Polystyrene-Supported α-Seleno Carbanions: Efficient Reagents for Highly Stereocontrolled Syntheses of Vinylphosphonates and Vinylsulfones

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Abstract: Polystyrene-supported selenomethyl-phosphonate and polystyrene-supported selenomethyl-sulfonates have been prepared. These novel reagents were treated with LDA (or n-BuLi) to produce polystyrene-supported α-seleno carbanions, which reacted with alkyl halides, followed by stereospecific selenoxide syn-elimination to give E-vinylphosphonates and E-vinylsulfones respectively. And also these novel polymer reagents can be regenerated and reused.

Keywords: polystyrene-supported, E-vinylphosphonates, E-vinylsulfones, selenoxide syn-elimination

Combinatorial chemistry has been rapidly and extensively applied to the preparation of small organic molecules recently.1 Drug development has significantly been accelerated by exploiting solid-phase synthetic methodologies.2 However, the carbon-carbon bond-forming solid-phase reactions are less common than the carbon-heteroatom bond-forming solid-phase reactions.1 Therefore the extension of the carbon-carbon bond-forming solid-phase reactions would allow further progress in combinatorial organic synthesis.

As an effective olefin-forming method, it might be argued that selenoxide syn-elimination provided the principal impetus of the coming organoselenium chemistry.3 Several early observations of this reaction4 were soon followed by more systematic investigations in the early 1970s that demonstrated the power of the selenoxide eliminations. The required selenoxides are readily available from the oxidation of the corresponding selenides, which in turn can be prepared by the reaction of selenium-stabilized carbanions with various electrophilic substrates.5 However, organic selenides are highly malodorous and generally unpleasant and difficult to handle, especially because of their toxicity.

Since the first organoselenium resin5 was reported in 1976, several groups have developed organoselenium resins as convenient linkers.7,8 Recently, our research group has been interested in the application of organic selenium resins in organic synthesis.9 Vinylsulfones have now become generally accepted useful intermediates in organic synthesis which can serve efficiently as both Michael acceptors and π partners in cycloaddition reaction.10 And the synthesis and use of vinylphosphonates have become of great importance because of their synthetic utilities11 and fungicidal and fungistatic activities.12 We wish to report here convenient syntheses of vinylphosphonates and vinylsulfones, which are based on polystyrene-supported α-seleno carbanions followed by alkylation and stereospecific selenoxide syn-elimination. The evident advantages of easy operation are the odorlessness and stability of the resin and the high yield and good purity of the products. An additional advantage is that the resin can be regenerated and reused.9a

Preparation and Application of Polystyrene-Supported Selenomethyl-Phosphonate

Polystyrene-supported selenomethyl-phosphonate (resin 2) was prepared by treating a THF–DMF-swollen suspension of resin 1 (Se: 1.38 mmol/g) with NaBH4 for twelve hours then followed by iodomethylphosphonate for another five hours (Scheme 1). This transformation could be monitored by FTIR. The appearance of three strong peaks at 1162 cm−1, 1024 cm−1 and 961 cm−1 indicated the absorption of the P(O)(OEt)2 group.

\[ \text{SeBr} \rightarrow \text{SeCH}_{2}P(O)(OEt)_{2} \]

a: (1) NaBH4, THF/DMF, 45 °C, 12 h, (2) ICH(PO(OEt)2), 45 °C, 5 h

Scheme 1

Resin 2 reacted smoothly with n-BuLi followed by substitution by alkyl halides to give resin 3, which was converted to vinylphosphonates 4 and resin 5 through selenoxide syn-elimination (Scheme 2). The results are summarized in the Table 1.

Preparation and Application of Polystyrene-Supported Selenomethyl-Sulfonates

Polystyrene-supported selenomethyl-sulfonates (resin 6) were accomplished by treating a THF–DMF-swollen suspension of resin 1 (Se: 1.38 mmol/g) with NaBH4 for twelve hours then followed by bromomethyl-sulfonates.
for another five hours (Scheme 3). This transformation also could be monitored by FTIR. The appearance of two strong peaks at 1318 cm$^{-1}$ and about 1145 cm$^{-1}$ indicated the absorption of the -SO$_2$- group.

**Scheme 3**

**Table 1** Yield and Purity of Vinylphosphonates

<table>
<thead>
<tr>
<th>Products</th>
<th>R</th>
<th>X</th>
<th>Yield (%)$^a$</th>
<th>Purity (%)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>Ph</td>
<td>Br</td>
<td>84</td>
<td>96</td>
</tr>
<tr>
<td>4b</td>
<td>2-NO$_2$C$_6$H$_4$</td>
<td>Cl</td>
<td>75</td>
<td>81</td>
</tr>
<tr>
<td>4c</td>
<td>CH$_2$=CH</td>
<td>Br</td>
<td>86</td>
<td>95</td>
</tr>
<tr>
<td>4d</td>
<td>H</td>
<td>I</td>
<td>81</td>
<td>94</td>
</tr>
<tr>
<td>4e</td>
<td>CH$_3$</td>
<td>Br</td>
<td>62</td>
<td>91</td>
</tr>
<tr>
<td>4f</td>
<td>Ph</td>
<td>Br</td>
<td>82</td>
<td>95</td>
</tr>
</tbody>
</table>

$^a$ Yields of products are based on the loading of the resin 2 or the original loading of resin 2 when regenerated resin was used. The products were identified by NMR, MS and IR spectroscopy.

$^b$ Determined by $^1$H NMR (400 MHz).

$^c$ Using regenerated resin 2.

Resin 6 reacted smoothly with LDA followed by substitution with alkyl halides to give resin 7, which was converted to vinylsulfones 8 and resin 5 through oxide-elimination using hydrogen peroxide (Scheme 4). The results are summarized in Table 2.

**Regeneration of Polystyrene-Supported Seleninic Acid (Resin 5)**

Resin 5 reacted with KI/Na$_2$S$_2$O$_3$ followed by NaBH$_4$ to furnish polymer-supported selenium sodium (resin 9). Resin 9 was further treated with iodomethylphosphonate
or bromomethylsulfonates to regenerate poly styrene-supported selenomethyl-phosphonate (resin 2) or poly styrene-supported selenomethyl-sulfonates (resin 6) respectively (Scheme 5).

![Scheme 5](image)

The melting points are uncorrected. $^1$H NMR (400 MHz) and $^{13}$C NMR (100 MHz) spectra were recorded on a Bruker Avance 400 spectrometer in CDCl$_3$ with TMS as the internal standard; chemical shifts were quoted in ppm and $J$ values were given in Hz. IR spectra recorded on a FTIR spectrometer, EIMS was run on a HP 5989B mass spectrometer. Elemental analysis was run on Thermofinnigan Flash EA 1112.

### Preparation of Polystyrene-Supported Selenomethyl-Phosphorous Acid (Resin 2); General Procedure

To a suspension of the swelled resin 1 (2 g) in anhyd THF–DMF (5:1, 30 mL) was added NaBH$_4$ (0.185 g) under N$_2$ atmosphere at 45 °C. After stirring for 12 h at 45 °C, iodomethylphosphonate (8 mmol) was added dropwise under N$_2$ atmosphere at 45 °C, and stirring was continued for another 5 h. The resin 2 was collected by filtration, washed and dried in vacuum, P: 1.21 mmol/g.

IR (KBr): 3440, 3058, 2921, 1599, 1567, 1451, 1318, 1301, 1145, 905, 823, 787, 757, 697, 540 cm$^{-1}$.

### Preparation of Vinyl phosphonates Through Resin 2; General Procedure

To a suspension of the swelled resin 2 (0.5 g) in anhyd THF, cooled to –60 °C, was added $n$-BuLi dropwise (2 M, 0.4 mL) under N$_2$ atmosphere. After stirring for 0.5 h at –60 °C, a solution of alkyl halide (4 mmol) in anhyd THF (3 mL) was added dropwise. The suspension was stirred for another 0.5 h at –60 °C. The resin 3 was collected by filtration and washed with THF (2 × 10 mL), MeOH (2 × 10 mL) and CH$_2$Cl$_2$ (2 × 10 mL). The washed resin was suspended in THF (15 mL) overnight. To the mixture was added 30% aq H$_2$O$_2$ (1 mL) and stirred for 1 h at 0 °C followed by 20 min at r.t. The mixture was filtered and the resin was washed with CH$_2$Cl$_2$ (15 mL × 2). The filtrate was washed with H$_2$O (30 mL × 2), dried over MgSO$_4$, and evaporated to dryness in vacuum.

### Phosphorous Acid 1-Phenylethyl Diethyl Ester (4a)

Oil.$^{13a}$

IR: 2982, 1616, 1495, 1247, 1097, 1026, 964, 744, 691 cm$^{-1}$.

$^1$H NMR (CDCl$_3$): $\delta = 7.53$–7.46 (m, 3 H), 7.38–7.34 (m, 3 H), 6.15 (t, $J = 17.2$ Hz, 1 H), 6.15 (t, $J = 7.2$ Hz, 6 H).

Resin 6a

S: 1.21 mmol/g.

IR (KBr): 3444, 3058, 2922, 1600, 1566, 1449, 1318, 1301, 1149, 905, 823, 787, 757, 697, 540 cm$^{-1}$.

### Preparation of Vinyl sulfones Through Resin 6; General Procedure

To a suspension of the swelled resin 6 (0.5 g) in anhyd THF, cooled to –60 °C, was added dropwise LDA (2 M, 0.4 mL) under N$_2$ atmosphere. After stirring for 0.5 h at –60 °C, a solution of alkyl halide (4 mmol) in anhyd THF (3 mL) was added. The suspension was stirred for another 0.5 h at –60 °C. The resin 7 was collected by filtration and washed with THF (2 × 10 mL), MeOH (2 × 10 mL) and CH$_2$Cl$_2$ (2 × 10 mL). The washed resin was suspended in THF (15 mL) overnight. To the mixture was added 30% aq H$_2$O$_2$ (1 mL) and stirring was continued for 0.5 h at 0 °C and then 2 h at r.t. The mixture was filtered and the resin was washed with CH$_2$Cl$_2$ (2 × 15 mL).
The filtrate was washed with H₂O (2 × 30 mL), dried over MgSO₄, and evaporated to dryness in vacuum.

(E)-1-Phenyl-2-(p-toluenesulfonyl)-ethene (8a)
White solid; mp 121–122 °C (lit.14a 121–122 °C).
IR: 3025, 2925, 1641, 1594, 1301, 1141, 809, 705, 661 cm⁻¹.

(E)-1-Phenyl-2-benzensulfonyl-ethene (8b)
White solid; mp 75–76 °C (lit.14b 76 °C).

(E)-1-(p-Toluenesulfonyl)-pentene (8c)
Oil.
IR: 2962, 1634, 1597, 1318, 1145, 813, 705 cm⁻¹.

(E)-1-(p-Toluenesulfonyl)-propene (8d)
White solid; mp 97–98 °C (lit.14c 97.5–98.5 °C).
IR: 3025, 2925, 1641, 1594, 1301, 1141, 809, 705, 661 cm⁻¹.

(E)-1-Cyano-2-p-toluenesulfonyl-ethene (8e)
White solid; mp 132–133 °C (lit.14d 132–134 °C).

(E)-1-Methoxycarbonyl-2-benzensulfonyl-ethene (8f)
White solid; mp 99–100 °C (lit.14e 99–101 °C).

(E)-2-Benzensulfonyl-ethenyl-oxirane (8g)
White solid; mp 82–83 °C.

(E)-2-(p-Toluenesulfonyl)-ethyl-oxirane (8h)
White solid; mp 67–68 °C (lit.14g 67–68 °C).

(E)-1-(p-Toluenesulfonyl)-3-methyl-1,3-butadiene (8i)
Oil.
IR: 2928, 1623, 1590, 1303, 1145, 909, 733 cm⁻¹.

(E)-1-Benzensulfonyl-propene (8j)
IR: 3025, 1641, 1304, 1146, 752, 686 cm⁻¹.

(E)-1-Benzensulfonyl-1,3-butadiene (8k)
Oil.
IR: 3062, 1631, 1584, 1306, 1147, 755, 689 cm⁻¹.

Regeneration of Polystyrene-Supported Seleninic Acid (Resin 5); General Procedure
The resin 5 (2 g) was swelled in anhyd DMF (30 mL) overnight. To the mixture was added a solution of K₂Na₂S₂O₃ (each 20 mmol) in DMF–H₂O (30 mL, 10:1). The suspension was stirred at r.t. for 24 h. The resin was collected by filtration and washed with THF (2 × 15 mL), MeOH (2 × 15 mL) and CH₂Cl₂ (2 × 15 mL). The washed resin was suspended in THF–DMF (4:1, 30 mL). To the mixture was added NaBH₄ (0.19 g, 5.1 mmol). After stirring for 10 h at 40 °C, iodomethylphosphonate (8 mmol) was added. The suspension was stirred at 45 °C for another 5 h. Polystyrene-supported selenomethyl-phosphonate (resin 2) was regenerated by filtration and washed with THF–H₂O (3:1, 2 × 15 mL), THF (2 × 15 mL). MeOH (2 × 15 mL), and CH₂Cl₂ (2 × 15 mL), and reused. The use of bro-momethyl-sulfonates in place of iodomethylphosphonate regenerated polystyrene-supported selenomethyl-sulfonates (resin 6) using the same procedure.
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References


