Synthesis of 3-Vinylisoxazole by a Nitrile Oxide Cycloaddition/Diels–Alder Cycloreversion Pathway

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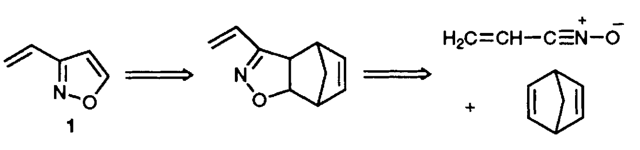
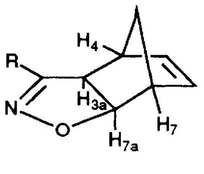
3-Vinylisoxazole is prepared by a sequence involving cycloaddition of acrylonitrile oxide, generated by dehydration of 1-nitropropene, to norbornadiene followed by Diels–Alder cycloreversion of the resulting 2-isoxazoline under flash vacuum pyrolysis conditions.

Several multistep synthetic sequences have been reported[1–3] for the preparation of 3-vinyl-substituted isoxazoles and 2-isoxazolines (4,5-dihydroisoxazoles). These involve construction of the heterocyclic ring, usually by nitrile oxide cycloaddition to the appropriate alkene or alkyne, followed by manipulation of the substituent at the 3-position by, for example, substitution of a sulfonyl group using vinyllithium[1] or dehydration of the hydroxyethyl compound[2] as the final step. A more elegant and direct route would be to introduce the vinyl moiety intact *via* the cycloaddition reactions of acrylonitrile oxide[4,5] ($CH_2{=}CHC{\equiv}N^+{-}O^-$). We have investigated the latter approach for the synthesis of 3-vinylisoxazole **1**, unsubstituted at both the 4- and 5-positions, which was required for polymerisation studies.[5] In this case the dipolarophile component would be acetylene which is, however, neither convenient to use nor sufficiently reactive for this purpose. To overcome this problem we have employed a two-step procedure involving initial cycloaddition of acrylonitrile oxide to norbornadiene, a highly reactive dipolarophile in nitrile oxide cycloadditions,[6–8] followed by thermal Diels–Alder cycloreversion of the resulting isoxazoline cycloadduct (Scheme 1). This technique, in which the norbornadiene is acting as an acetylene equivalent,[8,9] has previously been used for the preparation of several five-membered heterocyclic systems.[9–11]

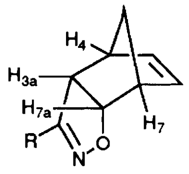
Acrylonitrile oxide was generated by isocyanate-mediated dehydration of 1-nitropropene and the reaction was carried out in the presence of an excess of the dipolarophile in order to minimise oligomerisation and dimerisation[12] to the furazan *N*-oxide. A benzene solution of 1-nitropropene (1 equiv.) was added slowly (18 h) to a solution of norbornadiene (5 equiv.), phenyl isocyanate (2 equiv.) and triethylamine (catalytic amount) in benzene at room temp. and the mixture stirred for a further 2 h. After removal of the precipitated diphenylurea, chromatography of the residue afforded *exo*- and *endo*-adducts **2** and **3** which were isolated in 35 and 11% yields, respectively. TLC of the reaction mixture showed the presence of several more polar byproducts which were attributed to 2 : 1 adducts resulting from further reaction of acrylonitrile oxide with either the vinyl substituent or the remaining endocyclic olefinic double bond in 1 : 1 products **2** and **3**. The individual isomers were identified from their characteristic ^1H NMR spectra.† For the *exo*-product **2** the isoxazoline protons 3*a*-H (δ_H 3.45) and 7*a*-H (δ_H 4.82, $J_{3a,7a}$ 8.0 Hz) have small couplings to the adjacent bridgehead protons 4-H and 7-H of 1.5 and 1.3 Hz, respectively. In contrast, for the *endo*-adduct **3** protons 3*a*-H (δ_H 3.87) and 7*a*-H (δ_H 5.29, $J_{3a,7a}$ 9.5 Hz) show much larger couplings to 4-H and 7-H (4.2 Hz in each case). The formation of both *exo*- and *endo*- products in 1,3-dipolar cycloadditions to norbornadiene has been noted previously.[6,7] In contrast, the corresponding reaction of acrylonitrile oxide with norbornene yielded only *exo*-adduct **4** [δ_H 3.13 (3*a*-H), 4.43 (7*a*-H); $J_{x\text{-}y}$ 3*a*–7*a* 8.3, 3*a*–4 1.6, 7–7*a* <1 Hz], in accord with previous reports[11,13] of π-facial specificity for 1,3-dipolar cycloaddition of nitrilium betaines to this dipolarophile.



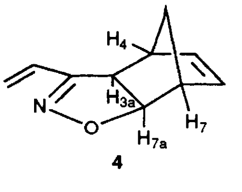
Scheme 1



2 R = CH=CH$_2$
5 R = Ph



3 R = CH=CH$_2$
6 R = Ph



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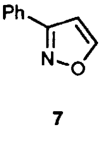

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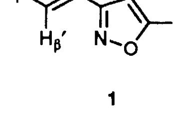

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Attempts to realise the retro-Diels–Alder fragmentation of isoxazoline **2** to cyclopentadiene and 3-vinylisoxazole **1** by heating in inert solvent were unsuccessful. Prolonged refluxing in mesitylene (163 °C, 19 h) resulted in decomposition of the starting material, but there was no evidence for the formation of **1**. To ensure a cleaner reaction we utilised the flash vacuum pyrolysis (FVP) technique which is known[14] to be well suited for accomplishing cycloreversions. Preliminary thermolysis experiments carried out with known[6] *exo*- and *endo*-norbornadiene–benzonitrile oxide adducts **5** and **6** showed that both isomers were cleaved cleanly, at 400 °C/0.003 mmHg and 350 °C/0.003 mmHg respectively, to 3-phenylisoxazole **7** in near quantitative yields (99% in each case). The reduced reaction temperature observed for *endo*-isomer **6** is consistent with the expected lower activation energy. Having established typical thermolysis conditions for compounds **5** and **6**, acrylonitrile oxide derived isoxazoline **2** was examined. FVP at 400 °C/0.001 mmHg resulted in partial consumption of the starting material and formation of a single product (by TLC). At 475 °C conversion was complete affording 3-vinylisoxazole as a pale-yellow oil (99% yield). The product was identified from its ^1H NMR spectrum [$CDCl_3$, 200 MHz; δ_H 8.32 (5-H), 6.8 (α-H), 6.47 (4-H), 5.90 (β′-H), 5.61 (β-H); $J_{x\text{-}y}$: 4–5 1.7, 5–α 0.8, α–β 10.9, α–β′ 17.8, β–β′ 0.9 Hz]. In addition to the expected signals for the vinyl moiety there is a characteristic AB pattern for the protons at the 4- and 5-positions of the isoxazole ring. The observed chemical shifts and coupling of 1.7 Hz are typical of 4/5-unsubstituted isoxazoles.[9,15] There is also an additional small (0.8 Hz) long-range five-bond coupling between H-5 and the vinylic proton α-H.

These results demonstrate that the dehydration of 1-nitropropene provides convenient access to acrylonitrile oxide and hence 3-vinyl-isoxazoles and isoxazolines, and are further evidence that FVP is uniquely well suited for achieving clean retro-Diels–Alder fragmentation reactions.

Received, 5th September 1994; Com. 4/05419I

Footnote

† All new compounds have been characterised by their ^1H and ^{13}C NMR spectra and their elemental compositions established by HRMS and/or combustion analysis.

References

1 P. A. Wade, J. F. Bereznak, B. A. Palfrey, P. J. Carroll, W. P. Dailey and S. Sivasubramanian, *J. Org. Chem.*, 1990, **55**, 3045.

2 P. A. Wade, N. V. Amin, H.-K. Yen, D. T. Price and G. F. Huhn, *J. Org. Chem.*, 1984, **49**, 4595.

3 H. Kano and I. Adachi, *Jap. Pat.* 23 172/1965; *Chem. Abstr.*, 1966, **64**, 15891.

4 A. Baranski, *Pol. J. Chem.*, 1984, **58**, 425.

5 P. W. Ambler, R. M. Paton and J. M. Tout, unpublished work.

6 R. Lazar and N. Barbulescu, *Rev. Roum. Chim.*, 1966, **11**, 1141; F. G. Cocu, R. Lazar and N. Barbulescu, *Rev. Roum. Chim.*, 1968, **19**, 625.

7 P. Sohar and I. Kövesdi, *Magn. Reson. Chem.*, 1990, **28**, 1023.

8 O. De Lucci and G. Modena, *Tetrahedron*, 1984, **40**, 2585.

9 R. Huisgen and M. Christl, *Angew. Chem., Int. Ed. Engl.*, 1967, **6**, 456; *Chem. Ber.*, 1973, **106**, 3291.

10 R. Huisgen, M. Seidel, G. Wallbillich and H. Knupfer, *Tetrahedron*, 1962, **17**, 3.

11 M. C. McKie and R. M. Paton, *J. Chem. Res.*, 1987, (*S*) 245.

12 C. Grundmann and P. Grünanger, *The Nitrile Oxides*, Springer, Berlin, 1971, ch. 4.

13 R. Huisgen, H. Stangl, H. J. Sturm, R. Raab and K. Bunge, *Chem. Ber.*, 1972, **105**, 1258; W. Fliege and R.Huisgen, *Liebigs Ann. Chem.*, 1973, 2038; R. Huisgen, P. H. J. Ooms, M. Mingin and N. L. Allinger, *J. Am. Chem. Soc.*, 1980, **102**, 3951.

14 M. Karpf, *Angew. Chem., Int. Ed. Engl.*, 1986, **25**, 414.

15 *E.g.* S. D. Sokolov, I. M. Yudintseva and P. V. Petrovskii, *Zh. Org. Khim.*, 1970, **6**, 2584; C. Dupuy and J.-M. Surzur, *Bull. Soc. Chim. Fr.* (*II*), 1980, 374.