Regioselective Synthesis of Highly Functionalized Arylphosphonates by Cyclocondensation of 1,3-Bis(trimethylsilyloxy)buta-1,3-dienes with 3-Ethoxy-2-phosphonylalk-2-en-1-ones

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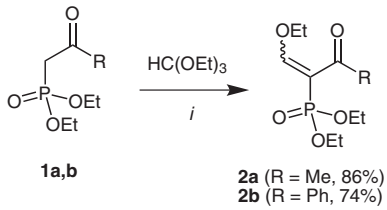
Abstract: Highly functionalized arylphosphonates were prepared by $TiCl_4$-mediated cyclocondensation of 3-ethoxy-2-phosphonylalk-2-en-1-ones with 1,3-bis(trimethylsilyloxy)buta-1,3-dienes.

Key words: cyclizations, regioselectivity, phosphonic acid derivatives, silyl enol ethers

Arylphosphonates are important core and lead structures in medicinal chemistry,[1] flame protection,[2] and polymer chemistry.[3] In addition, arylphosphonic acid derivatives play an important role as synthetic intermediates in organic chemistry.[4] Classic syntheses of arylphosphonates include, for example, the Friedel–Crafts reaction of phosphoric acid derivatives with aromatics,[5a] the copper-catalyzed reaction of phosphorus trichloride with diazonium salts,[5b,c] the nucleophilic aromatic substitution of sodium dialkylphosphites with electron-poor aryl halides,[5d] the nickel(II)- or copper(II)-mediated reaction of trialkyl phosphates with aryl halides,[5e–i] and the reaction of trialkyl phosphites with aromatic Grignard or organolithium compounds.[5j–l] A more recent approach to arylphosphonates relies on the palladium-catalyzed reaction of dialkyl phosphates with aryl halides.[6,7] Despite the great usefulness of all these methods for the formation of carbon–phosphorus bonds, they are generally limited by the fact that more complex starting materials, highly functionalized and substituted aryl halides, are not readily available. In fact, the halogenation and functionalization by aromatic electrophilic substitution reactions is often limited by their low *ortho*/*para* regioselectivity and other side reactions. In fact, most of the C–P bond-forming reactions outlined above have been carried out using simple, sterically unhindered, and commercially available substrates.

An alternative approach to more complex carba- and heterocyclic phosphonates relies on cyclocondensation reactions of suitable phosphonate-containing building blocks. Kouno and coworkers developed a versatile methodology based on the reaction of lithiated vinylphosphonates with electrophiles.[8] 3-Alkoxy-2-phosphonylalk-2-en-1-ones represent interesting dielectrophilic building blocks. However, reactions of these compounds have only scarcely been studied so far.[8a,9] Only one isolated example of a cyclocondensation, that is, the reaction of 3-ethoxy-2-(diethoxyphosphonyl)-1-phenylprop-2-en-1-one with hydrazine and hydroxylamine, has been reported.[8a] In recent years, we have studied the synthesis of arenes by titanium(IV) chloride mediated [3+3] cyclizations[10] of 1,3-bis(trimethylsilyloxy)buta-1,3-dienes.[11] Herein, we report what is, to the best of our knowledge, the first application of this methodology to the synthesis of arylphosphonates. The cyclocondensation of aliphatic and aromatic 3-ethoxy-2-phosphonylalk-2-en-1-ones with 1,3-bis(silyloxy)buta-1,3-dienes provides a convenient approach to highly functionalized arylphosphonates. These products, which have not been prepared so far, are not readily available by other methods.

Vinylphosphonates **2a**[12,9] and **2b**[13,8a] are available by reaction of β-ketophosphonates **1a**,**b** with triethyl orthoformiate (Scheme 1). 1,3-Bis(silyloxy)buta-1,3-dienes **3a–k** are prepared in two steps from the corresponding β-keto esters.[14–16]



1a,b

2a (R = Me, 86%)
2b (R = Ph, 74%)

Scheme 1 Synthesis of **2a**,**b**. *Reagents and conditions for compound **2a***: **1a** (1.0 equiv), $HC(OEt)_3$ (1.2 equiv), Ac_2O, reflux, 4 h. *Reagents and conditions for **2b***: **1b** (1.8 equiv) $HC(OEt)_3$, (2.8 equiv) Ac_2O, reflux, 36 h, then column chromatography; products **2a**,**b** were isolated as mixtures of *E*/*Z* isomers

The $TiCl_4$-mediated cyclization of vinylphosphonates **2a**,**b** with dienes **3a–k** afforded the novel arylphosphonates **4a–l** (Scheme 2, Table 1).[17,18] During the optimization it proved to be important to carry out the reaction in a highly concentrated solution (2 mL/1.0 mmol of **2a**,**b**). The cyclization can be explained by $TiCl_4$-mediated conjugate addition of the terminal carbon atom of the diene to the enone, cyclization by attack of the central carbon atom of the diene to the carbonyl group, and subsequent aromatization (before or during the aqueous workup using 10% HCl). The constitution of the products was proved by 2D NMR studies (HMBC, NOESY, analysis of P–C and P–H

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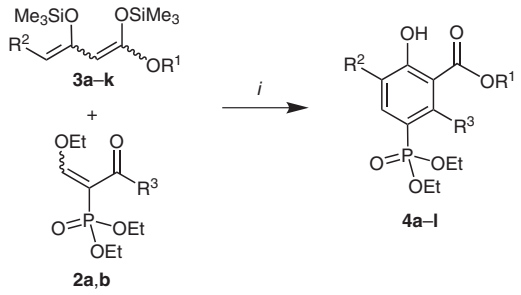
coupling constants). All reactions proceeded with excellent regioselectivity. In all products the substituent R^3 is located *ortho* to the ester group. The formation of the other regioisomer, containing the substituent R^3 located *para* to the ester group, was not observed. The moderate yields of the products can be explained by loss of material during the chromatography. In addition, the yields are decreased by some hydrolysis and $TiCl_4$-mediated oxidative dimerization of the diene and by decomposition. Similar yields were obtained for reactions of methyl and phenyl substituted vinylphosphonates **2a** and **2b**.



Scheme 2 Synthesis of **4a–l**. *Reagents and conditions*: *i*, 1) **2a**,**b** (1.0 equiv), **3a–k** (1.1 equiv), $TiCl_4$ (1.1 equiv), CH_2Cl_2, –78 °C to 20 °C, 12 h; 2) HCl (H_2O, 10%).

Table 1 Synthesis of **4a–l**

2	3	4	R^1	R^2	R^3	Yield of **4** (%)[a]
a	**a**	**a**	Me	H	Me	48
a	**b**	**b**	Et	Et	Me	52
a	**c**	**c**	Me	*n*-Hex	Me	54
a	**d**	**d**	Me	*n*-Oct	Me	58
b	**e**	**e**	Me	Me	Ph	56
b	**b**	**f**	Et	Et	Ph	51
b	**f**	**g**	Me	*n*-Pr	Ph	53
b	**g**	**h**	Me	*n*-Bu	Ph	57
b	**h**	**i**	Et	*n*-Hex	Ph	58
b	**i**	**j**	Et	*n*-Hept	Ph	55
b	**j**	**k**	Et	*n*-Dec	Ph	54
b	**k**	**l**	Et	*i*-Pr	Ph	47

[a] Yield of isolated products.

In conclusion, we have reported an efficient synthesis of highly functionalized arylphosphonates by cyclocondensation of 3-ethoxy-2-phosphonylalk-2-en-1-ones with 1,3-bis(trimethylsilyloxy)buta-1,3-dienes. These transformations represent a rare example for the synthesis of arylphosphonates based on the application of a building block approach. Reactions of 3-alkoxy-2-phosphonylalk-2-en-1-ones have only scarcely been reported to date. The products reported herein are not readily available by other methods. The scope and synthetic applications of this methodology are currently studied in our laboratory.

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(12) **Diethyl (1-Ethoxy-3-oxobut-1-en-2-yl)phosphonate (2a)**
A mixture of **1a** (1.10 g, 1.0 mL, 5.55 mmol), triethyl orthoformiate (1.1 mL, 6.62 mmol) and Ac_2O (1.5 mL, 16.0 mol) was stirred for 2 h at 120 °C and subsequently for 2 h at 140 °C. The resulting mixture was distilled to give **2a** as a brownish oil (1.20 g, 86%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.21–1.24 (m, 6 H, 2 × OCH_2CH_3), 1.36 (t, ^3J = 6.9 Hz, 3 H, OCH_2CH_3), 2.25 (s, 3 H, CH_3), 4.04–4.08 (m, 4 H, 2 × OCH_2CH_3), 4.23 (q, ^3J = 7.2 Hz, 2 H, OCH_2CH_3), 7.70 (d, $^3J_{P,H}$ = 11.4 Hz, 1 H, CH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 15.0, 15.9, 16.0, 20.6 (CH_3), 62.2, 62.4, 73.0 (OCH_2), 107.3 (d, $J_{C,P}$ = 191 Hz,C_q), 169.9 (d, $J_{CH,P}$ = 25.5 Hz, CH), 195.0 (CO). ^{31}P NMR (250 MHz, $CDCl_3$): δ = 19.64. GC-MS (EI, 70 eV): *m/z* (%) = 250 (5) [M$^+$], 235 (47), 221 (12), 207 (43), 205 (13), 179 (42), 177 (11), 151 (100), 123 (23), 121 (15), 105 (11), 81 (11), 53 (13), 43 (13), 29 (10). HRMS (EI): *m/z* calcd for $C_{10}H_{19}O_5P$ [M]$^+$: 250.09646; found: 250.09666.

(13) **Diethyl (1-Ethoxy-3-oxo-3-phenylprop-1-en-2-yl)phosphonate (2b)**
A mixture of **1b** (1.50 g, 1.27 mL, 5.85 mmol), triethyl orthoformiate (1.70 mL, 10.24 mmol), and Ac_2O (1.56 mL, 16.61 mmol) was stirred for 36 h at 140 °C. The mixture was cooled to 20 °C and purified by column chromatography to give **2b** as a brownish oil (1.350 g, 74%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.08 (t, ^3J = 7.1 Hz, 3 H, OCH_2CH_3), 1.21 (t, ^3J = 7.0 Hz, 6 H, 2 × OCH_2CH_3), 3.94 (q, ^3J = 7.1 Hz, 2 H, OCH_2CH_3), 4.01–4.10 (m, 4 H, 2 × OCH_2CH_3), 7.34–7.48 (m, 5 H, CH_{Ar}), 7.80–7.82 (m, 1 H, CH). ^{31}P NMR (250 MHz, $CDCl_3$): δ = 16.25 Hz. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.1, 16.1, 16.2 (CH_3), 62.3, 62.4, 71.4 (OCH_2), 106.4 (d, $J_{P,C}$ = 189.3 Hz), 128.2 (2 × CH_{Ar}), 129.3 (2 × CH_{Ar}), 133.0 (CH_{Ar}), 137.6 (d, $J_{P,C}$ = 4.3 Hz), 163.5 (d, $J_{P,C}$ = 21.0 Hz, CH), 192.2 (d, $J_{P,C}$ = 4.8 Hz, CO). IR (neat): 3060 (w), 2982 (w), 2932 (w), 2905 (w), 1716 (w), 1660 (m), 1597 (m), 1448 (m), 1391 (m), 1305 (w), 1244 (s), 1204 (m), 1145 (m), 1050 (m), 1016 (s), 959 (s), 853 (m), 790 (s), 723 (m), 690 (m), 659 (m), 564 (m), 534 (m) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 312 (4) [M$^+$], 297 (3), 283 (11), 267 (53), 239 (25), 211 (17), 183 (21), 159 (14), 151 (34), 129 (45), 105 (100), 77 (54). ESI–HRMS: *m/z* calcd for $C_{15}H_{22}O_5P$ [M + H]$^+$: 313.1199; found: 313.1198.

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(17) **General Procedure for the Synthesis of Arylphosphonates 4a–l**
To a CH_2Cl_2 solution (2 mL/1.0 mmol of **2a**,**b**) of **2a**,**b** was added **3a**–**k** (1.1 mmol) and, subsequently, $TiCl_4$ (1.1 mmol) at –78 °C. The temperature of the solution was allowed to warm to 20 °C over 12 h with stirring. To the solution was added HCl (10%, 20 mL), and the organic and the aqueous layer were separated. The latter was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and the filtrate was concentrated in vacuo. The residue was purified by chromatography (silica gel, *n*-heptane–EtOAc) to give **4a**–**l**.

(18) **Methyl 3-(Diethoxyphosphoryl)-6-hydroxy-2-methylbenzoate (4a)**
Starting with **2a** (0.375 g, 1.5 mmol) and **3a** (0.429 g, 1.65 mmol), **4a** was isolated after chromatography (silica gel, heptanes–EtOAc) as a yellowish oil (0.217 g, 48%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.24 (m, 6 H, 2 × OCH_2CH_3), 2.65 (s, 3 H, CH_3), 3.91 (s, 3 H, OCH_3), 3.99–4.07 (m, 4 H, 2 × OCH_2CH_3), 6.83 (dd, $^3J_{H,H}$ = 8.6 Hz, $^4J_{P,H}$ = 3.3 Hz, 1 H, CH_{Ar}), 7.90 (dd, $^3J_{H,H}$ = 9.0 Hz, $^3J_{P,H}$ = 14.0 Hz, 1 H, CH_{Ar}), 11.0 (s, 1 H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.2, 16.2, 20.6 (CH_3), 52.5 (OCH_3), 62.0, 62.0 (OCH_2), 114.9 (d, $J_{P,CH}$ = 15.2 Hz, CH_{Ar}), 115.9 (d, $J_{P,C}$ = 16.1 Hz), 119.0 (d, $J_{P,C}$ = 193.0 Hz), 139.3 (d, $J_{P,CH}$ = 11.0 Hz, CH_{Ar}), 145.8 (d, $J_{P,C}$ = 13.5 Hz), 164.0 (d, $J_{P,C}$ = 3.4 Hz, *C*OH), 171.2 (d, $J_{P,C}$ = 2.4 Hz, CO). ^{31}P NMR (250 MHz, $CDCl_3$): δ = 19.56. IR (neat): 2920 (m), 2851 (m), 1733 (m), 1660 (w), 1636 (w), 1580 (m), 1456 (m), 1437 (m), 1376 (w), 1308 (m), 1285 (m), 1199 (m), 1161 (m), 1158 (m), 1016 (s), 961 (m), 906 (m), 844 (m), 793 (m), 741 (m), 678 (w), 614 (w), 535 (m) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 302 (65) [M]$^+$, 287 (50), 274 (20), 270 (48), 259 (17), 242 (100), 229 (18), 227 (13), 214 (84), 197 (43), 186 (21), 167 (17), 161 (31), 158 (23), 134 (15), 105 (19), 77 (27), 65 (10), 51 (12), 29 (14). HRMS (EI): *m/z* calcd for $C_{13}H_{19}O_6P$ [M]$^+$: 302.09138; found: 302.09139.