A Convenient Synthesis of Free Vinyl Sulfoximines from Methyl Sulfoximines

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Received October 21, 1999

The sulfoximine\(^1\) as a functional group was unknown to organic chemistry until 1950, when Bentley and co-workers\(^2\) reported the structure elucidation of methionine sulfoximine (1), which is a potent inhibitor of the enzyme glutamate synthetase.\(^3\) Heterocyclic sulfoximines have also attracted considerable interest, because of a wide variety of biological activities.\(^4\) The remarkable biological activity of many sulfoximines, as well as the interesting diversity of reactions associated with the functionality itself, has stimulated continued interest in sulfoximine chemistry.\(^5\) We have been interested for some time in the preparation of functionalized sulfoximines\(^4\) starting from N-(trimethylsilyl)methyl phenylsulfoximine (3).\(^6\) Compound 3 was obtained almost quantitative yield simply by treating sulfoximine 2\(^7\) with either trimethylsilyldiethylamine or bis-(trimethylsilyl)acetamide. Lithiation of 3 and alkylation with various electrophiles followed by ready desilylation, provided simple access to a variety of free sulfoximines 4 that are not readily prepared by other methods (Scheme 1). Meanwhile, we needed several vinyl sulfoximines as a key intermediates for some cyclic sulfoximines.

This communication describes studies on the facile synthesis of free vinyl sulfoximines 6 by utilizing aforementioned carbanion chemistry of compound 3 (Scheme 2). Several methods for preparing vinyl sulfoximines\(^8\) have been reported. Those methods, however, provide access only to vinyl sulfoximines substituted at nitrogen with group which are difficult or impossible to be removed. Thus, lithiation of 3 followed by trapping with diethyl chlorophosphate gave phosphorylated compound 5 in > 80% yield. Subsequent treatment of 5 with n-butyllithium, aldehydes and then facile deprotection of the silyl group provided S-aryl-S-((E)-alkylvinyl sulfoximines (6) in 65-86% yields (Table 1).

Although this procedure provides a convenient access to the free vinyl sulfoximines 6, several points deserve some mentions regarding these process. First, compound 5 was unstable toward vacuum distillation, so it is desirable to use as crude product for the next step. A pure compound 5 can be obtainable by a flash column chromatography, but there is no practical value to do so. Second, direct conversion of 3 to 6, without isolation of 5, gave much inferior results (16-18% yield) to the present two step process. Third, an attempt to utilize Peterson extrusion\(^9\) of lithiated carbinol trimethylsilyl ether by trapping lithiated anion of 3 with trimethylsilyl chloride was unsuccessful. So the Peterson olefination procedure is not appropriate for this case. Finally, the stereochemistry of the vinyl region is exclusively E-configuration as judged by 200 MHz proton NMR spectrum. This result is not surprising in view of the steric bulk of the phosphoryl and sulfimidoyl group.

The finding that ketones gave very poor results under the same reaction condition for the aldehydes may indirectly support the rationale for the steric hindrance to get the exclusive E-isomer.

In conclusion, we have described a facile synthesis of free vinyl sulfoximines 6 starting from methylsulfoximine 2 through the phosphonomethylsulfoximine 5. With this vinyl sulfoximines in hand, the preparation of various heterocyclic sulfoximines will be reported in due course.

Table 1. Synthesis of free vinyl sulfoximines 6 from N-protected phosphonomethyl sulfoximines 5

<table>
<thead>
<tr>
<th>Compd.</th>
<th>X</th>
<th>R</th>
<th>Yield (%)(^a)</th>
<th>Compd.</th>
<th>X</th>
<th>R</th>
<th>Yield (%)(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6a</td>
<td>H</td>
<td>CH(_3)</td>
<td>66</td>
<td>6f</td>
<td>Cl</td>
<td>CH(_3)</td>
<td>86</td>
</tr>
<tr>
<td>6b</td>
<td>H</td>
<td>C(_6)(_6)</td>
<td>64</td>
<td>6g</td>
<td>Cl</td>
<td>CH(_3)</td>
<td>62</td>
</tr>
<tr>
<td>6c</td>
<td>H</td>
<td>CH(CH(_3))(_3)</td>
<td>68</td>
<td>6h</td>
<td>Cl</td>
<td>CH(CH(_3))(_3)</td>
<td>82</td>
</tr>
<tr>
<td>6d</td>
<td>H</td>
<td>C(CH(_3))(_3)</td>
<td>70</td>
<td>6i</td>
<td>Cl</td>
<td>C(CH(_3))(_3)</td>
<td>85</td>
</tr>
<tr>
<td>6e</td>
<td>H</td>
<td>CH(_2)CH(_3)</td>
<td>68</td>
<td>6j</td>
<td>Cl</td>
<td>CH(_2)CH(_3)</td>
<td>83</td>
</tr>
</tbody>
</table>

\(^a\)isolated yields calculated from the result that purity of 5 (X=H) is 82% pure. \(^b\)isolated yields calculated from the result that purity of 5 (X=Cl) is 80% pure.
Experimental Section

Mass spectra were recorded on a Shimadzu QP-1000 spectrometer (20 eV). High Resolution Mass Spectra (HRMS) were obtained on a JEOL JMS-DX-305 high resolution mass spectrometer. 1H-NMR spectra were recorded either on a JEOL-60 or on a Varian Gemini-200 MHz spectrometer. Chemical shifts were expressed in ppm downfield from TMS used as internal standard. Melting point was determined on an electrically heated Thomas-Hoover capillary melting point apparatus and uncorrected. All chromatographic separations were performed on Merck silica gel (Kieselgel 60, 230-400 mesh).

Preparation of diethylphosphonomethylsulfoximine 5 (X=H)

To a solution of N-trimethylsilyl sulfoximine 3 (X=H, 3.41 g, 15 mmol) in THF (25 mL) was added n-butyllithium (2.5 M in hexane, 6.60 mL, 17 mmol) over 3 min at -78 °C under nitrogen atmosphere. After addition was complete, the reaction mixture was stirred at -78 to 0 °C for 10 min, cooled back to -78 °C followed by addition of diethyl chlorophosphate (2.58 g, 15 mmol). The reaction mixture was stirred at -78 to 10 °C for 2h, quenched with saturated NH4Cl solution (10 mL), and then extracted with ethyl acetate (2 × 50 mL). The combined extracts were washed with cold water (1 × 20 mL) and brine (1 × 40 mL), and then filtered through MgSO4. The filtrate was concentrated in vacuo to leave faint yellow oil, which was chromatographed on silica gel with ethyl acetate as eluent to give pure products.

Preparation of diethylphosphonomethylsulfoximine 5 (X=Cl)

By the same procedure for the preparation of 5 (X=H), compound 5 (X=Cl) was obtained as a crude. 1H NMR (60 MHz, CDCl3): δ 0.13 (s, 9H), 1.25 (t, J = 7 Hz, 6H), 3.65 (d, J = 16 Hz, 2H), 4.10 (q, J = 7 Hz, 4H), 7.60 (m, 3H), 8.00 (m, 2H); MS: m/z 364 (M+ + 1). Again the crude compound 5 (X=Cl) was directly used for the next step without purification.

General method for the synthesis of vinyl sulfoximines 6 (6a-6j)

To a solution of crude compound 5 (X=H and Cl, 3.0 mmol) in THF (25 mL) was added n-butyllithium (2.5 M in hexane, 3.2 mmol) over 1 min at -78 °C under nitrogen atmosphere. The reaction mixture was stirred at -78 to 0 °C for 10 min, cooled back to -78 °C followed by addition of corresponding aldehydes (3.5 mmol). After stirring at ambient temperature for 10 h, the reaction mixture was quenched with saturated NH4Cl solution (5 mL) and then extracted with ethyl acetate (w × 50 mL). The combined extracts was washed with water (1 × 10 mL) and brine (1 × 20 mL), dried over MgSO4 and concentrated in vacuo to leave faint yellow oil, which was chromatographed on silica gel with ethyl acetate as eluent to give pure products.

(E)-1-(S-Phenylsulfonimidoyl)-1-propene (6a): yield 66%; oil; 1H NMR (200 MHz, CDCl3): δ 1.95 (dd, J = 6 Hz, 2 Hz, 3H), 2.70 (broad m, 1H), 6.40 (dq, J = 15 Hz, 2 Hz, 1H), 6.92 (dq, J = 15 Hz, 6 Hz, 1H), 7.50 (m, 3H), 7.85 (m, 2H); MS: m/z 181 (M+ + 1); HRMS: calcld for C12H13ONS: 181.0562, Found : 181.0567.

(E)-1-(S-Phenylsulfonimidoyl)-2-isopropyl-ethene (6b): yield 64%; mp 71-72 °C; 1H NMR (200 MHz, CDCl3): δ 3.00 (broad, m, 1H), 6.93 (d, J = 15 Hz, 1H), 7.35 (m, 5H), 7.50 (m, 3H), 7.63 (d, J = 15 Hz, 1H), 8.00 (m, 3H); MS: m/z 244 (M+ + 1); HRMS: calcld for C14H12OONS: 244.0718, Found: 244.0728.

(E)-1-(S-Phenylsulfonimidoyl)-2-isopropyl-ethene (6c): yield 68%; oil; 1H NMR (200 MHz, CDCl3): δ 8.90 (s, 9H), 3.35 (d, J = 15 Hz, 6 Hz, 1H), 2.80 (broad m, 1H), 6.30 (d, J = 15 Hz, 2 Hz, 1H), 6.65 (dd, J = 15 Hz, 6 Hz, 1H), 7.50 (m, 3H), 7.70 (m, 2H); MS: m/z 209 (M+); HRMS: calcld for C10H13ONS: 209.0874, Found: 209.0875.

(E)-1-(S-Phenylsulfonimidoyl)-2-t-butyl-ethene (6d): yield 70%; oil; 1H NMR (200 MHz, CDCl3): δ 1.10 (t, J = 8 Hz, 3H), 2.25 (qd, J = 8 Hz, 6 Hz, 2H), 2.80 (broad m, 1H), 6.38 (dt, J = 15 Hz, 2 Hz, 1H), 6.98 (dt, J = 15 Hz, 6 Hz, 1H), 7.50 (m, 3H), 7.95 (m, 2H); MS: m/z 196 (M+ + 1); HRMS: calcld for C11H14OONS: 195.0717, Found: 195.0722.

(E)-1-(S-Phenylsulfonimidoyl)-1-butenel (6e): yield 68%; oil; 1H NMR (200 MHz, CDCl3): δ 8.90 (s, 9H), 2.85 (broad, m, 1H), 6.30 (d, J = 15 Hz, 1H), 6.99 (d, J = 15 Hz, 1H), 7.55 (m, 3H), 8.00 (m, 2H); MS: m/z 224 (M+ + 1); HRMS: calcld for C11H15OONS: 223.1030, Found: 223.1032.

(E)-1-(S-Phenylsulfonimidoyl)-1-propene (6f): yield 66%; mp 71-72 °C; 1H NMR (200 MHz, CDCl3): δ 1.95 (dd, J = 6 Hz, 3H), 2.90 (broad m, 1H), 7.35 (m, 5H), 7.50 (m, 3H), 7.63 (d, J = 15 Hz, 1H), 7.95 (m, 2H); MS: m/z 216 (M+ + 1); HRMS: calcld for C12H15ONS: 215.0717, Found: 215.0719.

(E)-1-[S-(4-Chloropheny)sulfonylimidoyl]-1-propene (6g): yield 62%; mp 42-43 °C; 1H NMR (200 MHz, CDCl3): δ 3.15 (broad m, 1H), 6.93 (d, J = 15 Hz, 1H), 7.45 (m, 5H), 7.63 (d, J = 15 Hz, 1H), 7.95 (m, 2H); MS: m/z 278 (M+ + 1); HRMS: calcld for C13H14ClONS: 277.0326, Found: 277.0327.

(E)-1-[S-(4-Chloropheny)sulfonylimidoyl]-2-isopropyl-ethene (6h): yield 82%; oil; 1H NMR (200 MHz, CDCl3): δ 1.10 (d, J = 6 Hz, 6H), 2.50 (m, 1H), 2.95 (broad m, 1H), 6.30 (dd, J = 15 Hz, 2Hz, 1H), 6.65 (dd, J = 15 Hz, 6 Hz, 1H), 7.50 (m, 3H), 7.90 (d, J = 8 Hz, 2H); MS: m/z 244 (M+ + 1); HRMS: calcld for C14H16ClONS: 244.0493, Found: 244.0495.

(E)-1-[S-(4-Chloropheny)sulfonylimidoyl]-2-t-butyl-ethene (6i): yield 85%; mp 72-74 °C; 1H NMR (200 MHz, CDCl3): δ 1.10 (s, 9H), 2.90 (broad m, 1H), 6.25 (d, J = 15 Hz, 1H), 6.95 (d, J = 15 Hz, 1H), 7.45 (d, J = 8 Hz, 2H), 7.90 (d, J = 8 Hz, 2H); MS: m/z 258 (M+ + 1); HRMS: calcld for C15H16ClONS: 258.0517, Found: 258.0517.

Notes
ONSCl: 257.0641, Found: 257.0625
(E)-1-[S-(4-Chlorophenyl)sulfonimidoyl]-1-butene (6j); yield 83%; oil; ¹H NMR (200 MHz, CDCl₃): δ 1.05 (t, J = 8 Hz, 3H), 2.30 (qd, J = 8 Hz, 6Hz, 2H), 2.90 (broad m, 1H), 6.38 (dt, J = 15 Hz, 2Hz, 1H), 6.98 (dt, J = 15 Hz, 6 Hz, 1H), 7.55 (d, J = 8 Hz, 2H), 8.00 (d, J = 8 Hz, 2H); MS: m/z 230 (M⁺ + 1); HRMS: calcd for C₁₀H₁₂O₃NSCl: 229.0328, Found: 229.0330.

Acknowledgment. This work was in part supported by the Korean Research foundation made in program year of 1998. Author thanks N. K. Choi for her technical assistance.

References