Synthesis of Sedamine by Cycloisomerisation of an Allenic Hydroxylamine

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Abstract: Isoxazolidines have been prepared in a stereoselective manner by treatment of allenic hydroxylamines with silver(I). This methodology has been used in a short synthesis of the alkaloid (+)-sedamine.

Key words: cyclisation, allenes, heterocycles, alkaloids, stereoselectivity

We recently reported a synthesis of the alkaloid sedamine (1) (Figure 1), which involved the cyclocarbonylation of a hydroxylamine onto an alkene, with a subsequent cleavage of the N–O bond.¹ It may thus be considered as a variation on the idea of a tethered nitrogen.²

![Figure 1 Sedamine 1](image)

The drawback of this reaction is that, while it requires a palladium catalyst, more than two equivalents of copper(II) are required due to the redox nature of the process. We, therefore, sought a process which would deliver a similar cyclisation, but with greater atom efficiency. One way to do this would be by silver-mediated intramolecular addition to an allene, a reaction originally reported by Claesson, and extended by others, notably, Reissig, Arseniyadis and Gore, Gallagher, and Marshall.³ Such a process would be expected to yield an isoxazolidine bearing a pendant alkene substituent. It could, therefore, be conceived that the synthesis of sedamine could be continued using a ring-closing alkene metathesis reaction to introduce the additional carbon atoms.

Numerous syntheses of both racemic and optically active sedamine have been reported.⁴ While some potentially useful biological activity has been reported for sedamine (1),⁵ it has also become something of a ‘benchmark molecule’ for the demonstration of synthetic methodology.

The desired allenic hydroxylamines 3 could be prepared by Mitsunobu reaction of the corresponding allenic alcohols 2 with N-hydroxyphthalimide.⁶ Cleavage of the phthalimide (with hydrazine hydrate) yielded the free NH₂ compounds 2c, which could be N-functionalised as required (Scheme 1). To explore the generality of the reaction, the higher and lower homologues, 4 and 5, were also prepared, using analogous chemistry.⁷

The N-unsubstituted compound 2c and the N-sulfonyl compound 3c both failed to yield any cyclised product. In contrast, N-carbamates 3a and 3b cyclised cleanly but slowly on treatment with 10–20 mol% silver nitrate in wet acetone (Table 1) to give the isoxazolidines 6 (Scheme 2). The use of other silver salts, such as AgBF₄, gave no advantage. Pleasingly, the reactions required no protection

![Scheme 1 Reagents and conditions](image)

![Scheme 2](image)

<table>
<thead>
<tr>
<th>Allene</th>
<th>PG</th>
<th>R</th>
<th>Product, yield (%)</th>
<th>Ratio (cis/trans)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2c</td>
<td>H</td>
<td>Ph</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>3a</td>
<td>Boc</td>
<td>Ph</td>
<td>6a, 98</td>
<td>7:1</td>
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<tr>
<td>3b</td>
<td>Cbz</td>
<td>Ph</td>
<td>6b, 93</td>
<td>5:1</td>
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<tr>
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<td>Ph</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>7</td>
<td>Boc</td>
<td>Me</td>
<td>8, 83</td>
<td>4:1</td>
</tr>
</tbody>
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from oxygen or atmospheric moisture. The only precaution taken was the exclusion of light. In all cases, an inseparable mixture of cis- and trans-isoxazolidines 6 was formed in good yield. The cis-isomer was the major isomer in all cases, Gold(III) chloride8 was also employed as a catalyst. In this case the reaction was less clean, perhaps due to the stronger Lewis acidity of this reagent. The corresponding methyl substituted substrate 7 also cyclised with useful stereoselectivity.

The higher homologue 4 failed to cyclise and was recovered unchanged. The lower homologue 5 also failed to cyclise, but was converted into its hydration product, methyl ketone 9 (Scheme 3).

With the cyclisation methodology established, the synthesis of sedamine (1) commenced. While the initial studies of this methodology employed racemic compounds, for the purpose of the synthesis of sedamine, allene 3a was prepared as its S-enantiomer, starting from (S)-styrene oxide.9 Cyclisation as described, gave the isoxazolidine 6a as an inseparable cis/trans mixture. With the intention of construction of the six-membered ring, the Boc group was removed under the usual conditions and the nitrogen atom of isoxazolidine 10 was alkylated with 1-bromobut-3-ene (Scheme 4). At this point, the two stereoisomers of 11 could be easily separated by column chromatography. The major isomer was subjected to ring-closing metathesis,10 but no product could be obtained using either the first- or the second-generation Grubbs catalysts. As it is known that nitrogen lone pairs may coordinate to the ruthenium and inhibit catalysis,11 the nitrogen was quaternised by treatment with methyl tosylate. The quaternary salt 12 could be easily separated by column chromatography. The quaternary salt 12 was obtained as a mixture of diastereoisomers, the major one having the methyl cis to the vinyl group (NOE). Neither diastereoisomer, however, underwent ring-closing metathesis using either of the Grubbs catalysts.

Consequently, the N–O bond of isoxazolidine 11 was cleaved with zinc and acetic acid. The resulting amino alcohol 13 was reprotected as cyclic carbamate 14, which underwent ring-closing metathesis very efficiently on treatment with the Grubbs first-generation catalyst12 (Scheme 5). The synthesis was completed by reduction of the carbamate to the desired methyl group (LiAlH4) and reduction of the alkene (H2, Pd/C). No benzylic reduction was observed in this last transformation, presumably due to the presence of a basic nitrogen.13 The spectroscopic data for the synthetic sedamine (1) were in good agreement with those previously reported.

In conclusion, this variation on the Claesson cyclisation provides a simple and easily executed route to functionalised syn-1,3-amino alcohols that are useful intermediates for alkaloid synthesis. This allows an efficient synthesis of sedamine (1). The strategy is applicable to related alkaloids.

THF and CH2Cl2 were either distilled according to standard procedures or obtained from a solvent purifier. Other reagents and solvents were commercial and used as received. Petroleum ether (PE) used refers to the fraction boiling between 40 and 60 °C.

IR spectra were recorded on a Nicolet Magna 550 or Bio-Rad FTS 165 spectrometer, either neat or as Nujol mulls using NaCl plates.141H NMR spectra were recorded on a Bruker AM500 or DPX300 spectrometer at 300 MHz with residual protic solvent as the reference.1513C NMR spectra were recorded at the corresponding frequencies on the same spectrometers. Chemical shifts are in ppm and coupling constants; J are in Hz. Mass spectra were recorded on a Finnigan GCQ instrument at 70 eV and high-resolution mass spectra on a Micromass GCT instrument or a Finnigan MAT95XP instrument. Specific rotations, [α]D, were recorded on an Optical Activity Ltd AA-1000 or a Jasco P-1030 polarimeter and are given with units of 10−1 deg cm2g−1. Elemental analysis was carried out at the University of Exeter.

1H NMR (300 MHz, CDCl3): δ = 7.25–7.35 (5 H, m, ArH), 4.67 (1 H, d, J = 6.5 Hz, =CH), 4.76 (1 H, t, J = 1.6, 6.6 Hz, PhCH2), 2.54–2.70 (2 H, m, C=CH2), 1.87 (1 H, m, CH3), 1.47 (9 H, s, t-C5H11).

13C NMR (75 MHz, CDCl3): δ = 216.0, 148.9, 139.4, 137.0, 135.2, 134.4, 133.2, 130.8, 88.7, 86.1, 75.6, 34.9.

MS (Cl): m/z (%) = 361 (MH+, 100), 291 (92), 225 (16), 98 (14).

HRMS: m/z calcd for C19H20NO3 (MH+): 310.1489; found: 310.1489.

13-N-(1-phenylbuta-3,4-dienyl)hydroxylamine (5)

The title compound (312 mg, 76%) was obtained as a light yellow oil from the lower homologue of allene alcohol 2a via its hydroxylamine derivative by the method described for 3a.

1H NMR (300 MHz, CDCl3): δ = 7.39 (5 H, m, ArH), 7.14 (1 H, br s, NH), 5.48 (1 H, dt, J = 7.8, 6.6 Hz, CH=CH2), 5.32 (1 H, br d, J = 7.8 Hz, PhCH2), 4.89 (1 H, ddd, J = 1.6, 6.6, 11.4 Hz), 4.83 (1 H, ddd, J = 1.7, 6.6, 11.4 Hz), 1.48 (9 H, s, t-C5H11).

13C NMR (75 MHz, CDCl3): δ = 210.2, 156.9, 139.0, 128.9 (2 C), 127.9, 90.9, 85.9, 82.1, 77.3, 28.6.

MS (EI): m/z (%) = 582 (MH+, 20), 310 (11), 299 (100), 137 (45).

HRMS: m/z calcd for C15H19NO3 (MH+): 276.1443; found: 276.1450.
2-tert-Butyloxy carbonyl-5-phenyl-3-vinylsioxazolidine (6a): Typical Procedure

A solution of the Boc-protected hydroxylamine 3a (2.097 g, 7.63 mmol), AgNO₃ (0.259 g, 1.53 mmol) and 1,1,3,3-tetramethylguanidine (96 μL, 0.76 mmol) in acetone–H₂O (5:1, 25 mL) was stirred in the absence of light at r.t. for 30 h. The mixture was partitioned between EtOAc (20 mL) and H₂O (20 mL). The aqueous layer was extracted with EtOAc (2 × 20 mL). The organic extracts were combined, washed sequentially with H₂O (10 mL) and brine (10 mL), dried (MgSO₄), and the solvent removed in vacuo to give the title compound (2.087 g, 98%) as a colourless oil.

IR (neat): 3075, 1726 cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 7.35 (5 H, m, ArH), 5.91 (1 H, ddd, J = 7.0, 10.0, 17.1 Hz, CH₂=CH₂), 5.29 (2 H, dd, J = 10.0, 6.2 Hz, PhCH₂ON), 4.52 (1 H, dd, J = 10.4, 17.1 Hz, CH₂=), 4.50 (1 H, dd, J = 7.3, 12.6, 15.2 Hz, CH₂), 2.20 (1 H, m, CH), 2.14 (1 H, d, J = 7.0, 10.0, 12.5 Hz, CH₂).

13C NMR (75 MHz, CDCl₃): δ = 158.0, 137.7, 136.4, 129.1, 129.0, 128.9, 128.7, 127.3, 116.4, 83.8, 64.3, 43.1, 44.1.

MS (CI): m/z (%) = 310 (M⁺, 39), 266 (34), 107 (92).

HRMS: m/z calcd for C₁₉H₂₀NO₃ (MH⁺): 310.1443; found: 310.1441.

Treatment of allene 5 with AgNO₃ as described for the preparation of 6a gave the ketone 9.

1H NMR (300 MHz, CDCl₃): δ = 7.30 (5 H, m, ArH), 5.24 (1 H, dd, J = 5.5, 7.9 Hz, PhC=CH₂), 3.13 (1 H, dd, J = 8.1, 16.2 Hz, CH₂), 2.73 (1 H, dd, J = 5.5, 16.2 Hz, CH₂=), 2.21 (3 H, s, CH₃), 1.48 (9 H, s, t-C₄H₉).

13C NMR (75 MHz, CDCl₃): δ = 204.6, 155.5, 138.1, 127.6, 127.5, 126.0, 82.7, 80.9, 49.9, 29.6, 27.1.

Phenyl-3-vinylsioxazolidine (10)

Trifluoroacetic acid (3.2 mL, 42.1 mmol) was added dropwise to the isoxazolidine 6a (1.16 g, 4.21 mmol) with stirring, and the mixture was stirred at r.t. for 2 h. The volatiles were removed in vacuo and the residue was neutralised with aq sat. NaHCO₃ (1 mL). The mixture was partitioned between EtOAc (10 mL) and H₂O (5 mL). The aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic extracts were washed with H₂O (10 mL) and brine (5 mL), dried (MgSO₄), and the solvent removed in vacuo to give the title compound (0.737 g, 100%) as a light yellow oil.

IR (neat): 3202, 3007, 3063, 1644, 1603 cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 7.1–7.35 (5 H, m, ArH), 5.87 (1 H, ddd, J = 7.0, 10.2, 17.1 Hz, CH₂=CH₂), 5.28 (1 H, dd, J = 10.2, 17.1 Hz, CH₂=CH₂), 5.14 (1 H, br s, NH), 5.05 (1 H, t, J = 7.6 Hz, PhCH₃), 4.10 (1 H, q, J = 7.0, 7.0 Hz, CH₂), 2.88 (1 H, t, J = 7.6, 12.5 Hz, CH₂), 2.04 (1 H, dt, J = 7.6, 12.6 Hz, CH₂). [minor isomer: δ = 2.42 (2 H, dt, J = 7.3, 12.6, 15.2 Hz, CH₂)].

13C NMR (75 MHz, CDCl₃): δ = 141.1, 140.8, 129.0, 128.3, 126.6, 116.7, 84.2, 64.0, 45.0.

MS (Cl): m/z (%) = 176 (MH⁺, 100), 143 (65), 122 (100), 107 (27), 104 (40).

HRMS: m/z calcd for C₁₁H₁₄NO (MH⁺): 176.1075; found: 176.1082.

(3R,5S)-2-But-3-enyl-5-phenyl-3-vinylsioxazolidine (11)

1-Bromobut-3-ene (195 mmol) in DMF (16 mL) and the mixture was stirred at 50 °C for 14 h. An additional amount of 1-bromobut-3-ene (195 mmol) in DMF (16 mL) was added dropwise to the isoxazolidine 6a (1.16 g, 4.21 mmol) with stirring, and the mixture was stirred at r.t. for 2 h. The volatiles were removed in vacuo and the residue was neutralised with aq sat. NaHCO₃ (1 mL). The mixture was partitioned between EtOAc (10 mL) and H₂O (5 mL). The aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic extracts were washed with H₂O (10 mL) and brine (5 mL), dried (MgSO₄), and the solvent removed in vacuo to give the title compound (0.737 g, 100%) as a light yellow oil.

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13C NMR (75 MHz, CDCl₃): δ = 141.1, 140.8, 129.0, 128.3, 126.6, 116.7, 84.2, 64.0, 45.0.

MS (Cl): m/z (%) = 176 (MH⁺, 100), 143 (65), 122 (100), 107 (27), 104 (40).

HRMS: m/z calcd for C₁₁H₁₄NO (MH⁺): 176.1075; found: 176.1082.

Cycloisomerisation of Allenic Hydroxylamines

2-(But-3-ynyl)-2-methyl-5-phenyl-3-vinylisozaxolidin-2-im Tosylate (12)

A mixture of the isozaxolidine (11) (47 mg, 0.21 mmol) and methyl tosylate (39 mg, 0.21 mmol) was stirred at 70 °C for 2 days. The mixture was then dissolved in MeOH (5 mL) and partitioned with hexane (5 mL) to form two organic layers. The MeOH layer was evaporated in vacuo to give the title compound as a viscous oil, which was used without further purification.

1H NMR (400 MHz, CDCl3): δ (major isomer) = 7.76 (2 H, d, J = 8.1 Hz, tosyl ArH), 7.25–7.4 (5 H, m, ArH), 7.10 (2 H, d, J = 7.9 Hz, tosyl ArH), 6.14 (1 H, ddd, J = 8.3, 9.8, 17.1 Hz, CH=CH=CH2), 5.8–5.9 (2 H, m), 5.60–5.74 (3 H, s, =CH2 CHN), 5.12 (1 H, d, J = 12 Hz, =CH), 3.00 (1 H, d, J = 10.2 Hz, =CH2), 3.98–4.10 (1 H, m, CH), 2.37–2.38 (1 H, m, s, NCH2), 1.50–2.0 (3 H, m, CH3), 2.24 (3 H, m, ArCH).


13C NMR (75 MHz, CDCl3): δ = 126.4, 118.4, 116.1, 71.7, 56.9, 45.9, 33.2.

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References

(12) Cossey et al. also employed RCM to form the piperidine ring, but at a different position, see ref. 4i.