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Attempts to synthesize a benzofuran-3(2*H*)-one from eugenol, a key intermediate to potentially antimicrobial aurones

Micaela Marina Barbosa Nogueira*; Leonardo Scalione Tempesta; Dalila Junqueira Alvarenga; Lucas Lopardi Franco; Diogo Teixeira Carvalho
School of Pharmaceutical Sciences, Federal University of Alfenas, UNIFAL-MG, 37130-001
***e-mail:** micaela.nogueira@sou.unifal-mg.edu.br*

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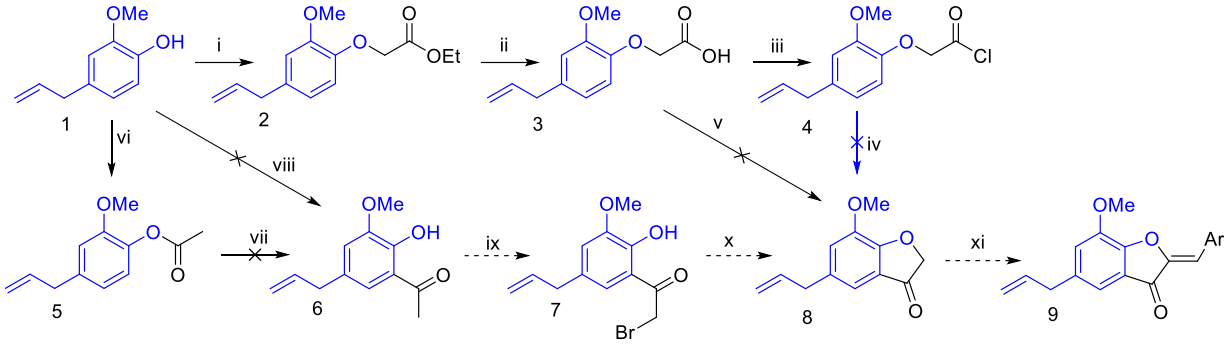
ABSTRACT

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.

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REFERENCES

(1) Lall, Namrita; Kishore, Navneet; Ndamase, Ayanda; et al. Natural products as potential antimicrobial agents. *Curr. Opin. Infect. Dis.* **2015**, *28* (6), 542-547
(2) El-Readi, Mahmoud Zaki; Wink, Michael; El-Shazly, Assem M.; et al. Eugenol exhibits antidepressant-like activity in mice and induces expression of metallothionein-III in the hippocampus. *Phytomedicine* **2011**, *18* (11), 1003-1008.
(3) Amankulova, D. et al. Recent advances in the synthesis of *m*-aryloxy phenols. Molecules. **2023**, 28, 2657-2676.