# Stereoselective Synthesis of Pyrrolizidine Alkaloids *via* Substituted Nitrones

**David Lathbury and Timothy Gallagher**

*School of Chemistry, University of Bath, Bath BA2 7AY, U.K.*

The 3,5-disubstituted pyrrolizidine alkaloid (**8**) has been synthesised using, as a key step, the cyclisation of the allenic oxime *E*-(**3**) to generate a 5-substituted nitrone (**4**); under the same cyclisation conditions *Z*-(**3**) reacts *via* oxygen to give (**9**).

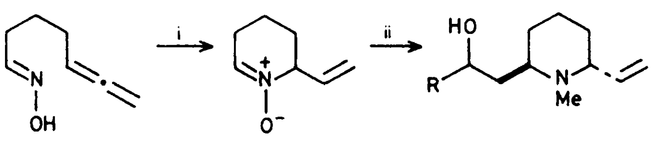


Nitrones, as a class of 1,3-dipoles, have increasingly proved to be valuable intermediates in the construction of a diverse range of alkaloids.[1] Although heterocyclic nitrones, especially unsubstituted examples, have also found applications in this area, general access to a variety of these cyclic dipoles is more limited. For example, oxidation of *N*-hydroxy-2-substituted piperidines or pyrrolidines with mercury(II) oxide is prone to give a mixture of isomeric nitrones.[2] A lack of regioselectivity in this oxidation step is the major shortcoming of using substituted nitrones of this type.[3]

The silver(I)-catalysed cyclisation of ω-allenic oximes [*e.g.* (**1**)] does, however, provide a route to isomerically pure cyclic nitrones.[4]† Intermediates such as (**2**) have been trapped by various 1,3-dipolarophiles to give, ultimately, *trans*-2,6-disubstituted piperidines (Scheme 1).[5]

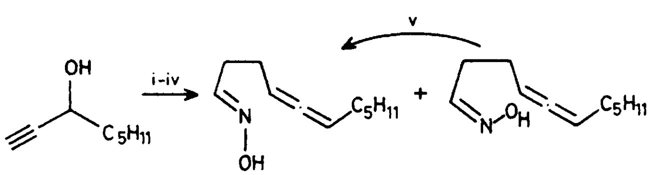
We now report that this methodology is also of value in the construction of *trans*-2,5-disubstituted pyrrolidines and this has been illustrated by a stereoselective synthesis of 3α,5α,7aβ-hexahydro-3-heptyl-5-methyl-1*H*-pyrrolizine (**8**). This unusual pyrrolizidine alkaloid was isolated from *Solenopsis xenoveneum* (a variety of thief ant) and has been assumed to be a component of the ant's venom.[6]

The racemic allenic oxime *E*-(**3**) was prepared, in five steps, from oct-1-yn-3-ol as a readily separable mixture of *E*- and *Z*-isomers (Scheme 2).‡ The efficiency of this sequence was improved by recycling *Z*-(**3**), by allowing a chloroform solution of *Z*-(**3**) to stand overnight. This resulted in a 1 : 1 equilibrium mixture of *E*- and *Z*-(**3**) which were once again separated by flash chromatography.



(**1**) (**2**)

**Scheme 1.** *Reagents*: i, $AgBF_4$, $CH_2Cl_2$, 20 °C, 2 h; ii, (a) $RCH{=}CH_2$, (b) MeI, (c) $LiAlH_4$.

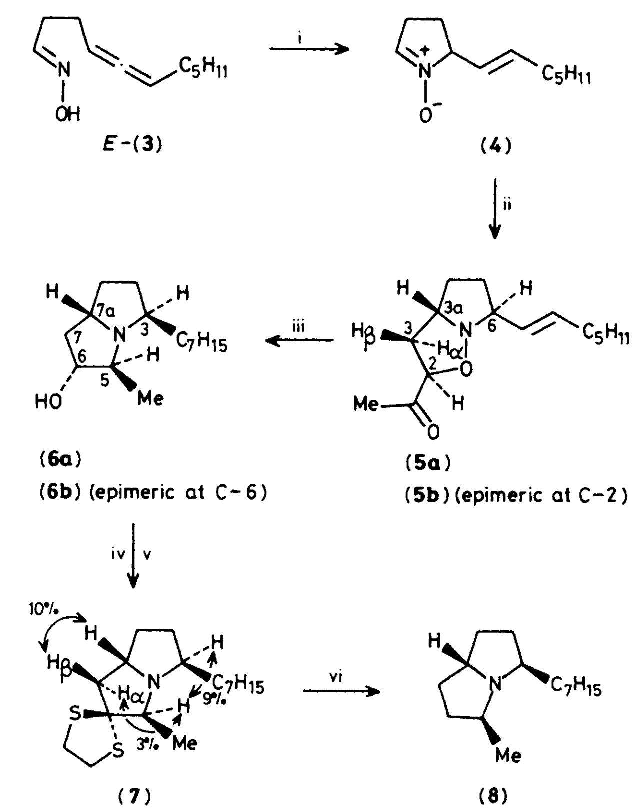


*E*-(**3**) *Z*-(**3**)

**Scheme 2.** *Reagents:* $MeC(OEt)_3$, pivalic acid, 110 °C, 15 h (77%); ii, $LiAlH_4$, ether, −60 to 20 °C over 30 min (97%); iii, $p$-$MeC_6H_4SO_2Cl$, pyridine, 0 °C, then KCN, $Me_2SO$, 75 °C, 2.5 h (78%); iv, $Bu^i{}_2AlH$, ether, 20 °C, 1 h and quenched with $NH_2OH{\cdot}HCl$, NaOAc, $H_2O$ (76%); v, chloroform, overnight, silica chromatography.

Cyclisation of *E*-(**3**) with a catalytic amount of silver tetrafluoroborate gave the 5-substituted nitrone (**4**) which was trapped with methyl vinyl ketone to give (**5a**)/(**5b**) (48% yield) as a 1 : 1 mixture of isomers (Scheme 3). The structure of (**5a**) was established by ¹H n.m.r. spectroscopy [nuclear Overhauser enhancement (n.O.e.) difference]. Irradiation of 2-H (δ 4.44, t, *J* 7.6 Hz) showed an enhancement of both 3α-H (5%, δ 2.17, ddd, *J* 4.6, 8.0, and 12.6 Hz) and 6-H (4%, δ 3.60, m) and irradiation of 3a-H resulted in enhancement of 3β-H (4.5%, δ 2.46, ddd, *J* 7.0, 8.0, and 12.6 Hz). The stereochemical assignment at C-6 of (**5b**) could not be unambiguously determined but the *trans* relationship between C-3a and C-6 was confirmed by subsequent transformation of (**5b**) to (**7**).

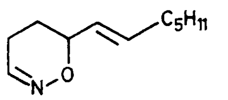
Hydrogenation of (**5a**) and (**5b**) resulted in (i) reduction of the unwanted double bond; (ii) N–O bond cleavage; and (iii) an intramolecular reductive amination to give (**6a**) and (**6b**)




**Scheme 3.** *Reagents*: i, $AgBF_4$, $CH_2Cl_2$, 20 °C, 3 h; ii, $MeC({:}O)CH{=}CH_2$, tetrahydrofuran, 20 °C, 15 h [48% from *E*-(**3**)]; iii, $H_2$, $PdCl_2$, ethanol, 20 °C, 18 h (76%); iv, Jones reagent, acetone, 1.5 h, followed by $HSCH_2CH_2SH$, $BF_3{\cdot}Et_2O$, $CH_2Cl_2$, 20 °C, 2.5 h (48%); v, W-2 Raney Ni, ethanol, 40 min (61%).

† The oxidation of isoxazolidines, with *m*-chloroperoxybenzoic acid, provides a valuable source of isomerically pure cyclic nitrones. See ref. 1 and N. A. LeBel, M. E. Post, and D. Hwang, *J. Org. Chem.*, 1979, **44**, 1819.

‡ All new compounds gave satisfactory spectral (i.r., ¹H n.m.r.) and high resolution mass data. All ¹H n.m.r. spectra refer to 400 MHz ($CDCl_3$).



(9)

respectively (76% yield). Jones oxidation of each of these alcohols gave the same unstable ketone [$\nu_{max.}$ (film) 1740 $cm^{-1}$] which was immediately converted into the 1,3-dithiolane (**7**) [48% from (**6a**)/(**6b**)]. The structure of (**7**) is consistent with its spectral parameters [δ 3.62 (1H, m, 7a-H), 3.28—3.18 (4H, m, $SCH_2CH_2S$), 2.98 (1H, q, *J* 6.2 Hz, 5-H), 2.70 (1H, m, 3-H), 2.50 (1H, dd, *J* 6.2 and 12.3 Hz, 3β-H), 1.99 (1H, dd, *J* 9.4 and 12.3 Hz, 3α-H), 2.03—1.90 (2H, m, 1β- and 2α-H), 1.54—1.41 (3H, m), 1.30—1.19 (11H, m), 1.21 (3H, d, *J* 6.2 Hz, 5-Me), and 0.86 (3H, t, *J* 7 Hz)]. The important nuclear Overhauser enhancements that were observed for (**7**) are also shown in Scheme 3. Desulphurisation of (**7**) gave (±)-(**8**) in 61% yield and the spectral data (i.r., mass, $^1H$ and $^{13}C$ n.m.r.) of synthetic (**8**) were identical to those previously reported.[6]

We have also examined the reaction of *Z*-(**3**) with silver(I). In this case a clean cyclisation ($AgBF_4$, $CH_2Cl_2$, 20 °C, 2 h) was observed to give (**9**) [90% yield, $\nu_{max.}$ (film) 1660 and 1615 $cm^{-1}$; δ 7.23 (1H, m), 5.80 (1H, dtd, *J* 0.9, 7.0, and 15.3 Hz), 5.49 (1H, tdd, *J* 1.5, 7.0, and 15.3 Hz), 4.20 (1H, ddd, *J* 2.3, 7.0, and 10.0 Hz), 2.35—1.70 (6H, m), 1.45—1.20 (6H, m), and 0.89 (3H, t, *J* 7 Hz)]. This is in contrast to the piperidine case illustrated in Scheme 1, in which cyclisation of the oxime, *via* oxygen, to generate a seven membered ring was not observed. Both *E*- and *Z*-(**1**) serve as precursors of the nitrone (**2**) presumably as a result of slow isomerisation of *Z*-(**1**) to *E*-(**1**) under the reaction conditions.

We thank Drs. O. Howarth and E. Curzon of Warwick University for high field $^1H$ n.m.r. spectra and the S.E.R.C. for generous financial support.

*Received, 14th March 1986; Com. 335*

## References

1 J. J. Tufariello, *Acc. Chem. Res.*, 1979, **12**, 396; J. J. Tufariello, H. Meckler, and K. P. A. Senoratne, *Tetrahedron*, 1985, **41**, 3447.

2 The limitations of this oxidation process have been recognised: see J. J. Tufariello in '1,3-Dipolar Cycloaddition Chemistry,' ed. A. Padwa, Wiley, New York, 1984, ch. 9.

3 For related oxidation processes see H. Mitsui, S. Zenki, T. Shiota, and S.-I. Murahashi, *J. Chem. Soc., Chem. Commun.*, 1984, 874, and references therein.

4 D. Lathbury and T. Gallagher, *Tetrahedron Lett.*, 1985, 6249; J. Grimaldi and A. Cormons, *ibid.*, 1985, 825.

5 For recent approaches to the stereoselective synthesis of 2,6-disubstituted piperidines see Y. C. Hwang, M. Chu, and F. W. Fowler, *J. Org. Chem.*, 1985, **50**, 3885; K. Fugami, Y. Morizawa, K. Oshima, and H. Nozaki, *Tetrahedron Lett.*, 1985, 857; S. Arsenijadis and J. Sartoretti, *ibid.*, 1985, 729; W. Carruthers, M. J. Williams, and M. T. Cox, *J. Chem. Soc., Chem. Commun.*, 1984, 1235.

6 T. H. Jones, M. S. Blum, H. M. Fales, and C. R. Thompson, *J. Org. Chem.*, 1980, **45**, 4778. A synthesis of (−)-(**8**) has been reported: S. Takano, S. Otaki, and K. Ogasawara, *J. Chem. Soc., Chem. Commun.*, 1983, 1772.