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A NEW APPROACH TO CYCLIC NITRONES: APPLICATION TO THE SYNTHESIS OF α,α'-DISUBSTITUTED PIPERIDINES AND PYRROLIDINES

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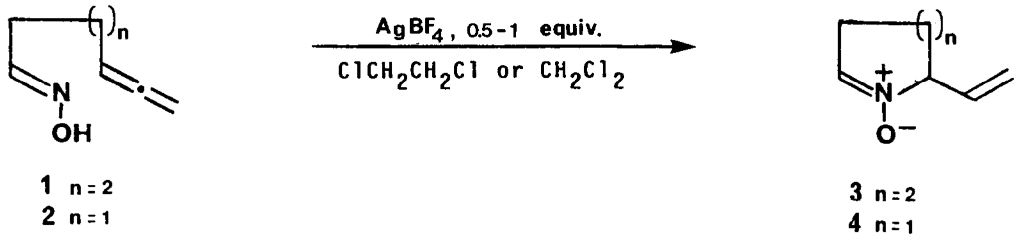
Summary. A new synthesis of nitrones is described. This involves the Ag(I)-catalysed cyclisation of allenic oximes, the resulting nitrones being trapped by various 1,3-dipolarophiles.

The importance, in both an inter- and intramolecular sense, of the 1,3-dipolar cycloaddition reaction in organic synthesis is well documented.[1] Nitrones have proven to be a particularly useful class of 1,3-dipoles since they are relatively stable and have been shown to give cycloadducts that are synthetically quite flexible.[2] However, methods of preparing nitrones, especially cyclic members of the group, are limited to relatively few routes.[3] Although the alkylation of an oxime with, for example, an alkyl halide or tosylate is attractive, the major disadvantage of this route is that oximes, being ambident nucleophiles, can react at either oxygen or nitrogen. The efficiency of this process for nitrone formation, i.e. alkylation on nitrogen, depends on both the substrates and the conditions used.[4] Successful application of this reaction to the synthesis of several cyclic nitrones has been reported although examples where the product carries further functionality, in addition to the 1,3-dipole itself, are rare.[5]

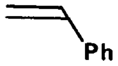
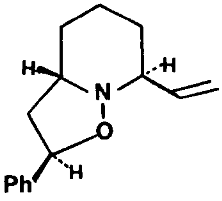
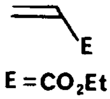
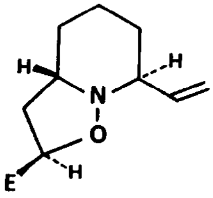
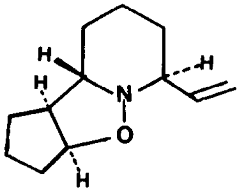
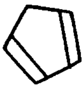
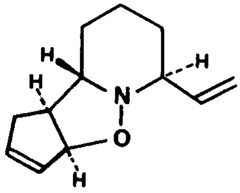
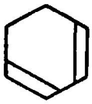
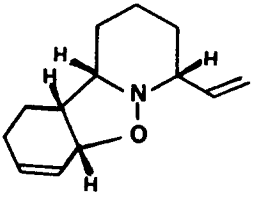
As part of a programme directed towards the use of allenes in the synthesis of functionalised heterocycles we have prepared the allenic oximes, **1** and **2**. We now report that both **1** and **2** undergo a facile silver(I)-catalysed cyclisation, via nitrogen, to give the novel vinyl substituted nitrones, **3** and **4**, respectively (Scheme 1).

SCHEME 1



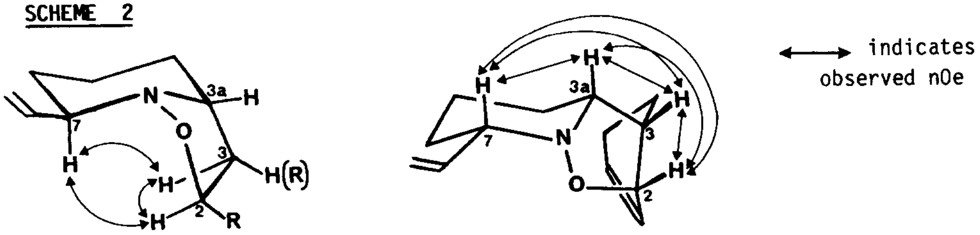
Oxime **1** was prepared from 5,6-heptadienal as a 1:1 mixture of E- and Z-isomers. Although these could be separated, both isomers underwent cyclisation in the presence of silver tetrafluoroborate.[6] The resulting nitrone **3**, though not sufficiently stable to isolate, was trapped, in fair yield, with a range of 1,3-dipolarophiles to give adducts **5(a-e)** (Table 1).

TABLE 1

1,3-Dipolarophile	Cycloadduct	**5** (yield)
		**5a** (42%)
		**5b** (25%)
		**5c** (29%)
		**5d** (43%)
		**5e** (35%)

An important feature of the dipolar cycloaddition reaction is the generation of two stereocentres at C_{3a} and C_7 in **5(a-e)**. Thus reductive cleavage of the N-O bond allows access to a 2,6-disubstituted piperidine (or 2,5-disubstituted pyrrolidine, see **6** below) with defined stereochemistry at both carbon atoms flanking nitrogen as well as in the side chain itself.[7] Determination of the structure of adducts **5(a-e)**, both the regiochemistry and relative stereochemistry, is therefore crucial when considering any application of this overall sequence. The assignment of **5(a-e)** is based primarily upon 2D COSY and NOE difference spectroscopy (NOEDS).[8] In the case of **5(a-d)** irradiation of H_2 resulted in an enhancement of the signals corresponding to $H_{3(endo)}$ and H_7. In addition, irradiation of H_7 gave no nOe to H_{3a}. These results, shown in Scheme 2, would indicate that the dipolarophile approaches the nitrone in an 'exo' mode on the side remote from the vinyl substituent.

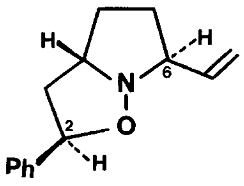
SCHEME 2



5 a-d **5e**

An exception to this mode of reaction is seen with **5e** (cyclohexadiene adduct). Here NOEDS showed an enhancement of the H_{3a} signal when H_2, H_3 and H_7 were each separately irradiated (Scheme 2). The reasons behind this apparent stereochemical anomaly are as yet unclear and further investigations are in progress.

Cyclisation of oxime **2**, prepared again as a 1:1 mixture of E- and Z-isomers from 4,5-hexadienal, was carried out under similar conditions (Scheme 1). However, nitrone **4** was found to be more stable than **3** and reacted with styrene at 70°C to give adduct **6** in 42% yield. Assignment of **6** is again based on NOEDS data. Irradiation of H_2 showed an enhancement of signals corresponding to $H_{3(endo)}$ and H_6.[8]



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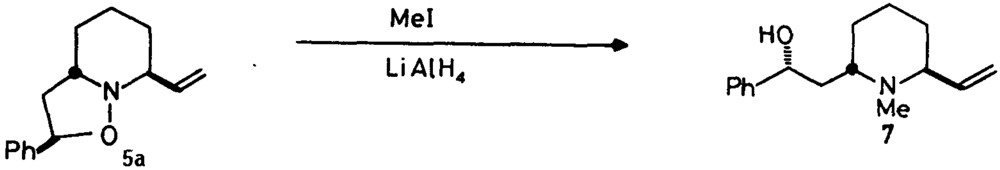
Extension of this methodology to olefinic oximes has so far been unsuccessful. The palladium-induced cyclisation of γ,δ-unsaturated ketoximes has however been reported. The products were either pyridines or isoxazoles, depending on the reaction conditions, and nitrones would not appear to be involved as intermediates.[9]

In conclusion the cyclisation of readily available allenic oximes[10] gives regiostable nitrones bearing a potentially useful vinyl group. These nitrones are trapped by a range of 1,3-dipolarophiles to give cycloadducts of defined stereochemistry. Extensions of this work including the use of electrophiles other than silver(I) are currently being explored.[11]

References and Notes

1. A. Padwa, *Angew.Chem., Int.Ed.Engl.,* **15**, 123, (1976);
   W. Oppolzer, *ibid.,* **16**, 10, (1977).
2. D. St. C. Black, R.F. Crozier and V.C. Davis, *Synthesis,* **1975**, 205;
   J.J. Tufariello, *Acc.Chem.Res.,* **12**, 396, (1979).
3. G. Tennant in *"Comprehensive Organic Chemistry"*, D.H.R. Barton and W.D. Ollis, Eds., Pergamon Press, 1979, Vol. 2, pt. 8, p.500; see also S. Murahashi, H. Mitsui, T. Watanabe and S. Lenki, *Tetrahedron Letters,* **1983**, 1049.
4. O-Trimethylsilyloximes are alkylated on nitrogen with trialkyloxonium tetrafluoroborates or alkyl triflates to give acyclic nitrones. N.A. LeBel and N. Balasubramanian, *Tetrahedron Letters,* **1985**, 4331.
5. G. Stork, S.D. Darling, L.T. Harrison and P.S. Wharton, *J.Amer.Chem.Soc.,* **84**, 2018, (1962); H.R. Brandsma and R.T. Conley, *J.Org.Chem.,* **38**, 2236, (1973); D. St. C. Black, R.F.C Brown, B.T. Dunstan and S. Sternhell, *Tetrahedron Letters,* **1974**, 4283.
6. Both isomers of **1** have been separated and each cyclised, in the presence of styrene, to give **5a**. The E-isomer gave **5a** in 83% yield after 15 hr. The Z-isomer, which undergoes a slow isomerisation under the reaction conditions gave **5a** in 27% yield after 96 hr. Usually the E- and Z-isomers of **1** (and of **2**) were not separated and the yields shown in Table 1, which have not been optimised, reflect incomplete conversion of the Z-isomer. All cycloadducts gave satisfactory ^{1}HNMR, IR and high resolution mass spectral data.
7. Reductive cleavage of the N-O bond of isoxazolines is well known.[2] We have illustrated this by conversion of **5a** to **7** in two steps (88%).



   Another approach to 2,6-disubstituted piperidines using an amine-allene cyclisation gives comparable amounts of both the *cis* and *trans* isomers. S. Arseniyadis and J. Sartoretti, *Tetrahedron Letters,* **1985**, 729.
8. For **5a**, **5b** and **5e** well resolved ^{1}HNMR spectra could only be obtained at -50°C. For other applications of NOEDS to nitrone cycloadducts see P. DeShong, C.M. Dicken, R.R. Staib, A.J. Freyer and S.M. Weinreb, *J.Org.Chem.,* **47**, 4397, (1982). Numbering system used is based upon 2H-isoxazolo(2,3-a)pyridine for **5(a-e)** and pyrrolo(1,2-b)-isoxazole for **6**.
9. T. Hosokawa, N. Shimo, K. Maela, A. Sonoda and S. Murahashi, *Tetrahedron Letters,* **1976**, 383.
10. The allenic substrates were easily prepared on a multigram scale by conventional methods (PCC oxidation followed by NH$_2$OH) based on the corresponding allenic alcohols. L. Brandsma and H.D. Verkruijsse, "Synthesis of acetylenes, allenes and cumulenes", Studies in Organic Chemistry, Elsevier, 1981, **8**, p.30.
11. The reductive cyclisation of an oxime to an alkyne has been reported, S.K. Pradhan, K.G. Akamanchi and P.P. Divakaran, *Tetrahedron Letters,* **1982**, 5017. This was presumed to involve the intermediacy of a nitrone, the final product being a hydroxylamine. However, under the conditions reported (NaBH$_4$/MeOH) both **1** and **2** were recovered unchanged.

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