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Facile Solid-Phase Synthesis of Cycloalkylphosphonates and 1-Cycloalkenylphosphonates Using Polymer-Supported Phenylsulfonylmethylphosphonates

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Facile Solid-Phase Synthesis of Cycloalkylphosphonates and 1-Cycloalkenylphosphonates Using Polymer-Supported Phenylsulfonylmethylphosphonates

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Abstract: A facile procedure for the solid-phase synthesis of cycloalkylphosphonates and 1-cycloalkenylphosphonates in good yields and high purities using polystyrene-supported phenylsulfonylmethylphosphonates with traceless sulfone linker strategy is described.

Keywords: 1-cycloalkenylphosphonate, cycloalkylphosphonate, polymer-supported phenylsulfonylmethylphosphonate, solid-phase organic synthesis

Fueled by a rapidly growing interest in combinatorial chemistry, solid-phase organic synthesis (SPOS) is of current interest.[1] SPOS enjoys several advantages over solution-phase synthesis, such as easy manipulation and purification of the organic products, greatly simplified through the use of polymer-bound reagents. Phosphonate derivatives are important biologically active compounds[2] and synthetic intermediates, which can he converted into a variety of other organophosphorus compounds using well-established protocols.[3] Solution-phase synthetic methods for cycloalkylphosphonates[4] and 1-cycloalkenylphosphonates[5] are well documented; however, efforts

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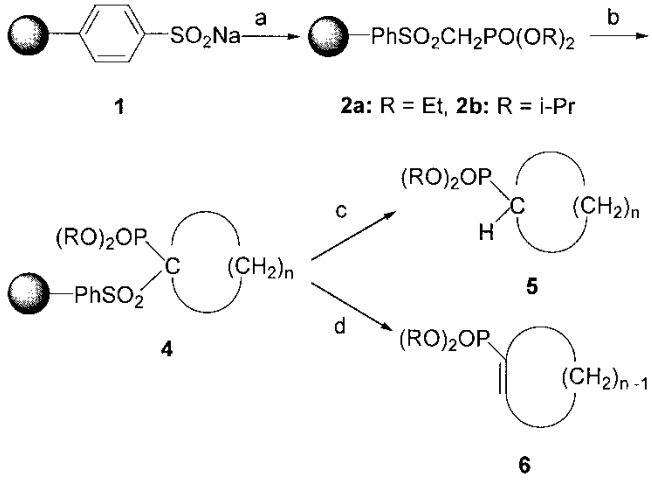
are continuing for the development of more efficient, simple methods. To our knowledge, they have not been prepared via SPOS. Recently, several groups have developed the traceless sulfone linker, which was shown to be a robust and versatile tether that offers various resin functionalizations or cleavage with additional changes.[6] In continuation of our interest in SOPS with sulfone linker,[7] we herein report the extension of this sulfone-based chemistry to a convenient, traceless, solid-phase synthesis of cycloalkylphosphonates and 1-cycloalkenylphosphonates using polystyrene-supported phenylsulfonylmethylphosphonate. The procedure for the synthesis of target compounds from polystyrene/1% divinylbenzene sodium phenylsulfinate (**1**) include (a) sulfinate *S*-alkylation, (b) the sulfonyl anion *bis*-alkylations with dihaloalkanes, and (c) traceless product release by desulfonation (Scheme 1).

The polystyrene-supported diethyl (phenylsulfonyl)methylphosphonate **2a** (R = Et) and diisopropyl (phenylsulfonyl)methylphosphonate **2b** (R = *i*-Pr) were easily accessible, both in 95% yield, by the reaction of a THF-swollen suspension of resin **1** with diethyl iodomethylphosphonate and diisopropyl iodomethylphosphonate, respectively, at 80°C for 12 h. The FT-IR spectrum of resin **2a**–**2b** with a loading of 0.86 and 0.84 mmol P/g determined by elemental analysis exhibited characteristic absorptions near 1240 cm^{-1} and 1150 cm^{-1} due to a P═O double bond and the sulfone groups, respectively. Moreover, resin **2** can be stored at room temperature for a long time without diminution of capacity. With the resin **2** in hand, the sulfonyl anion *bis*-alkylation with dihaloalkanes, the key step for the



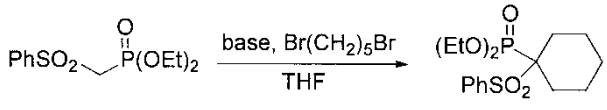
Scheme 1. Reagents and conditions: (a) $ICH_2PO(OR)_2$, THF/DMF (2/1), 80°C, 12 h; (b) (i) *n*-BuLi, −78°C, THF, 30 min; (ii) X $(CH_2)_n$ X (**3a**–**3e**), THF, −78°C, 1 h, then rt, 10 h; (c) $Mg/HgCl_2$, EtOH/THF, rt, 16 h; (d) Et_3N, CH_2Cl_2, rt, 10 h.

success of this protocol, was investigated. Apparently, previous solution-phase studies[4f] with aqueous sodium hydroxide solution as a base and dodecyltrimethylammounium chloride as phase-transfer catalyst could not survey this SPOS reaction. Here, we started optimization of solution-phase *bis*-alkylation reaction conditions by treatment of diethyl (phenylsulfonyl) methylphosphonate 7 with ω-dibromopentane **3c** using different bases (Scheme 2, Table 1). As shown in Table 1 (Entry 4), the *bis*-alkylation product **8** was obtained in high yield (95%) when *n*-BuLi was used as base at $-78^{\circ}C$ for 1 h and then at room temperature for 10 h.

Subsequent solid-phase *bis*-alkylation of resin **2** with dihaloalkanes using the similar solution-phase methodology generated the corresponding resin **4** in good yields (94–96%). Because this transformation exhibited no reliably diagnostic absorption peaks in the single-bead FTIR spectrum, the final cleavage of **4** was carried out directly. The resin **4ac** was further employed as a model to investigate the cleavage conditions. When using the classical one-electron reducing agent Na/Hg[8] in MeOH/DMF in the presence of Na_2HPO_4 at room temperature for 18 h, SmI_2[9] in MeOH/THF at $-78^{\circ}C$ or $0^{\circ}C$, **5ac** was produced via concomitant linker cleavage in 60–70% overall yield from starting resin **1**. Furthermore, the residual resin still exhibited a weak P═O absorption near 1240 cm^{-1} in FT-IR, which indicated the cleavage was not complete. To our delight, when magnesium power with a catalytic amount of $HgCl_2$ in EtOH/THF[10] was adopted at room temperature for 16 h, **5ac** was obtained in 90% yield with 95% purity. The optimized synthetic strategy was applied to the preparation of **5aa**–**5bd**, and the results are summarized in Table 2. This protocol gave the crude products in good yields (82–90%) with high purity (>92% by HPLC analysis).

Finally, we switched to another cleavage strategy wherein the polymeric sulfone **4** was treated with an excess of triethylamine[7] at room temperature for 12 h to give the 1-cycloalkenylphosphonates **6** in good yields and purities. Several typical examples are described in Table 3.

In summary, we have developed a novel method for the solid-phase synthesis of cycloalkylphosphonates and 1-cycloalkenylphosphonates in good yields and purities using a sulfone-linker strategy. This methodology is applicable for combinatorial library preparation.



7 **8**

Scheme 2.

Table 1. Solution-phase *bis*-alkylation of **7** with ω-dibromopentane

Entry	Base[a]	Temp./time	Yield of **8**[b] (%)
1	LDA	−30°C/1 h	68
2	LDA	−78°C/1 h	70
3	LDA	−78°C/1 h to rt/10 h	80
4	*n*-BuLi	−78°C/1 h to rt/10 h	95
5	*n*-BuLi	−78°C/1 h to rt/10 h	90
6	*n*-BuLi	rt/10 h	78
7	*t*-BuOK	0°C/1 h to rt/10 h	85
8	NaH	0°C/1 h to rt/10 h	80

[a]Four equiv of base and 8 equiv of ω-dibromopentane.
[b]Isolated yield.

EXPERIMENTAL

Melting points were determined on an X_4 melting-point apparatus and are uncorrected. ^{1}H NMR (400 MHz) spectra were recorded on a Bruker Avance (400-MHz) spectrometer, using $CDCl_3$ as the solvent and TMS as internal standard. FT-IR spectra were taken on a Perkin–Elmer SP One FT-IR spectrophotometer. Microanalyses were performed with a PE 2400 elemental analyzer. All final products are known, and their spectra (^{1}H NMR and IR) were compared with authentic samples. Polystyrene (100–200 mesh, cross-linked with 1% divinylbenzene) sodium sulfinate was purchased from Tianjin Nankai Hecheng Science and Technology Co.

Table 2. Yields and purities of cycloalkylphosphonates **5**

Entry	Dihaloalkane	R	Product	Yield[a] (%)	Purity[b] (%)
1	Br $(CH_2)_3$ Br (**3a**)	Et	**5aa**	83	93
2	Cl $(CH_2)_4$ Cl (**3b**)	Et	**5ab**	84	94
3	Br $(CH_2)_5$ Br (**3c**)	Et	**5ac**	90	95
4	Br $(CH_2)_6$ Br (**3d**)	Et	**5ad**	82	94
5	Br $(CH_2)_7$ Br (**3e**)	Et	**5ae**	83	95
6	Br $(CH_2)_3$ Br (**3a**)	*i*-Pr	**5ba**	84	92
7	Cl $(CH_2)_4$ Cl (**3b**)	*i*-Pr	**5bb**	86	95
8	Br $(CH_2)_5$ Br (**3c**)	*i*-Pr	**5bc**	90	96
9	Br $(CH_2)_6$ Br (**3d**)	*i*-Pr	**5bd**	87	94

[a]Overall yield based on the loading of the resin **1**.
[b]Purity determined by HPLC of crude cleavage product.

Table 3. Yields and purities of 1-cycloalkenylphosphonates **6**

Entry	Resin **4** (**n**)	R	Product	Yield[a] (%)	Purity[b] (%)
1	**4aa** (n = 3)	Et	**6aa**	80	90
2	**4ab** (n = 4)	Et	**6ab**	95	96
3	**4ac** (n = 5)	Et	**6ac**	94	94
4	**4ad** (n = 6)	Et	**6ad**	90	95

[a]Overall yield based on the loading of the resin **1**.
[b]Purity determined by HPLC of crude cleavage product.

(catalog no. HC8201-1). All chemicals were obtained from commercial suppliers and used without purification.

General Procedure for the Preparation of Polystyrene-Supported Phenylmethylsulfone 2

Polystyrene/1% divinyl benzene sodium sulfinate **1** (1.0 g, 2.1 mmol) was swollen under nitrogen in THF/DMF (2 : 1, 15 mL). Either diethyl iodomethylphosphonate (4.0 mmol) or diisopropyl iodomethylphosphonate (4.0 mmol) was added, and the reaction mixture was stirred at 80°C for 12 h, after which the reaction mixture was cooled to room temperature, quenched with water, and filtered. The resin was washed successively with THF/H_2O (2 : 1, 3 × 10 mL), THF (2 × 5 mL), CH_2Cl_2 (2 × 5 mL), and ether (2 × 5 mL) and then dried under vacuum overnight to afford the pale yellow resin **2**. **2a**: FT-IR (single bead reflection) 1600, 1495, 1452, 1313, 1240, 1150, 1025 cm^{-1}, Anal. P, 2.67% (0.86 m equiv/g); **2b**: FT-IR (single bead reflection) 1600, 1498, 1450, 1315, 1242, 1151, 1026 cm^{-1}, anal. P, 2.60% (0.84 mequiv/g).

General Procedure for the Preparation of Cycloalkylphosphonates (5aa–5bd)

A suspension of polymer **2** (1.0 mmol) in THF (8 mL) at −78°C was treated with a solution of *n*-BuLi in hexane (1.6 M, 2.5 mL, 4.0 mmol) under nitrogen. After stirring for 30 min, a solution of dihaloalkane (8.0 mmol) in THF (5.0 mL) was added dropwise. The mixture was stirred for another 1 h at −78°C and then at room temperature for 10 h. The reaction was quenched with 10% HCl (aq.) after 10 min, and the resin was filtered, washed successively with H_2O (3 × 10 mL), THF (3 × 5 mL), and CH_2Cl_2 (3 × 5 mL), and dried in a vacuum to afford resin **4** as pale yellow beads. Subsequently the resin **4** was swollen in THF (8 mL) and treated with Mg (0.24 g, 10 mmol, powder, 50 mesh) and a catalytic amount of $HgCl_2$ in EtOH–THF (3 : 1, 12 mL) under

nitrogen. The mixture was stirred at room temperature for 16 h. Then the reaction mixture was added with cold 0.5 N HCl solution and stirred for 10 min. The residual resin was collected by filtration and washed with Et_2O (3 × 10 mL). The organic extracts were washed with saturated aqueous $NaHCO_3$ solution, dried over anhydrous $MgSO_4$, and concentrated to afford crude product **5aa**–**5bd** with 92–96% purity as determined by HPLC, which was further purified by flash-column chromatography using petroleum ether–ethyl acetate (1 : 1) as an eluent, affording the pure products for their structure analysis, if necessary.

Data

O,*O*-Diethyl cyclobutylphosphonate (**5aa**): Colorless oil (lit.[4d] oil); ^{1}H NMR: $\delta = 4.06–4.02$ (m, 4H), 2.71–2.68 (m, 1H) 2.50–1.96 (m, 6H), 1.31 (t, $J = 7.1$ Hz, 6H); IR (film): 2930, 1385, 1240, 1160, 1040 cm^{-1}. Anal. calcd. for $C_8H_{17}O_3P$: C, 50.00; H, 8.92. Found: C, 49.96; H, 8.99.

O,*O*-Diethyl cyclopentylphosphonate (**5ab**): Colorless oil (lit.[4d] oil); ^{1}H NMR: $\delta = 4.12–4.08$ (m, 4H), 2.19–1.46 (m, 9H), 1.31 (t, $J = 7.1$ Hz, 6H); IR (film): 2928, 1384, 1238, 1155, 1040 cm^{-1}. Anal. calcd. for $C_9H_{19}O_3P$: C, 52.42; H, 9.29. Found: C, 52.45; H, 9.36.

O,*O*-Diethyl cyclohexylphosphonate (**5ac**): Colorless oil (lit.[4d] oil); ^{1}H NMR: $\delta = 4.07–4.02$ (m, 4H), 2.12–1.43 (m, 11H), 1.30 (t, $J = 7.0$ Hz, 6H); IR (film): 2931, 1385, 1235, 1158, 1036 cm^{-1}. Anal. calcd. for $C_{10}H_{21}O_3P$: C, 54.53; H, 9.61. Found: C, 54.60; H, 9.72.

O,*O*-Diethyl cycloheptylphosphonate (**5ad**): Colorless oil (lit.[4d] oil); ^{1}H NMR: $\delta = 4.02–3.98$ (m, 4H), 2.18–1.33 (m, 13H), 1.29 (t, $J = 7.0$ Hz, 6H); IR (film): 2933, 1385, 1241, 1162, 1042 cm^{-1}. Anal. calcd. for $C_{11}H_{23}O_3P$: C, 56.40; H, 9.90. Found: C, 56.47; H, 9.97.

O,*O*-Diethyl cyclooctylphosphonate (**5ae**): Colorless oil; ^{1}H NMR: $\delta = 4.13–3.05$ (m, 4H), 1.98–1.54 (m, 15H), 1.31 (t, $J = 6.8$ Hz, 6H); IR (film): 2932, 1386, 1239, 1162, 1045 cm^{-1}. Anal. calcd. for $C_{12}H_{25}O_3P$: C, 58.05; H, 10.15. Found: C, 58.12; H, 10.26; EIMS: m/z: 248 (M^+).

O,*O*-Diisopropyl cyclobutylphosphonate (**5ba**): Colorless oil (lit.[4d] oil); ^{1}H NMR: $\delta = 4.70–4.62$ (m, 2H), 2.60–2.48 (m, 1H), 2.37–1.91 (m, 6H), 1.21 (d, $J = 6.1$ Hz, 12H); IR (film): 2927, 1383, 1375, 1237, 1160, 1046, 988 cm^{-1}. Anal. calcd. for $C_{10}H_{21}O_3P$: C, 54.53; H, 9.61. Found: C, 54.61; H, 9.73.

O,*O*-Diisopropyl cyclopentylphosphonate (**5bb**): Colorless oil (lit.[4d] oil); ^{1}H NMR: $\delta = 4.45–4.38$ (m, 2H), 1.24–1.20 (m, 9H), 1.21 (d, $J = 6.0$ Hz, 12H); IR (film): 2930, 1385, 1376, 1240, 1164, 1050, 985 cm^{-1}. Anal. calcd. for $C_{11}H_{23}O_3P$: C, 56.40; H, 9.90. Found: C, 56.49; H, 9.99.

O,*O*-Diisopropyl cyclohexylphosphonate (**5bc**): Colorless oil (lit.[4d] oil); ^{1}H NMR: $\delta = 4.66-4.61$ (m, 2H), 1.27–1.22 (m, 11H), 1.25 (d, $J = 6.1$ Hz, 12H); IR (film): 2935, 1385, 1375, 1238, 1162, 1045, 986 cm^{-1}. Anal. calcd. for $C_{12}H_{25}O_3P$: C, 58.05; H, 10.15. Found: C, 58.15; H, 10.24.

O,*O*-Diisopropyl cycloheptylphosphonate (**5bd**): Colorless oil (lit.[4d] oil); ^{1}H NMR: $\delta = 4.60-4.52$ (m, 2H), 1.35–2.01 (m, 13H), 1.23 (d, $J = 6.0$ Hz, 12H); IR (film): 2934, 1383, 1374, 1240, 1160, 1044, 990 cm^{-1}. Anal. calcd. for $C_{13}H_{27}O_3P$: C, 59.54; H, 10.38. Found: C, 59.62; H, 10.46.

General Procedure for the Preparation of 1-Cycloalkenylphosphonates (6aa–6bd)

The resin **4** was swollen in CH_2Cl_2 (10 mL) and treated with triethylamine (5.0 mmol) at room temperature for 12 h. The residual resin was collected by filtration and washed with CH_2Cl_2 (2 × 3 mL). The organic extracts were washed with water, dried over anhydrous $MgSO_4$, and concentrated to afford crude product **6** with 90–96% purity determined by HPLC, which was further purified by silica-gel chromatographic column (hexane–ethyl acetate = 1 : 1), affording the pure products for their structure analysis, if necessary.

Data

O,*O*-Diethyl cyclobutenylphosphonate (**6aa**): Colorless oil (lit.[5a] oil); ^{1}H NMR: $\delta = 6.72$ (ddt, $J = 21.6$, 17.0, 6.6, 1H), 4.06–4.02 (m, 4H), 2.19–2.23 (m, 2H), 1.87–1.96 (m, 2H), 1.31 (t, $J = 7.1$ Hz, 6H); IR (film): 2895, 1620, 1386, 1241, 1160, 1053, 1027 cm^{-1}; anal. calcd. for $C_8H_{15}O_3P$: C, 50.53; H, 7.95. Found: C, 50.62; H, 8.03.

O,*O*-Diethyl cyclopentenylphosphonate (**6ab**): Colorless oil (lit.[5a] oil); ^{1}H NMR: $\delta = 6.75$ (ddt, $J = 22$, 17.1, 6.7, 1H), 4.10–4.06 (m, 4H), 2.18–2.22 (m, 2H), 1.87–1.95 (m, 2H), 1.25–1.40 (m, 2H), 1.31 (t, $J = 7.1$ Hz, 6H); IR (film): 2892, 1618, 1385, 1239, 1160, 1053, 1027, 821 cm^{-1}. Anal. calcd. for $C_9H_{17}O_3P$: C, 52.94; H, 8.39. Found: C, 52.99, H, 8.48.

O,*O*-Diethyl cyclohexenylphosphonate (**6ac**): Colorless oil (lit.[5b] oil); ^{1}H NMR: $\delta = 6.74$ (ddt, $J = 21.8$, 17.2, 6.7, 1H), 4.12–4.07 (m, 4H), 2.19–2.22 (m, 2H), 1.83–1.93 (m, 2H), 1.22–1.41 (m, 4H), 1.30 (t, $J = 7.1$ Hz, 6H); IR (film): 2893, 1621, 1387, 1240, 1159, 1052, 1028 cm^{-1}. Anal. calcd. for $C_{10}H_{19}O_3P$: C, 55.04; H, 8.78. Found: C, 55.15; H, 8.86.

O,*O*-Diethyl cycloheptenylphosphonate (**6ad**): Colorless oil (lit.[5a] oil); ^{1}H NMR: $\delta = 6.72$ (ddt, $J = 21.9$, 17.0, 6.6, 1H), 4.11–4.08 (m, 4H), 2.17–

2.20 (m, 2H), 1.82–1.91 (m, 2H), 1.20–1.39 (m, 6H), 1.30 (t, $J = 7.1$ Hz, 6H); IR (film): 2895, 1619, 1388, 1241, 1160, 1054, 1025 cm^{-1}. Anal. calcd. for $C_{11}H_{21}O_3P$: C, 56.88; H, 9.11. Found: C, 56.98; H, 9.23.

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