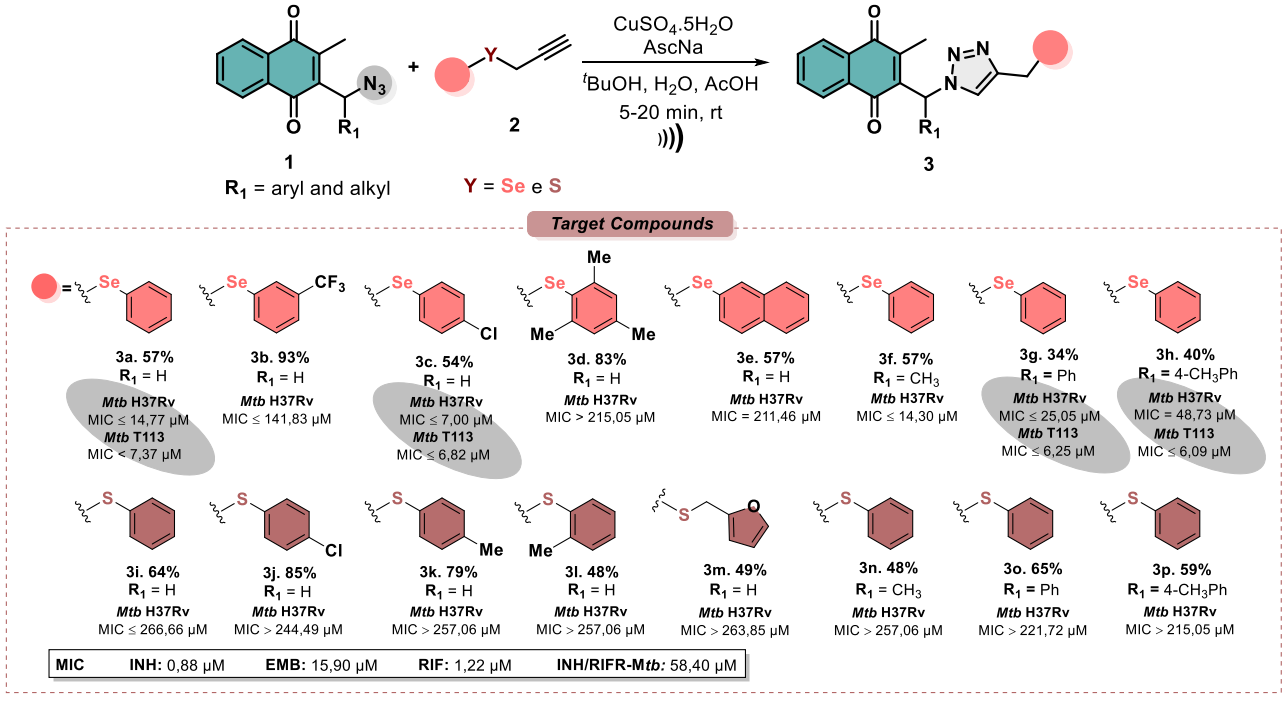

Figure 1. Synthetic route for obtaining chalcogenonaphthoquinone-1,2,3-triazole derivatives.

ACKNOWLEDGEMENTS

PPGQ-UFF, CAPES, FAPERJ and CNPq.

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Electroreduction of elemental Sulphur for the synthesis of 2,5-disubstituted thiophenes

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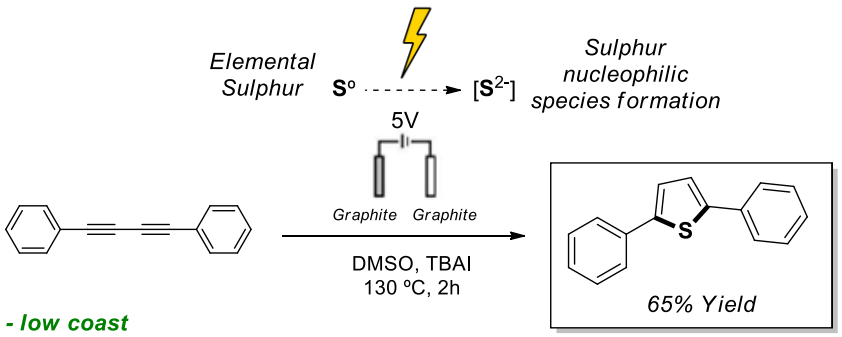
Keywords: *Chalcogenophenes, electrocatalysis, cyclization.*

ABSTRACT

2,5-Disubstituted chalcogenophenes are a class of compounds widely explored and applied in many research fields, particularly in materials science.[1] The main motivation for synthesizing these heterocycles is their π-conjugation and rigidity, which are often associated with conductive materials in optoelectronic devices.[2] On the other hand, electrocatalysis is an important and growing field in organic chemistry, offering greener and innovative synthetic routes with high selectivity and efficiency,[3] It is well-known that sulphur can be reduced to their binucleophilic species with an applied potential.[4] In this context, a new system for obtaining 2,5-disubstituted chalcogenophenes through electroreduction of elemental chalcogen using graphite as electrode and cyclization from 1,3-butadiynes has been developed. The optimal reaction conditions were established using elemental sulphur and grafite as electrode. The corresponding 2,5-diphenylthiophene was obtained in 65% yield. With these exciting results, the prospects include varying the scope of 2,5-diarylthiophenes and expanding the reaction to synthesize selenophenes analogues.



- low coast
- fast time reaction
- strong reducing agents and additive free conditions

Several examples were synthesized with this metodology

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Synthesis of Tetrahydroimidizalone-Dihydropyrimidinone hybrids

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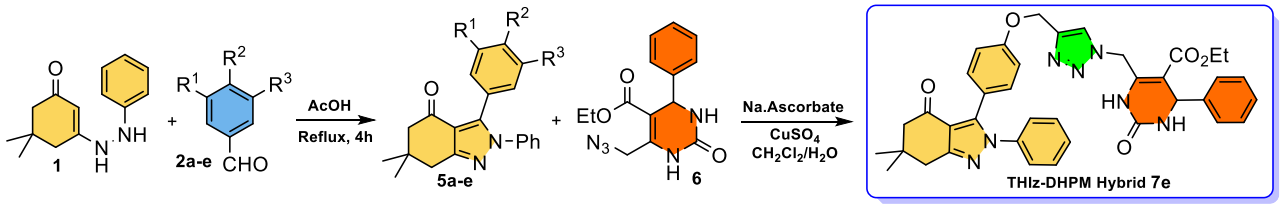
Keywords: *Molecular Hybridization, Tetrahydroindazolones, Dihydropyrimidinones.*

ABSTRACT

Tetrahydroimidizalones (THIz) are important scaffolds in Medicinal Chemistry. They are active as protein kinases inhibitors,[1] anti-cancer agents[2] or antimicrobials.[3] Likewise, Dihydropyrimidinones (DHPM) are cytotoxic against several cancer cell lines.[4]

The hybridization of these two heterocyclic compounds may lead to the discovery of more efficient drugs with reduced side effects.[5] Thus, the easy access of THIz from the reaction of enamino-hydrazine **1** and substituted aldehydes **2a-e**, prompt us to prepare a set of 2,3-diaryl-tetrahydroindazol-4-ones **5a-e** in good yields. The click CuAAC reaction[6] of THIz **5e** and azido-DHPM **6** afforded the hybrid compound **7e** with a non hydrolyzable triazole link in 81% yield after purification (Scheme 1 and Table 1).



Scheme 1: General scheme for the synthesis of **THIz-DHPM** hybrid compounds **7e**.

Table 1. Yield of compounds **5a-e** and hybrid THIz-DHPM **7e**

Entry	Compound	R1	R2	R3	Yield (%)
1	**5a**	H	H	H	70
2	**5b**	H	OMe	H	69
3	**5c**	H	OMe	OMe	72
4	**5d**	OMe	OMe	OMe	75
5	**5e**	H	OPropargyl	H	77
6	**7e**	-	-	-	79

The antibacterial and anticancer activities of THIz and THIz-DHPM hybrid against Gram positive/negative and a set of tumoral cell lines, respectively, are under current investigation.

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One-Pot Synthesis of (+)-Nootkatone via Photooxidation of (+)-Valencene

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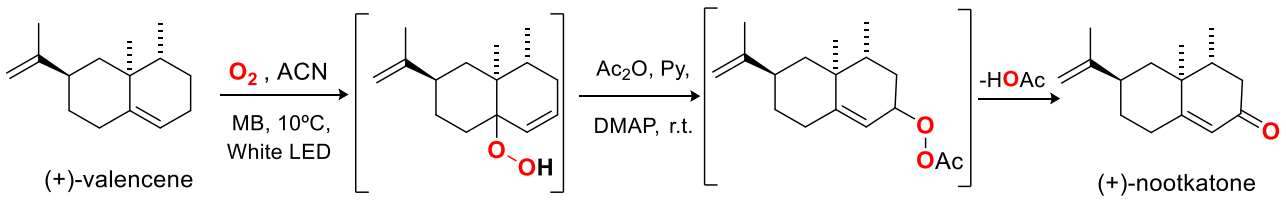
Keywords: *photooxygenation, one-pot synthesis, Nootkatone.*

ABSTRACT

(+)-Nootkatone is a high-value compound, very regarded in the flavoring and fragrance industry for its characteristic grapefruit aroma and low perception threshold. Additionally, (+)-nootkatone is used as a food additive and possesses insecticidal activity[1], which highlights its versatility and contributes to its significant commercial value, especially given its low natural abundance. Herein, we describe the semi-synthesis of (+)-nootkatone from commercial (+)-valencene using a one-pot photooxygenation followed by an allylic rearrangement and E_2 elimination.

Our protocol involves the photooxidation of (+)-valencene with O_2 and methylene blue (MB), followed by the Schenk rearrangement, acetylation of the hydroperoxides and HOAc elimination for the formation of (+)-nootkatone (Scheme 1), using an adapted methodology previously developed in our laboratory.[2] To date, we have succeeded in obtaining (+)-nootkatone in overall yields up to 13% in batch. We are currently optimizing this protocol in batch to evaluate the initial reaction conditions, and subsequently translate this to continuous flow conditions.



Scheme 1. (+)-Nootkatone synthesis.

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Benzo[*f*]indole-4,9-dione derivatives: synthesis and evaluation as potent antitumor agents to suppress the growth of triple-negative breast cancer

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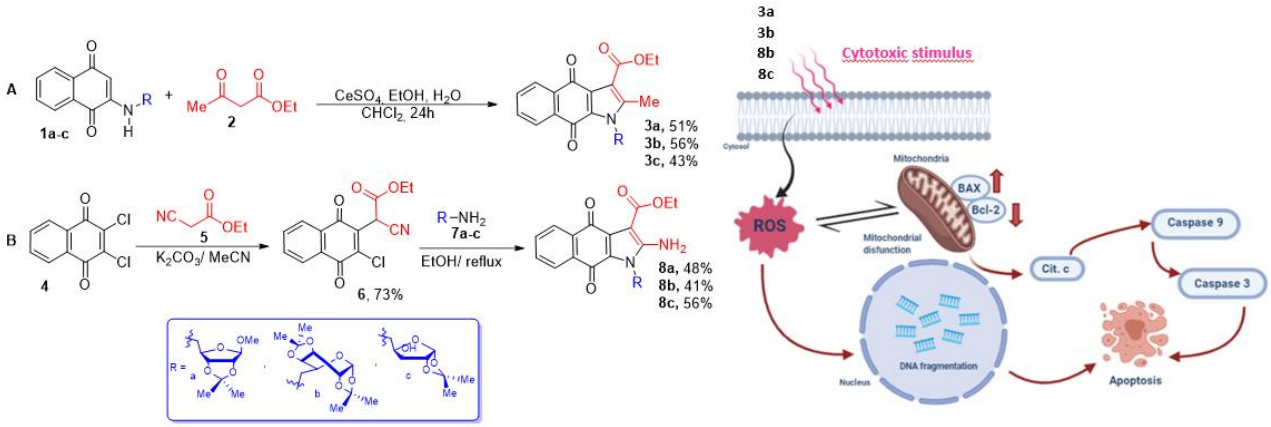
Keywords: *benzo[f]indole-4,9-dione, antitumor activity, triple-negative breast cancer.*

ABSTRACT

This work describes the synthesis and evaluation of the antitumor activity against triple-negative breast cancer (TNBC) of two classes of benzo[*f*]indole-4,9-dione glycoconjugates **3a-c** and **8a-c**. The first route utilizes cerium(IV)-mediated oxidative free radical cyclization involving 1,4-amino-naphthoquinones and ethyl acetoacetate (Scheme 1A). The second consists of the nucleophilic substitution of 2,3-dichloro-naphthoquinone by the ethyl cyanoacetate (Scheme 1b), followed by the replacement of the second chlorine atom by the aminocarbohydrates.

Glycoconjugated quinones **3a-c/8a-c** have been tested for TNBC and four derivatives can induce apoptotic cell death by increasing reactive oxygen species (ROS), causing DNA damage and inducing cell cycle arrest in the G2/M phase. Furthermore, we showed that the four benzo[*f*]indole-4,9-dione derivatives can induce caspase cleavage, thereby activating the intrinsic apoptosis pathway. These results suggest that compounds are potent cytotoxic agents and offer new possibilities for the development of a series of compounds for the treatment of TNBC and other cancers.



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Ruthenium-Catalyzed Chemo- and Regioselective Alkenylation of Flavones with Alkenes through C-H Activation

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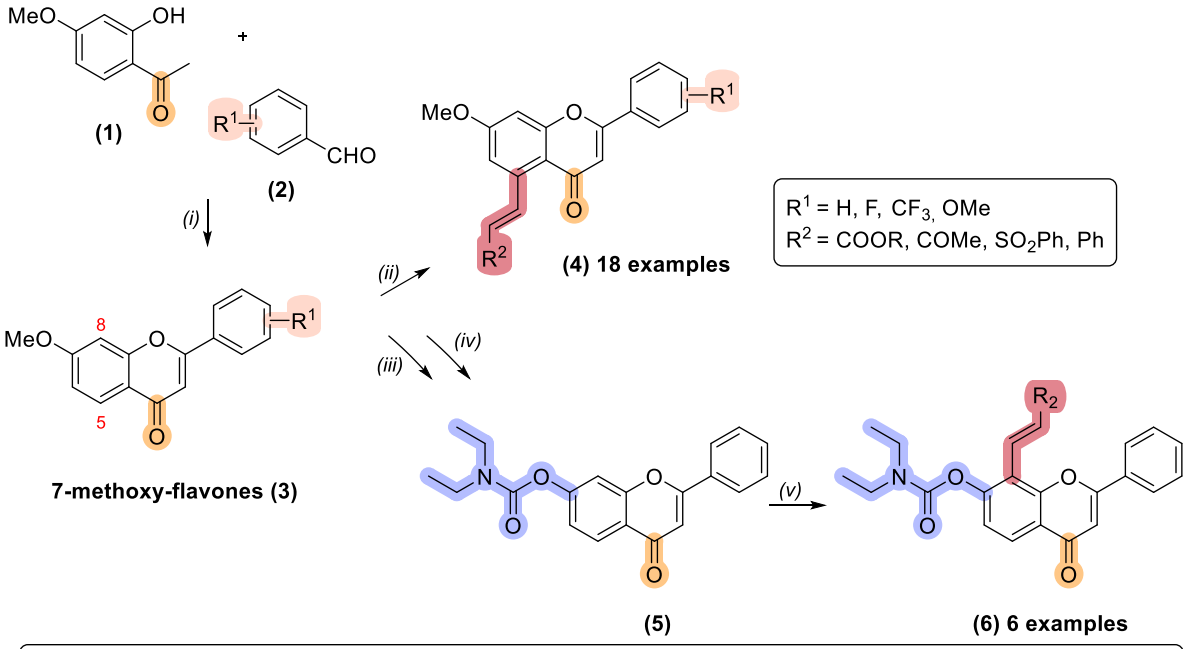
Keywords: *C-H activation, Ruthenium, Alkenylation.*

ABSTRACT

Flavones are a diverse group of natural products commonly found in plants. These secondary metabolites exhibit several biological activities such as anti-inflammatory, antioxidant, and antitumor. Therefore, developing methods for the synthesis of functionalized flavones is extremely relevant.[1] Transition-metal-catalyzed C-H bond olefination of arenes has been reported by employing several directing groups such as carbamates using ruthenium and rhodium complexes as catalysts. [2-4] In this work, alkenylated flavones were prepared by ruthenium catalyst with good yields (up to 92%) (**Scheme 1**). The 7-methoxy flavones **(3)** were obtained using **(1)** and **(2)**.[5] Then, 5-alkenylated **(4)** and 8-alkenylated **(6)** flavones were synthesized by the keto and *O*-carbamate-directing group, respectively. In addition, in the presence of the carbamate group at C7 a chemo and regioselective process was observed. The flavone **5** coupled with alkenes exclusively to give 8-alkenylated products.



Scheme 1: Synthesis Alkenylated Flavones.

ACKNOWLEDGEMENTS

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Mechanistic investigation of Pd-photocatalyzed Heck reaction

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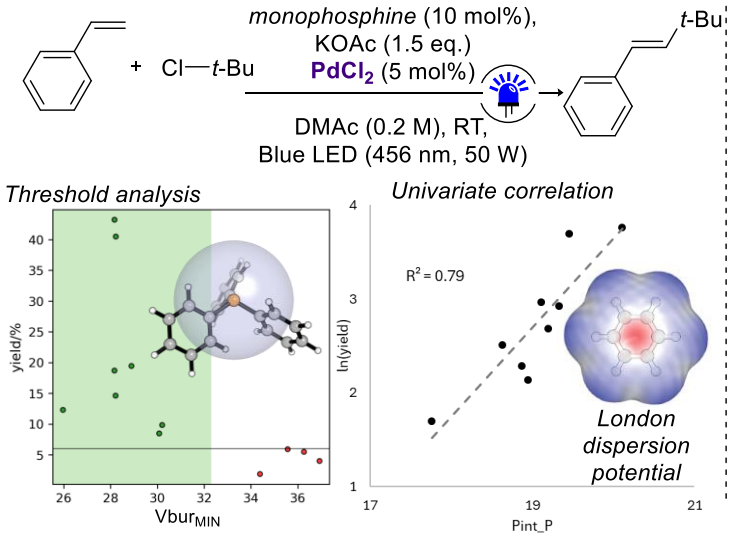
Keywords: *Photocatalysis, Palladium, Parametrization.*

ABSTRACT

Coupling reactions have proven to be incredibly useful in organic synthesis, both in academia and industry, and palladium as a catalyst proves to be extremely efficient and versatile, where in addition to coupling it is also capable of cascade reactions.[1] The development of these reactions via photochemical pathway allows access to reactivities not possible via traditional thermal route.[2] The understanding of how the palladium is modulated by the phosphine ligands is essential for an efficient synthesis. In this context, key steps for understanding the catalytic cycle were investigated.[3] Reactivity threshold analysis indicated the presence of a maximum volume of phosphine is required to complete the catalytic cycle, which corroborates the literature of the requirement for a bisligated palladium.[4] The correlation of the reactive phosphines indicated a univariate trend between yield and the non-covalent interaction London dispersion potential.[5] NMR and DFT studies are being carried out to full elucidate the mechanism.



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Base mediated divergent intramolecular cyclization of β-enamino diketones: a diversity-oriented synthesis of *N*-heterocycles

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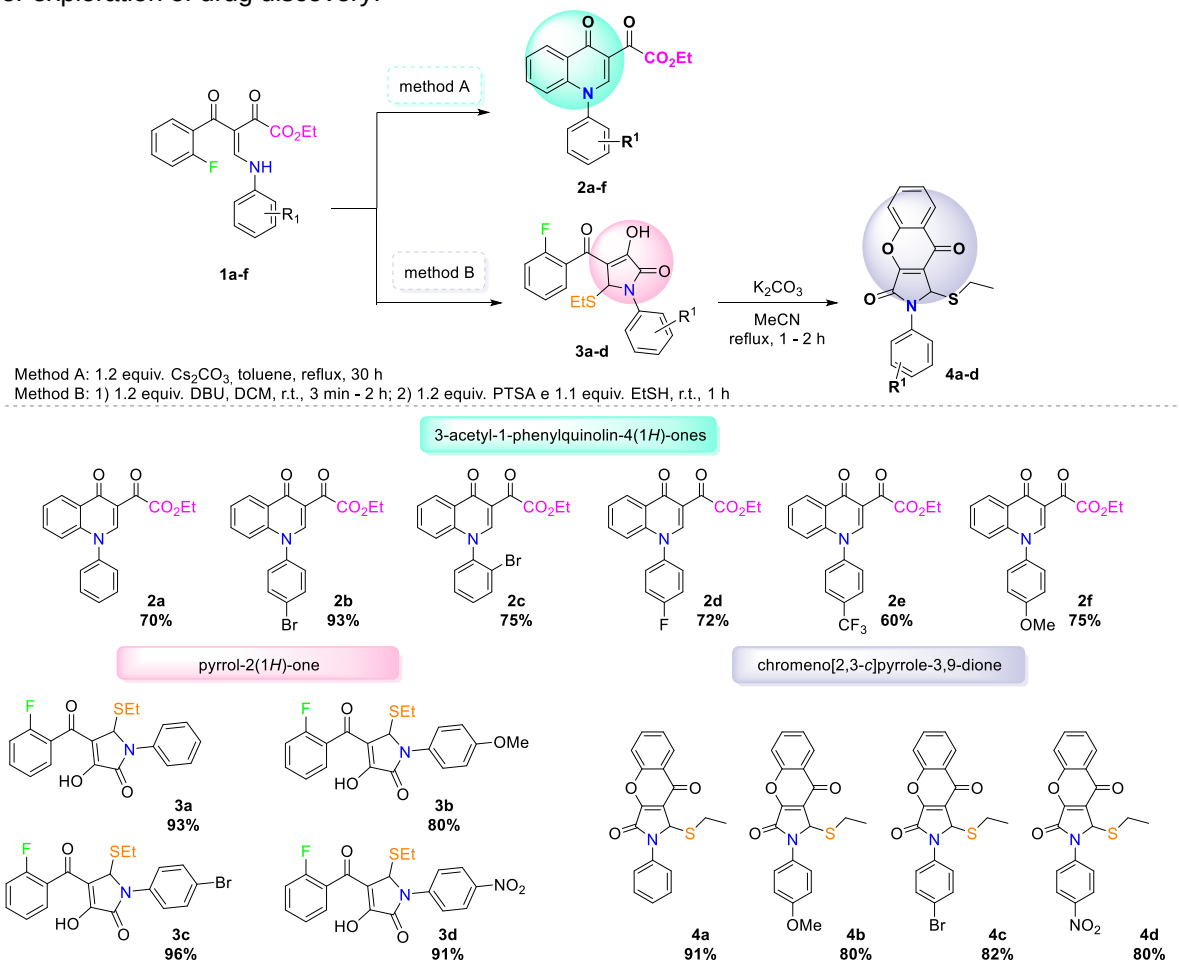
Keywords*: regioselective*, *diversity-oriented synthesis, β-enamino diketone*

ABSTRACT

This work describes the diversity-oriented synthesis of quinolin-4(1*H*)-one vs. pyrrol-2(1*H*)-one or chromeno[2,3-*c*]pyrrole-3,9-dione derivatives through base-mediated intramolecular cyclization of β-enamino diketones. A series of 3-acetyl-1-phenylquinolin-4(1*H*)-ones **2** was prepared using Cs_2CO_3 as a promoter of the intramolecular nucleophilic aromatic substitution of β-enamino diketone **1** in toluene at reflux. In contrast, starting material **1** in DCM at room temperature in the presence of DBU[1] gave the corresponding pyrrol-2(1*H*)-one **3** via intramolecular nucleophilic acyl substitution and a sequential reaction with ethanethiol. In addition, the intramolecular annulation of **3** using K_2CO_3 in MeCN at reflux provides a fascinating fused chromeno[2,3-*c*]pyrrole-3,9-dione **4**. This diversification process provides access to an expanded chemical space for the further exploration of drug discovery.



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Molecular docking and dynamics of AKT1 and *N*-heterocycles on the search for novel anticancer compounds

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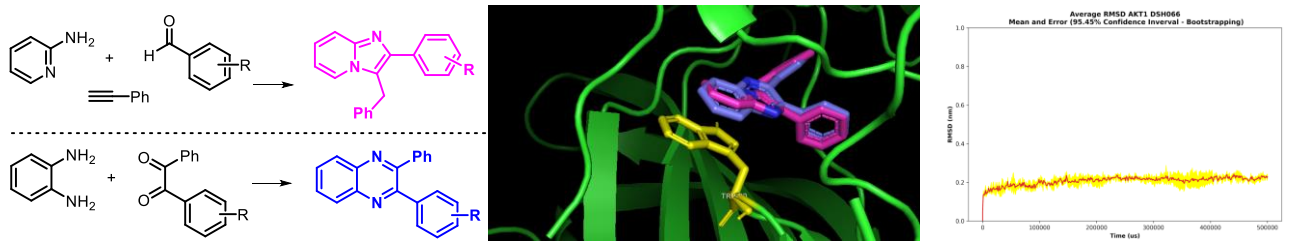
Keywords: *anticancer, heterocycles, simulation, molecular docking, molecular dynamics*

ABSTRACT

The AKT1 human serine/threonine kinase has a main role in the anticancer activity and its inhibition was described by heterocyclic compounds. These allosteric inhibitors effectively bind to tryptophan-80 among other aminoacids in the receptor active site. In this work we have investigated the interaction between modified crystallographic AKT1 (PDB:4EJN) and two classes of *N*-heterocycles (imidazo[1,2-*a*]pyridines and diarylquinoxaline) by *in silico* methods. Model compounds were previously synthesized by cyclization reactions in good yields. Molecular docking (AutoDock software) resulted in high affinity with the active site with free energies between -11.0 and -9.5 kcal/mole for both classes of compounds, with similar π–π interactions between the heteroaromatic rings and Trp-80. Molecular dynamics (GROMACS software) in aqueous solution resulted in high stability of the substrate-receptor complex after 500 ns as depicted by the protein RMSD. From these promising results targeted-oriented design and synthesis of new compounds prior to *in vitro* evaluation are being developed.



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A Visible Light-Mediated Strategy for the Cyclopropenation of Ynamides with Aryldiazoacetates

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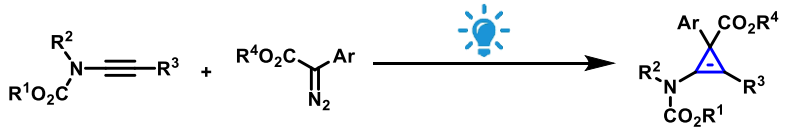
Keywords: *Ynamides, blue light, Carbenes, Cyclopropenation.*

ABSTRACT

Ynamides are a special class of alkynes attached to a nitrogen atom bearing an electron-withdrawing group. Over the past years, these compounds have been widely used as building blocks for promoting many transformations in organic chemistry.[1] In particular, their unique structure and reactivity allow these substrates to be efficiently reacted with different electrophiles or in tandem reaction sequences, thus allowing a plethora of transformations. On the other hand, the chemistry of aryldiazoacetates under blue light irradiation has also emerged as a powerful strategy[2,3] to afford different heterocycles. In this context, we became interested on the chemistry of ynamides under such photochemical conditions using aryldiazoacetates to produce densely substituted cyclopropenes under mild conditions.



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We are grateful to Fapesp for a post-doctoral Fellowship (2022/01750-2) to Tales A. C. Goulart and a Thematic Research grant (2019/17721-9) and a Regular Research grant (2022/01104-3) to Igor D. Jurberg

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Development of organocatalyst-loaded electrospun nanofibers to improve heterogeneous catalysis

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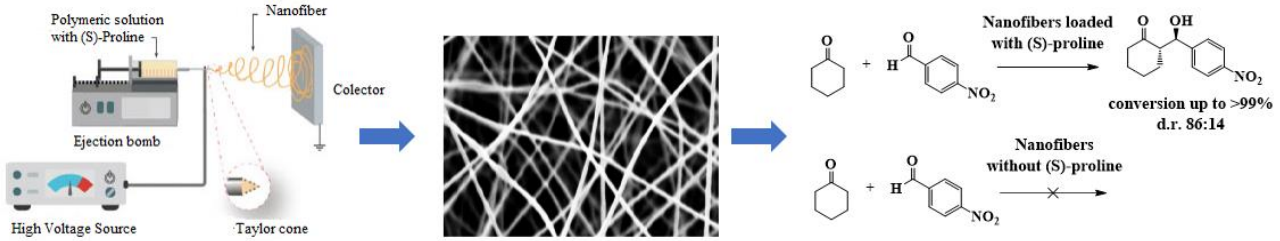
Keywords: *Nano-organocatalysis, electrospinning, assymetric aldol reaction, (S)-proline*

ABSTRACT

In recent years, the development of heterogeneous catalysts has been gaining prominence in the field of organocatalysis, due to the limitations of homogeneous catalysis, such as challenges in separation and recycling.[1] Thus, heterogeneous catalysis on solid supports emerges as an alternative. In this sense, electrospinning is a simple and versatile process used to fabricate polymeric nanofibers with high surface area that can be used as solid support in heterogeneous catalysis.[2] Therefore, the objective of this work was to develop a nano-organocatalyst from the electrospinning of a PVA and PVP nanofiber loaded with (*S*)-proline (**Scheme 1**).

Scheme 1.



The nano-organocatalyst was successfully prepared and its efficiency was verified against a the asymmetric aldol reaction between cyclohexanone and *p*-nitrobenzaldehyde was evaluated.[3] The conversion observed for the reaction was >99% after 11 h, with an increase in diastereoselectivity (86:14) when compared to homogeneous organocatalyst (76:24). At the end of the reaction, the nano-organocatalyst was recovered by simple filtration.

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SEPTEMBER 23-27 2024
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Synthesis of new eugenol derivatives using microwave and ultrasound irradiation.

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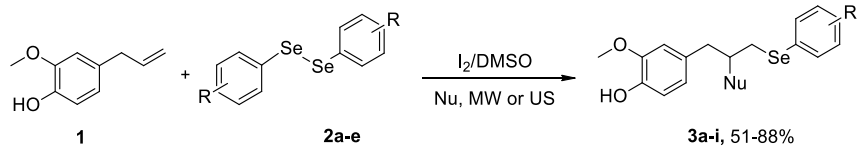
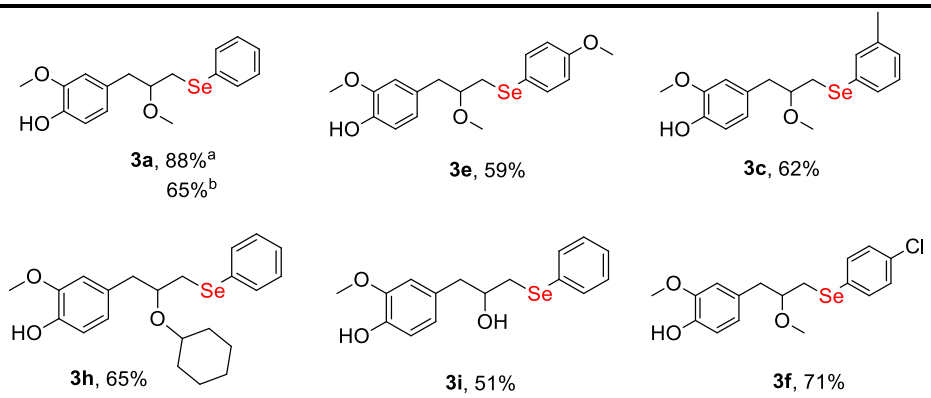
Keywords: *Green synthesis, Natural product, Selenium compounds.*

ABSTRACT

Microwave and ultrasound irradiation are powerful tools for synthesizing organic compounds, due to their environmental benefits, easy operation, and cost-effectiveness.[1] To enhance eco-friendly synthesis, derivatives of natural products are synthesized to improve their biological properties. Eugenol is a natural product with good anti-inflammatory and antioxidant properties.[2] However, your easy oxidation and high volatility limit the use of this compound.[3] Selenium compounds are widely studied due to their anti-neuroprotective and antioxidation properties.[4] Herein, we showed the synthesis of new eugenol derivatives with selenium using microwave (a) and ultrasound (b) irradiation. Eugenol (**1**) was extracted from the clove using the hydrodistillation method (Scheme 1). Microwave synthesis followed the conditions proposed by Braga et al.[5] and ultrasound irradiation, proposed in this work, it proved to be a cheaper methodology for the synthesis compared with microwave device.

Scheme 1.





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Molecular Docking of new eugenol derivatives with selenium like Catechol O-methyltransferase inhibitors

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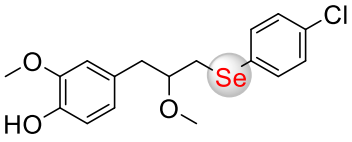
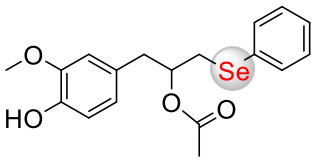
Keywords: *Molecular Docking, Parkinson's Disease, Selenium compounds.*

ABSTRACT

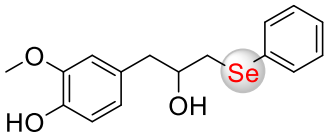
Parkinson's Disease is the second neurodegenerative disease most frequent in people over 60 years old. Tremors, rigidity, and postural instability are common symptoms of the disease, in addition to emotional disturbs, due to a decrease of dopamine levels in the brain.[1,2] The combination of L-Dopa with Dopa decarboxylase and catechol O-methyltransferase (COMT) inhibitors is used to repair the dopamine level. Tolcapone, Entacapone, and Opicapone are COMT inhibitors approved by FDA, however have some problems like hepatotoxicity and less potential.[3] To initialize the studies of new inhibitors of COMT, molecular docking is an important tool in drug discovery, due to less necessity of investment, fast results, and support for the synthesis of the compounds more important for the study.[4] This work realized the docking study of eugenol derivatives with selenium like COMT inhibitors. Software used for molecular docking was MOPAC 22.0.6, AutoDock Tools 1.5.7., Biovia Discovery Studio 2021 and PyMol.



3a



3b



3c

Compound	ΔG (kcal-mol^{-1})	Distance (Å)
Tolcapone	-6.16	2.92
Entacapone	-5.59	3.58
3a	-6.19	2.86
3b	-6.60	3.02
3c	-6.63	2.84

Compounds **3a**, **3b,** and **3c** showed excellent results, acquiring good binding energy and approximation of the cofactor SAM and Mg^{2+} in Molecular Docking. As a result, these compounds show potential to advance for *in vitro* and *in vivo* tests.

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Synthesis Arylselanyl Acrylates promoted by electrosynthesis

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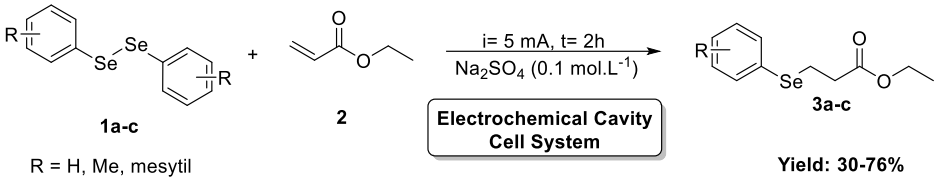
Keywords: *Electrosynthesis, Arylselanyl Acrylates, Greener Approach*

ABSTRACT

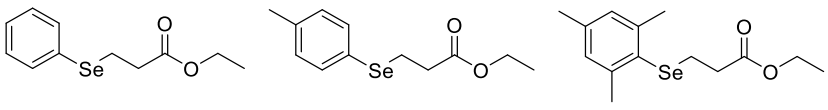
Organic electrosynthesis (OES) is a simple methodology that can waive use of some auxiliary agents, what makes it potentially less hazardous for the environment and the operator and can be applied to the preparation of several compounds including organic[1,2] and inorganic[3] as well as pharmaceutical compounds.[4] Besides, electrochemistry provides a green and efficient method of synthesis,[5] particularly due to good yields, current efficiency, and control of the process.[6] A preliminary study was conducted to establish the best condition reactions, using diphenyl diselenide **1a**, ethyl acrylate **2**, and graphite powder were mixed and then transferred to the macroelectrode cavity. It was evaluated the influence of stoichiometry of diphenyl diselenide **1a** and **2**, graphite powder amount, type of electrolyte solution and current intensity. This greener approach involves mild reaction conditions, short reaction time, without organic solvent use, under open-to air conditions and provides the arylselanyl acrylates products in good yields (Scheme 1).

Scheme 1. Study of electrosynthesis of arylselanyl acrylates in cavity cell system.



Entry	1a (mmol)	2 (mmol)	graphite (g)	Solvent/Electrolyte (0.1 mol.L^{-1})	Current (mA)	time (h)	Yield (%)
1	0,14	0,25	1,2	H_2O/Na_2SO_4	10	1	21
2	0,14	0,25	1,2	H_2O/Na_2SO_4	20	0,8	28
3	0,14	0,25	0,6	H_2O/Na_2SO_4	5	1	57
4	0,14	0,25	0,6	H_2O/Na_2SO_4	10	1	48
5	0,14	0,25	0,6	$CH_3CN/LiClO_4$	10	1	46
6	0,14	0,25	0,6	$DMF/TBAClO_4$	10	1	47
7	0,5	1	0,3	H_2O/Na_2SO_4	10	1	68
8	0,25	0,5	0,6	H_2O/Na_2SO_4	10	1	58
9	0,25	0,5	0,6	H_2O/Na_2SO_4	20	0,5	38
10	0,25	0,5	0,6	H_2O/Na_2SO_4	5	2	76
11	0,5	1	0,3	H_2O/Na_2SO_4	5	2	70

Yields:



3a: 76% **3b**: 60% **3c**: 30%

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SEPTEMBER 23-27 2024
19BMOS
BRAZILIAN MEETING ON ORGANIC SYNTHESIS
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Synthesis of fluorescent supramolecular complexes containing pillar[5]arenes and benzothiadiazoles

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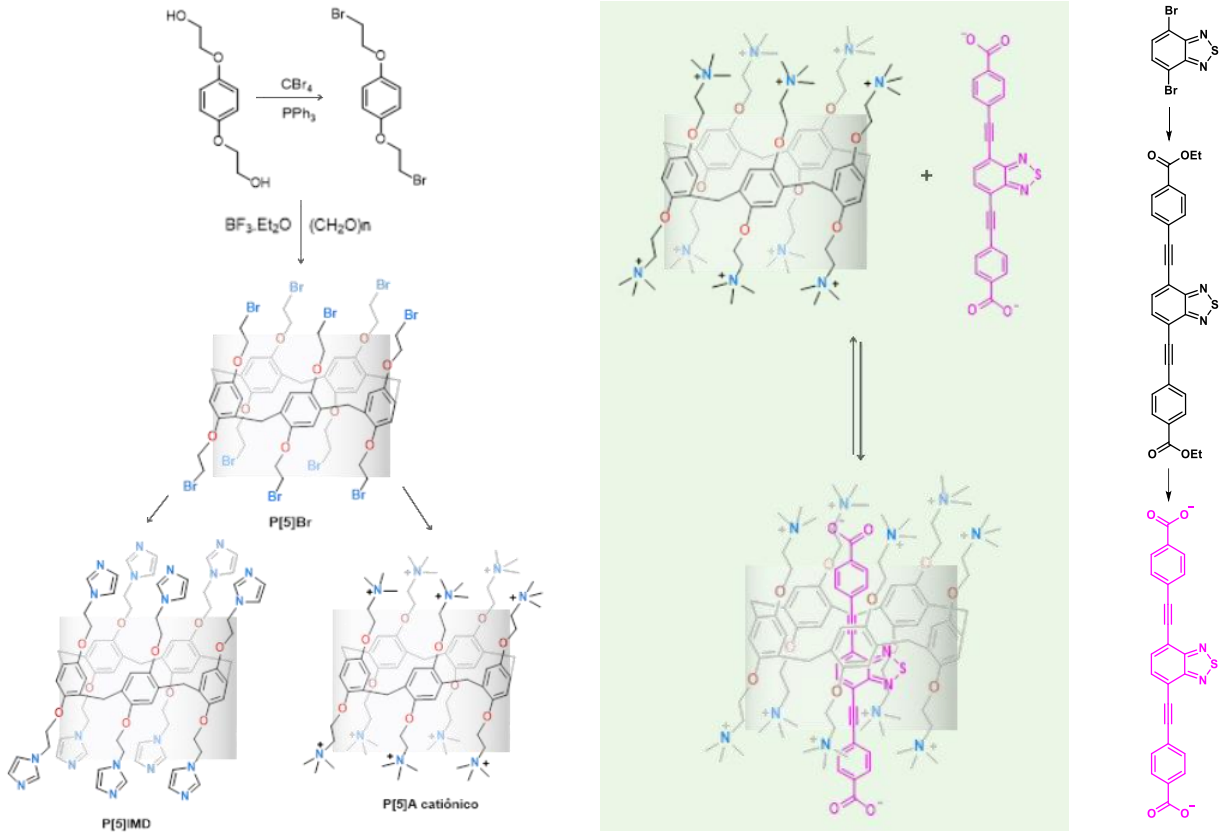
Keywords: *Pillar[5]arene, Benzothiadiazole*, *Supramolecular Chemistry, Fluorescence.*

ABSTRACT

Pillararenes are a class of hosts widely used in the formation of host-guest complexes due to their versatile functionalization.[1] Additionally, the benzothiadiazole (BTD) core possesses characteristics that make it an excellent luminescent material, with its derivatives typically being efficient fluorophores capable of being excited by visible light and exhibiting large Stokes shifts.[2] The introduction of organic fluorescent molecules into macrocycles through non-covalent interactions can change the photophysical properties of fluorophores.[3] In this context, our work explored a synthetic route for the preparation of supramolecular complexes containing pillar[5]arenes and benzothiadiazoles. The characterization of BTD derivatives and verification of the formation of supramolecular systems were performed using ^{1}H NMR, UV-Vis absorption spectrophotometry, and fluorescence emission spectroscopy. Tests are ongoing to verify if the formed complex can act as a natural fluorescence sensor for DNA.



ACKNOWLEDGEMENTS

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SEPTEMBER 23-27 2024
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Chalcogen Bond-Mediated Alkylation Catalysis: Selenoxide-Pillar[5]arene as a Recyclable Catalyst in Aqueous Solutions

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Keywords: *Chalcogen bonding, Supramolecular Catalysis, Aqueous medium, Organic shyntesis*

ABSTRACT

In this study, we introduce a novel strategy for catalyzing alkylation reactions via chalcogen bond interactions using a chalcogen-macrocyclestructure. Chalcogen bonding (ChB), involving elements like sulfur, selenium, and tellurium, is defined as the interaction between a positively polarized chalcogen atom and a Lewis base. This electrostatic attraction and charge-transfer component make ChB a powerful tool for achieving high yields and controlling selectivity.[1-3] Employing a macrocyclic pillar[5]arene decorated with organoselenium, we achieved efficient catalysis of benzyl bromide cyanation in water using only1.0 mol% selenoxide-pillar[5]arene (**P[5]SeO**) as the recyclable catalyst. Supported by control experiments and theoretical models, ^{1}H NMR analysis revealed that **P[5]SeO** facilitated inclusion complex formation, enabling nucleophilic displacement. The reaction protocol proved applicable to a broad range of nucleophiles and substrates, including aromatic, heteroaromatic, and alpha-carbonyl derivatives. Notably, the method is scalable, and the catalyst **P[5]SeO** can be effectively recovered and reused for multiple cycles, showcasing its sustainability.

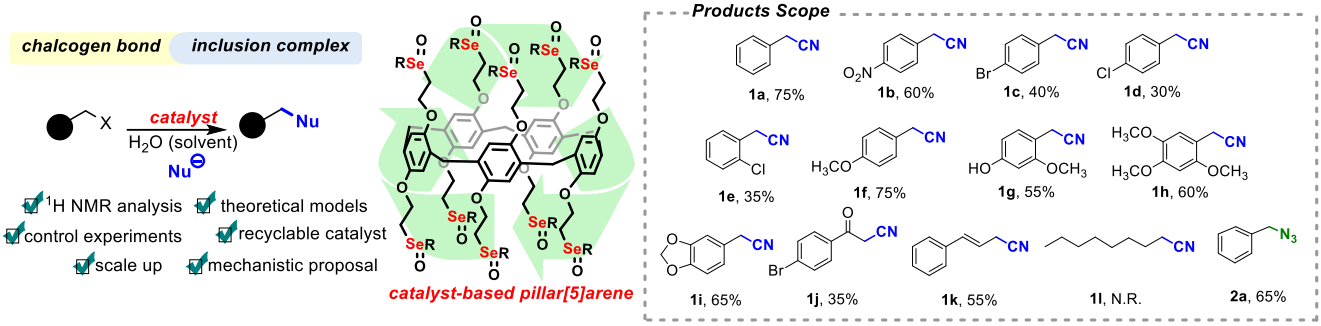

Figure 1. Representation of the work and achieved scope.

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SEPTEMBER 23-27 2024
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Synthesis and Photophysics of novel 4-aryl-polyhydroacridinodiones: Fluorescence confinement effect

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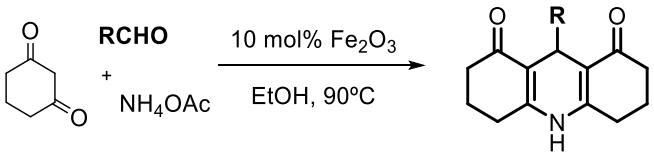
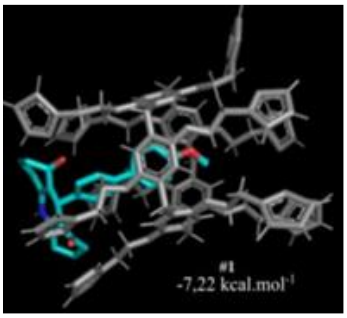
Keywords: *Polyhydroacridinodiones, Multicomponent Reaction, Pillararenes, Substrate-receptor, Fluorescence*

ABSTRACT

Polyhydroacridinodiones (**PHA**) are compounds derived from 1,4-dihydropyridines, an important class of bioactive molecules with wide applicability in medicinal chemistry. Pillararenes are a recent class of macrocycles that allow complexation with other molecules through the substrate-receptor system, resulting in a series of applications. We have successfully synthesized new **PHA** derivatives by Hantzsch multicomponent reaction using maghemite (γ-Fe_2O_3) as a catalyst, with yields between 40 and 91%. Optimized geometries of products and intermediates were calculated by DFT. Photophysical study of **PHA** in ethanol was also carried out in the presence of the macrocycle pillar[5]arene imidazole (**P[5]Im**), which indicated the possibility of formation of an inclusion complex with structure **2a'**. All compounds are fluorescent in the blue region (~420 nm) and the presence of the macrocycle selectively increased the fluorescence emission intensity of the biphenyl derivative. The interaction was evidenced by NOESY NMR analysis, and a plausible structure was achieved by molecular docking.



1a' - R = 2,3,5-trimethoxyphenyl 40%
2a' - R = 4-methoxybiphenyl 91%
3a' - R = 3-trifluoromethoxyphenyl 56%
4a' - R = 4-methoxyphenyl 78%



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SEPTEMBER 23-27 2024
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Scope of the Diels-Alder reactions of potassium furanyl trifluoroborates

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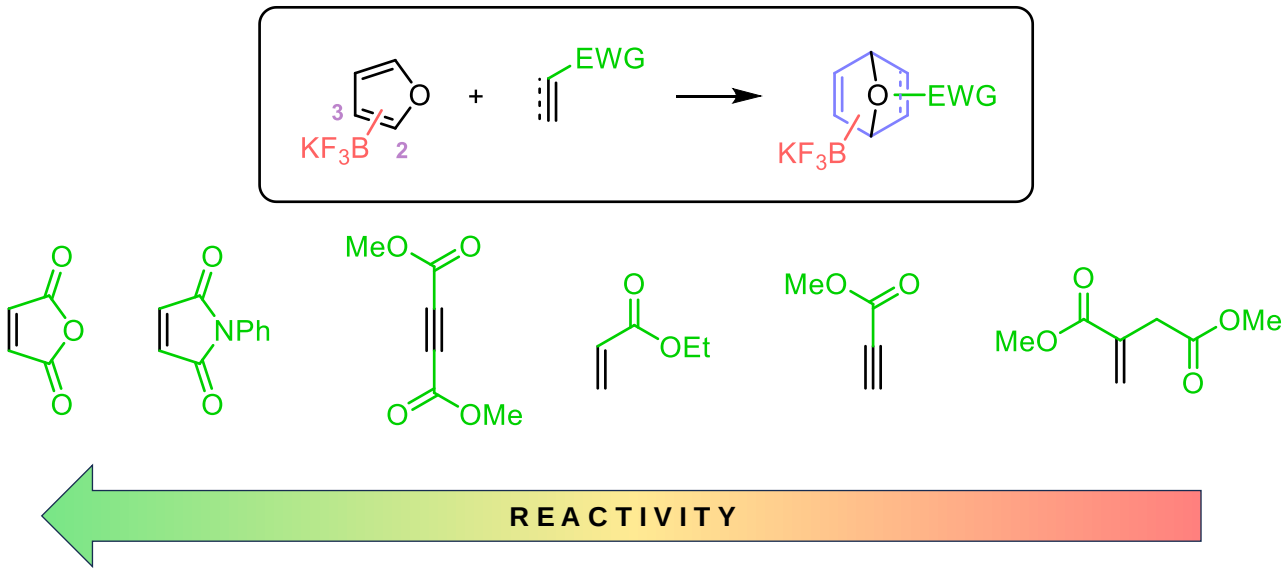
Keywords: *furanyl trifluoroborates, cycloadduct, reactivity.*

ABSTRACT

Diels-Alder reactions involving organoboron compounds as dienes allow the generation of six-membered rings with interesting substitution patterns that can be exploited in further reactions, generating highly complex structures in a few synthetic steps.[1] In our research group we described for the first time the use of boron-substituted heteroaromatic compounds as dienes in Diels-Alder reactions.[2] In particular, potassium 3-furanyl trifluoroborate showed exceptional reactivity towards maleic anhydride, giving the *exo* cycloadduct quantitatively after 15 min at room temperature. The present work describes the Diels-Alder reactions of 2- and 3-furanyl trifluoroborates with several activated dienophiles. In general, potassium 3-furanyl trifluoroborate generated the cycloadducts more efficiently than its C-2 counterpart. The use of computational tools allowed a more detailed understanding of the factors governing these reactions. In addition, some derivatization reactions of the cycloadducts are described.



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SEPTEMBER 23-27 2024
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Study of the reactivity and the selectivity of the Diels-Alder reactions of furanylboron compounds with maleimides

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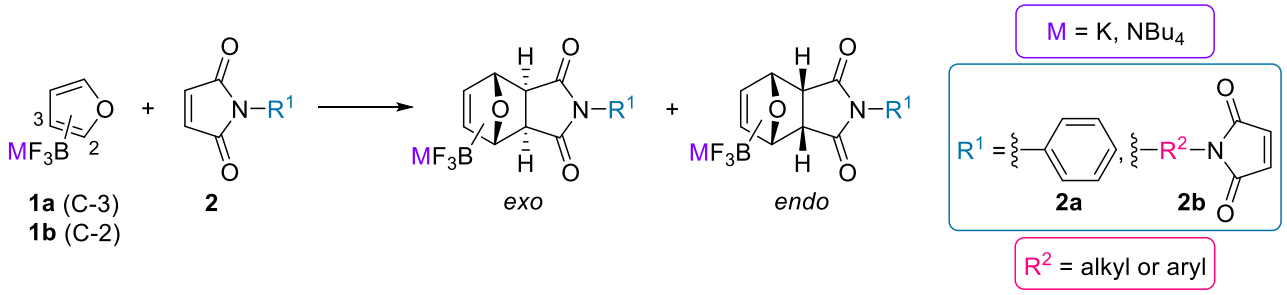
Keywords: *furanylboron compounds, Diels-Alder reactions, maleimides.*

ABSTRACT

Organoboranes are highly versatile and widely available reagents to carry out carbon-carbon bond-forming reactions and also to prepare a wide variety of functional groups. Although the Diels-Alder reactions using unsaturated organoboron compounds as dienophiles have been widely studied, those in which they participate as dienes are less abundant.[1] Recently, our research group described for the first time the use of furanylboron compounds (**1**) as dienes in Diels-Alder reactions with maleic anhydride.[2] Next, the reaction of **1** with *N*-phenylmaleimide (**2a**) was investigated. Fortunately, we were able to obtain the *exo* products with excellent diastereoselectivities and yields. In addition, their enhanced stability in solution relative to their maleic anhydride counterparts allowed their subsequent derivatizations. Furthermore, given the reversibility of these cycloadditions, the use of various bismaleimides (**2b**) is being explored and will possibly pave the way to applications in the preparation of cross-linked self-healing polymeric networks.[3]



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SEPTEMBER 23-27 2024
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Ru(II)-Catalyzed Asymmetric Transfer Hydrogenation of Polymethoxylated 3-Arylidene Chromanones via Dynamic Kinetic Resolution.

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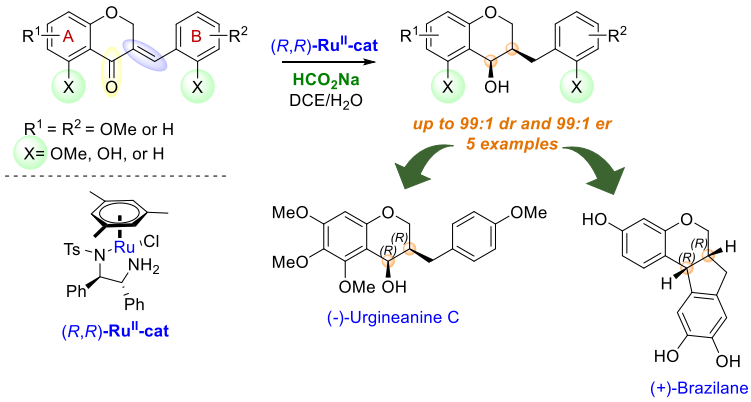
Keywords: *ATH-DKR, Noyori-Ikariya catalyst, ruthenium; asymmetric catalysis, hydrogen bounding*

ABSTRACT

The asymmetric transfer hydrogenation (ATH) of carbonyl compounds catalyzed by chiral transition-metal complexes is a powerful tool for obtaining key intermediates in the synthesis of optically pure pharmaceutical and natural products.[1–4] Mono-, di-, and trimethoxylated 3-arylidenechromanones at the A-ring were hydrogenated to *cis*-benzylic alcohols with high diastereomeric ratios (91:9 to 99:1) and enantiomeric excess (up to 99:1). This transformation was achieved via a one-pot reduction of the conjugated C=C and C=O bonds in the presence of 2-5 mol% of a Ru(II) chiral complex and HCO_2Na as the hydrogen source, under ATH-DKR conditions in a DCE:H_2O solvent mixture. Electronic effects (C7 and C5) and steric effects (C5) of these substituents controlled the reaction outcome. Notably, the presence of phenol groups at C5 or C2' in these 3-(benzylidene)chroman-4-ones enhanced the reaction rate, diastereo- and enantioselectivity through intramolecular hydrogen bonding. Furthermore, the oxidation of these aryl alcohols led to the enantioselective synthesis of natural homoisoflavanones with promising anticancer activities.[5,6] Additionally, the formal synthesis of the tetracyclic homoisoflavonoid (+)-brazilane was successfully accomplished.



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SEPTEMBER 23-27 2024
19BMOS
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Sulfonic Acid-functionalized Chitosan as a Biodegradable Heterogeneous Organocatalyst in O-alkylation and A3 coupling Reactions

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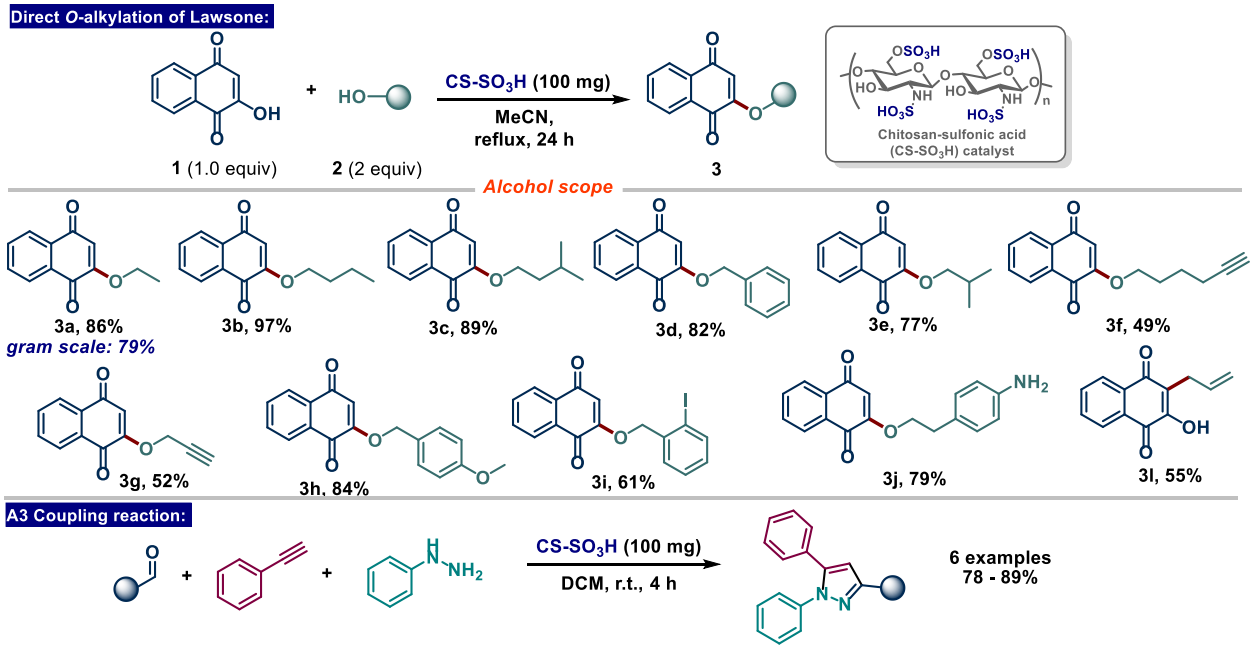
Keywords: *Lawsone, Acidic Chitosan, Alkylation Heterogenous Organocatalyst, A3 reactions.*

ABSTRACT

Advances in the field of heterogeneous catalysis have expanded the synthetic toolbox available for the preparation of densely functionalized molecules. Thus, the development and application of polymer-bound catalysts have increased over the past years.[1] In this context, chitosan (CS) is a good candidate for solid catalyst since it is natural, biocompatible, reusable and biodegradable. The numerous basic groups in this polysaccharide provide active sites for chemical modifications and stabilization of homogeneous catalysts.[2] One such chemical modification is sulfonation to produce chitosan-SO_3H (CS-SO_3H) which has been used as a solid acid catalyst in organic reactions.[3] Herein, we describe the use of CS-SO_3H as a heterogenous organocatalyst in a direct *O*-alkylation of lawsone with different alcohols and *A3* coupling reaction for the synthesis of 1,3,5-substituted pyrazoles. The scope of both transformations showed good tolerance to the presence of different functional groups affording the corresponding products in satisfactory yields.



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Expanding the Chemical Space of Electrophilic β-Glycosyl β-Lactams through Photoinduced Diastereoselective Functionalization

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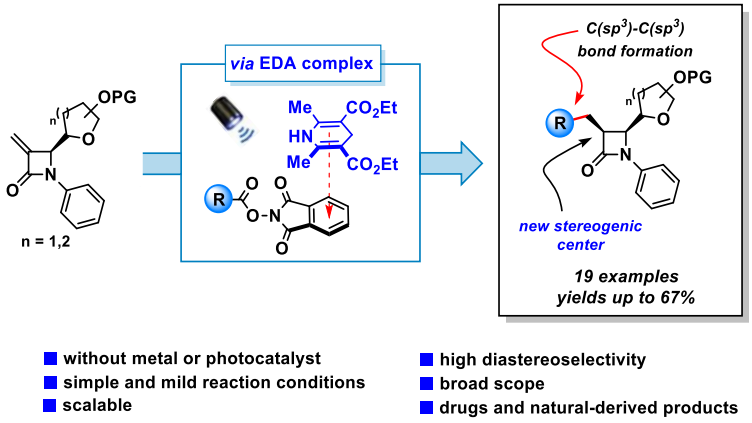
Keywords: *EDA complex, β-Glycosyl β-Lactams, high diastereoselectivity synthesis.*

ABSTRACT

A photoinduced diastereoselective C-3 functionalization of electrophilic β-glycosyl β-lactams is presented. The developed protocol is simple, mild and explores the use of 3-exomethylene β-lactams, which are still unexplored under photochemical conditions, as reaction partners in a Giese type reaction. The key nucleophilic alkyl radical is generated by a photoinduced electron transfer process in the *EDA* complex formed by NHPI and Hantzsch esters. The diastereoselective hydrogen atom transfer to the β-lactam radical intermediate enables the synthesis of various *N*-phenyl β-glycosyl β-lactams. This strategy features excellent functional group tolerance, scalability, and high diastereoselectivity and offers an alternative way to functionalize position C-3 in the β-lactams core, wich is increasingly recognized as crucial given its direct correlation with the biological efficacy of these compounds.[1]



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Fast and efficient one-pot ultrasound-mediated synthesis of solid state (full color tunable) fluorescent indolizine derivatives

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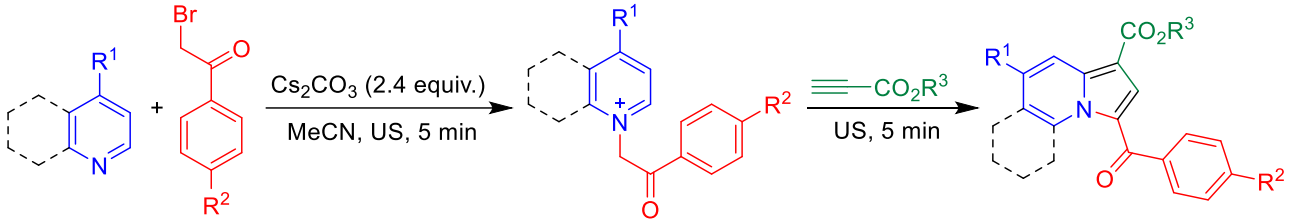
Keywords: *One-pot, Indolizines, Ultrasound*

ABSTRACT

The class of heterocyclic compounds has gained prominence in recent decades due to its wide range of applications. Among these, indolizines are highly versatile, presenting different pharmacological properties and applications such as on/off fluorescent sensors, dye-sensitized solar cells (DSSCs), among others.[1] Given the importance of this class of compounds, we developed an efficient, rapid, and sustainable method for the preparation of fluorescent indolizine derivatives under ultrasound (US) irradiation, using a one-pot, multicomponent methodology. Using this method, it was possible to synthesize ten different indolizines containing electron-donating and electron-withdrawing groups in yields ranging from 21% to 99%. The synthesized compounds were subjected to comprehensive photophysical studies, revealing that the substituents used influenced the photophysical properties. In solution, indolizine derivatives exhibit absorption in the UV region and fluorescence emission in the violet-to-blue region. In the solid state, the derivatives exhibit fully adjustable color fluorescence.[2]



R^1 = H, NMe_2, CN;
R^2 = H, NO_2, OMe,
R^3 = Me, Et;

21 - 99%
10 examples

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We thank UFRGS, FAPERGS, CAPES and CNPQ.

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SEPTEMBER 23-27 2024
19BMOS
BRAZILIAN MEETING ON ORGANIC SYNTHESIS
BENTO GONÇALVES, RS - BRAZIL

Synthesis and *In Vitro* Studies of Chalcogenophenes Containing Quinoline.

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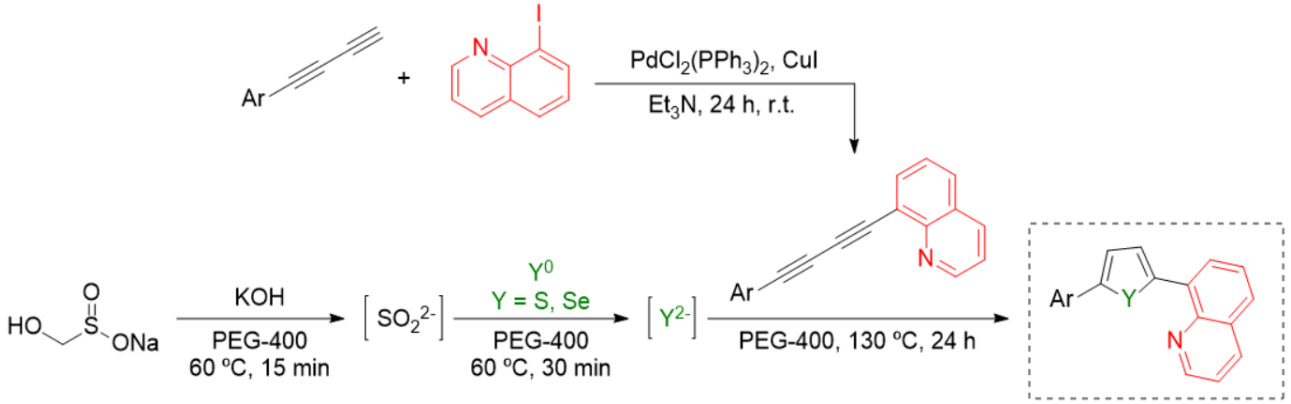
Keywords: *Chalcogenophene, Quinoline, Cyclization.*

ABSTRACT

Research interest on chalcogenophenes increased in recent years due to their wide range of applications. This class of heterocycles are vastly investigated in different fields such as material science, organic chemistry and medicinal chemistry.[1,2] Considering their versatility, we designed a new class of compounds, combining thiophenes and selenophenes with quinoline, which is well known for its photophysical and biological activity. These compounds were synthesized from elemental chalcogen and novel 1,3-butadiynes, previously synthesized, containing the quinoline core using a green methodology developed by our research group, which uses PEG-400 as solvent. This method promotes the diynes cyclization utilizing Rongalite, a cheap and non-toxic reagent, that promotes the formation of the chalcogens nucleophilic species *in situ*.[3] Preliminary results indicate that the synthesized chalcogenophenes, particularly selenophenes, exhibit antiproliferative activity against the breast tumor cell line MDA-MB-231, as assessed by the MTT method.



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Synthesis of new derivatives of salicylic acid with potential bioactivity

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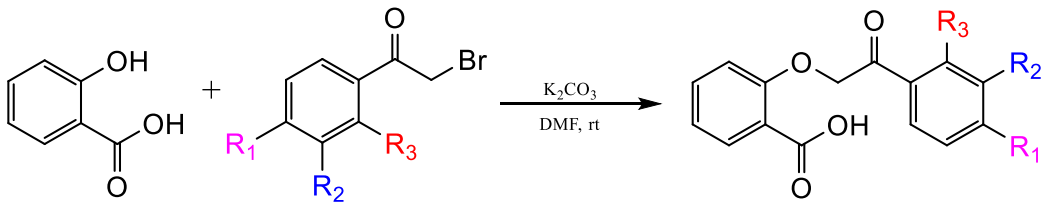
Keywords: *Salicylic acid, ether derivatives, Williamson reaction.*

ABSTRACT

The synthesis of derivatives of natural products offers the possibility of generating unprecedented molecules through low-complexity reactions that provide an excellent platform of the introduction of new functional groups, allowing the creation of libraries of compounds with structural diversity. Derivatives of salicylic acid are used for the treatment of various diseases; currently the best known is acetylsalicylic acid, one of the most widely used anti-inflamatory drug.[1] Other derivatives, as methyl salicylate, salol and salicylanilide, are known for their analgesic, antipyretic, antimicrobial, antiproliferate and cytotoxic activities.[2] In this study, ten new series of ether analogues of salicylic acid were prepared via the Williamson reaction, as the side chain of the salicylic ethers can influence their biological capacities.[3] The chemical structures were determined by NMR, and some of their crystallographic structures are determined by X-ray crystallography. This approach will allow us to evaluate the structure-activity relationship and improve pharmacological activities.

GRAPHICAL ABSTRACT



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FAPES
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Copper Catalyzed Direct Chalcogenylation of Chalcogenophenes C(sp^2)-H Bonds Using a 2-Amino Oxazole Directing Group

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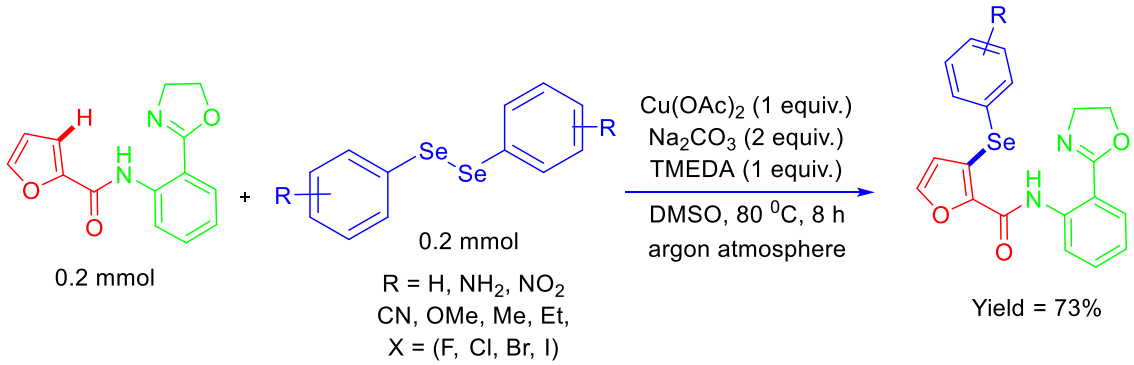
Keywords: *Catalysis, C-H activation, Directing group*

ABSTRACT

In recent decades, organoselenides with potential pharmaceutical uses have been identified. Many others have demonstrated bioactivities for various applications, including agricultural chemicals and fluorescent probes for bioimaging.[1] Recent advancements in transition metal-catalyzed direct chalcogenylations via C-H activation using directing groups have created a dynamic field. [2] The importance of the given methodology of direct chalcogenylations via C-H activation for the synthesis of organoselenides, different aryl and heteroaryl chalcogens compounds using copper acetate as catalyst and 2-(4,5-dihydrooxazol-2-yl)amides as directing group was prepared. Under the best optimized condition, it provides 73% yield. The reaction scope will be further elaborate by using different heterocyclic substrates and diphenyl diselenides. Including electron donating and withdrawing groups. Initially the compounds also showed fluorescence emission under UV in the violet to blue region that can be further elaborated for fluorescence study. The compounds will be further analyzed for the photophysical properties.



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Design, Synthesis, and Structure-Activity Relationship Study of Thiohydantoin Derivatives

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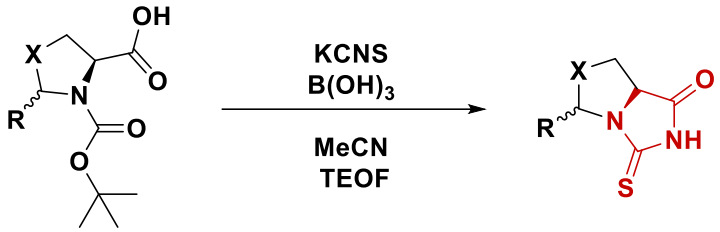
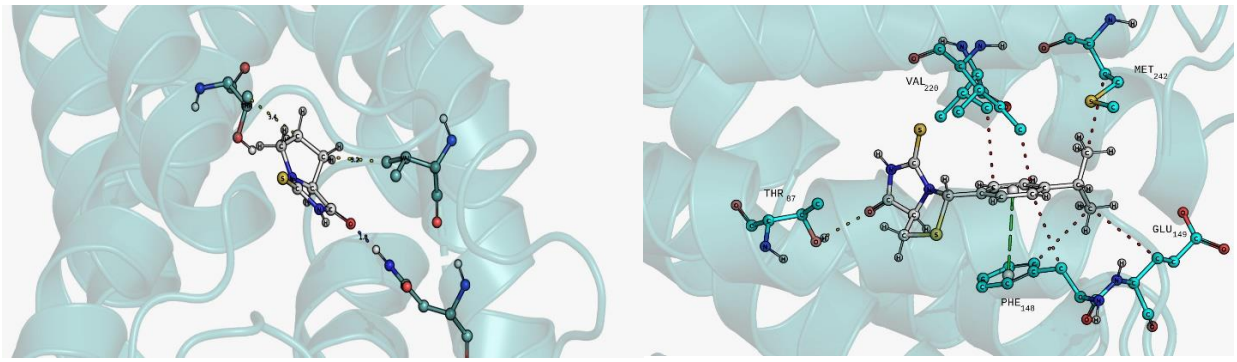
Keywords: *Catalysis, fused hydantoins, study in silico.*

ABSTRACT

Hydantoins and thiohydantoins are recognized as "privileged structures" due to their significant chemical and pharmacological applications, appearing in various biological matrices with medicinal properties.[1] These structures are present in several high-value drugs, such as phenytoin, mephenytoin, and nitrofurantoin.[2] Despite the availability of three classical synthesis reactions for these molecules,[3] there remains a demand for new methodologies that are simpler, more cost-effective, and in line with green chemistry principles, particularly for the synthesis of fused bicyclic thiohydantoins. This study focused on the synthesis and optimization of reaction conditions, exploring variables such as reagent concentration, the use of $B(OH)_3$ as a catalyst,[4] and different solvents, with thiazolidines as the starting materials to obtain fused thiohydantoins. Additionally *in silico* methods were employed to predict and analyze the physicochemical and biological properties of the synthesized compounds, laying a solid foundation for their future therapeutic applications and offering new perspectives for the development of innovative drugs.





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Towards greener MCRs: use of renewable reactants in Ugi and Passerini reactions

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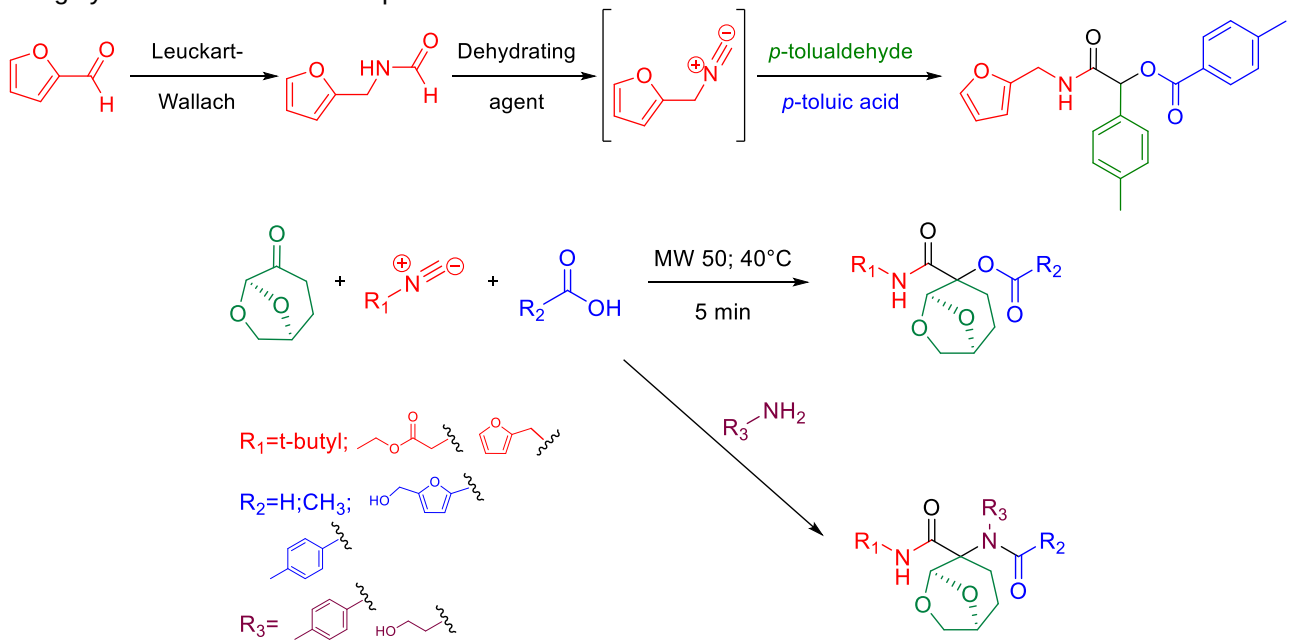
Keywords: *Multicomponent Reactions, cyrene, green chemistry.*

ABSTRACT

Multicomponent reactions (MCRs) such as Passerini and Ugi are invaluable in organic synthesis, enabling high molecular complexity in a single step. Considering the challenges associated with toxic reactans (isocyanides, aldehydes, etc.),[1] we demonstrate the use of biomass-derived reactants in 3MCRs and 4MCRs. We explored *in situ* produced, biomass-derived isocyanides[2] as Passerini reactants and we utilized cyrene[3] (a chiral ketone) with commercial isocyanides examining diastereomeric outcomes and the effect of chiral catalysts. Reactions were performed in a Monowave 50 reactor to reduce heating times.
These greener strategies yielded 8 products excluding diastereomers, optimizing the Passerini strategy with cyrene. Current efforts focus on the *in situ* generation of greener isocyanides and the synthesis of Ugi products using cyrene as the ketone component.



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