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A New Synthetic Route of 2-Aroyl- and 2-Benzyl-Benzofurans and their Application in the Total Synthesis of a Metabolite Isolated from *Dorstenia gigas*

Christian Correa,[A] *María del Carmen Cruz*,[B,C] *Fabiola Jiménez*,[A] *L. Gerardo Zepeda*,[A] *and Joaquín Tamariz*[A,C]

[A]Departamento de Química Orgánica, Escuela Nacional de Ciencias Biológicas, Instituto Politécnico Nacional Prol. Carpio y Plan de Ayala, 11340 México, DF, Mexico.

[B]Centro de Investigación en Biotecnología Aplicada, Instituto Politécnico Nacional, Carretera Estatal Sta Inés Km 1.5, Tepetitla, 90700 Tlaxcala, Mexico.

[C]Corresponding authors. Email: jtamariz@woodward.encb.ipn.mx; carmencruz25@yahoo.com.mx

The Lewis acid-catalyzed cyclization of the (*Z*)-3-(dimethylamino)-2-aryloxy-1-arylprop-2-en-1-ones **4a**–**h** leads to a regioselective and short synthesis of 2-aroylbenzofurans **2a**–**h**. The Wolff–Kishner reduction of the latter yielded a series of substituted 2-benzylbenzofurans **3a**–**h**. This methodology was applied in the first total synthesis of the metabolite 2-(4-hydroxybenzyl)-6-methoxybenzofuran **1**, which was isolated from the tropical plant *Dorstenia gigas*, and obtained through a six-step route and in a 24% overall yield.

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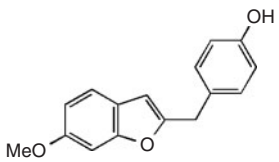
Introduction

The genus *Dorstenia* (Moraceae) has attracted special interest due to the isolation of a large variety of heterocyclic compounds such as furocoumarins, benzofurans, and flavonoids.[1–7] The presence of these metabolites has been associated with the biological properties exhibited by some species of this genus, when used in folk medicine, mainly for the treatment of skin diseases.[8–12] Among the metabolites isolated from *Dorstenia gigas*, a succulent shrub growing on Socotra Island whose extracts have shown anti-inflammatory and antibiotic activities,[13] one can find 2-(4-hydroxybenzyl)-6-methoxybenzofuran **1** (Scheme 1),[13] which is a natural product exhibiting antifungal activity in the *Cladosporium* bioassay, and which displays an uncommon 2-benzylbenzofuran framework.[14] Owing to the medicinal and horticultural interest of *D. gigas*, a micropropagation technique has been developed with the intention of reproducing this threatened species.[15]

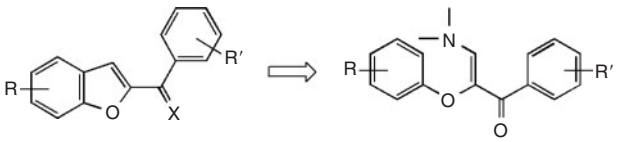
However, 2-aroylbenzofurans and 2-benzylbenzofurans have been synthesized, and some of them have exhibited significant biological properties, such as estrogenic, spasmolytic, antiviral, antimicrobial, and anticancer activities.[16–20] In an intense effort to synthesize 2-substituted benzofurans,[21–24] many methodologies that lead to the preparation of 2-aroylbenzofurans have been reported,[16–20,23,25–29] whereas only a few approaches have been found for the synthesis of 2-benzylbenzofurans.[16,26,30–33]

Recently, we reported a new straightforward synthesis of 2-carbomethoxy- and 2-acetyl-benzofurans, through an intramolecular cyclization of enaminones promoted by Lewis acids.[34] This strategy allowed us to prepare a series of natural benzofurans in good overall yields.[35] Therefore, the ready access to the construction of the benzofuran scaffold by this



1

Scheme 1.



2 X = O
3 X = H, H

4

Scheme 2.

methodology prompted us to extend it to the preparation of the substituted 2-aroyl- and 2-benzyl-benzofurans **2** and **3**, respectively, by using enaminones **4** as their precursors (Scheme 2), as well as to the development of the first total synthesis of natural compound **1**.

Results and Discussion

Phenoxyacetophenones **8a**–**h** were prepared in high yields (80–88%) by treating the corresponding 2-bromoacetophenones **6a**–**e** with phenols **7a**,**b** in the presence of potassium carbonate in acetone at reflux for 12 h (Scheme 3). 2-Bromoacetophenones

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