

Alma Mater Studiorum Università di Bologna
Archivio istituzionale della ricerca

Unexpected migration of a benzoyl group in the intramolecular Wittig reaction of o-acyloxybenzylidenephosphoranes with benzoyl chlorides: One-pot synthesis of isomeric 3-benzoyl-2-phenylbenzofurans

This is the final peer-reviewed author's accepted manuscript (postprint) of the following publication:

Published Version:

Begala, M., Mancinelli, M., Delogu, G.L. (2020). Unexpected migration of a benzoyl group in the intramolecular Wittig reaction of o-acyloxybenzylidenephosphoranes with benzoyl chlorides: One-pot synthesis of isomeric 3-benzoyl-2-phenylbenzofurans. TETRAHEDRON LETTERS, 61(12), 1-4 [10.1016/j.tetlet.2020.151634].

Availability:

This version is available at: <https://hdl.handle.net/11585/782951> since: 2020-12-02

Published:

DOI: <http://doi.org/10.1016/j.tetlet.2020.151634>

Terms of use:

Some rights reserved. The terms and conditions for the reuse of this version of the manuscript are specified in the publishing policy. For all terms of use and more information see the publisher's website.

This item was downloaded from IRIS Università di Bologna (<https://cris.unibo.it/>).
When citing, please refer to the published version.

(Article begins on next page)

This is the final peer-reviewed accepted manuscript of:

Begala, M., Mancinelli, M., Delogu, G.L., 2020. Unexpected migration of a benzoyl group in the intramolecular Wittig reaction of o-acyloxybenzylidenephosphoranes with benzoyl chlorides: One-pot synthesis of isomeric 3-benzoyl-2-phenylbenzofurans. Tetrahedron Letters 61, 151634.

The final published version is available online at:
<https://doi.org/10.1016/j.tetlet.2020.151634>

Rights / License:

The terms and conditions for the reuse of this version of the manuscript are specified in the publishing policy. For all terms of use and more information see the publisher's website.

This item was downloaded from IRIS Università di Bologna (<https://cris.unibo.it/>)

When citing, please refer to the published version.

Unexpected migration of a benzoyl group in the intramolecular Wittig reaction of *o*-acyloxybenzylidenetriphenylphosphoranes with benzoyl chlorides: one-pot synthesis of isomeric 3-benzoyl-2-phenylbenzofurans

Michela Begala^{a,*}, Michele Mancinelli^b and Giovanna Lucia Delogu^{a,†}

^aDepartment of Life and Environmental Sciences, University of Cagliari, Via Ospedale 72, 09124 Cagliari, Italy

^bDepartment of Industrial Chemistry "Toso Montanari", University of Bologna, Viale del Risorgimento, 4, 40136 Bologna, Italy

ha formattato: Non Apice / Pedice

Formattato: Normale, SpazioDopo: 0 pt

ARTICLE INFO

ABSTRACT

Article history:

Received

Received in revised form

Accepted

Available online

The reaction of *o*-acyloxybenzylidenetriphenylphosphoranes with substituted benzoyl chlorides in an aprotic solvent led, together with the expected 2-phenylbenzofuran, to isomeric 3-benzoyl-2-phenylbenzofuran derivatives. This result formally corresponds to intramolecular migration of the benzoyl group from the *ortho* oxygen atom to the ylide carbanion *via* cyclization and ring opening of the starting *o*-acyloxybenzylidenetriphenylphosphoranes.

Keywords:

Wittig reaction

Phosphoranes

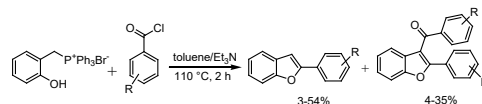
2-phenylbenzofurans

3-arylbenzofurans

Introduction

3-Aroyl[*b*]benzofurans are present in the structural cores of a large number of bioactive molecules in current pharmaceutical use and development (Fig. 1) [1-4]. As a result, numerous approaches towards the synthesis of 3-acylbenzofurans have been disclosed in the literature [5,6]; however, most of them are only suitable for the preparation of 2-arylb-3-benzoylbenzofuran derivatives bearing electron-donating groups [7].

leads to 3-benzoyl-2-phenylbenzo[*b*]furans via ylide acylation in addition to the expected 2-phenylbenzofurans (Scheme 1) [8,9].



Scheme 1. Synthetic route towards 2-phenylbenzofurans and 3-benzoyl-2-phenylbenzofurans.

Hercouet and Le Corre [10] reported that the intramolecular Wittig reaction of *o*-acyloxybenzylidenetriphenylphosphoranes leads to the corresponding benzofurans in aprotic medium (toluene) or to acylated products in protic medium (*t*-BuOH). Therefore, we became interested in verifying whether the *o*-[(benzyloxy)benzyl]-triphenyl-phosphorane was the key intermediate leading to the 3-benzoyl derivatives. Our results showed that benzoyl chloride reacts with phosphorane **I** to give a mixture of 2-phenylbenzofuran and 3-benzoyl-2-phenylbenzofuran, thus confirming this hypothesis (Scheme 2).

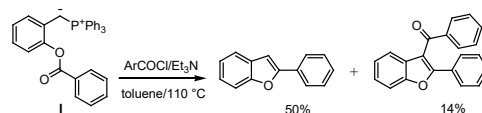


Figure 1. Representative 3-arylb[*b*]benzofurans of pharmacological interest.

In our previous work, we found that the reaction of 2-hydroxybenzyltriphenylphosphonium bromide with benzoyl chlorides and triethylamine in an aprotic solvent (*i.e.* toluene),

* Corresponding author.

e-mail address: michelabegala@unica.it (M. Begala).

† These authors contributed equally to the work.

Scheme 2. Formation of 2-phenylbenzofuran and 3-benzoyl-2-phenylbenzofuran from **I**.

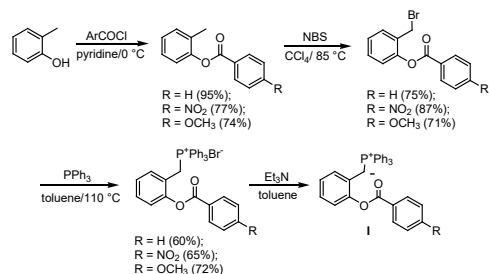
3-Benzoyl-2-phenylbenzofuran derivatives with strongly electron-withdrawing groups (*e.g.* NO₂ and CN) on the 2-phenyl or 3-benzoyl ring, could provide convenient intermediates in the preparation of more complicated compounds [11]. However, no methods for the synthesis of such deactivated benzofurans have been described. For instance, during the Friedel-Crafts acylation of 2-phenylbenzofuran with nitrobenzoyl chloride, other 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 [12]. Thus, the development of new synthetic routes, especially those that allow access to deactivated analogues, is of considerable interest.

In this context, we envisaged that the reaction of *o*-acyloxybenzylidenetriphenylphosphoranes with substituted benzoyl chlorides would provide access to the corresponding 3-benzoyl-2-phenylbenzofurans bearing different substituents on the 2-phenyl and/or the 3-benzoyl ring.

In the present work, we describe our efforts toward the synthesis of diversely 2,3-disubstituted benzofurans with particular attention given to the preparation of 3-benzoyl-2-phenylbenzofuran derivatives bearing electron-withdrawing groups. Moreover, the unexpected formation of the 3-acyl isomers, prompted us to further investigate the Wittig reaction.

Results and Discussion

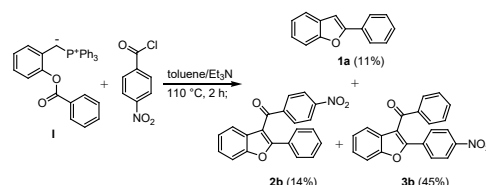
o-[(Benzoyloxy)benzyl]-triphenyl-phosphoranes **I**, prepared from *ortho*-cresol [8,13,14] (Scheme 3), were reacted with benzoyl chlorides substituted with electron withdrawing or donating groups.



Scheme 3. Synthetic route towards *o*-[(benzoyloxy)benzyl]-triphenyl-phosphoranes **I** (R = H, NO₂, OCH₃).

When **I** (R = H) was reacted with 4-nitrobenzoyl chloride in the presence of triethylamine in toluene, the reaction mixture

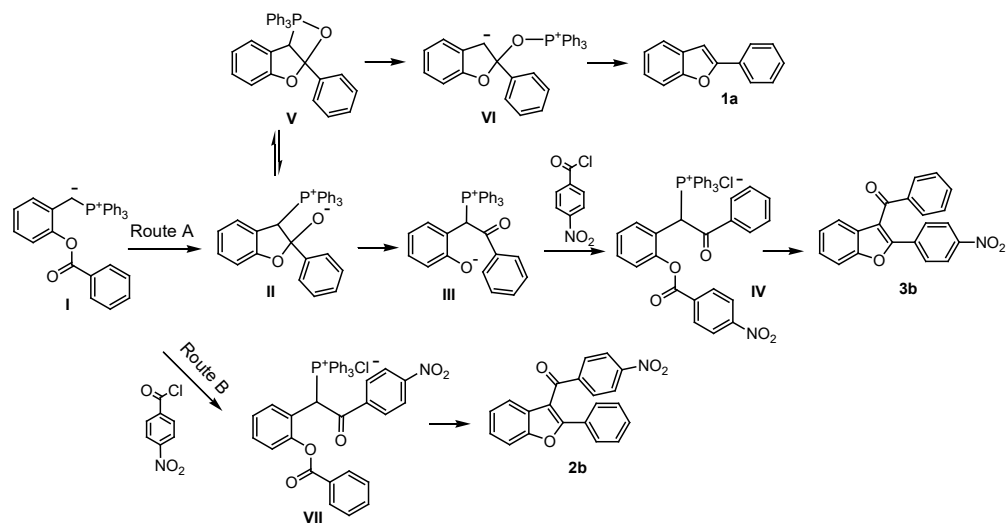
showed the formation of two 3-acyl isomers (Scheme 4), *i.e.* the expected 3-(4-nitrobenzoyl)-2-phenylbenzofuran **2b** and 3-benzoyl-2-(4-nitrophenyl)benzofuran **3b**, as identified by NMR spectroscopy and GC/MS analysis.



Scheme 4. Synthesis of isomeric compounds **2b** and **3b**.

The same behaviour was also observed when a variety of 4-substituted benzoyl chlorides were used (*vide infra*). These results clearly suggest that benzoyl group migration occurred to some extent. Interestingly, Hercouet and Le Corre reported such a transposition only under protic condition (*t*-BuOH) and using a strong base (*t*-BuOK) [10]. An analogous 1,5-transposition of an ester acyl functional group was also observed by Gorgues and co-workers for the σ -bonded organochromium-(III) complex resulting from the reduction of *ortho*-bromomethylphenyl benzoate with CrCl₂ [15].

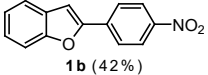
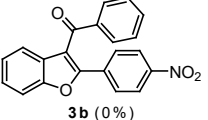
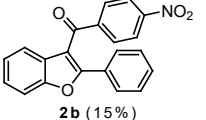
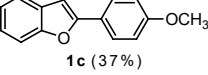
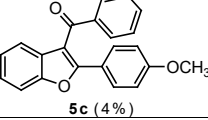
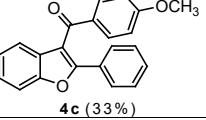
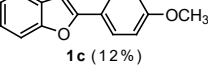
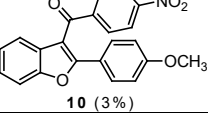
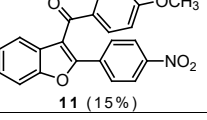
A plausible mechanism is depicted in Scheme 5. Carbanion **I** reacts with the corresponding acyl chloride to give the isomer **2b** (Route B), as previously proposed by us [8]. Alternatively, the O-acylated phosphorane **I** can also cyclize directly into intermediate **II** (Route A) to give either the 2-phenylbenzofuran **1a** or undergo ring-opening to the C-acylated phenolate **III**. Intermediate **III** is O-acylated to give the phenol ester **IV**, that leads to the isomeric 3-benzoyl-2-phenylbenzofuran **3b** via a ylide intermediate.



Scheme 5. Proposed mechanism of benzoyl group migration from ylide **I** and the formation of isomeric compounds **2b** and **3b**.

Table 1. Synthetic route towards 2-phenylbenzofurans **1a-c**, and 3-benzoyl-2-phenylbenzofurans **2-9a-e**, **10** and **11**.^a

ENTRY	SUBSTRATES	PRODUCTS (YIELDS %)		
1	R = H; R' = NO ₂			
2	R = H; R' = OCH ₃			
3	R = H; R' = Br			
4	R = H; R' = CN			

5	R = NO ₂ ; R' = H	 1b (42%)	 3b (0%)	 2b (15%)
6	R = OCH ₃ ; R' = H	 1c (37%)	 5c (4%)	 4c (33%)
7	R = OCH ₃ ; R' = NO ₂	 1c (12%)	 10 (3%)	 11 (15%)

^a**1** (1 equiv.), benzoyl chlorides (2.5 equiv.), Et₃N (2.5 equiv.), toluene 110 °C, 2 h.

Interestingly, the isomer arising from benzoyl migration **3b** (45%) was the main product; therefore Route A was more favored than Route B. These data clearly indicate that the O-acylated phosphorane **I** spontaneously cyclizes into **II**, presumably because intramolecular attack of the ylide carbanion to the *ortho* carbonyl group is favoured by their proximity (Scheme 5 and Table 1, entry 1).

This behaviour was even more pronounced when 4-nitrobenzoyl chloride was replaced by 4-methoxybenzoyl chloride (Table 1, entry 2). In the latter case, the reaction of **I** with the less electrophilic 4-methoxybenzoyl chloride (Route B) was suppressed (**4c**, 3%) in favour of Route A (**1a**, 20%; **5c**, 15%). These results clearly indicate that deactivated benzoyl chlorides allow the formation of both isomeric 3-acyl derivatives, most likely because **I** and **III** rapidly attack the highly electrophilic carbonyl of the 4-nitrobenzoyl chloride. Accordingly, analogous trends were also observed with 4-bromo and 4-cyanobenzoyl chlorides (Table 1, entries 3 and 4).

When substituted *o*-[(benzoyloxy)benzyl]-triphenyl-phosphoranes were used (R = NO₂, OCH₃, entries 5 and 6), we observed that the electron withdrawing group further suppressed Route B in favour of cyclization to **II** (Route A), as reflected by the higher yield of 2-(4-nitrophenyl)benzofuran **1b** (42%) and the absence of 3-benzoyl-2-(4-nitrophenyl)benzofuran **3b** (Table 1, entry 5). This behaviour could be rationalized by the fact that the 4-nitro group increases the electrophilicity of the carbonyl group of **I** (R = NO₂), making it easier for the ylide carbanion to attack this electrophilic centre. Accordingly, *o*-[(benzoyloxy)benzyl]-triphenyl-phosphorane bearing an electron donating group (R = OCH₃) still resulted in the formation of isomer **5c**; albeit in low yield (4%) (Table 1, entry 6).

The reaction of substituted *o*-[(benzoyloxy)benzyl]-triphenyl-phosphoranes **I** (R = OCH₃) with 4-nitrobenzoyl chloride (Table

1, entry 7) again leads predominantly to 2-(4-methoxyphenyl)benzofuran **1c** (12%) and isomer **11** (15 %) *via* Route A.

Conclusion

Our previous results demonstrated that under aprotic conditions 3-acylbenzofurans can be obtained from the reaction of *o*-[(benzoyloxy)benzyl]-triphenyl-phosphoranes with benzoyl chlorides. We have also demonstrated that under these conditions phosphoranes preferentially undergo intramolecular migration of the benzoyl group *via* cyclization and ring opening. This behaviour clarifies the unexpected formation of two sets of 3-acylbenzofuran isomers when phosphoranes react with benzoyl chlorides.

In particular, we found that the isomer arising from benzoyl migration is further favoured by the use of deactivated benzoyl chlorides or by phosphoranes **I** with a 4-methoxy group. This finding is of considerable interest as it allows preparation of a wide variety of 3-acylbenzofuran derivatives which are difficult to obtain using alternative methods.

Acknowledgments

The present work was partially supported by FIR (Fondo Integrativo per la Ricerca – annualità 2018) - University of Cagliari.

References and notes

- [1] Singh SN, Fletcher RD, Fisher SG, Singh BN, Lewis HD, Deedwania PC, Massie BM, Colling C, Layyeri D. *N. Eng. J. Med.* **1995**;333:77-82; (b) Kálai T, Várbió G, Bognár Z, Pálfi A, Hantó K, Bognár B, Ósz E, Smegi B, Hideg K. *Bioorg. Med. Chem.* **2005**;13:2629-2636; (c) Hartong R,

- Wiersinga WM, Plomp TA. *Horm. Metab. Res.* **1990**;22:85-89; (d) Basaria S, Cooper DS. *Am. J. Med.* **2005**;118:706-714.
- [2] Felder CC, Joyce KE, Briley EM, Glass M, Mackie KP, Fahey KJ, Cullian GJ, Hunden DC, Johnson DW, Chaney MO, Koppel GA, Brownstein M J. *Pharmacol Exp Ther.* **1998**;284(1):291-297.
- [3] Heel RC, Brogden RN, Speight TM, Avery GS. *Drugs* **1977**;14:349-366.
- [4] (a) Brenner LM, Brush CK. US Pat. 4,001,426 (**1997**); (b) Howlett DR, Perry AE, Godfrey F, Swatton JE, Jennings KH, Spitzfaden C, Wadsworth H, Wood SE, Markwell RE. *Biochem. J.* **1999**;340:283-289.
- [5] Gong W, Liu D, Li F, Gao J, Li H, Lang J. *Tetrahedron* **2015**;71:1269-1275.
- [6] (a) Nakamura M, Ilies L, Otsubo S, Nakamura E. *Org Lett.* **2006**;8:2803-2805; (b) Zhao J, Fang H, Xie C, et al. *Org Chem.* **2013**;2:1044-1047; (c) Farrar MW, Levine R. *J Am Chem Soc.* **1950**;72:4433-4436.
- [7] (a) Oda K, Machida M. *Chem. Pharm. Bull.* **1993**;41:1299-1301; (b) Yuan H, Bi K, Li B, Yue R, Ye J, Shen Y, Shan L, Jin H, Sun Q, Zhang W. *Org. Lett.* **2013**;15:4742-4745; (c) Arcadi A, Cacchi S, Del Rosario M, Fabrizi G, Marinelli F. *J. Org. Chem.* **1996**;61:9280-9288. (d) Jason H, Chaplin JH, Flynn BL. *Chem. Commun.* **2001**;1594-1595; (e) Mothe SR, Susanti D, Hong Chan PW. *Tetrahedron Lett.* **2010**;51:2136-2140.
- [8] Begala M, Caboni P, Matos MJ, Delogu GL. *Tetrahedron Lett.* **2018**;59:1711-1714.
- [9] Begala M, Delogu GL. *J. Mass Spectrom.* **2019**;54(9):750-760.
- [10] (a) Hercouet A, Le Corre M. *Tetrahedron Lett.* **1979**;23:2145-2148; (b) Hercouet A, Le Corre M. *Tetrahedron* **1981**;37(16):2867-2873.
- [11] (a) Kabalka GW, Varma RS. *Comprehensive Organic Synthesis*; Trost BM, Fleming I, eds, 8. Oxford: Pergamon Press; 1991:363-379; (b) Rappoport Z, ed. *Chemistry of the Cyano Group*. London: John Wiley & Sons; 1970.
- [12] (a) Twyman LJ, Allsop D. *Tetrahedron Lett.* **1999**;40:9383-9384; (b) Thévenin M, Thoret S, Grellier P, Dubois J. *Bioorg. Med. Chem.* **2013**;21(17):4885-4892.
- [13] Ghosh S, Das J. *Tetrahedron Lett.* **2011**;52:1112-1116.
- [14] Routasalo T, Helaja J, Kavakka J, Koskinen AMP. *Eur. J. Org. Chem.* **2008**;18:3190-3199.
- [15] Ledoussal B, Gorgues A, Le Coq A. *Tetrahedron* **1987**;43:5841-5852.

Supporting Information

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