Facile Intramolecular O→C Ester Migration in Benzylphosphonium Salts

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Received April 10, 2000

Compared to aldehydes and ketones, esters are usually poor substrates for Wittig reactions unless an intramolecular process is involved. A typical example of an efficient nonclassical Wittig reaction[1] is the conversion of (2-acyloxybenzyl)triphenylphosphonium salts into 2-substituted benzofurans.[2] With regard to carbonates, there are only two reports on olefinations with phosphonium salts[3,4] and in both cases an intramolecular Wittig reaction is used to generate the cyclic ketene acetal functionality of 2-phenoxy-4*H*-1-benzopyran-4-ones.

We now report that, in contrast to the observations cited above, carbonate-containing benzylphosphonium salts **4** do not undergo an intramolecular Wittig reaction to produce 2-alkoxybenzofurans, but follow a different reaction pathway on treatment with base (Scheme 1, 2).

When commercially available **1** was reacted with methyl chloroformate (**2a**) and excess triethylamine at room temperature, we observed further transformation of the initially formed acylated phosphonium salt **4a** already under these conditions. The reaction finally yielded methyl (2-hydroxyphenyl)acetate **3a**[5] and triphenylphosphine oxide (Scheme 1). For confirmation, the postulated intermediate **4a** was prepared in pure state using a different route (3 steps starting from *o*-cresol; acylation with methyl chloroformate, NBS-bromination, reaction with triphenylphosphine; 68% overall yield; Scheme 1) and treated with triethylamine. Again **3a** (82%) was obtained after aqueous workup, ruling out the possibility that the product was generated via direct acylation at the benzylic position of the phosphonium component.

The scope of the conversion of **1** into **3** was investigated by variation of the R group in the acylating agent **2** (Scheme 2). As shown in Table 1, alkyl chloroformates **2a,b,d,e** and dialkyl dicarbonate **2c** gave the corresponding alkyl (2-hydroxyphenyl)acetates **3a**−**e** in moderate to good yields. In some experiments trace amounts (<7%) of apolar byproducts were obtained which were identified as the *O*-acylated product analogues, resulting from reaction of phenolic products **3** with residual acylating agent **2**. However, when **1** was treated with phenyl chloroformate (**2f**) and 4-nitrophenyl chloroformate (**2g**),

Scheme 1. Formation of 3a from Either 1 or 4a as Precursor

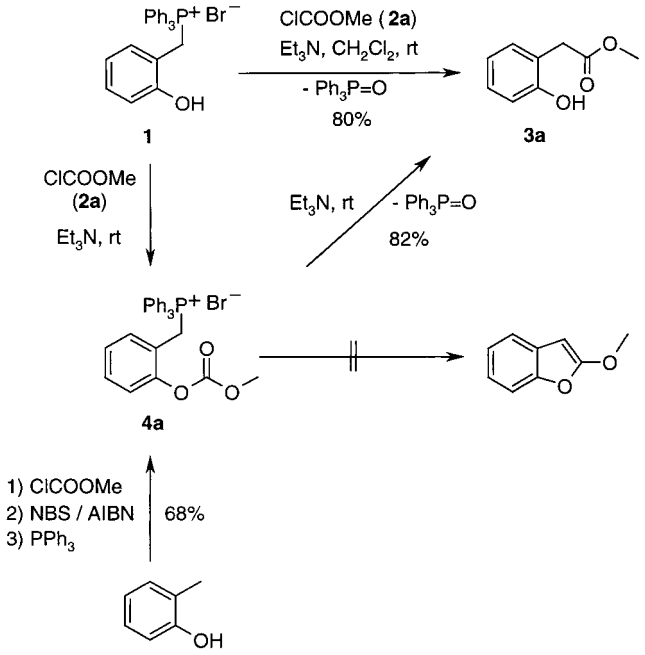


Table 1. Yields Obtained in the Reaction of Phosphonium Salt 1 with Acylating Agents 2a−g

R	ClCOOR or $(ROCO)_2O$[a]	product (% yield)[b,c]
methyl	**2a**	**3a** (80)
i-propyl	**2b**	**3b** (63)
tert-butyl	**2c**	**3c** (55)
benzyl	**2d**	**3d** (75)
allyl	**2e**	**3e** (77)
phenyl	**2f**	**5** (90)
4-NO_2-phenyl	**2g**	**5** (83)

[a] Compounds **2a,b,d**−**g** were used as chloroformates, **2c** as dicarbonate. [b] Nonoptimized yields of isolated, analytically pure products. [c] Analytical data of products **3a**−**d** agreed with published information; **3e** and **5** were characterized by ^{1}H NMR, ^{13}C NMR, and C, H analysis.

respectively, in the presence of excess triethylamine the stabilized phosphonium ylide **5** was obtained in high yield. The structure of **5**[6] was confirmed by two independent syntheses (Scheme 3) starting either with 3-bromo-2(3*H*)benzofuranone (**6**) and triphenylphosphine or with **1** and carbonyldiimidazole.

Our mechanistic rationale for the formation of **3** and **5** is depicted in Scheme 2 and involves nonisolable intermediates **Ia**−**d**. Acylation of the hydroxy group in **1** produces the carbonate-containing phosphonium salt **4**. The mild reaction conditions (triethylamine, rt) are sufficient to allow further transformation of **4**. Deprotonation generates ylide **Ia**, which upon intramolecular cyclization yields betaine **Ib**. This intermediate does not eliminate triphenylphosphine oxide to give 2-alkoxybenzofurans as expected for a Wittig-type reaction. Instead, opening of the heavily substituted five-membered ring generates intermediate **Ic**, provided that R = alkyl. The

(1) For recent reviews, see: (a) Murphy, P. J.; Lee, S. E. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3049−3066. (b) Heron, B. M. *Heterocycles* **1995**, *41* (10), 2357−2386. (c) Le Corre, M. *Janssen Chim. Acta* **1985**, *3* (2), 4−8.

(2) Hercouet, A.; Le Corre, M. *Tetrahedron* **1981**, *37*, 2867−2873.

(3) Takeno, H.; Hashimoto, M. *Chem. Commun.* **1981**, 282−283.

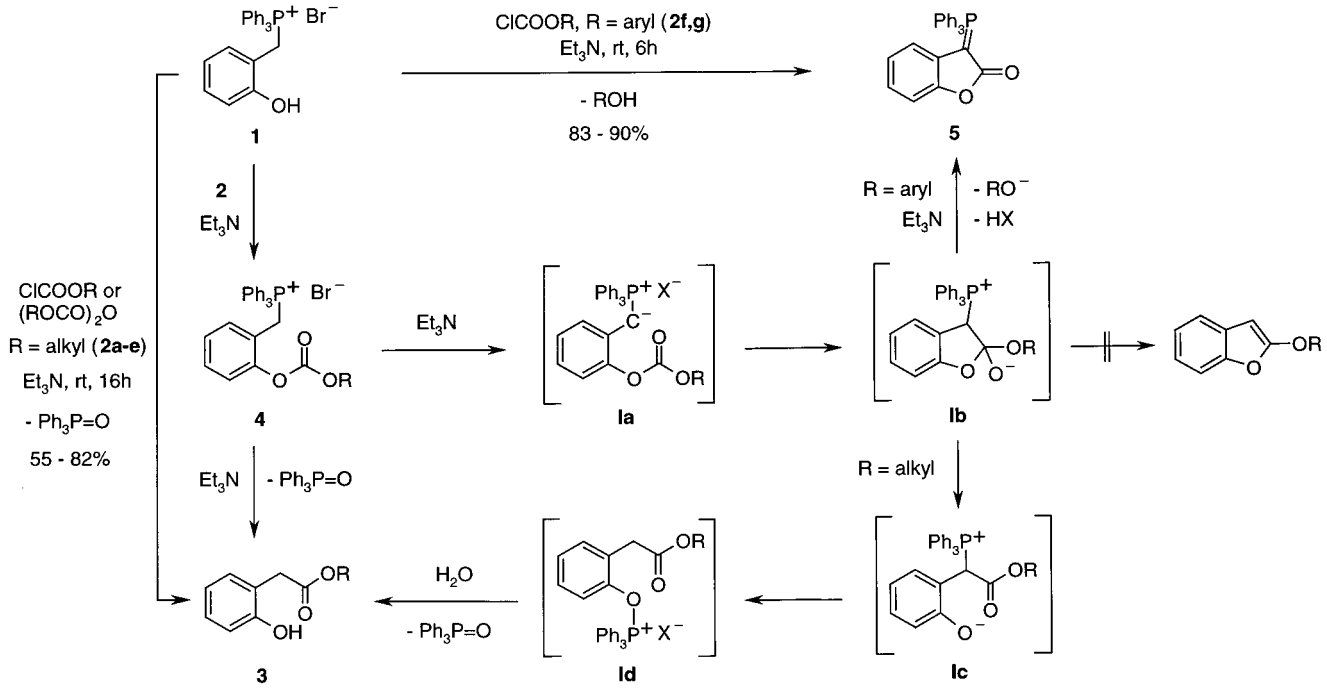
(4) Takeno, H.; Hashimoto, M.; Koma, J.; Horiai, H.; Kikuchi, H. *Chem. Comm.* **1981**, 474−475.

(5) Compound **3a** proved to be analytically identical (TLC, mp, ^{1}H NMR, MS) to a sample prepared by esterification of (2-hydroxyphenyl)-acetic acid.

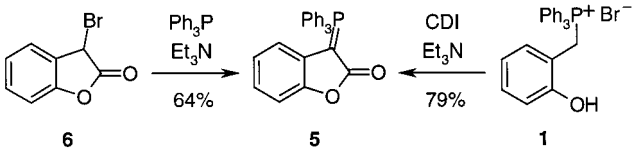
(6) The chemical shift of 13.3 ppm observed for stabilized ylide **5** in the ^{31}P NMR spectrum agreed well with published data of similar structures: Saalfrank, R. W.; Ackermann, E.; Winkler, H.; Paul, W.; Böhme, R. *Chem. Ber.* **1980**, *113*, 2950−2958.

10.1021/jo000532y CCC: $19.00
Published on Web 10/11/2000

Scheme 2. Postulated Mechanism for the Formation of 3 (R = alkyl) and 5 (R = aryl)



Scheme 3. Alternative Syntheses of Stabilized Ylide 5



better leaving group character of the phenolate relative to the alkoxide is believed to be the driving force behind this pathway. In accordance with the mechanism discussed by Le Corre,[2] intermediate **Ic** then rearranges into the hydrolytically labile[7,8] phenoxyphosphonium salt **Id**, which gives **3** and triphenylphosphine oxide on aqueous workup. The formal result of this sequence is an oxygen to carbon (O → C) migration of an alkyl ester fragment in **4** with concomitant loss of triphenylphosphine oxide.

When R = phenyl in intermediate **Ib**, irreversible elimination of the unsubstituted phenolate residue (introduced by the acylating agent **2**) generates a phosphonium salt which is deprotonated by excess triethylamine to yield the stabilized ylide **5**.

Thus, formation of both products **3** and **5** can be explained from one common intermediate, i.e., **Ib**. The course of the reaction appears to be rather selective, since production of **5** was never observed in the alkyl series (products **3a**−**e**) and the treatment of **1** with either **2f** (R = phenyl) or **2g** (R = 4-nitrophenyl) produced **5** in high yield with no detectable amount of the corresponding phenylacetate.

In summary, we discovered that (2-alkoxycarbonyloxybenzyl)triphenylphosphonium bromides (**4**, R = alkyl), which can be generated in situ from commercially available (2-hydroxybenzyl)triphenylphosphonium salt **1**, undergo base-induced rearrangement with concomitant elimination of triphenylphosphine oxide under very mild conditions to give alkyl (2-hydroxyphenyl)acetates **3** in good yields. In contrast, the reaction of **1** with phenyl chloroformates follows a different course producing the stabilized phosphonium ylide **5** by elimination of the corresponding phenols.

Experimental Section

(2-Hydroxybenzyl)triphenylphosphonium bromide, alkyl and aryl chloroformates, di-*tert*-butyl dicarbonate, and 3-bromo-2(3*H*)benzofuranone were purchased from Aldrich.

General Procedure for the Synthesis of Alkyl (2-Hydroxyphenyl)acetates 3. Synthesis of Allyl (2-Hydroxyphenyl)acetate (3e). Allyl chloroformate (**2e**; 130 mg dissolved in 2 mL of dry dichloromethane, 1.1 mmol) was added via syringe to a solution of (2-hydroxybenzyl)triphenylphosphonium bromide (**1**; 500 mg, 1.1 mmol) and triethylamine (340 mg, 3.3 mmol) in dry dichloromethane at room temperature under argon atmosphere. The mixture was stirred for 16 h and then poured into aqueous pH 7 buffer solution. Extraction with ethyl acetate followed by chromatography on silica gel (cyclohexane/ethyl acetate = 4/1) gave pure **3e** (160 mg, 77%) as light yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.23 (dt, J = 1.7, 7.9 Hz, 1H), 7.11 (dd, J = 1.7, 7.4 Hz, 1H), 6.94 (dd, J = 1.2, 7.9 Hz, 1H), 6.88 (dt, J = 1.2, 7.4 Hz, 1H), 5.90 (ddt, J = 5.8, 10.4, 17.2 Hz, 1H), 5.33 (dqua, J = 1.3, 17.2 Hz, 1H), 5.27 (dqua, J = 1.3, 10.4 Hz, 1H), 4.64 (dt, J = 1.3, 5.8 Hz, 2H), 3.71 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 173.46, 155.06, 131.37, 131.00, 129.17, 120.87, 120.54, 118.99, 117.51, 66.29, 37.69. Anal. Calcd. for $C_{11}H_{12}O_3$ (mw 192.22): 68.73, C; 6.29, H. Found: 69.01, C; 6.15, H.

In analogy to the synthesis decribed for **3e** the following compounds were obtained starting from **1** and the respective acylating agents **2a**−**d**.

Methyl (2-hydroxyphenyl)acetate (3a): colorless crystals, mp 69−71 °C (lit.[9] mp 69−71 °C); ^{1}H NMR ($CDCl_3$) δ 7.35 (br s, 1H), 7.20 (dt, J = 1.6, 7.7 Hz, 1H), 7.10 (dd, J = 1.6, 7.4 Hz, 1H), 6.94 (dd, J = 1.2, 7.7 Hz, 1H), 6.89 (dt, J = 1.2, 7.4 Hz, 1H), 3.75 (s, 3H), 3.69 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 174.20, 155.00, 130.94, 129.12, 120.81, 120.53, 117.40, 52.64, 37.44.

(7) Sensitivity of phenoxyphosphonium salts to hydrolysis: Appel, R.; Warning, K.; Ziehn, K. D. *Liebigs Ann. Chem.* **1975**, 406−409.

(8) TLC analysis supported the presence of a hydrolytically labile intermediate (i.e., **Id**) when comparing samples taken directly from the reaction mixture and run without aqueous treatment in aprotic and protic solvent systems.

(9) Gringauz, A. *J. Med. Chem.* **1968**, 611−612.

2-Propyl (2-hydroxyphenyl)acetate (3b): colorless oil; ^{1}H NMR ($CDCl_3$) δ 7.20 (dt, J = 1.6, 7.7 Hz, 1H), 7.10 (dd, J = 1.6, 7.4 Hz, 1H), 6.96 (dd, J = 1.2, 7.7 Hz, 1H), 6.88 (dt, J = 1.2, 7.4 Hz, 1H), 5.04 (hept, J = 6.3 Hz, 1H), 3.64 (s, 2H), 1.27 (d, J = 6.3 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 173.63, 155.33, 130.93, 129.11, 120.75, 117.71, 69.72, 38.47, 21.65.

***tert*-Butyl (2-hydroxyphenyl)acetate (3c):** reaction time 72 h, colorless oil; ^{1}H NMR ($CDCl_3$) δ 7.98 (br s, 1H), 7.20 (dt, J = 1.7, 7.7 Hz, 1H), 7.08 (dd, J = 1.7, 7.4 Hz, 1H), 6.97 (dd, J = 1.2, 7.7 Hz, 1H), 6.88 (dt, J = 1.2, 7.4 Hz, 1H), 3.59 (s, 2H), 1.47 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 173.60, 155.44, 130.96, 129.04, 121.06, 120.70, 117.78, 82.89, 39.62, 27.95.

Benzyl (2-hydroxyphenyl)acetate (3d): colorless crystals, mp 99−100 °C (lit.[9] mp 98−100 °C); ^{1}H NMR ($CDCl_3$) δ 7.30−7.42 (m, 5H), 7.21 (dt, J = 1.6, 7.7 Hz, 1H), 7.11 (dd, J = 1.6, 7.5 Hz, 1H), 6.84 (dd, J = 1.2, 7.7 Hz, 1H), 6.89 (dt, J = 1.2, 7.5 Hz, 1H), 5.18 (s, 2H), 3.72 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 173.63, 155.07, 135.06, 131.01, 129.19, 128.61, 128.50, 128.32, 120.89, 120.51, 117.56, 67.50, 37.78.

Synthesis of 3-(Triphenylphosphoranylidene)-2(3*H*)-benzofuranone (5). Following the procedure described for the synthesis of **3e** the reaction of equimolar amounts of phosphonium salt **1** with either phenyl chloroformate (**2f**), 4-nitrophenyl chloroformate (**2g**), or 1,1′-carbonyldiimidazole yielded **5** in 90, 83, and 79% yields, respectively, as yellowish crystals: mp 206−209 °C; ^{1}H NMR ($CDCl_3$) δ 7.63−7.81 (m, 9H), 7.52−7.60 (m, 6H), 7.04−7.12 (m, 1H), 6.82 (dt, J = 1.3, 7.6 Hz, 1H), 6.62 (dt, J = 1.2, 7.6 Hz, 1H), 5.64 (dd, J = 1.2, 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 171.82, 171.50, 149.37, 149.12, 134.11, 133.95, 133.33, 133.28, 132.36, 132.15, 129.39, 129.18, 123.90, 122.42, 121.36, 119.09, 114.04, 108.78, 48.74, 46.56; ^{31}P NMR ($CDCl_3$) δ 13.3.[6] Anal. Calcd for $C_{26}H_{19}PO_2$ (mw 394.41): 79.18, C; 4.86, H. Found: 79.21, C; 5.26, H.

Reaction of commercially available 3-bromo-2(3*H*)benzofuranone (**6**) with equimolar amounts of triphenylphosphine and triethylamine in toluene at 80 °C for 6 h followed by chromatographic purification on silica gel (cyclohexane/ethyl acetate = 4/1) yielded **5** in 64% yield.

Synthesis of (2-Methoxycarbonyloxyphenyl)triphenylphosphonium Bromide (4a). Methyl chloroformate (2.88 g, 30.5 mmol) was added to a solution of *o*-cresol (3 g, 27.7 mmol) and triethylamine (3.36 g, 33.3 mmol) in dry dichloromethane (50 mL) at 5 °C under argon atmosphere. The mixture was stirred for 30 min at this temperature and then for 1 h at room temperature. The solvent was distilled off in vacuo, and the residue was partitioned between ethyl acetate and water. The organic layer was separated, washed with brine, dried over magnesium sulfate, and evaporated to dryness to give crude methyl 2-methylphenyl carbonate (4.4 g, 95%). Without further purification the crude intermediate, *N*-bromosuccinimide (4.7 g, 26.5 mmol) and a catalytic amount of benzoyl peroxide were heated in tetrachloromethane for 4 h at 80 °C. After the reaction was cooled, the succinimide was removed by filtration and the filtrate was evaporated in vacuo. The crude methyl 2-bromomethylphenyl carbonate (6 g) thus obtained was dissolved in dry toluene (50 mL) and heated together with triphenylphosphine (6.43 g, 24.5 mmol) to 80 °C for 6 h, followed by heating to 100 °C for 1 h. After this solution was cooled, the precipitate was collected by filtration, washed with diethyl ether, and dried in vacuo to yield pure **4a** (9.56 g, 68% over all steps starting from *o*-cresol) as colorless crystals: mp 147−148 °C; ^{1}H NMR ($CDCl_3$) δ 7.54−7.83 (m, 15H), 7.42−7.50 (m, 1H), 7.23−7.32 (m, 1H), 7.18 (d, J = 8 Hz, 1H), 7.05 (t, J = 7.5 Hz, 1H), 5.41 (d, J = 14.3 Hz, 2H), 3.70 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 152.33, 149.78, 149.69, 135.08, 135.03, 134.33, 134.17, 133.17, 133.09, 130.28, 130.08, 129.80, 129.74, 126.31, 126.26, 121.32, 121.27, 119.05, 118.92, 118.17, 116.82, 55.54, 25.99, 25.22; ^{31}P NMR ($CDCl_3$) δ 22.8. Anal. Calcd for $C_{27}H_{24}O_3P\cdot Br$ (mw 507.37): 63.92, C; 4.77, H; Found: 63.64, C; 4.91, H.

JO000532Y