

Unexpected migration of benzoyl group in the synthesis of 3-benzoyl-2-phenylbenzofurans under Wittig conditions

Giovanna Lucia Delogu* and Michela Begala

Dipartimento di Scienze della Vita e dell' Ambiente, Università degli Studi di Cagliari, 09124 Cagliari, Italy.

* Correspondence: delogug@unica.it; Tel.: +39-070-675-8566; michelabegala@unica.it; Tel.: +39-070-675-8678

Abstract: In the present work we report the unexpected formation of isomeric 3-benzoyl-2-phenylbenzo[b]furans using triphenylphosphonium salt and benzoyl chlorides under Wittig conditions. In particular, we found that the *o*-[(benzoyloxy)benzyl]-triphenyl-phosphoranes constitute the key intermediate that reasonably undergoes benzoyl group migration.

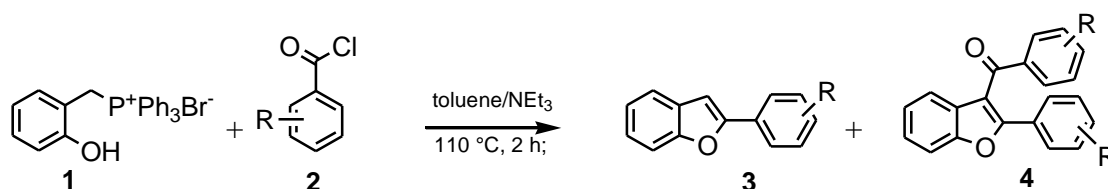
Keywords: Wittig reaction, 3-acyl-2-phenylbenzofurans, phosphorane

1. Introduction

3-Aroyl[b]benzofurans represent the structural cores of a large number of bioactive molecules in current pharmaceutical use or development. As a result, numerous approaches towards the synthesis of 3-acylbenzofurans have been disclosed in the literature.

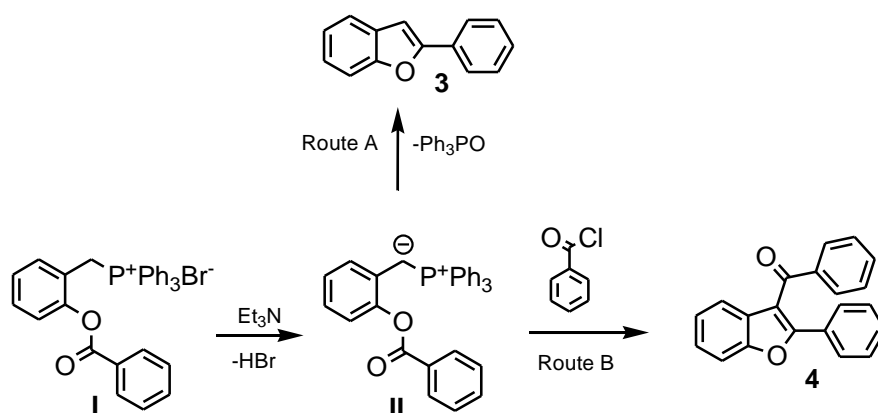
The Wittig reaction, is an easy procedure to the benzofuran ring system. In a previous paper Hercouet and Le Corre reported that the intramolecular condensation of *o*-acyloxybenzylidenetriphenylphosphoranes **II** leads to the benzofuran in aprotic medium (toluene) or to acylated product in protic medium (t-BuOH) [1].

We recently found that the reaction of the triphenylphosphonium salt and aroyl chlorides in toluene leads together with the expected 2-phenylbenzofurans **3**, also to 3-benzoyl-2-phenylbenzo[b]furans **4** via ylide acylation under Wittig conditions (Scheme 1) [2].



Scheme 1: Synthetic route towards 2-phenylbenzofurans **3** and 3-benzoyl-2-phenylbenzofurans **4**

We proved that the key intermediate that leads to the 3-benzoyl derivatives was the *o*-[(benzoyloxy)benzyl]-triphenyl-phosphoranes **II** (Scheme 2).



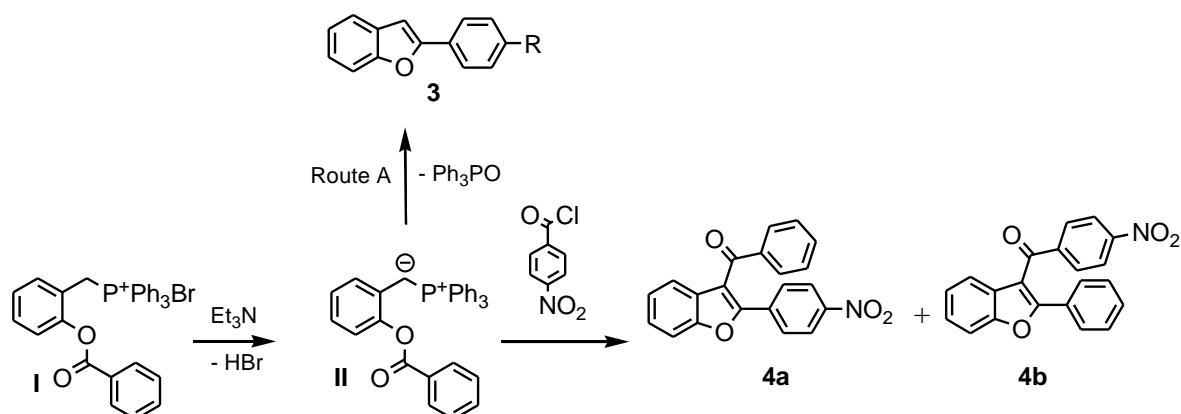
Scheme 2: Proposed reaction mechanism.

However, the reaction of the phosphorane **II** with substituted benzoyl chloride, unexpectedly showed the formation of two sets of 3-acyl isomers (Route B). These data prompted us to investigate the Wittig reaction.

2. Results and Discussion

O-[(benzoyloxy)benzyl]-triphenyl-phosphoranes **II** was reacted with benzoyl chlorides substituted with electron withdrawing and donating groups.

O-[(benzoyloxy)benzyl]-triphenyl-phosphoranes **II** was prepared starting from *ortho* cresol [3,4]. Subsequently, **II** was reacted with 4-nitrobenzoyl chloride in the presence of triethylamine in toluene. The reaction mixture showed the formation of two 3-acyl isomers (Scheme 3), *i.e.* the 3-benzoyl-2-(4'-nitrophenyl)benzofuran **4a** and 3-(4'-nitrobenzoyl)-2-phenylbenzofuran **4b**, as identified by GC/MS analysis.



Scheme 3: Preparation of compounds **4a** and **4b** from intermediate **II**

The same behaviour was also observed when 4-methoxybenzoyl chloride was used. These results clearly suggest that the regioselective benzoyl group migration occurred in some extent.

3. Conclusion

Our preliminary results demonstrated that, under aprotic conditions, also 3-acyl derivative can be obtained from phosphoranes and that the intramolecular migration of the benzoyl group occurred. This finding is of considerable interest as it allows to prepare a wide variety of 3-acylbenzofuran derivatives difficult to obtain with alternative synthetic methods.

4. 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 N₂ 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. 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). 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 50°C (held for 2 min) to 210°C at 20°C/min (held for 15 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 280°C

General procedure for the preparation of 2-methylphenylbenzoate [3,4]: *ortho*-cresol (1 g, 0.92 mmol) was taken in pyridine (10 ml) and to it benzoyl chloride (1.2 g, 0.92 mmol) was added drop wisely at 0 °C with stirring and kept overnight. The reaction mixture was warmed on a water bath for 10 min and decomposed with ice cold hydrochloric acid (1:1), followed by extraction with ether (3 x 15 ml), washed with brine (3 x 10 ml) and dried over anhydrous sodium sulphate. Yield: 95%.

General procedure for the preparation of 2-bromomethylphenylbenzoate [3,4]: 2-methylphenyl benzoate (1.5 g, 7 mmol) and *N*-bromosuccinimide (NBS) (1.28 g, 7.2 mmol) were taken in dry CCl₄ (15 ml). The mixture was heated to 85 °C before azobisisobutyronitrile (AIBN) was added in few crystals. After heating at reflux for 1 h, more AIBN was added. The flask was kept at reflux for 5 h. The reaction mixture was cooled down to room temperature and precipitated succinimide was filtered off. The solvent was removed in *vacuo* and the residue was chromatographed on silica gel (Hexane/EtOAc 2:1) to give 2-bromomethylphenylbenzoate, as colorless crystals. Yield: 75%; mp 79 °C.

General procedure for the preparation of 2-benzyloxy-benzyl triphenyl phosphonium bromide I [1]: a mixture of 2-bromomethylphenylbenzoate (5.1 mmol) and PPh₃·HBr (5.1 mmol) in toluene (60 mL) was stirred under reflux for 4 h. The solid formed was filtered and washed with toluene to give the desired compounds. White solid; yield: 60%.

General procedure for the preparation of 2-phenylbenzofuran 3 and 3-(4'-Nitrobenzoyl)-2-phenylbenzofuran 4a and 3-benzoyl-2-(4'-nitrophenyl)benzofuran 4b: a mixture of 2-benzyloxy-benzyl triphenyl

phosphonium bromide **I** (0.6 mmol) and 4-nitrobenzoyl chloride (1.5 mmol) in a mixed solvent (toluene 15 mL and Et₃N 0.4 mL) was stirred under reflux for 2 h. The precipitate was removed by filtration. The filtrate was concentrated, and the mixture containing the three reaction products, **3**, **4a** and **4b**, were analysed by GC/MS.

2-(4'-Nitrophenyl)benzofuran **3**: MS (EI, 70eV): *m/z* (%): 239 (100) [M⁺], 209 (37), 165 (26).

3-Benzoyl-2-(4'-nitrophenyl)benzofuran **4a**: MS (EI, 70eV): *m/z* (%): 343 (100) [M⁺], 221 (70).

3-(4'-Nitrobenzoyl)-2-phenylbenzofuran **4b**: MS (EI, 70eV): *m/z* (%): 343 (100) [M⁺], 266 (65).

References

1. (a) Hercouet, A.; Le Corre, M. *Une nouvelle voie d'accès aux benzofurannes*. *Tetrahedron Lett.* **1979**, *23*, 2145-2148; DOI: 10.1016/S0040-4039(01)86285-7 (b) Hercouet, A.; Le Corre, M. *Acyloxyalkylidènéphosphoranes—III: Etude des ω-acyloxybenzylidènetriphénylphosphoranes.nouvelle voie d'accès aux benzofurannes*. *Tetrahedron* **1981**, *37* (16), 2867-2873. DOI: 10.1016/S0040-4020(01)92357-9
2. Begala, M.; Caboni, P.; Matos, M.J.; Delogu, G.L. *Unexpected one-step synthesis of 3-benzoyl-2-phenylbenzofurans under Wittig conditions*. *Tetrahedron Lett.* **2018**, *59*, 1711-1714. DOI: 10.1016/j.tetlet.2018.03.048
3. Ghosh, S.; Das, J. *A novel photochemical Wittig reaction for the synthesis of 2-aryl/alkylbenzofurans*. *Tetrahedron Lett.* **2011**, *52*, 1112-1116. DOI: 10.1016/j.tetlet.2010.12.104
4. Routasalo, T.; Helaja, J.; Kavakka, J.; Koskinen, A. M. P. *Development of Bis(2-picoyl)amine-Zinc Chelates for Imidazole Receptors*. *Eur. J. Org. Chem.* **2008**, *18*, 3190-3199. DOI: 10.1002/ejoc.200700926