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Unexpected one-step synthesis of 3-benzoyl-2-phenylbenzofurans under Wittig conditions

Michela Begala [a,*,c], Pierluigi Caboni [a], Maria João Matos [b], Giovanna Lucia Delogu [a,c]

[a] Department of Life and Environmental Sciences, University of Cagliari, Via Ospedale 72, 09124 Cagliari, Italy
[b] Department of Organic Chemistry, University of Santiago de Compostela, Campus Vida, 15782 Santiago de Compostela, Spain

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ABSTRACT

The reaction of 2-hydroxybenzyltriphenylphosphonium bromide with substituted benzoyl chlorides under Wittig conditions, led to 2-phenylbenzofuran derivatives **4a**–**p** and the unexpected formation of 3-benzoyl-2-phenylbenzofuran derivatives **5a**–**p**. Benzoyl chlorides possessing electron-withdrawing groups afforded 3-benzoyl-2-phenylbenzofuran derivatives in higher yields than those with electron-donating groups. This reaction represents a simple and regioselective, one-pot route towards the preparation of deactivated 3-benzoyl-2-phenylbenzofuran compounds which are difficult to obtain by the direct acylation of 2-phenylbenzofurans.

Introduction

3-Aroyl[*b*]benzofurans represent the structural cores of a large number of bioactive molecules in current pharmaceutical use or development. Representative examples of this family include amiodarone (**A**), a clinically used drug for controlling intractable cardiac arrhythmias,[1] LY 320135 (**B**), a potent cannabinoid CB_1 receptor antagonist,[2] benzbromarone (**C**), an uricosuric agent,[3] and SKF-64346 (**D**), an amyloid binding agent with neuroprotective and antitumor activities[4] (Fig. 1).

As a result, numerous approaches towards the synthesis of 3-acylbenzofurans have been disclosed in the literature; however, most are only suitable for the preparation of 2-aryl-3-benzoyl benzofuran derivatives bearing electron-donating groups.[5]

Many synthetic methods to prepare 3-acylbenzofurans introduce the C3-substituent to the preformed benzo[*b*]furan ring at the end of the synthsis.[5c,6] Among these, the simplest and most straightforward method is the Friedel-Crafts reaction using acyl chlorides.[7] However, this method suffers from limitations, *e.g.,* the use of excess Lewis acid, the formation of gaseous HCl and poor regioselectivity, especially when strongly deactivated acyl chlorides are used. In fact, during the Friedel-Crafts acylation of 2-phenylbenzofuran with nitrobenzoyl chloride, many positions of the benzofuran ring were also acylated, leading to a complex mixture of regioisomers where the expected derivative was formed as a minor product.[8]

2-Aryl-3-benzoylbenzofuran derivatives bearing strongly electron-withdrawing groups on both phenyl rings, such as NO_2 and CN, could provide convenient intermediates in the preparation of more complicated compounds.[9] However, no methods for the synthesis of such deactivated benzo[*b*]furans have been described. Thus, the development of synthetic routes, especially those that allow access to deactivated analogues, is of considerable interest.

Herein, we report a simple and regioselective, one-pot route for the preparation of deactivated 2-phenyl-3-benzoylbenzo[*b*]furans *via* ylide acylation under Wittig conditions.

Results and discussion

In the course of a program directed towards the synthesis of novel monoamine oxidase (MAO) inhibitors,[10] we planned to synthesize 2-phenylbenzofurans using an intramolecular Wittig procedure due to the accessibility and simplicity of this methodology.[11]

The desired Wittig reagent was readily prepared in high yield from 2-hydroxybenzyl alcohol **1** and triphenylphosphine hydrobromide (Method A, Table 1).[12,13] Compounds **4** and **5a**–**p** were prepared from the appropriate triphenylphosphonium salt **2** and the commercially available aroyl chlorides **3a**–**p**.[14–21]

However, while developing this procedure, GC/MS analysis of the reaction mixture using triphenylphosphonium salt **2** and benzoyl chloride **3a**, revealed that, together with the desired product of cyclization **4a**, the unexpected side-product **5a** was present. This

* Corresponding author.
E-mail address: michelabegala@unica.it (M. Begala).
[c] This author equally contributed to the work.

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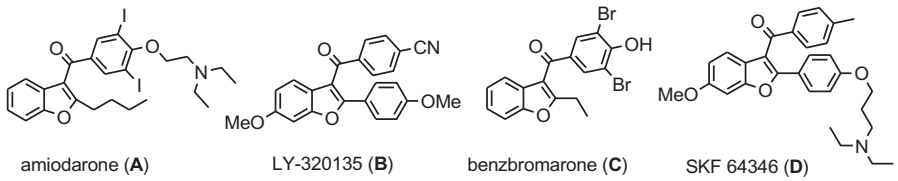
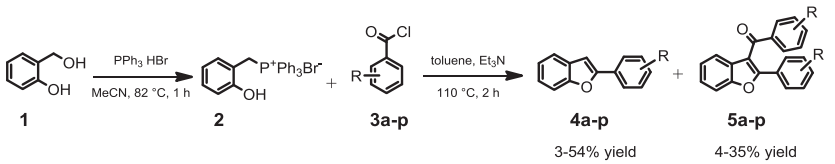
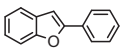
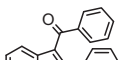
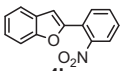
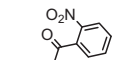
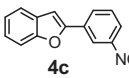
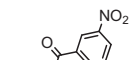
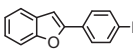
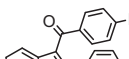
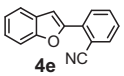
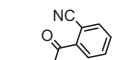
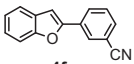
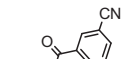
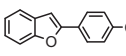
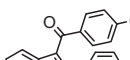
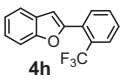
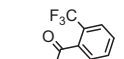
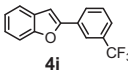
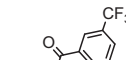


Fig. 1. Representative 3-aroyl[*b*]benzofurans of pharmacological interest.

Table 1
Synthetic route towards 2-phenylbenzofurans **4a**–**p** and 3-benzoyl-2-phenylbenzofurans **5a**–**p** (Method A). Effect of various benzoyl chlorides on the ratio of **4** and **5**.[a]



Entry	Product		Product	Yield (%)[b] (ratio **4**:**5**)
1	 **4a**	+	 **5a**	93 (9:1)[c] 88 (1.5:1)
2	 **4b**	+	 **5b**	–
3	 **4c**	+	 **5c**	38 (1:5)
4	 **4d**	+	 **5d**	16 (1:5)
5	 **4e**	+	 **5e**	–
6	 **4f**	+	 **5f**	27 (1:3)
7	 **4g**	+	 **5g**	46 (1:2)
8	 **4h**	+	 **5h**	–
9	 **4i**	+	 **5i**	21 (1:5)