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

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

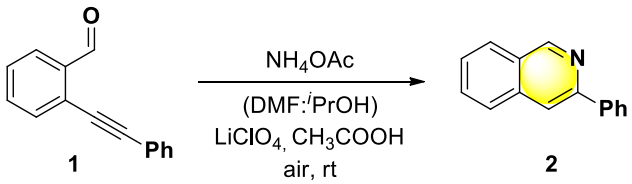
Eliakin Sato de Borba[1], Guilherme Machado Martins[2] Samuel Rodrigues Mendes[1]*
1) Department of Chemistry, University of the State of Santa Catarina, UDESC, 88035-901.
***2) Department of Chemistry*, Federal University of Sao Carlos (UFSCar), 13565-905.**
e-mail: samuel.mendes@udesc.br

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.

ACKNOWLEDGEMENTS

CMU/UDESC, UFSCar, FAPESC, CAPES

REFERENCES

(1) Vinoth, P.; Karuppasamy, M.; Gupta, A.; Nagarajan, S.; Maheswari, C. U.; Sridharan, V. Intramolecular Oxypalladation-Initiated Domino Sequence: One-Pot, Two-Step Regioselective Synthesis of Isoquinolines. *Tetrahedron* **2023**, *134*. https://doi.org/10.1016/j.tet.2023.133272.

(2) Tan, X.; Hou, X.; Rogge, T.; Ackermann, L. Ruthenaelectro-Catalyzed Domino Three-Component Alkyne Annulation for Expedient Isoquinoline Assembly. *Angewandte Chemie - International Edition* **2021**, *60* (9), 4619–4624. https://doi.org/10.1002/anie.202014289.