A New Method for the Preparation of (*E*)-2-(Styrylsulfonyl)acetic Acid Esters and Their Reactions with Hydrazine Hydrate

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Abstract: A new route to esters of (*E*)-2-(styrylsulfonyl)acetic acid has been developed. Treatment of the methyl ester with hydrazine hydrate gave the six-membered 4-amino-5-phenylthiomorpholine-3-one 1,1-dioxide (**1**), and not the seven-membered 6-phenyl-1,4,5-thiadiazepane-3-one 1,1-dioxide (**2**) as previously described by others. In contrast, treatment of the ethyl ester with the same reagent provided a separable 1:1.2 mixture of **1** and **2**. The NMR spectra of both **1** and **2** differed substantially from that described for **2** in the previous report.

Key words: cyclizations, sulfones, heterocycles, esters

In the course of our literature survey on diazepanes, we were intrigued by a recently reported synthesis of 6-phenyl-1,4,5-thiadiazepan-3-one 1,1-dioxide (**2**). Padmavathi and co-workers reported that dioxide **2** was produced by treatment of methyl (*E*)-2-(styrylsulfonyl)acetate with hydrazine hydrate in refluxing methanol.[1] The reported formation of this seven-membered ring was somewhat surprising to us, because previous experience seemed to indicate that reactions of hydrazine with 1,5-dielectrophiles strongly favors the formation of the six-membered-ring adducts.[2] Furthermore, an examination of Padmavathi's ^{1}H NMR data reinforced our concerns, in that one broad singlet at δ = 10.58 ppm was assigned to two NH protons. A single peak for both of these protons is not what one would expect, because the two NH groups in **2** are quite different. We suspected that the product might be the isomeric six-membered 4-amino-5-phenylthiomorpholine-3-one 1,1-dioxide (**1**), the NH_2 protons of which would be expected to appear as a broad singlet. However, a value of δ = 10.58 ppm would be too high for such an amino group by comparison with some known analogues (Figure 1).[2c,3] Because we were unable to contact the author, we decided to reinvestigate this reaction experimentally to check the identity of the product.

Padmavathi and co-workers did not report any experimental procedure for the preparation of their starting material, methyl (*E*)-2-(styrylsulfonyl)acetate (**6**). The most closely related substrate that has appeared in the literature is (*E*)-2-(4-methylstyrylsulfonyl)acetic acid, which was prepared by Bhaskar Reddy and co-workers from sodium (*E*)-4-methylstyrylsulfinate and chloroacetic acid.[4] Our attempts to follow this route were unsuccessful because of a lack of experimental details for the preparation of sodium (*E*)-4-methylstyrylsulfinate. This problem prompted us to design a new and more reliable synthesis of methyl ester **6** and its analogues from the readily commercially available starting materials methyl sulfanylacetate, diethyl (chloromethyl)phosphonate, and benzaldehyde.

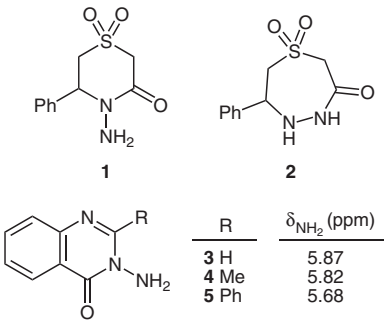
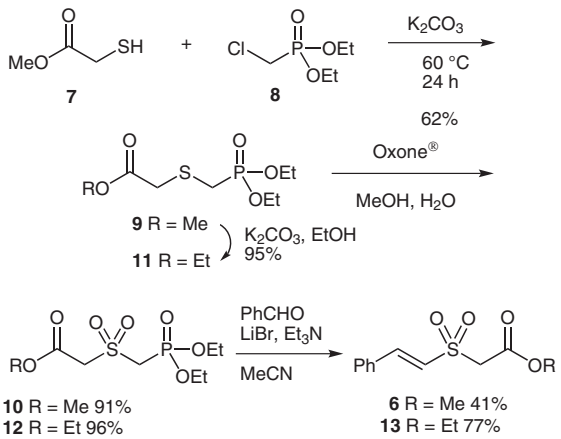


Figure 1



Scheme 1

The synthesis began with treatment of methyl sulfanylacetate (**7**) with diethyl (chloromethyl)phosphonate (**8**) to give the sulfide **9** in 62% yield. Oxidation of **9** with Oxone gave the corresponding sulfone **10** in 91% yield. Treatment of **10** with benzaldehyde in the presence of triethylamine and lithium bromide gave methyl ester **6** in 41% yield. The corresponding ethyl ester **13** could also be conveniently prepared in good yield by the same route. We believe that this route could be used to generate a library of useful compounds simply by changing the aldehyde in the last step. It was also possible to convert the methyl es-

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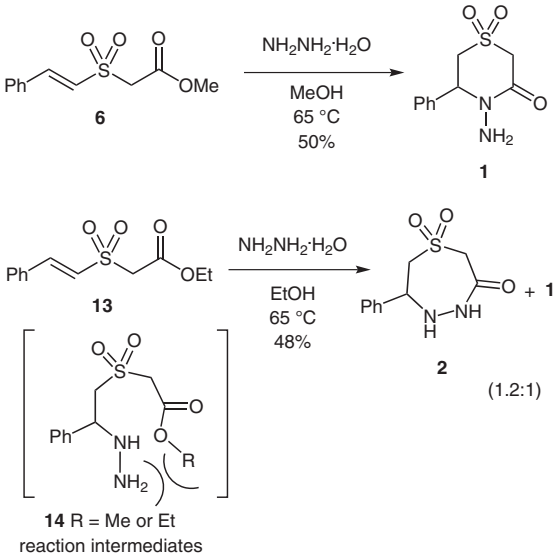
ter **6** into the ethyl ester **13** by treatment with potassium carbonate and ethanol, albeit in a lower yield (48%).

Treatment of ester **6** or **13** with hydrazine hydrate provided interesting results. The six-membered-ring product **1** was obtained almost exclusively from the reaction of ester **6** with hydrazine hydrate, whereas a mixture of products **1** and **2** was obtained from the reaction of ester **13** with hydrazine hydrate (Scheme 2). The structures of **1** and **2** were elucidated by ^{1}H NMR, ^{13}C NMR, and IR spectroscopy and by HRMS. The results matched our expectations in all respects. The ^{1}H NMR spectrum of **1** showed a broad singlet for two (exchangeable) NH protons at δ = 4.65 ppm, whereas the spectrum of **2** showed two (exchangeable) NH signals at δ = 9.42 ppm and δ = 5.79 ppm. At this point, the identity of the product reported by Padmavathi and co-workers remains elusive, because the NMR data in their report is not consistent with our NMR results for either **1** or **2**.



Scheme 2

Whereas we expected the formation of the six-membered-ring product, we did not expect the formation of the seven-membered ring, because the formation of the six-membered ring should be entropically favored. The change in the product distribution caused by a subtle change in the ester structure implies that the cyclization event occurs after the conjugate addition of hydrazine and that it is sensitive to the steric bulk of the ester moiety. On the basis of our results, we predict that the reaction of the corresponding isopropyl ester should give **2** as the major product, but we did not attempt this reaction.

In conclusion, we established a new and reliable route to methyl (*E*)-2-(styrylsulfonyl)acetic acid methyl (**6**) and the corresponding ethyl ester **13**. 1,1-Dioxo-4-amino-5-phenylthiomorpholine-3-one (**1**) and 1,1-dioxo-6-phenyl-1,4,5-thiadiazepan-3-one (**2**) were prepared and fully characterized; neither of these compounds displayed spectral data consistent with those previously reported for compound **2** by Padmavathi and co-workers.[1]

All commercially obtained solvents and reagents were used as received. ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Bruker 300 MHz instrument. Chemical shifts are given as δ values referenced to the internal standard TMS. Mass spectra were recorded on an Agilent ESI-TOF instrument or a Waters Micromass Quattro Ultima MS instrument, and HRMS spectra were recorded on a Bruker Daltonic High Resolution Q-FTMS instrument. FTIR spectra were recorded on a Perkin Elmer Spectrum 400 instrument.

Methyl {[(Diethoxyphosphoryl)methyl]sulfanyl}acetate (9)

K_2CO_3 (5 g, 36.2 mmol) was added to a mixture of $ClCH_2P(O)(OEt)_2$ (**8**; 4.94 g, 26.5 mmol) and $HSCH_2CO_2Me$ (**7**; 5 g, 47.1 mmol), and the mixture was stirred and heated at 70 °C for 24 h. The mixture was then diluted with CH_2Cl_2 (20 mL), filtered, and concentrated by rotary evaporation. The residue was purified by column chromatography (silica gel, 20–50% EtOAc–hexanes) to give a colorless oil; yield: 4.22 g (62%); R_f = 0.28 (hexanes–EtOAc, 1:1).

^{1}H NMR ($CDCl_3$): δ = 4.18 (m, 4 H), 3.74 (s, 3 H), 3.50 (s, 2 H), 2.89 (d, *J* = 12.9 Hz, 2 H), 1.35 (t, *J* = 7.2 Hz, 6 H).

^{13}C NMR ($CDCl_3$): δ = 170.4, 62.7, 52.4, 33.6, 24.8 (d, *J* = 149 Hz), 16.5.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_8H_{18}O_5PS$: 257.0607; found: 257.0613.

Ethyl {[(Diethoxyphosphoryl)methyl]sulfanyl}acetate (11)

K_2CO_3 (15 mg, 0.1 mmol) was added to a soln of ester **9** (1.78 g, 6.9 mmol) in EtOH (15 mL), and the mixture was stirred for 16 h then filtered. The filtrate was concentrated by rotary evaporation. The residue was dissolved in CH_2Cl_2 (10 mL) and filtered again to remove traces of K_2CO_3. The filtrate was concentrated by rotary evaporation and dried in a high vacuum to give a pale yellow oil; yield: 1.79 g (95%); R_f = 0.36 (hexanes–EtOAc, 1:1).

^{1}H NMR ($CDCl_3$): δ = 4.18 (m, 6 H), 3.48 (s, 2 H), 2.89 (d, *J* = 12.9 Hz, 2 H), 1.35 (t, *J* = 7.2 Hz, 6 H), 1.29 (t, *J* = 7.2 Hz, 3 H).

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_9H_{20}O_5PS$: 271.1; found: 271.0.

Methyl {[(Diethoxyphosphoryl)methyl]sulfonyl}acetate (10); Typical Procedure

A soln of Oxone (3.1 g, 5.0 mmol) in H_2O (13 mL) was added dropwise to a soln of ester **9** (0.86 g, 3.35 mmol) in MeOH (10 mL) at 0 °C, and the resulting suspension was allowed to warm to r.t. over 1 h and then stirred for 16 h. The white solid was removed by filtration, and the filtrate was concentrated to about 10 mL by rotary evaporation. The cloudy soln was extracted with EtOAc (4 × 30 mL), and the extracts were dried ($MgSO_4$) and concentrated by rotary evaporation. The residue was purified by gel column chromatography (silica gel, 50–75% EtOAc–hexanes) to give a colorless oil; yield: 0.88 g (91%); R_f = 0.32 (hexanes–EtOAc, 1:1).

^{1}H NMR ($CDCl_3$): δ = 4.48 (s, 2 H), 4.25 (m, 4 H), 3.95 (d, *J* = 16.2 Hz, 2 H), 3.83 (s, 3 H), 1.38 (t, *J* = 7.2 Hz, 6 H).

^{13}C NMR ($CDCl_3$): δ = 164.0, 63.8, 57.4, 53.3, 50.1 (d, *J* = 138 Hz), 49.2, 16.3.

HRMS (ESI): *m/z* [M + H]$^+$: calcd for $C_8H_{18}O_7PS$: 289.0505; found: 289.0518.

Ethyl {[(Diethoxyphosphoryl)methyl]sulfonyl}acetate (12)

Ester **12** was prepared by the same procedures as above, starting from **11** (1.79 g, 6.63 mmol) and Oxone (6.11 g, 9.9 mmol).

Colorless oil; yield: 1.91 g (96%); R_f = 0.23 (hexanes–EtOAc, 1:1).

^{1}H NMR ($CDCl_3$): δ = 4.45 (s, 2 H), 4.25 (m, 6 H), 3.95 (d, *J* = 16.2 Hz, 2 H), 1.40–1.30 (m, 9 H).

MS (ESI): *m/z* [M + H]$^+$ calcd for $C_9H_{20}O_7PS$: 303.1; found: 303.0.

Methyl (*E*)-2-(Styrylsulfonyl)acetate (6); Typical Procedure

LiBr (0.38 g, 4.41 mmol) was added to a soln of ester **10** (0.85 g, 2.94 mmol), PhCHO (0.33 mL, 3.2 mmol), and Et_3N (1.23 mL, 9.7 mmol) in MeCN (7 mL). The resulting suspension was stirred for 16 h at r.t. and then diluted with MeCN (10 mL). The white solid was removed by filtration and rinsed with MeCN (5 mL). The combined organic phases were concentrated by rotary evaporation and the residue was purified by column chromatography (silica gel, 25–50% EtOAc–hexanes) to give a waxy solid; yield: 0.29 g (41%); R_f = 0.52 (hexanes–EtOAc, 1:1).

^{1}H NMR ($CDCl_3$): δ = 7.64 (d, *J* = 15.6 Hz, 1 H), 7.56–7.53 (m, 2 H), 7.47–7.43 (m, 3 H), 7.07 (d, *J* = 15.6 Hz, 1 H), 4.10 (s, 2 H), 3.82 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 163.4, 145.8, 132.0, 131.7, 129.2, 128.8, 124.5, 59.9, 53.3.

MS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{11}H_{12}NaO_4S$: 263.0; found: 263.1.

Ethyl (*E*)-2-(Styrylsulfonyl)acetate (13)

Ester **13** was prepared by using the same procedures as above, starting from **12** (1.0 g, 3.3 mmol), PhCHO (0.37 mL, 3.6 mmol), Et_3N (0.69 mL, 4.95 mmol), and LiBr (0.43 g, 4.95 mmol).

Viscous colorless oil; yield: 0.65 g (77%); R_f = 0.61 (hexanes–EtOAc, 1:1).

^{1}H NMR ($CDCl_3$): δ = 7.65 (d, *J* = 15.3 Hz, 1 H), 7.56–7.53 (m, 2 H), 7.48–7.43 (m, 3 H), 7.06 (d, *J* = 15.3 Hz, 1 H), 4.25 (q, *J* = 7.2 Hz, 2 H), 4.09 (s, 2 H), 1.29 (t, *J* = 7.2 Hz, 3 H).

MS (ESI): *m/z* [M + H]$^+$ calcd for $C_{12}H_{15}O_4S$: 255.1; found: 255.0.

4-Amino-5-phenylthiomorpholine-3-one 1,1-Dioxide (1); Typical Procedure

$N_2H_4{\cdot}H_2O$ (24 L, 0.50 mmol) was added to a cloudy soln of ester **6** (60 mg, 0.25 mmol) in MeOH (15 mL). The mixture was heated at 65 °C for 15 h and then concentrated by rotary evaporation. The residue was purified by column chromatography (silica gel, 0–60% EtOAc–hexanes) to give a white solid; yield: 30 mg (50%); mp 208–211 °C; R_f = 0.22 (hexanes–EtOAc, 1:1).

FTIR (KBr): 3305.0 (m), 2984.6 (m), 2933.5 (w), 2898.2 (w), 1639.1 (s), 1587.7 (s) cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 7.39–7.28 (m, 5 H, Ph), 4.85 [dd, *J* = 10.8, 5.1 Hz, 1 H, C(5)H], 4.80 [d, *J* = 15.8 Hz, 1 H, C(2)H_a], 4.65 (br s, 2 H, NH_2, exch. D_2O), 4.18 [dd, *J* = 15.8, 3.9 Hz, C(2)H_b], 3.90 [ddd, *J* = 14.4, 4.8, 3.9 Hz, 1 H, C(6)H_a], 3.81 [dd, *J* = 14.4, 10.8 Hz, 1 H, C(6)H_b].

^{13}C NMR (DMSO-d_6): δ = 160.5, 138.4, 128.5, 127.9, 127.2, 61.6, 55.3, 53.6.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{10}H_{13}N_2O_3S$: 241.0641; found: 241.0643.

6-Phenyl-1,4,5-thiadiazepan-3-one 1,1-Dioxide (2)

Thiadiazepan **2** was prepared as a mixture with **1** by using the same procedures as above, starting from ester **13** (0.3 g, 1.18 mmol), $N_2H_4{\cdot}H_2O$ (86 L, 1.77 mmol), and EtOH (30 mL).

1: White solid; yield: 67 mg (24%).

2: White solid; yield: 85 mg (30%); mp 194–197 °C; R_f = 0.14 (hexanes–EtOAc 1:1).

FTIR (KBr): 3330.6 (m), 3285.7 (m), 3003.0 (w), 2942.6 (w), 1697.1 (br, vs), 1602.4 (vw), 1583.2 (vw) cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 9.42 [br s, 1 H, N(4)H, exch. D_2O], 7.42–7.28 (m, 5 H, Ph), 5.79 [br s, 1 H, N(5)H, exchangeable with D_2O], 5.13 [br d, *J* = 13.8 Hz, 1 H, C(2)H_a], 4.33 [d, *J* = 11.7 Hz, 1 H, C(6)H], 3.93 [dd, 1 H, *J* = 13.8, 11.7 Hz, C(7)H_a], 3.69 [br dd, *J* = 13.8, 2.4 Hz, 1 H, C(2)H_b], 3.53 [dt, *J* = 13.8, 2.4 Hz, 1 H, C(7)H_b].

^{13}C NMR (DMSO-d_6): δ = 165.5, 139.1, 128.6, 127.9, 126.9, 62.9, 62.1, 59.6.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{10}H_{13}N_2O_3S$: 241.0641; found: 241.0640.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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