β-Tosylethylhydroxylamine: Preparation and Use as a Hydroxylamine Equivalent in Amidyl Radical-Olefin Cyclizations

Gerald D. Artman III, Jacob H. Waldman, Steven M. Weinreb*

Department of Chemistry, The Pennsylvania State University, University Park, Pennsylvania 16802, USA
Fax +1(814)8638403; E-mail: smw@chem.psu.edu

Received 8 February 2002

Abstract: An efficient three-step procedure has been developed for synthesis of β-tosylethylhydroxylamine from commercially available starting material. This compound forms hydroxamic acids which undergo amidyl radical-olefin cyclizations promoted by diethyl chlorophosphite to give functionalized β-tosylethyl-protected lactams, which can be deprotected under mild basic conditions.

Key words: lactams, radical reactions, protecting groups, cyclizations

Amidyl radical-olefin cyclizations provide useful synthetic methodology for preparation of lactams and related compounds.1,2 We recently devised a new strategy for effecting such reactions as outlined in Scheme 1.3 Treatment of an olefinic hydroxamic acid 1 with t-butylsulfinyl chloride4 in the presence of Hunig’s base and a radical trapping agent such as diphenyl diselenide, diphenyl disulfide or TEMPO leads to a functionalized lactam cyclization product 5. Mechanistically, this process involves initial formation of a sulfinate ester 2 which upon warming undergoes spontaneous homolysis to form a radical pair 3.5 Cyclization of the nitrogen radical to give carbon radical 4, followed by trapping, leads to the observed product 5. More recently, we have discovered a significant improvement in convenience and in product yields in most cases if one uses commercially available diethyl chlorophosphite as the initiator in place of t-butylsulfinyl chloride, which must be prepared.3b,4 Presumably this phosphorus-based modification occurs via a pathway similar to that shown in Scheme 1.6

As an extension of this methodology we were interested in effecting these cyclizations starting from a hydroxamic acid, which does not bear a nitrogen substituent (i.e. R = H), leading to secondary lactams. Interestingly, no examples of cyclizations of primary amidyl radicals appear to exist in the literature.1,7 Therefore, as an alternative we considered using a nitrogen protecting group which might be easily removed under conditions compatible with the type of functionality present in cyclization products 5. A few years ago we reported that the β-tosylethyl group (TSE) was useful in N-protection of various amido compounds and lactams, and can be removed via a β-elimination upon treatment with potassium t-butoxide.8,9

In order to apply this type of protection to our amidyl radical chemistry it was therefore necessary to access β-tosylethylhydroxylamine (9). In this paper we describe a convenient synthesis of this previously unknown compound and its use in amidyl radical cyclizations.

Our initial approach for preparing the hydroxylamine 9 began with commercially available 2-tosylethanol (6), which was oxidized with the Dess–Martin periodinane to afford the unstable aldehyde 7 (Scheme 2).10,11 This compound was immediately converted to the corresponding oxime 8 and then reduced with sodium p-toluenesulfinate in a methylene chloride–water mixture to yield the requisite tosyl-substituted oxime 9 in high overall yield on a multigram scale.13

Amidyl radical cyclization precursors were synthesized by first converting the appropriate γ,δ-unsaturated acid 12 to the acid chloride, and then acylating with hydroxylamine 9 to produce the TSE hydroxamic acid 13 (Scheme 3). We initially explored the cyclization of substrate 13a using t-butylsulfinyl chloride with diphenyl diselenide as the trapping reagent under our original conditions,14 which produced a 60% isolated yield of se-
leiden lactam 14a (Table 1). However, with diethyl chlorophosphite as the initiator, the yield of product 14a improved dramatically to 78%. We therefore conducted all subsequent cyclization experiments with the phosphite as the trap are listed in Table 1. We have also look briefly at some cyclizations with diphenyl disulfide and these results are also listed in the Table 1. Removal of the TSE group from the cyclization products 14 was effected by treatment with potassium tert-butoxide in THF initially at –30 °C and then slowly warming to room temperature to afford the NH lactams 15. The results of these deprotections with the various substrates, which generally proceeded in high yield, are also shown in Table 1.

Scheme 2

In conclusion, we have developed an efficient synthesis of a new hydroxyamine equivalent, β-tosylethydroxy- 
lamine (9), and have shown that it is useful in cyclizations of amidyl radicals generated via hydroxamic acids by our 
recently reported methodology. We intend to investigate other synthetic applications of this reagent.

1H and 13C NMR spectra were recorded on Bruker DPX-300, AMX-360 or DRX-400 spectrometers with TMS as an internal standard. Infrared spectra were obtained using a Perkin-Elmer 1600 FTIR. High-resolution mass spectra were performed by the Intercollegiate Mass Spectrometry Center at the Pennsylvania State University. Melting points are uncorrected. All solvents were dried and distilled according to standard procedures. Flash column chromatography was carried out using scientific Absorbents silica gel (32–63μm). Analytical and preparative thin-layer chromatography (TLC) was performed on EM Science silica gel 60 PF254 plates.

Preparation of (Toluene-4-sulfonyl)-acetalddehyde Oxime (8) from Alcohol 6

To a suspension of Dess–Martin periodinane (14.4 g, 33.9 mmol) in CH2Cl2 (100 mL), was added 6-BuOH (3.0 mL, 31 mmol). After 20 min, 2-(p-toluene sulfonyl)jethanol (6, 4.84 g, 24.2 mmol) in CH2Cl2 (40 mL) was slowly added to the suspension. After 1 h the reaction was diluted with aq. sat. NaHCO3 (50 mL) and H2O (50 mL). The resulting precipitate was filtered off and the aq layer was extracted with CH2Cl2 (3 × 50 mL). The combined organic extracts were dried (MgSO4) and concentrated to give the crude aldehyde 7. The crude aldehyde 7 was taken up in EtOH (150 mL), and hydroxylamine hydrochloride (3.29 g, 47.4 mmol) and pyridine (5.0 mL, 62 mmol) were added. The mixture was stirred for 4 h at r.t. and concentrated under reduced pressure. The resulting oil was partitioned between CH2Cl2 (100 mL) and H2O (100 mL) and the aq layer was extracted with CH2Cl2 (3 × 50 mL). The combined organic extracts were dried (MgSO4) and concentrated in vacuo. The crude aldehyde 7 was purified by flash chromatography (EtOAc–hexanes, 1:2) to give the oxime 8 as a pale yellow solid (4.35 g, 84% over two steps, 1:1 syn:anti); mp 92–94 °C.

Bromooacetalddehyde Oxime (11)

Bromooacetalddehyde dimethyl acetal (10, 35.0 mL, 0.30 mol) was added to hydroxylamine hydrochloride (100 g, 1.44 mol) in H2O (400 mL) and aq HCl (1 M, 200 mL). The biphasic solution was stirred until it became homogenous [TLC: EtOAc–hexanes, 1:2 (Rf 0.65 for oxime)] at which time the reaction mixture was diluted and extracted with EtO (3 × 500 mL). The combined organic extracts were dried (MgSO4) and concentrated to give the oxime 11 as a volatile liquid, which was used without further purification.

1H NMR (300 MHz, CDCl3): δ = 2.44 (s, 3 H), 3.94 (d, J = 6.5 Hz, 1 H), 4.21 (d, J = 5.7 Hz, 1 H), 6.89 (t, J = 5.7 Hz, 0.5 H), 7.34 (d, J = 8.4 Hz, 2 H), 7.38 (t, J = 6.5 Hz, 0.5 H), 7.73 (d, J = 8.4 Hz, 1 H), 7.78 (d, J = 8.3 Hz, 1 H), 8.31 (br s, 0.5 H), 8.55 (br s, 0.5 H).

13C NMR (75 MHz, CDCl3): δ = 145.9, 145.8, 141.1, 139.3, 136.1, 135.5, 130.5, 130.4, 128.8, 128.6, 57.3, 52.2, 22.1.


Synthesis of (Toluene-4-sulfonyl)-acetalddehyde Oxime (8) from Oxime 11

Sodium p-toluenesulfinate (80.3 g, 0.45 mol) was added rapidly to the oxime 11 in CH2Cl2–H2O (1:1, 500 mL), and the mixture was stirred at r.t. until the starting oxime was consumed based on TLC analysis [EtOAc–hexanes, 1:2 (Rf 0.45, ~4 h)]. The biphasic solu-
Table 1 Amidyl Radical Cyclizations and Subsequent Deprotections of TSE-Protected Hydroxamic Acids

<table>
<thead>
<tr>
<th>Entry</th>
<th>Hydroxamic Acid (13)</th>
<th>Cyclization (14)</th>
<th>Deprotection (15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td><img src="image1" alt="Structure" /></td>
<td><img src="image2" alt="Structure" /> 78%</td>
<td><img src="image3" alt="Structure" /> 81%</td>
</tr>
<tr>
<td>b</td>
<td><img src="image4" alt="Structure" /></td>
<td><img src="image5" alt="Structure" /> 69%</td>
<td><img src="image6" alt="Structure" /> 83%</td>
</tr>
<tr>
<td>c</td>
<td><img src="image7" alt="Structure" /></td>
<td><img src="image8" alt="Structure" /> 72%</td>
<td><img src="image9" alt="Structure" /> 77%</td>
</tr>
<tr>
<td>d</td>
<td><img src="image10" alt="Structure" /></td>
<td><img src="image11" alt="Structure" /> X = Se: 89% 69%</td>
<td><img src="image12" alt="Structure" /> X = Se: 79% 80%</td>
</tr>
<tr>
<td>e</td>
<td><img src="image13" alt="Structure" /></td>
<td><img src="image14" alt="Structure" /> 68%</td>
<td><img src="image15" alt="Structure" /> 77%</td>
</tr>
<tr>
<td>f</td>
<td><img src="image16" alt="Structure" /></td>
<td><img src="image17" alt="Structure" /> X = Se: 80%</td>
<td><img src="image18" alt="Structure" /> 80%</td>
</tr>
<tr>
<td>g</td>
<td><img src="image19" alt="Structure" /></td>
<td><img src="image20" alt="Structure" /> 67%</td>
<td><img src="image21" alt="Structure" /> X = Se: 76% 62%</td>
</tr>
<tr>
<td>h</td>
<td><img src="image22" alt="Structure" /></td>
<td><img src="image23" alt="Structure" /> X = Se: 68% 91%</td>
<td><img src="image24" alt="Structure" /> X = Se: 76% 81%</td>
</tr>
</tbody>
</table>

Sodium cyanoborohydride (3.31 g, 52.7 mmol) was added in one portion to the oxime 8 (5.70 g, 26.7 mmol) in MeOH (100 mL) with a trace of methyl orange at 0 °C. The pH was adjusted periodically to the red-yellow transition point by addition of 25% HCl in MeOH (prepared from acetyl chloride/MeOH) until the oxime had been consumed based on TLC analysis (EtOAc–hexanes, 1:2). The solution was diluted with H₂O (200 mL) and extracted thoroughly with CH₂Cl₂ (3 × 500 mL). The combined organic extracts were dried (MgSO₄) and concentrated to afford the desired oxime 11 (57.4 g, 91%, 1:1 syn:anti) as a pale yellow solid, which had data as reported above.

\(\text{N-[2-(Toluene-4-sulfonyl)-ethyl]-hydroxylamine (9)}\)

Sodium cyanoborohydride (3.31 g, 52.7 mmol) was added in one portion to the oxime 8 (5.70 g, 26.7 mmol) in MeOH (100 mL) with a trace of methyl orange at 0 °C. The pH was adjusted periodically to the red-yellow transition point by addition of 25% HCl in MeOH (prepared from acetyl chloride/MeOH) until the oxime had been consumed based on TLC analysis (EtOAc–hexanes, 1:2). The solution was diluted with H₂O (200 mL) and extracted thoroughly with CH₂Cl₂ (3 × 500 mL). The combined organic extracts were dried (MgSO₄) and concentrated to afford the desired oxime 11 (57.4 g, 91%, 1:1 syn:anti) as a pale yellow solid, which had data as reported above.
tion was basified with 1 M NaOH (pH > 10) and extracted with Et2O (5 × 50 mL). The combined extracts were dried (MgSO4) and concentrated to give the hydroxylamine 9 (5.66 g, 98%) as a colorless to light yellow solid, which was used immediately without further purification.

1H NMR (300 MHz, CDCl3): δ = 2.35 (s, 3 H), 3.19 (t, J = 6.5 Hz, 2 H), 3.35 (t, J = 6.5 Hz, 2 H), 5.33 (br, 2 H), 7.27 (d, J = 8.1 Hz, 2 H), 7.69 (d, J = 8.3 Hz, 2 H).

13C NMR (90 MHz, CDCl3): δ = 145.5, 136.3, 130.5, 128.3, 53.4, 47.5, 22.0.

HRMS: m/z [M]+ calcd for C16H21NO4S: 312.1270; found: 312.1272.

Cyclohex-3-eneacrylic Acid Hydroxy-[2-(toluene-4-sulfonyl)-ethyl]-amide (13d)
Yield: 74%; white solid; mp 125–126 °C.

1H NMR (300 MHz, CDCl3): δ = 1.63 (br m, 1 H), 1.85 (br d, J = 11.1 Hz, 1 H), 2.05–2.22 (m, 4 H), 2.44 (s, 3 H), 3.10 (br s, 1 H), 3.39 (br s, 2 H), 4.05 (t, J = 6.0 Hz, 2 H), 5.67 (s, 2 H), 7.37 (d, J = 8.0 Hz, 2 H), 7.76 (d, J = 8.0 Hz, 2 H), 7.99 (br s, 1 H).

13C NMR (75 MHz, CDCl3): δ = 177.3, 146.0, 135.5, 130.6, 128.4, 127.0, 125.9, 54.4, 43.2, 36.3, 27.5, 25.2, 21.1.

HRMS: m/z [M]+ calcd for C16H17NO3S: 324.1270; found: 324.1262.

5-Methylcyclohex-4-ene Acrylic Acid Hydroxy-[2-(toluene-4-sulfonyl)-ethyl]-amide (13e)
Yield: 57%; white solid; mp 93–94 °C.

1H NMR (400 MHz, CDCl3): δ = 1.59 (s, 3 H), 1.66 (s, 3 H), 2.20–2.29 (m, 2 H), 2.36–2.47 (m, 5 H), 3.37–3.42 (br m, 2 H), 4.01 (t, J = 5.6 Hz, 2 H), 5.08 (t, J = 6.5 Hz, 1 H), 7.36 (d, J = 8.0 Hz, 2 H), 7.76 (d, J = 8.0 Hz, 2 H), 8.18 (br s, 1 H).

13C NMR (100 MHz, CDCl3): δ = 174.9, 145.8, 135.6, 133.1, 130.6, 134.9, 123.2, 54.0, 43.0, 33.0, 26.1, 23.6, 22.1, 18.1.

HRMS: m/z [M]+ calcd for C16H17NO3S: 326.1426; found: 326.1418.

2-Methylcyclohex-4-ene Acrylic Acid Hydroxy-[2-(toluene-4-sulfonyl)-ethyl]-amide (13f)
Yield: 71%; yellow oil.

1H NMR (300 MHz, CDCl3): δ = 1.10 (d, J = 6.8 Hz, 3 H), 2.10–2.17 (m, 1 H), 2.34–2.46 (m, 4 H), 3.10–3.17 (br m, 1 H), 3.34–3.39 (br m, 2 H), 4.00–4.09 (br m, 2 H), 5.00–5.10 (m, 1 H), 7.37 (d, J = 7.8 Hz, 2 H), 7.76 (d, J = 7.9 Hz, 2 H), 7.84 (br s, 1 H).

13C NMR (75 MHz, CDCl3): δ = 176.8, 145.5, 135.9, 135.0, 130.2, 128.0, 116.5, 54.3, 42.7, 37.4, 34.8, 21.7, 16.3.

HRMS: m/z [M]+ calcd for C16H17NO3S: 312.1270; found: 312.1271.

2-Cyclopent-2-enyl-N-hydroxy-N-[2-(toluene-4-sulfonyl)ethyl]-acetamide (13g)
Yield: 70%; white solid; mp 99–100 °C.

1H NMR (400 MHz, CDCl3): δ = 1.48 (m, 1 H), 1.90 (m, 1 H), 2.35 (m, 3 H), 2.47 (m, 3 H), 3.10 (m, 1 H), 3.40 (m, 4 H), 4.08 (m, 2 H), 5.70 (br s, 1 H), 5.77 (br s, 1 H), 7.39 (d, J = 8.3 Hz, 2 H), 7.79 (d, J = 8.1 Hz, 2 H).

13C NMR (100 MHz, CDCl3): δ = 173.7, 145.6, 135.1, 134.1, 131.3, 130.2, 128.0, 54.3, 42.7, 41.6, 38.4, 31.8, 29.8, 21.7.

HRMS: m/z [M]+ calcd for C14H13NO3S: 324.1270; found: 324.1270.

Bicyclo[2.2.1]hept-5-ene-2-carboxylic Acid Hydroxy-[2-(toluene-4-sulfonyl)-ethyl]-amide (13h)
Yield: 60%; yellow gum.

IR (thin film): 3424, 1631 cm⁻¹.

1H NMR (360 MHz, CDCl3): δ = 1.34 (d, J = 8.0 Hz, 1 H), 1.45 (dd, J = 7.7, 1.9 Hz, 2 H), 1.94 (dt, J = 7.5, 3.7 Hz, 1 H), 2.47 (s, 3 H), 2.93 (s, 1 H), 3.32 (m, 4 H), 4.09 (br s, 2 H), 5.89 (br s, 1 H), 6.22 (t, J = 3.0 Hz, 1 H), 7.40 (d, J = 8.0 Hz, 2 H), 7.49 (br s, 1 H), 7.79 (d, J = 8.3 Hz, 2 H),
PAPER

β-Tosylethylhydroxylamine: Preparation and Use as a Hydroxylamine Equivalent

2061

Radical Cyclization of Hydroxamic Acids; General Procedure

The hydroxamic acid (0.3 mmol) was dissolved in CH₂Cl₂ (10 mL) with either (PhSeCl)₂ (0.6 mmol) or PhSeCl (6 mmol) and cooled to −50 °C. DIEA (0.8 mmol), (EtO)₂PCl (0.5 mmol) was slowly added and the solution warmed to r.t. over 1 h. After stirring the mixture for an additional hour at r.t., the volatile organics were removed under reduced pressure and the remaining residue was purified by flash silica gel chromatography (EtOAc–hexanes, 20:80→50:50) to afford the desired lactam.

3,3-Dimethyl-5-phenylselanyl-1-[2-(toluene-4-sulfonyl)-ethyl]-pyrrolidin-2-one (14a)

Yield: 78%, oil.

IR (thin film): 2970, 1675, 1290, 1140 cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 1.00 (s, 3 H), 1.08 (s, 3 H), 1.63 (d, J = 12.9, 7.3 Hz, 1 H), 2.02 (dd, J = 12.8, 7.3 Hz, 1 H), 2.38 (s, 3 H), 2.88 (m, 1 H), 3.20 (m, 3 H), 3.62 (m, 2 H), 3.88 (m, 1 H), 7.24 (m, 4 H), 7.46 (m, 1 H), 7.70 (m, 4 H).

13C NMR (75 MHz, CDCl₃): δ = 27.1, 26.8, 21.8, 21.2, 14.3.

13C NMR (100 MHz, CDCl₃): δ = 177.0, 145.6, 136.4, 133.7, 130.6, 129.8, 129.5, 128.0, 118.1, 54.8, 53.4, 41.2, 40.3, 35.4, 32.6, 25.4, 25.3, 22.1.


Endo isomer:

1H NMR (400 MHz, CDCl₃): δ = 1.48–1.58 (m, 3 H), 1.90 (br, s, 1 H), 2.13 (m, 2 H), 2.41 (br, s, 1 H), 2.42 (s, 3 H), 3.38 (m, 2 H), 3.56 (m, 1 H), 3.84 (br, s, 1 H), 3.93–4.00 (m, 2 H), 7.30–7.34 (m, 5 H), 7.53–7.55 (m, 2 H), 7.77 (d, J = 8.2 Hz, 2 H).

13C NMR (100 MHz, CDCl₃): δ = 177.2, 145.1, 134.7, 134.5, 130.0, 129.7, 128.8, 128.3, 128.2, 60.7, 60.6, 54.2, 43.7, 40.3, 39.4, 38.0, 27.1, 26.8, 21.8, 21.2, 14.3.


4-Phenylsulfanyl-6-[2-(toluene-4-sulfonyl)-ethyl]-6-azabicyclo[3.2.1]octan-7-one (14d, X = S)

Yield: 72%, oil, 1:1 mixture of diastereomers.

Endo Isomer:

1H NMR (400 MHz, CDCl₃): δ = 1.70–1.89 (m, 5 H), 2.17 (d, J = 11.4 Hz, 1 H), 2.42 (br, s, 1 H), 2.47 (s, 3 H), 3.29–3.36 (m, 2 H), 3.43–3.49 (m, 2 H), 3.83 (t, J = 4.5 Hz, 1 H), 3.88–3.94 (m, 1 H), 7.30–7.45 (m, 7 H), 7.77 (d, J = 8.3 Hz, 2 H).

13C NMR (100 MHz, CDCl₃): δ = 177.5, 145.1, 136.1, 134.5, 131.7, 130.0, 129.3, 127.8, 127.5, 50.4, 43.2, 35.4, 31.8, 24.8, 22.1, 21.6.

Exo Isomer:

1H NMR (400 MHz, CDCl₃): δ = 2.25–2.30 (m, 1 H), 2.42–2.48 (m, 3 H), 3.58 (pent, J = 7.1 Hz, 1 H), 3.82 (d, J = 5.8 Hz, 1 H), 3.89–3.99 (m, 2 H), 7.28–7.42 (m, 7 H), 7.77 (d, J = 8.3 Hz, 2 H).

13C NMR (100 MHz, CDCl₃): δ = 176.9, 144.8, 138.6, 133.8, 131.9, 129.9, 129.3, 127.9, 127.5, 59.7, 53.9, 48.1, 39.9, 38.1, 38.0, 25.9, 21.6, 14.1.


5-(1-Methyl-1-phenylselanylethyl)-1-[2-(toluene-4-sulfonyl)-ethyl]-pyrrolidin-2-one (14e)

Yield: 80%; oil, 1:1 mixture of diastereomers.

4-Methyl-5-phenylselanyl-1-[2-(toluene-4-sulfonyl)-ethyl]-pyrrolidin-2-one (14f)

Yield: 89%; oil, 1:5:1 mixture of diastereomers.

Exo isomer:

1H NMR (300 MHz, CDCl₃): δ = 1.13 (s, 3 H), 1.16 (s, 3 H), 2.04 (d, J = 16.6 Hz, 1 H), 2.43–2.53 (m, 4 H), 3.08–3.32 (m, 5 H), 3.55–3.63 (m, 2 H), 7.27–7.37 (m, 5 H), 7.51–7.54 (m, 2 H), 7.73 (d, J = 8.3 Hz, 2 H).

13C NMR (75 MHz, CDCl₃): δ = 174.4, 144.9, 135.8, 133.4, 130.1, 130.0, 129.5, 129.3, 127.9, 127.7, 66.9, 53.3, 45.2, 36.7, 35.3, 29.6, 28.9, 23.1, 21.6.

HRMS: m/z [M⁺] calcd for C₂₂H₂₅NO₃Se: 452.0956; found: 452.0966.
7.36 (m, 5 H), 7.57–7.60 (m, 2 H), 7.70 (d, J = 8.0 Hz, 2 H), 3.52–3.57 (m, 1 H), 7.26–7.33 (m, 5 H), 7.38–7.40 (m, 2 H), 2.75–2.86 (m, 4 H), 2.90–2.96 (m, 1 H), 3.40 (d, J = 4.9 Hz, 1 H), 2.42 (s, 3 H), 2.50 (dd, J = 12.2, 4.5 Hz, 1 H), 2.45 (t, J = 6.9 Hz, 2 H). HRMS: m/z [M+] calcd for C13H17NOSe: 284.0554; found: 284.0555.

4-Methyl-5-phenylselenylmethylpyrrolidin-2-one (15c)
Yield: 77%; oil; 1:5:1 mixture of diastereomers.
1H NMR (400 MHz, CDCl3): δ = 1.05 (s, 3 H), 1.11 (s, 3 H), 2.19 (s, 2 H), 2.68 (dd, J = 12.4, 11.2 Hz, 1 H), 3.09 (dd, J = 12.5, 2.9 Hz, 1 H), 3.36 (dd, J = 11.2, 2.9 Hz, 1 H), 6.03 (br s, 1 H), 7.27–7.30 (m, 3 H), 7.48–7.52 (m, 2 H).
13C NMR (100 MHz, CDCl3): δ = 176.0, 133.4, 129.4, 128.3, 127.8, 63.0, 46.3, 38.8, 29.1, 27.2, 22.6.
HRMS: m/z [M+] calcd for C14H13NOSe: 280.0554; found: 280.0569.

4-Phenylselenyl-6-azabicyclo[3.2.1]octan-7-one (14f)
Yield: 67%; oil.
1H NMR (360 MHz, CDCl3): δ = 1.45 (m, 1 H), 1.79 (m, 1 H), 1.96–2.05 (m, 2 H), 2.17 (m, 1 H), 2.42 (s, 3 H), 2.50 (dd, J = 17.8, 10.5 Hz, 1 H), 2.77 (m, 1 H), 3.04 (m, 1 H), 3.13–3.20 (m, 2 H), 3.51 (m, 1 H), 3.82 (m, 1 H), 3.94 (dd, J = 7.8, 1.9 Hz, 1 H), 7.32–7.35 (m, 5 H), 7.58–7.61 (m, 2 H), 7.73 (d, J = 8.3 Hz, 2 H).
13C NMR (90 MHz, CDCl3): δ = 174.5, 144.9, 135.9, 135.0, 129.9, 129.5, 128.4, 128.3, 127.9, 69.2, 52.0, 45.7, 37.5, 35.6, 34.1, 32.9, 31.1, 21.6.
HRMS: m/z [M+] calcd for C10H8NOSe: 246.0810; found: 246.0816.

Removal of the TSE Group; General Procedure
The TSE-protected lactam (1 equiv) was dissolved in THF (5 mL) and cooled to –30 °C. t-BuOK (4 equiv, 1M in THF) was then added and the mixture was slowly warmed to r.t.. Following 1 h at r.t., H2O (20 mL) was added to the mixture and the resulting ag solution was extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried (MgSO4) and concentrated in vacuo. The residue was purified by flash silica gel chromatography to afford the desired lactam.
1H NMR (400 MHz, CDCl₃): δ = 1.30 (s, 3 H), 1.34 (s, 3 H), 1.89–1.96 (m, 1 H), 2.00–2.09 (m, 1 H), 2.35–2.41 (m, 1 H), 3.60 (t, J = 7.2 Hz, 1 H), 6.33 (br s, 1 H), 7.29–7.33 (m, 2 H), 7.40 (tt, J = 7.5, 1.2 Hz, 1 H), 7.60 (dd, J = 7.9, 1.2 Hz, 2 H).

13C NMR (100 MHz, CDCl₃): δ = 178.0, 138.7, 129.6, 129.4, 126.6, 62.1, 39.6, 31.5, 26.5, 23.3, 22.6.


3-Methyl-5-phenylselenylmethylpyrrolidin-2-one (15f)

Yield: 80%; oil; 1:1 mixture of diastereomers.

1H NMR (360 MHz, CDCl₃): δ = 1.09–1.13 (m, 3 H), 1.29–1.32 (m, 0.5 H), 1.83–1.89 (m, 0.5 H), 2.00–2.03 (m, 0.5 H), 2.36–2.49 (m, 1.5 H), 2.75–2.86 (m, 1 H), 2.91–3.01 (m, 1 H), 3.59–3.67 (m, 1 H), 4.00 (dd, J = 7.8, 2.6 Hz, 1 H), 6.07 (br s, 1 H), 7.21–7.26 (m, 3 H), 7.49–7.51 (m, 2 H).

13C NMR (100 MHz, CDCl₃): δ = 152.1, 39.6, 31.5, 26.5, 23.3, 22.6.


2-Phenylsulfanyl-4-azatricyclo[4.2.1.0²,⁰]nonan-5-one

Synthesis 2002, No. 14, 2057–2063 ISSN 0039-7881 © Thieme Stuttgart · New York

Acknowledgement

We are grateful to the National Institutes of Health (CA-34303) for financial support of this research.

References


(7) We have made a few attempts to effect such a cyclization but without success.


(10) Attempted PCC oxidation of alcohol 6 led only to the dimeric ester i. Swern oxidation led to a complex mixture (Figure). 

Figure


(13) This reaction might involve nucleophilic addition to an intermediate vinylnitroso compound: Gilchrist, T. L. Chem. Soc. Rev. 1983, 11, 53; and references cited.