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

Philip W. Ambler, ^b R. Michael Paton*^a and Jaki M. Tout^a

^a Department of Chemistry, The University of Edinburgh, West Mains Road, Edinburgh, UK EH9 3JJ ^b BP International Ltd, Sunbury Research Centre, Chertsey Road, Sunbury-on-Thames, Middlesex, UK TW16 7LN

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 reported¹⁻³ 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 vinyllithium¹ or dehydration of the hydroxyethyl compound² 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} (CH₂=CHC=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 dimerisation¹² 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 3a-H ($\delta_{\rm H}$ 3.45) and 7a-H ($\delta_{\rm H}$ 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 3a-H (δ_{H} 3.87) and 7*a*-H ($\delta_{\rm H}$ 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 exoand 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-y} 3a-7a 8.3, 3a-4 1.6, 7-7a <1 Hz], in accord with previous reports^{11,13} of π -facial specificity for 1,3-dipolar cycloaddition of nitrilium betaines to this dipolarophile.

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 known¹⁴ to be well suited for accomplishing cycloreversions. Preliminary thermolysis experiments carried out with known⁶ 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 endoisomer 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 [CDCl₃, 200 MHz; δ_H 8.32 (5-H), 6.8 (α-H), 6.47 (4-H), 5.90 $(\beta'-H)$, 5.61 $(\beta-H)$; J_{x-y} : 4–5 1.7, 5– α 0.8, $\alpha-\beta$ 10.9, $\alpha-\beta'$ 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.

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Footnote

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

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