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An efficient synthesis of benzofurans and their application in the preparation of natural products of the genus *Calea*

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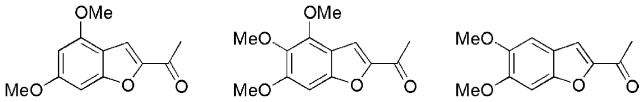
Dedicated to Professor Gustavo García de la Mora on his 60th birthday

Abstract—The intramolecular cyclization of the β-substituted olefins methyl 2-aryloxy-3-dimethylaminopropenoates **3a**–**3f** catalyzed by Lewis acids leads to a short and novel synthesis of benzofurans **2a**–**2f**. When the olefins 4-dimethylamino-3-aryloxy-3-buten-2-ones **4a**–**4f** were used, the cyclization process was faster and provided the corresponding substituted 2-acetylbenzofurans **1a**–**1f**. Among the latter, naturally occurring compounds calebertin (**1a**), caleprunin A (**1b**), and caleprunin B (**1c**) were prepared in good overall yields. These benzofurans were also obtained by direct treatment under MW irradiation of the precursors 1-aryloxypropan-2-ones **7a**–**7c** with DMFDMA, followed by addition of the catalyst, resulting in a route that was one step shorter.

1. Introduction

An intense effort has been made directed towards the synthesis of benzofurans,[1] due to their biological activity as potential pharmacological agents,[2] and to their occurrence in nature.[3] Among the reported synthetic strategies, those approaches designed for building the heterocyclic ring have been widely preferred, because of their simplicity when the starting materials are already carrying the functionalized benzene moiety. Thus, a great number of methods have been developed for the heterocyclic ring closure,[1,4] being particularly versatile those approaches leading to the C3–C3a bond formation as the key step.[5]

Natural 2-acetylbenzofurans calebertin (**1a**), caleprunin A (**1b**), and caleprunin B (**1c**) have been isolated from *Calea* species.[6] Caleprunin B (**1c**) had been previously isolated from *Eupatorium sternbergianum* and called eupatarone.[7] The syntheses of these compounds were carried out through an aldolic condensation of the corresponding *ortho*-formylphenoxyketone.[8] Partial synthesis of compound **1c** has also been reported by oxidation of natural 5,6-dimethoxy-2-isopropylbenzofuran.[9]



1a **1b** **1c**

Recently, we reported our preliminary results about a new straightforward synthesis of benzofurans **2**,[10] taking advantage of the high reactivity of captodative olefins in Friedel–Crafts reactions.[11] Thus, the intramolecular cyclization of the previously functionalized methyl 2-aryloxy-3-dimethylaminopropenoates (**3**) promoted by a Lewis acid ($ZnCl_2$) allowed for the preparation of benzofurans **2** in good yields (Scheme 1). Compounds **3** are acting as enaminones, which have proved to be privileged Michael acceptors for the addition of a large number of nucleophiles.[12]

With the aim of optimizing and extending our methodology, we hereby describe the development of some alternative conditions for the preparation of benzofurans **2**, and the study of preparation and intramolecular cyclization of 3-aryloxy-4-dimethylamino-3-buten-2-ones **4** as versatile and reactive precursors of compounds **1** (Scheme 1), including the total synthesis of natural products **1a**–**1c**.

Keywords: 2-Aryloxy-3-dimethylaminopropenoates; Natural 2-acetylbenzofurans; Cyclization; Lewis acid catalysis; Microwaves.
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