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Direct synthesis of α-substituted phosphonates

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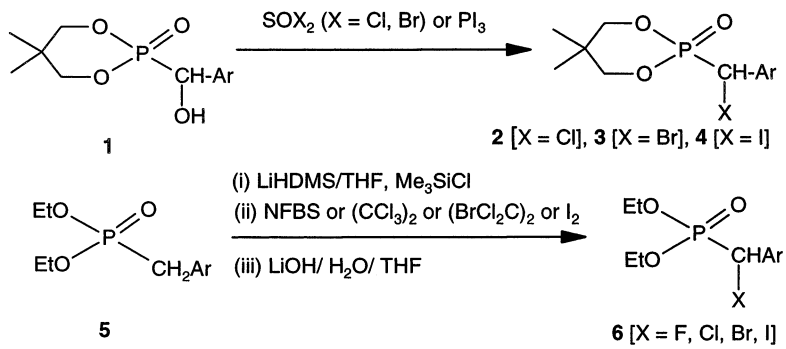
Abstract—The α-substituted phosphonates $(OCH_2CMe_2CH_2O)P(O)CH(X)(Ar)$ [X = Cl, OMe, NMe_2 and $OSiMe_3$], useful precursors for Horner–Wadsworth–Emmons reactions, are readily prepared by treating $(OCH_2CMe_2CH_2O)PX$ with an aromatic aldehyde. In the reaction of $(OCH_2CMe_2CH_2O)PCl$ with furfuraldehyde and cinnamaldehyde, the 5-chlorofurfurylphosphonate $(OCH_2CMe_2CH_2O)P(O)CH_2(5\text{-Cl-}C_4H_2O)$ and the γ-chlorophosphonate $(OCH_2CMe_2CH_2O)P(O)CH{=}CH\text{-}CH(Cl)Ph$, respectively, are formed in good yields. © 2001 Published by Elsevier Science Ltd.

Phosphonates are popular precursors in organic synthesis for C–C bond forming reactions and, hence, new reagents that will be useful for specific synthetic goals are still being discovered.[1–3] The α-substituted phosphonates $(RO)_2P(O)CH(X)Ar$ constitute a subclass of phosphonates having the advantage of the additional functional group 'X' already being incorporated. Two general routes have been reported for the synthesis of such phosphonates, where X is a halogen (cf. Scheme 1).[2–4]

For the synthesis of compounds $(RO)_2P(O)CH(X)Ar$ (**I**), where X is a group other than a halogen, a procedure that uses a common, readily accessible precursor is not available.[5–8] Species **I** can be regarded as an addition product of the corresponding phosphite $(RO)_2PX$ and an aldehyde ArCHO, formed by a modified Abramov reaction. Since the compound $(OCH_2CMe_2CH_2O)PX$ (**7a**: X = Cl) is conveniently prepared, cheap and amenable to substitution (by OR, NRR′, etc.), we felt that under suitable conditions, various α-substituted phosphonates may be directly accessible using this as a precursor. The six-membered ring in **7** normally remains intact and, hence, side reactions occur less often when using these compounds. In this paper, we report the use of **7** in the synthesis of various α-substituted phosphonates that have high potential for use in Horner–Wadsworth–Emmons reactions (see Scheme 2 and Table 1).[1h,8–10]

The precursors **7** [X = Cl (**a**),[11] OMe (**b**),[12] NMe_2 (**c**)[13]] were prepared by literature procedures; compound **7d**



Scheme 1.

Keywords: phosphonates; Abramov reaction.

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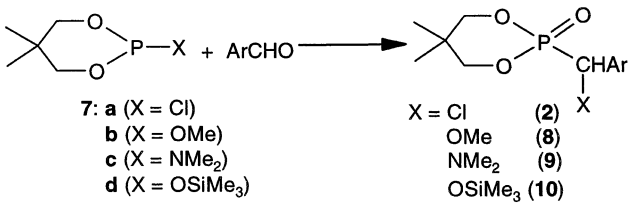

Scheme 2.

[X = $OSiMe_3$; bp 75°C/0.5 mmHg, δ(P) 108.4] was prepared in 94% yield by treating $(OCH_2CMe_2CH_2O)P(O)H$ with Me_3SiCl/Et_3N in toluene. Compounds **7a–d** were stirred with the respective aldehyde at room temperature for 72 h to afford the phosphonates **8–12**; for the synthesis of the chloro compounds **2**, a mixture of **7a** and the aldehyde was first heated at 60°C for 1 h and then stirred at room temperature for 72 h. Although the reactions worked well with aromatic aldehydes, a pure phosphonate could not be isolated when **7a–c** were treated with the aliphatic aldehyde, Me_2CHCHO; only **7d** gave the phosphonate $(OCH_2CMe_2CH_2O)P(O)CH(OSiMe_3)(CHMe_2)$ (**10f**) as an isolable product.[14]

Important points to be noted are the following:

1. The present method offers an excellent route to α-methoxy-, α-dimethylamino- and α-trimethylsilyloxy-substituted phosphonates. The simplicity of the method, coupled with the readily accessible starting materials, makes this approach an elegant choice to obtain synthetically useful phosphonates. In fact, our preliminary results suggest that **8d** is an excellent precursor for 2-methoxy-1,3-dienes.[15]
2. The yield of α-chlorophosphonates **2** was only moderate under the conditions employed. As explained elsewhere,[16] several products are possible in these reactions, one of them being **2**. Isolation of **2** is facilitated in our case as they are stable solids.
3. In the reaction of **7a** with furfuraldehyde and cinnamaldehyde, we obtained the products **11** (65% yield) and **12** (60% yield), respectively; these compounds were recently prepared by us using a different route.[1h] In these products, the incoming chlorine goes to the 5-position of the furan ring or the γ-position of the cinnamyl residue instead of the normal α-position. The formation of **11** and **12** also contrasts with the isolation of the normal products **8d** and **9e**, respectively, in analogous reactions using **7b** and **7c**. A possible intermediate in these reactions is (**II**); formation of the phosphoryl bond, as well as the transfer of the X group, can occur subsequently as shown in the structural diagram. This will explain the formation of **2** and **8–10**. For X = Cl, contribution by the ionic form (**II′**) could be significant;[16] Cl^- may then attack at the available 5-position of the furan ring or the γ-position of the cinnamyl group leading to **11** or **12**, respectively.

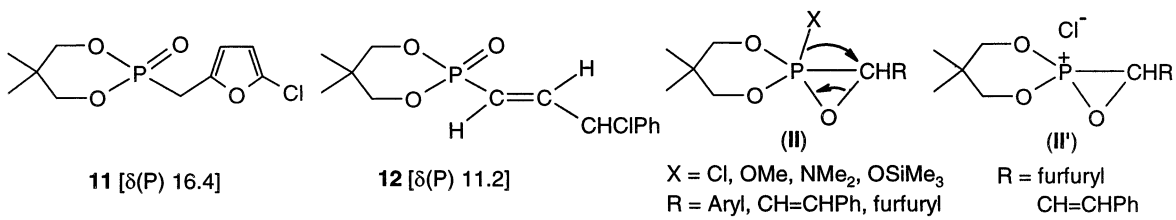

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Table 1. Data for α-substituted phosphonates **2** and **8–10** (cf. Scheme 2)

Compound	Ar	δ(P) (ppm)	Yield (%)	Compound	Ar	δ(P) (ppm)	Yield (%)
2 (X = Cl)				**9** (X = NMe_2)			
2a[a]	Ph	8.1	45	**9a**	Ph	17.4	67
2b[a]	4-Me-C_6H_4	8.4	55	**9b**	4-Me-C_6H_4	17.1	72
2c	4-OMe-C_6H_4	8.4	60	**9c**	4-OMe-C_6H_4	17.4	75
2d[a]	4-Cl-C_6H_4	7.5	45	**9d**	4-Cl-C_6H_4	16.9	73
2e[a]	1-Naphthyl	8.6	40	**9e**	Furfuryl	14.4	80
8: (X = OMe)				**10**: (X = $OSiMe_3$)			
8a	Ph	9.8	92	**10a**	Ph	11.0	89
8b	4-Me-C_6H_4	9.9	88	**10b**	2,4-Cl_2-C_6H_3	8.9	91
8c	4-OMe-C_6H_4	10.2	86	**10c**	4-Cl-C_6H_4	10.6	90
8d	PhCH=CH	10.0	85	**10d**	1-Naphthyl	10.8	92
				10e	4-Br-C_6H_4	10.4	90

[a] These compounds have been prepared by a different route by us before.[1h,2]

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10. Typical procedure for **8a**: A mixture of **7b** (2.0 g, 12.16 mmol) and benzaldehyde (1.3 g, 12.16 mmol) was stirred at room temperature for 3 days. Then the product was crystallized from toluene until a sharp melting point and a single spot in TLC was obtained.

    A similar procedure was adopted to synthesize **8b–d**, **9a–e**, **10a–e**, **11** and **12**; in the case of **10a–e** the product mixture was first washed with heptane and crystallized from a mixture of CH_2Cl_2 and heptane. For the chloro derivatives **2a–d** an equimolar mixture of the chlorophosphite and the aldehyde was heated at 60°C for 1 h and stirred at room temperature for a further 3 days; column chromatography (silica gel; CH_2Cl_2–hexane) was used to obtain the pure product. We have reported physical data for compounds **2a**,**b**,**d**,**e**, **11** and **12** before.[1h,2] Selected data for other representative compounds are given below; ^{31}P NMR chemical shifts are given in Table 1.

    Compound **8a**: mp 120–122°C; ^1H NMR: 0.88, 1.20 (2s, 6H, $2CH_3$), 3.41 (s, 3H, OCH_3), 4.05–4.31 (m, 4H, OCH_2), 4.73 (d, $J=16.5$ Hz, 1H, P-C*H*), 7.35–7.43 (m, 5H, Ar-*H*); ^{13}C NMR: 20.8, 21.9, 32.4 (d, $J=7.7$ Hz, CMe_2), 58.6 (d, $J=14.2$ Hz, P-COCH_3), 77.5, 78.1, 82.3 (d, $J=162.2$ Hz, P-*C*), 127.7, 127.8, 128.5, 134.0. Anal. calcd for $C_{13}H_{19}O_4P$: C, 57.77; H, 7.03. Found: C, 57.86; H, 7.09.

    Compound **9a**: mp 156–158°C; ^1H NMR: 1.01 (s, 6H, $2CH_3$), 2.42 (s, 6H, N-$(CH_3)_2$), 3.65–3.85 (m, 2H, OCH_2), 3.97 (d, $J=20$ Hz, 1H, P-C*H*), 4.09–4.29 (m, 2H, OCH_2), 7.35–7.48 (m, 5H, Ar-*H*); ^{13}C NMR: 21.6 (CH_3), 32.7, 43.8 (d, $J=9.4$ Hz, N-$(CH_3)_2$), 67.3 (d, $J=156.8$ Hz, P-*C*), 75.5, 128.3, 130.4, 130.6. Anal. calcd for $C_{14}H_{22}NO_3P$: C, 59.35; H, 7.82; N, 4.94. Found: C, 59.40; H, 7.85; N, 4.98.

    Compound **10e**: mp 164–166°C; ^1H NMR: 0.20 (s, 9H, $SiCH_3$), 0.93 (s, 3H, CH_3), 1.20 (s, 3H, CH_3), 3.95–4.39 (m, 4H, OCH_2), 5.10 (d, 1H, ^2J(P-H)=15.0 Hz, C*H*), 7.30–7.50 (m, 4H, Ar-*H*); ^{13}C NMR: −0.2, 20.9, 21.9, 32.4 (d, $J=7.5$ Hz, CMe_2), 72.8 (d, $J=166.2$ Hz, P-*C*), 77.7, 77.9, 78.4, 78.5, 122.1, 128.5, 131.4, 136.0. MS: 406, 408 {$[M]^+$}.
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14. Compound **10f** (yield: 0.86 g (90%) using 0.726 g (3.27 mmol) of **7d**; mp 74–75°C): ^1H NMR: 0.25 (s, 9H, $SiCH_3$), 1.00–1.10 (2 s+merged d, 12H, CH_3), 2.11–2.20 (m, 1H, C*H*Me_2), 3.80–4.25 (m, 5H, P-C*H*+2 OCH_2); ^{13}C NMR: 0.3, 18.1, 18.2, 19.7, 19.8, 21.6, 21.7, 31.0, 32.6 (d, $J=7.5$ Hz, CMe_2), 75.9 (d, $J=160.0$ Hz, P-*C*), 75.6, 75.8, 76.2; ^{31}P NMR: 18.4.
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