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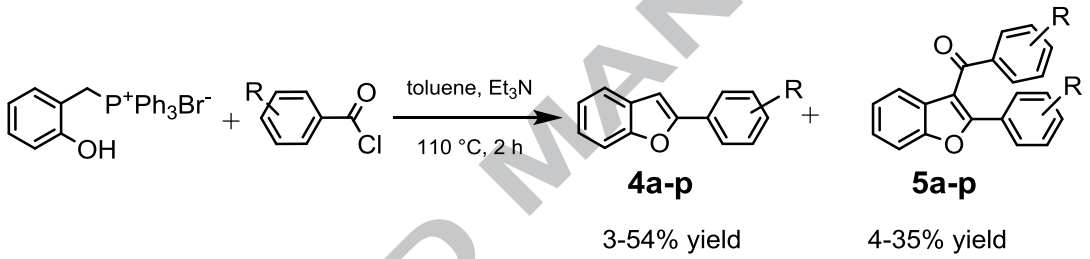

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ABSTRACT

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).

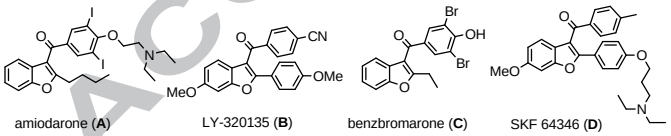

Figure 1. Representative 3-aroyl[*b*]benzofurans of pharmacological interest.

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.

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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]

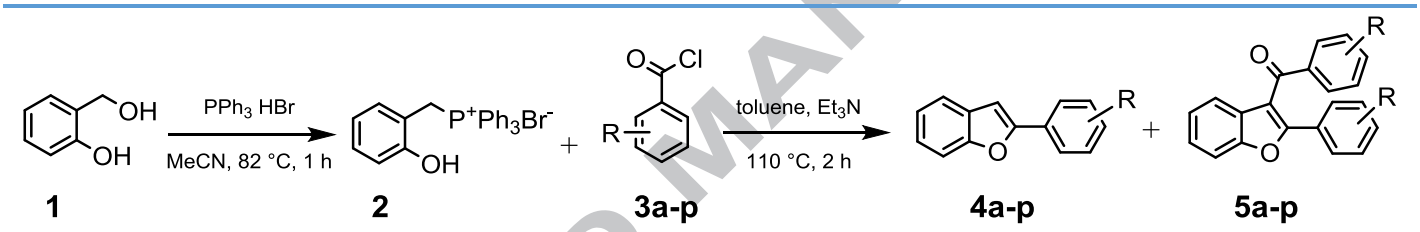
However, while developing this procedure, GC/MS analysis of the reaction mixture using triphenylphosphonium salt **2** and benzoyl chloride **3a**, revealed that, together with the desired product of cyclization **4a**, the unexpected side-product **5a** was present. This product, after purification and extensive analysis by NMR and mass spectrometry, was determined to be 2-phenyl-3-benzoylbenzofuran (see ESI for full spectroscopic data).

Although the Wittig reaction has been described in several papers regarding the preparation of 2-arylbenzofuran derivatives, the formation of secondary products was not mentioned.[11] These findings encouraged us to investigate the formation of 2-phenyl-3-acylbenzofurans under Wittig conditions.

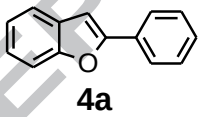
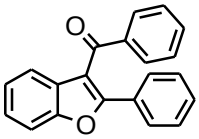
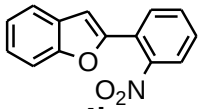
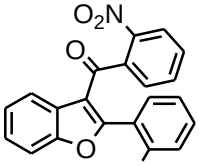
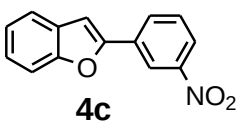
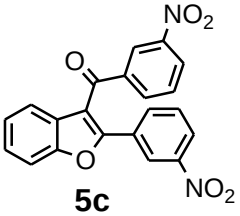
Initially, triphenylphosphonium salt **2** was treated with benzoyl chloride **3a** (1.0 equiv.) and triethylamine in dry toluene for 2 hours at 110 °C. The obtained products were easily purified by silica gel chromatography, using a mixture of hexane/ethyl acetate (9:1) as the eluent system.

Under these conditions, **5a** was isolated as the minor product along with 2-phenylbenzofuran **4a**. A higher ratio of compound **5a** was achieved by altering the ratio of reagents. Upon increasing the equivalents of both benzoyl chloride **3a** and triethylamine (3.0 equiv.), the total yield remained practically unchanged, whereas the ratio of **4a** and **5a** significantly changed from 9:1 to 1.5:1 (Table 1, entry 1). Unfortunately, attempts to prepare a single benzofuran derivative by varying the other reaction parameters failed. Next, we investigated the effect of various benzoyl chlorides on the ratio of **4** and **5** after purification (Table 1).

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



1 **2** **3a-p** **4a-p** 3-54% yield **5a-p** 4-35% yield

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)

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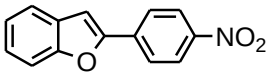
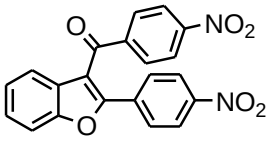
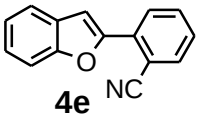
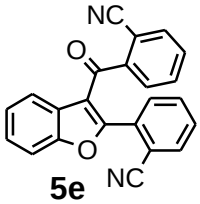
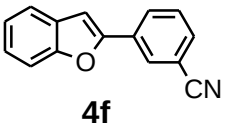
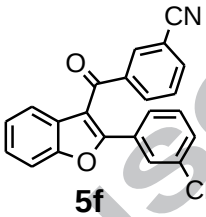
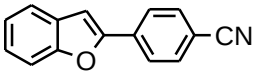
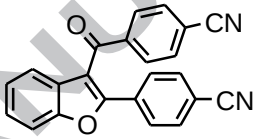
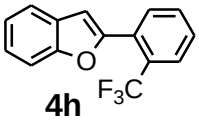
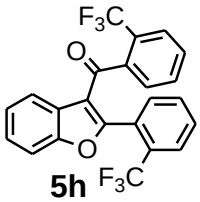
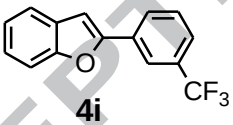
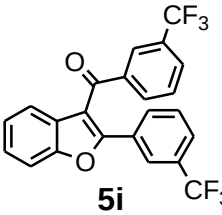
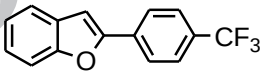
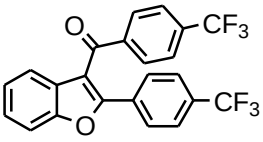
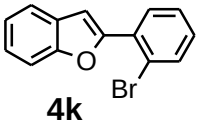
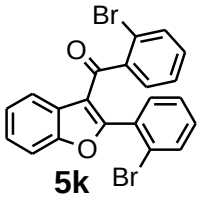
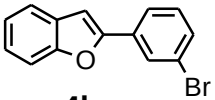
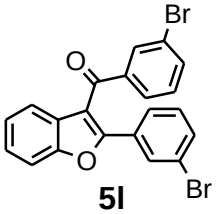
4	 **4d**	+	 **5d**	16 (1:5)
5	 **4e**	+	 **5e**	-
6	 **4f**	+	 **5f**	27 (1:3)
7	 **4g**	+	 **5g**	46 (1:2)
8	 **4h**	+	 **5h**	-
9	 **4i**	+	 **5i**	21 (1:5)
10	 **4j**	+	 **5j**	18 (1:3)
11	 **4k**	+	 **5k**	-
12	 **4l**	+	 **5l**	49 (1:1.5)

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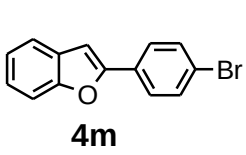
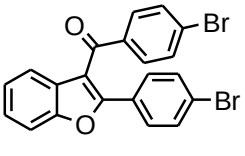
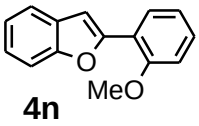
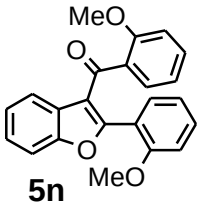
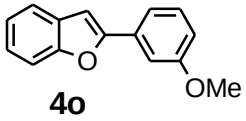
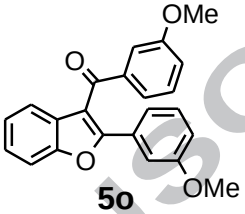
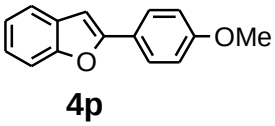
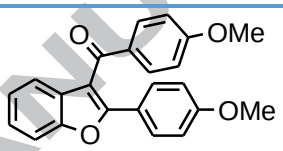
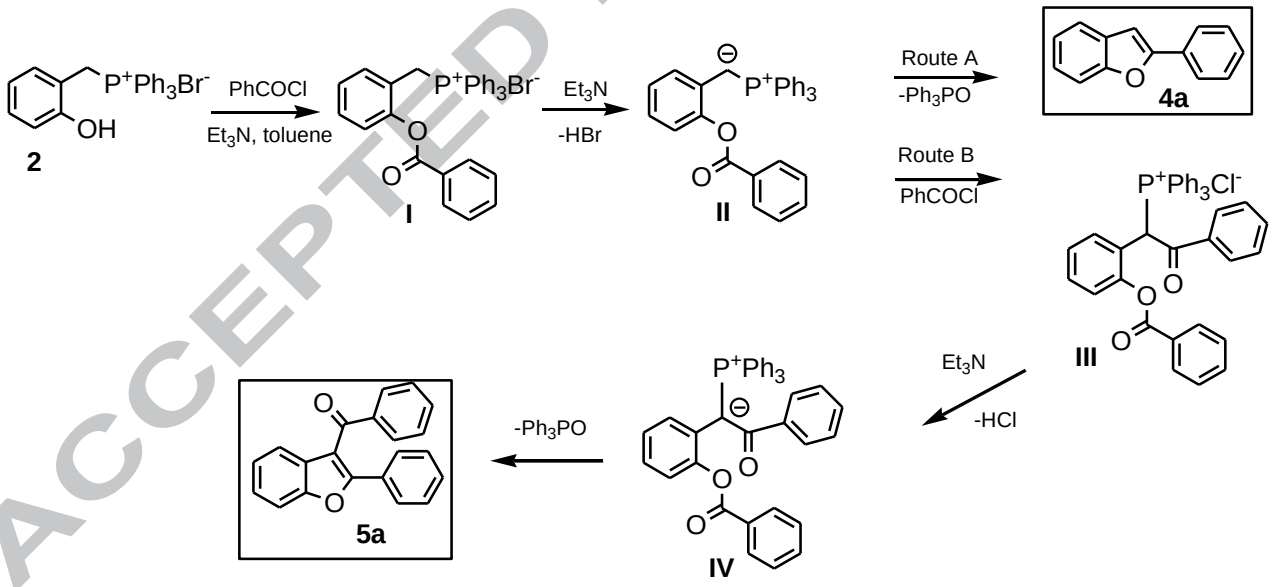
13	 **4m**	+	 **5m**	46 (1:1.3)
14	 **4n**	+	 **5n**	25 (2:1)
15	 **4o**	+	 **5o**	34 (5.5:1)
16	 **4p**	+	 **5p**	29 (2.5:1)

[a] Reagents and conditions: **2** (1 equiv.), benzoyl chloride **3a-p** (3 equiv.); [b] Total yield of products **4** and **5**. [c] Reagents and conditions: **2** (1 equiv.), benzoyl chloride **3a** (1 equiv.).



Scheme 1. Proposed reaction mechanism.

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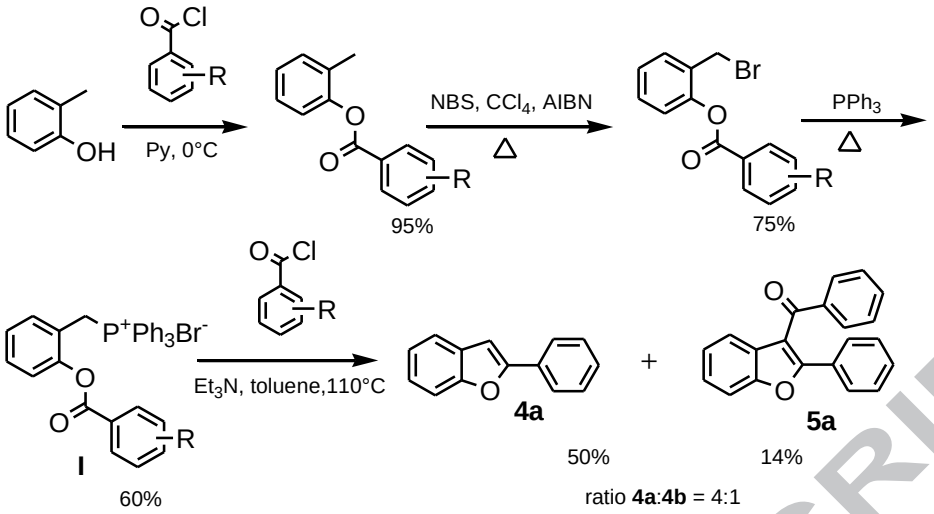

Scheme 2. Preparation of compounds **4a** and **5a** from intermediate **I** (Method B).

Compounds **4a-p** and **5a-p** were prepared using triphenylphosphonium salt **2** (1 equiv.), benzoylchlorides **3a-p** (3 equiv.) and triethylamine. In general, the electronic nature of the substituents on the phenyl ring has a strong influence on the reaction. Benzoyl chlorides possessing electron-withdrawing groups gave the corresponding 3-acyl derivatives **5** as the major products. However, *ortho*-substituted benzoyl chlorides with electron-withdrawing groups (NO_2, CN, CF_3 and Br), failed to form the acylation product (Table 1, entries 2, 5, 8, and 11).

A plausible mechanism is depicted in Scheme 1. According to the literature,[11] the phosphonium salt **2** is *O*-acylated in the presence of triethylamine to afford the corresponding *o*-(benzoyloxy)benzyl)-triphenyl-phosphonium salt **I**. Then, salt **I** is converted to the desired phosphorane **II** using triethylamine as a base. Subsequently, phosphorane **II** could either directly cyclize to give 2-phenylbenzofuran **4a** (Route A) or react with a second molecule of the acyl chloride to afford the α-ketophosphonium salt **III** (Route B). Compound **III** then readily eliminates HCl to give the stabilized *C*-acylated ylide **IV**. In the final step, intramolecular nucleophilic attack of the ylide carbanion onto the carboxylate group leads to 3-aroylbenzofuran **5a**.

The formation of intermediate **I** was supported by the fact that, under the same conditions, this compound prepared from *o*-cresol,[22,23] reacts with benzoyl chloride (2 equiv.) to afford a mixture of 2-phenylbenzofuran **4a** and 3-benzoyl-2-phenylbenzofuran **5a** (Method B, Scheme 2). It should be noted that this synthetic approach cannot be considered a convenient route to the preparation of compounds **4a** and **5a** as it requires three additional synthetic steps and toxic reagents, when compared with Method A (Table 1).

Conclusion

A series of 2-phenylbenzofurans and unexpected 3-benzoyl-2-phenylbenzofurans were synthesized under Wittig conditions. This operationally simple procedure, requires short reaction times and does not involve the use of expensive reagents. The principal advantage of this synthetic method consists of the synthesis of 3-benzoyl-2-phenylbenzofuran derivatives with electron-withdrawing groups, which are difficult to obtain by the direct acylation of the 2-phenylbenzofurans.

Acknowledgments

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References and notes

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Supporting Information

Details of the experimental procedure and spectral data for new compounds. This material is available free of charge in the online version [http://].

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Highlights

•The Wittig reaction affords 3-benzoyl-2-phenylbenzofurans from triphenylphosphonium salt and commercially available aroyl chlorides

•A variety of new deactivated 3-benzoyl-2-phenylbenzofurans were obtained

•The present protocol offers direct and facile access to 3-benzoyl-2-phenylbenzofurans and good tolerance towards strongly deactivated functional groups

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