Synthesis of 2-Phenyl-3-benzoylbenzofurans under Wittig Conditions

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Abstract:

3-Benzoyl[*b*]benzofurans are structural cores to a host of bioactive molecules in pharmaceutical use or development. Representative examples include amiodarone, a clinically used drug for controlling intractable cardiac arrhythmias, LY 320135, a potent cannabinoid CB_1 receptor antagonist, and benzbromarone, an uricosuric agent.

Numerous approaches to the benzofurane scaffold have been disclosed in the literature. Most synthetic approaches to 2,3-disubstituted benzofurans introduce the C3-substituent on the preformed benzo[*b*]furan ring at the end of the synthesis. Traditionally, the simple and straightforward method for the C3 acylation of benzofurans appeared to be the Friedel-Craft reaction using acylchlorides. However this method suffer from some limitations *e.g.* the poor regioselectivity, especially when strongly deactivated acylchloride are used.

In the course of our program directed at the synthesis of novel MAO inhibitors, we planned to synthesize 2-phenylbenzofuranes using the intramolecular Wittig procedure due to its ease and simplicity.

Using this procedure, we found that the GC/MS analysis of the crude reaction mixture revealed, together with the desired product of cyclization (2-phenylbenzofuran), one unexpected side product, which, after extensive analysis by NMR and mass spectrometry, turned out to be the 2-phenyl-3-benzoyl benzofurane.

In this scenario, our findings could be extended to design and develop new potentially therapeutic molecules, especially useful in neurodegenerative diseases.

Keywords: Synthetic method, 3-Aroylbenzofuranes, intramolecular Wittig reaction

Introduction:

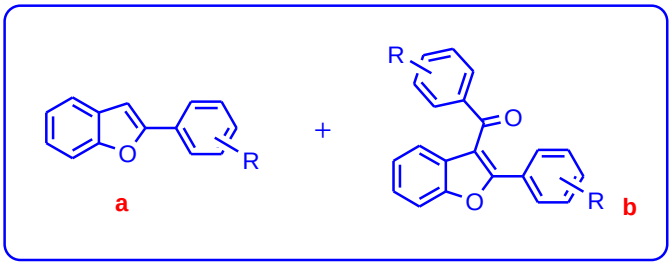
Many important biochemical compounds and drugs of natural origin contain heterocyclic ring structures. The presence of heterocyclic structure in such different type of compounds is strongly indicative of the diverse pharmacological activities and recognition of this is reflected in efforts to find useful synthetic drugs.

3-Benzoyl[*b*]benzofurans are structural cores to a host of bioactive molecules in pharmaceutical use or development. Representative examples include amiodarone,[1] a clinically used drug for controlling intractable cardiac arrhythmias, LY 320135,[2] a potent cannabinoid CB_1 receptor antagonist, and benzbromarone,[3] an uricosuric agent.

Most synthetic approaches to 3-acyl benzofurans introduce the C3-substituent on the preformed benzo[*b*]furan ring at the end of the synthesis.[4] Traditionally, the simple and straightforward method for the C3 acylation of benzofurans appeared to be the Friedel-Crafts reaction using acylchlorides.[5] However this method suffer from some limitations *e.i* the use of excess of Lewis acid, the formation of harmful gaseous HCl and poor regioselectivity, especially when strongly deactivated acyl chloride are used.

In the course of our program directed towards the synthesis of novel MAO inhibitors, we planned to synthesize 2-phenylbenzofuranes using the intramolecular Wittig procedure due to its ease and simplicity.[6,7]

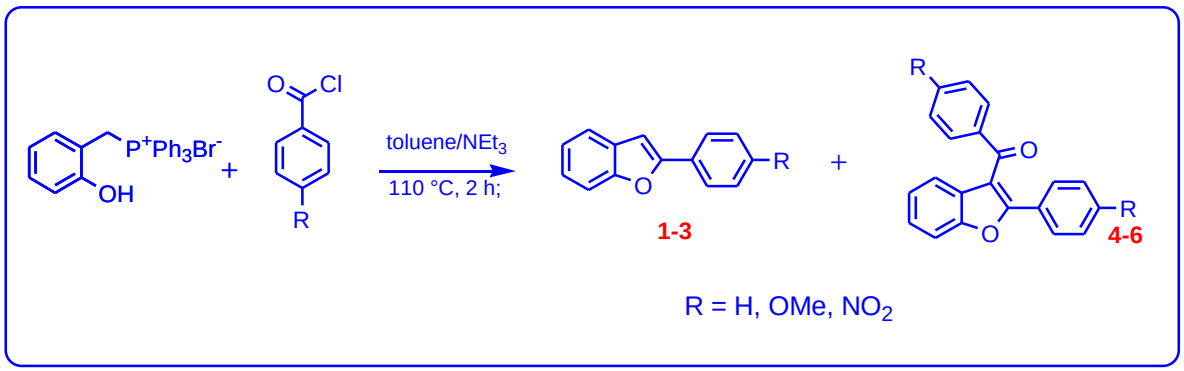
Using this procedure, we found that the GC/MS analysis of the crude reaction mixture revealed, together with the desired product of cyclization (2-phenylbenzofuran **a**), one unexpected side product, which, after extensive analysis by NMR and mass spectrometry, turned out to be the 2-phenyl-3-benzoyl benzofurane **b**.



Results and discussion

Compounds **1–3ab** were efficiently synthesized according to the synthetic strategy outlined in Scheme 1. The key step for the formation of the benzofuran moiety was achieved by an intramolecular Wittig reaction between *ortho*-hydroxybenzyltriphosphonium salt and the appropriate aroylchloride.[8]

The desired Wittig reagent was readily prepared from the conveniently substituted *ortho*-hydroxybenzyl alcohol and $PPh_3 \cdot HBr$.[9,10]



Scheme 1

While developing our project using this procedure, we found that the GC/MS analysis of the crude reaction mixture revealed, together with the desired product of cyclization **a** (**1-3a**), the unexpected side product **b** (**1-3b**), which, after extensive analysis by NMR and mass spectrometry, turned out to be the 2-phenyl-3-benzoyl benzofurane.

The benzofuran structures were confirmed by mass spectrometry, elemental analyses, one-dimensional resonance techniques. In table 1 we reported isolated overall yields and mp obtained for compound **1-3ab**.

compounds	R	% Yeld (a:b)	Mp
1a	H	88%	118-120 °C
1b			148-149 °C
2a	OMe	30%	181-182 °C
2b			98-99 °C
3a	NO_2	20%	80-83 °C
3b			258-260 °C

Table 1

The Wittig reaction has been already described in several papers dealing with the preparation of 2-arylbenzofurane derivatives, however the formation of secondary products was not mentioned.[8] These findings encouraged us to investigate the formation of 2-phenyl-3-acylbenzofurane under this condition.

Conclusion

In the present piper a series of 2-phenylbenzofurans and unexpected 3-benzoyl-2-phenylbenzofurans, were synthesized by Wittig reaction. The reaction is very easy and does not involve the use of any expensive reagents, The principal advantage of this synthetic method consist in the synthesis of 3-benzoyl-2-phenylbenzofuran derivatives with electron-withdrawing groups, difficult to obtain by a direct acylation of 2-phenylbenzofuran nucleus. These promising results are paving the way for the introduction of a significant array of substituents at C3 of the benzofuran scaffold, and the investigation on the activity of new poly-substituted benzofuran derivatives.

Materials and Methods

Starting materials, solvent and reagents were obtained from commercial suppliers (Sigma-Aldrich) and were used without further purification. All reactions were performed under N_2 atmosphere. Analytical thin layer chromatography (TLC) was carried out on silica gel 60 F254 plates (0.25 mm), visualized by exposure to UV light. Column chromatography purifications were performed using. Aldrich silica gel (60–120) mesh size. Melting points were determined on a Stuart Scientific SMP 11 melting point apparatus and are uncorrected. Concentration and evaporation of the solvent after reaction or extraction were carried out on a rotary evaporator (Büchi Rotavapor) operating at reduced pressure. ^{1}H NMR and ^{13}C NMR spectra were recorded with a Varian INOVA 500 spectrometer using [D_6]DMSO or $CDCl_3$ as solvent. Chemical shifts (δ) are expressed in parts per million (ppm) using TMS (tetramethylsilane) as an internal standard. Coupling constants *J* are expressed in hertz (Hz). Spin multiplicities are given as s (singlet), d (doublet), dd (doublet of doublets), and m (multiplet). GC-MS: low resolution mass spectrometric experiments were carried out on a Saturn 2000 ion-trap coupled with a Varian 3800 gas chromatograph (Varian, Walnut Creek,

CA) operating under EI conditions (electron energy 70 eV, emission current 20 mA, ion-trap temperature 200°C, manifold temperature 80°C, automatic gain control (AGC) target 21.000) with the ion trap operating in scan mode (scan range from m/z 40–400 at a scan rate of 1 scan/s). Aliquots of 1 µL of solutions 1.0 x 10^{-5} M in chloroform have been introduced into the gas chromatographer inlet. A CIP Sil-8 CB Lowbleed/MS capillary column (30 m, 0.25 mm i.d., 0.25 mm film thickness) was used. The oven temperature was programmed from 150°C (held for 2 min) to 310°C at 30°C/min (held for 2 min). The temperature was then ramped to 350 at 20°C/min. The transfer line was maintained at 250°C and the injector port (30:1 split) at 230°C

General procedure for the preparation of 2-hydroxybenzylalcohols: $NaBH_4$ (6.60 mmol) was added to a stirring solution of 2-hy-droxybenzaldehyde (6.60 mmol) in EtOH (20 mL) in an ice bath. The reaction mixture was stirred at room temperature for 1 h. After that, the solvent was removed, 1n aqueous HCl (40 mL) was added to the residue and extracted with Et_2O. The solvent was evaporated under vacuum to give the desired compounds

General procedure for the preparation of 2-hydroxybenzyltri-phenylphosphonium bromide: A mixture of 2-hydroxybenzylalcohol (24.6 mmol) and $PPh_3 \cdot HBr$ (24.6 mmol) in CH_3CN (50 mL) was stirred under reflux for 2 h. The solid was filtered and washed with CH_3CN to give the desired compounds.

General procedure for the preparation of 2-phenylbenzofuran ***1-3*** *and 3-benzoyl-2-phenylbenzofuran* ***4-6***: A mixture of 2-hydroxybenzyltriphenylphosphonium bromide (1.11 mmol) and benzoyl chloride (3.33 mmol) in a mixed solvent (toluene 30 mL and Et_3N 0.6 mL) was stirred under reflux for 2 h. The precipitate was removed by filtration. The filtrate was concentrated, and the residue was purified by silica gel chromatography (hexane/EtOAc 9:1) to give the desired compounds.

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