# *N*-Vinyl-Nitroimidazole Cycloadditions: Potential Routes to Nucleoside Analogues

Russell Clayton, Christopher A. Ramsden*

Lennard-Jones Laboratories, School of Chemistry and Physics, Keele University, Keele, Staffordshire ST5 5BG, UK
Fax +44(1782)712378; E-mail: c.a.ramsden@chem.keele.ac.uk

*Received 20 April 2005*

**Abstract:** Cycloaddition reactions of 4-nitro- and 5-nitro-1-vinylimidazoles have been investigated. The cycloadducts obtained are potential intermediates for synthesis of purine nucleoside analogues via reduction to the corresponding aminoimidazoles. A byproduct obtained using benzonitrile oxide as 1,3-dipolarophile has been identified as a novel tricyclic isomer **12** of the cycloadduct **11**.

**Key word:** nitroimidazole, vinylimidazole, 1,3-dipolar cycloadditions, isoxazoline, nucleoside analogues

4-Unsubstituted-5-aminoimidazoles **1**[1] are useful synthetic intermediates. Early workers claimed that these simple amines are very unstable[2] and, although they were implicated in the anaerobic antibacterial activity of 5-nitroimidazoles such as metronidazole (**2**)($R^1$ = Me, $R^2$ = $CH_2CH_2OH$),[3] their chemistry remained largely unexplored. We have subsequently shown that 5-nitroimidazoles **2** are readily reduced to 5-aminoimidazoles **1** (Figure 1), which can be isolated[4,5] or trapped by soft electrophiles[6] giving convenient precursors to purine nucleosides and their analogues. Using this approach we have reported the preparation of a variety of purine derivatives and related heterocycles.[6,7] We now report the results of an investigation of cycloaddition reactions of *N*-vinyl-nitroimidazoles that are potential routes to nucleoside analogues.

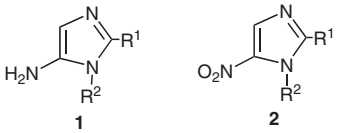
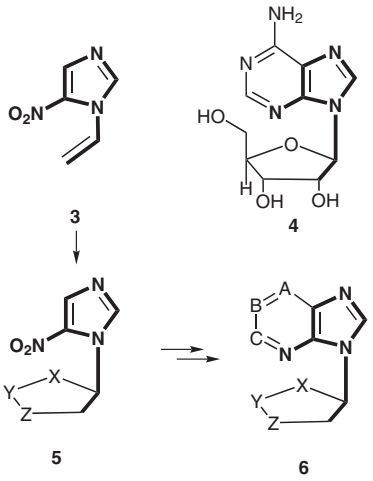



**Figure 1**

Inspection of Scheme 1 shows that the *N*-vinyl-5-nitroimidazole molecule **3** has the same molecular skeleton as a central portion of purine nucleosides such as adenosine (**4**). 1,3-Dipolar cycloaddition of the *N*-vinyl substituent in principle gives sugar mimics **5** which can be further elaborated, via the corresponding 5-aminoimidazoles, to purine nucleoside analogues of general structure **6**. We have therefore investigated the preparation and chemistry



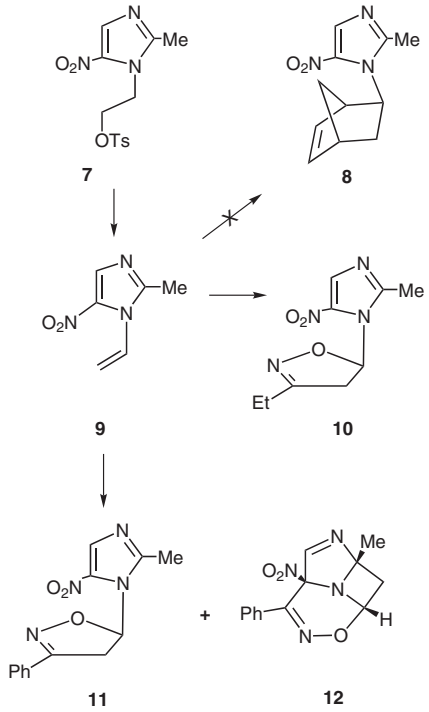

**Scheme 1**

of selected *N*-vinyl derivatives of both 4- and 5-nitroimidazoles and now report our findings.

Because of the ready availability of metronidazole **2** ($R^1$ = Me, $R^2$ = $CH_2CH_2OH$) we initiated our studies by investigating cycloadditions of the 2-methyl-1-vinyl derivative **9** (Scheme 2). This was prepared by treatment of the tosyl derivative **7** with base using the procedure of Ross and coworkers.[8] Since 5-nitroimidazoles are electron-deficient heterocycles and the nitrogen lone pair is in conjugation with the nitro group, we made no assumptions about the nature of the C=C bond and investigated potential reactions with a range of dienes and 1,3-dipolarophiles. No formation of the cycloadduct **8** occurred when the alkene **9** was reacted with freshly prepared cyclopentadiene, even in the presence of acid catalysts ($AlCl_3$, $TiCl_4$, aq HCl). Similarly, no cycloaddition products were identified using phenyl azide or the four 1,3-dipoles $RHC{=}(Me)N^+X^-$ (X = O or $CH_2$, R = H or Ph) under various conditions. These negative results suggested that the imidazole **9** contains an electron-rich vinyl substituent and we therefore directed our attention to reactions with nitrile oxides (low LUMO).

When compound **9** was reacted with propanenitrile oxide ($EtC{\equiv}N^+O^-$), generated in situ by treatment of a mixture of 1-nitropropane and phenyl isocyanate with a catalytic amount of $Et_3N$,[9] a small amount of cycloadduct **10** was isolated using column chromatography. The yield of this product (< 3%) was too low for full characterization but the $^1H$ NMR spectrum supported the structural assign-

**SYNTHESIS** 2005, No. 16, pp 2695–2700
Advanced online publication: 20.07.2005
DOI: 10.1055/s-2005-872083; Art ID: P05405SS



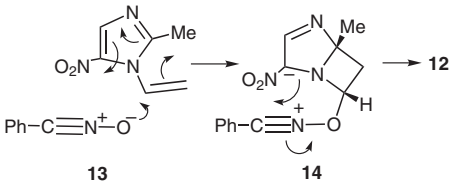
**Scheme 2**

ment **10**. In particular the isoxazoline ring protons were observed at δ = 3.53 (*J* = 5, 18.5 Hz, CHC$H_2$(*trans*)], 4.08 (*J* = 10, 18.5 Hz, CHC$H_2$(*cis*)] and 7.33 (*J* = 5, 10 Hz, C*H*C$H_2$]. A regioisomer was not detected and the only other reaction products were diphenylurea and nitrile oxide dimer. Dimerisation of the 1,3-dipole appeared to be the preferred reaction pathway,[10] even in the presence of a large excess of alkene **9**. We therefore investigated a more sterically hindered derivative (i.e. PhC≡$N^+O^-$) hoping that this might reduce the relative rate of dimerisation.

Benzonitrile oxide was generated in situ in the presence of the alkene **9** by treatment of benzylhydroximinoyl chloride with $Et_3N$.[11] Again, dimerisation competed with cycloaddition but a cycloadduct (mp 118 °C) was isolated in 31% yield and assigned structure **11**. The $^1$H NMR spectrum of the product **11** showed the mutually coupled (*J* = 18 Hz) methylene protons of the 2-isoxazoline ring at δ = 3.53 and 4.08. These signals are further split by coupling to the proton at position 1′ [*J* = 10 (*cis*), 5 (*trans*) Hz, respectively]. As expected the anomeric proton (1′) appears at low field (δ = 7.33) as a doublet of doublets (*J* = 5, 10 Hz). The imidazole proton at position 4 and the methyl substituent at position 2 appear as singlets at δ = 7.91 and δ = 2.49. All these features are entirely consistent with the cycloadduct having structure **11**. The regioisomeric structure can be eliminated since the 2-isoxazoline methylene protons, being adjacent to an oxygen, would be significantly shifted to lower field. The $^{13}$C NMR spectrum confirms these conclusions. The 2′-$CH_2$ and 1′-CH isoxazoline carbons are observed (DEPT) at 43.7 and 87.5 ppm, respectively. In the regioisomer the $OCH_2$ signal would be expected at lower field, due to the adjacent oxygen, and the anomeric CH signal at higher field. All other aspects of the $^{13}$C spectrum were consistent with structure **11**. The mass spectrum of the product **11** showed a weak molecular ion [*m*/*z* (%) = 272 (1)] together with fragment ions, corresponding to cleavage of the C(1′)N bond, at *m*/*z* (%) = 146 (26) and *m*/*z* (%) = 127 (100). The constitution $C_{13}H_{12}N_4O_3$ was confirmed by microanalysis. The similarity between the spectra of the products **10** and **11** strongly supports the structural assignment **10**.

In an attempt to reduce dimerisation the preparation was repeated using only a catalytic amount of $Et_3N$ with stirring over excess solid $NaHCO_3$. The yield slightly increased but in this case the cycloadduct **11** was accompanied by a second product (ca 9:1) that was separated by chromatography. Initially we thought that this minor product (mp 113 °C) was the regioisomer. Subsequently, a more critical analysis of the $^1$H and $^{13}$C NMR spectra eliminated the regioisomer and suggested the unexpected tricyclic structure **12**. The $^1$H NMR spectrum of this minor product shows a three proton doublet (*J* = 1 Hz) at δ = 1.35. This is at too high field to be a simple 2-methyl-5-nitroimidazole signal (ca δ = 2.5) and suggests a methyl group attached to a saturated carbon atom. A singlet at δ = 8.30, which superficially appears to be an imidazole 4-H signal, is not coupled with this methyl signal. The product is clearly not an aromatic 5-nitroimidazole and this is confirmed by the $^{13}$C NMR spectrum which does not show a signal at ca 138 ppm, highly characteristic of the C-5 carbon atoms of 5-nitroimidazoles.[12] In addition to the phenyl protons, three other protons are observed at δ = 2.16 (ddd, *J* = 14, 4, 1 Hz), δ = 3.70 (dd, *J* = 14, 6 Hz) and δ = 7.71 (dd, *J* = 6, 4 Hz). A DEPT spectrum confirmed that the protons at δ = 2.16 and δ = 3.70 are associated with a methylene group ($J_{AB}$ = 14 Hz, $CH_AH_B$). One of these protons (δ = 2.16) is weakly coupled (*J* = 1 Hz) to the methyl substituent suggesting bond formation between the vinyl 2′-carbon and the imidazole 2-carbon of the precursor **9**. The only structure that satisfactorily accounts for all aspects of the NMR spectra is structure **12**. The proton singlet at δ = 8.30 is the imine proton. In the $^{13}$C spectrum the two imine carbons appear at 153.5 (t) and 152.5 (q) ppm and there are three other quaternary carbons at δ = 135.5, 121.6 and 98.7 ppm. The mass spectrum showed a protonated molecular ion [$MH^+$] at *m*/*z* = 273 with the constitution $C_{13}H_{13}N_4O_3$. Formation of the product **12** is repeatable but attempts to increase the yield by varying the conditions were unsuccessful. The cycloadduct **11** does not appear to be a precursor of the isomer **12**.

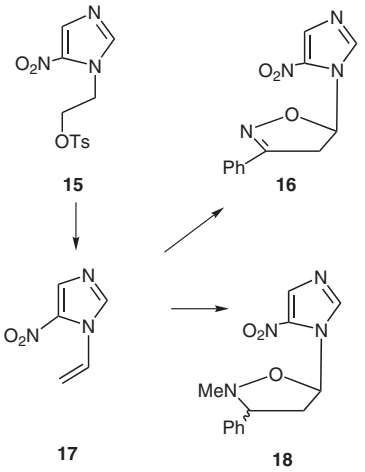
Although only a minor side-product, the unusual structure **12** merits some mechanistic justification. We suggest that addition of the nitrile oxide (or the anion of its oxime precursor) to the vinyl group (**13**) produces an anionic species (e.g. **14**) in which negative charge is resonance stabilised. Intramolecular cyclisation then gives the product **12**. This mechanistic pathway (Scheme 3) shows that there is a structural and mechanistic relationship between the products **11** and **12**.



**Scheme 3**

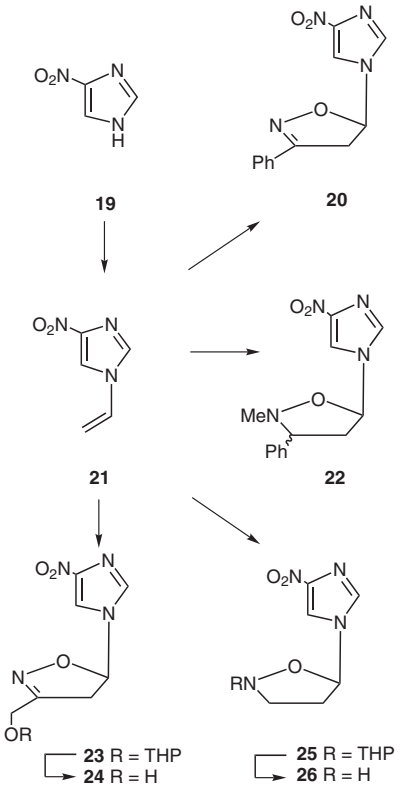
At this stage we turned our attention to 5-nitro-1-vinylimidazole (**17**), which is a potential precursor to purine nucleoside analogues as shown in Scheme 1. The tosylate **15** was prepared from the alcohol. Elimination of *p*-toluenesulfonic acid using EtOH–EtONa was achieved in 51% yield provided that the EtOH was anhydrous and all traces of water were removed from the apparatus. Alternatively the vinyl derivative **17** can be prepared from the chloride using a procedure that we have described elsewhere.[13] For a comparative study we have also investigated 4-nitro-1-vinylimidazole (**21**), which is readily prepared from 4-nitroimidazole (**19**).[13]

Reaction of the alkene **17** with benzonitrile oxide gave the cycloadduct **16** (36%) as a pale yellow solid (Scheme 4). All spectroscopic properties of the adduct **16** were similar to those of the 2-methyl derivative **11**. We then investigated other 1,3-dipoles. *N*-Methyl benzaldehyde nitrone was prepared in toluene solution using the method of De Shong and Leginus.[14] When the *N*-vinylimidazole **17** was added and the solution heated under reflux (72 h) a single product was formed. After isolation by column chromatography this was identified as the adduct **18** (21%). $^1$H NMR showed that the 5-nitroimidazole fragment was present (δ = 8.0, 8.3) together with a phenyl group (δ = 7.2–7.4) and an *N*-methyl singlet (δ = 2.7). The methylene group of the isoxazolidine ring appears as coupled ($J$ = 14 Hz) non-equivalent protons at δ = 2.4 and δ = 3.5. These chemical shifts eliminate the regioisomeric structure in which the chemical shifts of the $OCH_2$ protons would be at significantly lower field. The anomeric proton is observed at δ = 6.6 and the PhCH proton is at δ = 3.8.



**Scheme 4**

When 4-nitro-1-vinylimidazole (**21**) was reacted with benzonitrile oxide and *N*-methyl benzaldehyde nitrone under the same conditions as for the 5-nitro derivative **17**, the corresponding adducts **20** and **22** were obtained in similar yields (Scheme 5). The position of the nitro substituent appears to have little influence on these cycloaddition reactions.



**Scheme 5**

The presence of a phenyl substituent in the cycloadducts described above is undesirable in nucleoside precursors and we next investigated the in situ use of unstabilised nitrile oxides and nitrones. (Tetrahydropyran-2-yl)oxyacetonitrile oxide [THP-$OCH_2CNO$][15] was formed by reaction of 2-(2-nitroethoxy)tetrahydropyran with PhNCO–$Et_3N$ and reacted with 4-nitro-1-vinylimidazole (**21**) at room temperature (24 h). Column chromatography and acid workup (to deprotect the initial product **23**) gave the adduct **24** (61%) as yellow crystals.

The spectroscopic features of product **24** were analogous to the adducts previously described and fully support the assigned structure **24**. The $CH_2OH$ substituent was observed as a two proton multiplet at δ = 4.39 and a triplet (OH) at δ = 5.6. When this procedure was repeated using 5-nitro-1-vinylimidazole (**17**) $^1$H NMR analysis of the reaction mixture suggested that cycloaddition had occurred but the only product isolated after workup was 4-nitroimidazole (**19**). Repetition and chromatography of the reaction mixture before acid work-up gave a yellow oil that was identified as the crude THP protected adduct **27**. Deprotection under mild conditions (MeOH–$HCO_2H$)

followed by chromatography gave a low yield (7%) of a yellow oil. This was identified as the product **28** by $^1$H NMR and mass spectrometry but a pure sample could not be obtained. We have previously encountered high instability of sugar derivatives of 5-nitroimidazoles to acid conditions under which the 4-nitro isomers are stable.[7b] This is attributed to protonation of the imidazole and 4-nitroimidazole acting as a very good leaving group assisted by the ring oxygen atom.

Finally, we investigated the reaction of *N*-(tetrahydropyran-2-yl)formaldehyde nitrone [$H_2C$=(THP)$N^+O^-$] generated in situ from *N*-(tetrahydropyran-2-yl)hydroxylamine and *para*-formaldehyde.[16] Reaction of this reagent with the 4-nitro dipolarophile **21** in hot THF gave the adduct **25** (62%), which was isolated by column chromatography as a crystalline solid (mp 98 °C) and identified by $^1$H NMR. Deprotection (MeOH–concd HCl) of this product and chromatographic purification gave the isoxazoline **26** (71%) as a colourless oil. The structure was confirmed by NMR spectroscopy and mass spectrometry. Attempts to repeat this procedure with the 5-nitro isomer **17** were unsatisfactory. Although the adduct **29** was formed in reasonable yield and identified by $^1$H NMR it could not be isolated in pure form. Deprotection of the crude mixture (MeOH–$HCO_2H$) gave mainly 4-nitroimidazole (**19**) and a low yield (ca. 3%) of material tentatively identified as the desired product **30** (Figure 2). Like adduct **27**, the product **29** is extremely sensitive to acid.[7b]

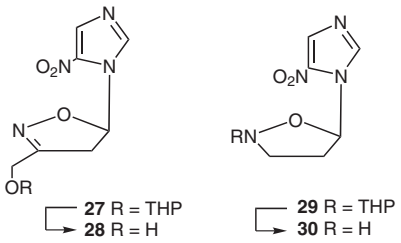



**Figure 2**

The $^1$H and $^{13}$C NMR spectra were recorded on a Bruker Avance DPX300 NMR spectrometer at 300 MHz and 50 MHz, respectively, in $CDCl_3$ (TMS as internal standard). IR spectra were recorded on a Perkin-Elmer Paragon 1000 FT-IR spectrophotometer, and microanalyses on a Perkin-Elmer 240 Elemental Analyser. Unless otherwise stated, IR spectra were measured as thin films (liquids) or KBr discs (solids). Only significant bands for the IR spectra are quoted. Melting points were determined on a Reichert–Kofler block apparatus and are uncorrected. Chromatotron chromatography was performed on plates prepared using silica gel 60 $PF_{254}$ containing $CaSO_4$.

**5-Nitro-1-(2-tosyloxyethyl)imidazole (15)**

*p*-TsCl (11.4 g, 60 mmol) was added to 1-(2-hydroxyethyl)-5-nitroimidazole[17] (8.0 g, 50 mmol) in anhyd pyridine (75 mL) and the mixture was stirred (7 h). A further portion of *p*-TsCl (2.85 g, 15 mmol) was then added and stirring was maintained overnight. The precipitate was collected, recrystallised from MeOH and identified as the 5-nitroimidazole **15** (13.1 g, 84%); colourless rectangular crystals; mp 129 °C.

IR (KBr): 650, 661, 823, 896, 1179, 1366, 1469, 1524, 1596, 1772, 2924 cm$^{-1}$.

$^1$H NMR ($CDCl_3$–TMS): δ = 2.39 (s, 3 H, $CH_3$), 4.31 (t, 2 H, $NCH_2$), 4.54 (t, 2 H, $OCH_2$), 7.23 (d, *J* = 8.3 Hz, 2 H, arom-H), 7.53 (d, *J* = 8.3 Hz, 2 H, arom-H), 7.57 [s, 1 H, imidazole C(4)H], 7.81 [s, 1 H, imidazole C(2)H].

$^{13}$C NMR ($CDCl_3$–TMS): δ = 21.66 (Ar*C*$H_3$), 46.99 ($NCH_2$), 66.87 ($OCH_2$), 127.69 (arom-CH), 130.13 (arom-CH), 131.84 (arom-C), 133.88 [C(4)H], 137.99 [C(5)], 142.59 [C(2)H], 145.68 (arom-C).

MS (EI): *m*/*z* (%) = 311 (62) [M$^+$], 310, 155, 140, 139, 92, 91 (100), 90, 65, 53.

Anal. Calcd for $C_{12}H_{13}N_3O_5S$ (311.31): C, 46.30; H, 4.21; N, 13.50. Found: C, 46.64; H, 4.26; N, 13.28.

**2-Methyl-5-nitro-1-(2-tosyloxyethyl)imidazole (7)**

Following the method described for compound **15**, the title compound was obtained from metronidazole (15.0 g, 82.5 mmol); yield: 22.67 g (85%); pale cream needles from EtOH; mp 151 °C (Lit.[8] 153 °C).

IR (KBr): 898, 1174, 1366, 1430, 1460, 1526, 1596 cm$^{-1}$.

$^1$H NMR ($CDCl_3$–TMS): δ = 2.45 (s, 3 H, $CH_3$), 2.52 (s, 3 H, $CH_3$), 4.37 (t, 2 H, $NCH_2$), 4.54 (t, 2 H, $OCH_2$), 7.30 (d, *J* = 8.3 Hz, 2 H, arom-H), 7.60 (d, *J* = 8.3 Hz, 2 H, arom-H), 7.79 [s, 1 H, imidazole C(4)H].

$^{13}$C NMR ($CDCl_3$–TMS): δ = 13.91 (Ar-*C*$H_3$), 21.01 [C(2)*C*$H_3$], 44.61 ($NCH_2$), 68.38 ($OCH_2$), 127.21 (arom-CH), 129.24 (arom-CH), 131.50 (arom-C), 133.04 [C(4)H], 138.03 [C(5)], 145.22 (arom-C), 151.57 [C(2)].

MS (EI): *m*/*z* (%) = 325 (11) [M$^+$], 199, 170 (100), 155, 91, 65, 53.

Anal. Calcd for $C_{13}H_{15}N_3O_5S$ (325.34): C, 47.99; H, 4.65; N, 12.92. Found: C, 47.99; H, 4.59; N, 12.63.

**5-Nitro-1-vinylimidazole (17)**

NaOEt (1.10 g, 16 mmol) was added to a solution of 1-(2-tosyloxyethyl)-5-nitroimidazole (**15**; 5.00 g, 16 mmol) in anhyd EtOH (100 mL) heated under reflux. Heating of the resulting orange solution was maintained (30 min), before cooling to r.t. and stirring overnight. The precipitate was removed and the volume was reduced (ca. 10 mL). The concentrated solution was diluted with $H_2O$ (200 mL) and $Et_2O$ (200 mL). The organic phase was separated, dried ($MgSO_4$) and evaporated to give a yellow oil. Column chromatography (silica gel; $Et_2O$ as eluent) gave the vinylimidazole **17** (1.15 g, 51%); yellow crystals; mp 24 °C.

IR (film): 643, 826, 1119, 1526, 1376, 1473, 1530, 1641, 3127 cm$^{-1}$.

$^1$H NMR ($CDCl_3$–TMS): δ = 5.36 [dd, *J* = 1.8, 8.4 Hz, 1 H, CH=C$H_2$(*cis*)], 5.57 [dd, *J* = 1.8, 15.5 Hz, 1 H, CH=C$H_2$(*trans*)], 7.44 (dd, *J* = 8.4, 15.5 Hz, 1 H, NC*H*=$CH_2$), 7.85 [d, *J* = 0.8 Hz, 1 H, imidazole C(4)H], 8.00 [d, *J* = 0.8 Hz, 1 H, imidazole C(2)H].

$^{13}$C NMR (DMSO-$d_6$–TMS): δ = 110.09 (C=*C*$H_2$), 128.82 (C=*C*H), 133.20 [C(4)H], 137.95 [C(5)], 140.23 [C(2)H].

MS (EI): *m*/*z* (%) = 139 (48) [M$^+$], 94, 82, 67, 66, 55, 54, 40, 39 (100), 28, 27.

Anal. Calcd for $C_5H_5N_3O_2$ (139.11): C, 43.17; H, 3.62; N, 30.21. Found: C, 43.44; H, 3.50; N, 30.19.

**2-Methyl-5-nitro-1-vinylimidazole (9)**

Following the method described for compound **17**, the title compound was obtained from the 5-nitroimidazole **7** (20.0 g, 61.5 mmol) and NaOEt (4.60 g, 65.0 mmol). After reduction of the volume (ca. 60–70 mL) and dilution with $H_2O$ (200 mL), the solution was extracted with $Et_2O$ (3 × 100 mL). The combined organic extracts were dried and concentrated (40 mL). Careful trituration with

*n*-hexane gave a red oil which was discarded. Further dilution with *n*-hexane yielded the vinylimidazole **9** (5.32 g, 55%); pale yellow needles; mp 48 °C (Lit.[8] 49–50 °C).

IR (KBr): 962, 1204, 1260, 1369, 1472, 1525, 1636, 3119 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$–TMS): δ = 2.51 (s, 3 H, $CH_3$), 5.41 [dd, *J* = 1.3, 15.6 Hz, 1 H, CH=C$H_2$(*trans*)], 5.64 [dd, *J* = 1.3, 8.2 Hz, 1 H, CH=C$H_2$(*cis*)], 7.06 (dd, *J* = 8.2, 15.6 Hz, 1 H, NC*H*=$CH_2$), 7.93 [s, 1 H, imidazole C(4)H].

$^{13}C$ NMR ($CDCl_3$–TMS): δ = 15.13 (2-$CH_3$), 116.40 (C=*C*$H_2$), 129.59 (C=*C*H), 131.80 [C(4)H], 138.98 [C(5)], 149.52 [C(2)].

MS (EI): *m*/*z* = 153 (61) [$M^+$], 67, 54, 43, 42, 39 (100), 27.

Anal. Calcd for $C_6H_7N_3O_2$ (153.14): C, 47.06; H, 4.61; N, 27.44. Found: C, 47.00; H, 4.49; N, 27.17.

### 1,3-Dipolar Cycloaddition Reactions of 4- and 5-Nitro-1-vinylimidazoles

#### (a) With Benzonitrile Oxide

#### 5-(2-Methyl-5-nitroimidazol-1-yl)-3-phenyl-4,5-dihydroisoxazole (11)

2-Methyl-5-nitro-1-vinylimidazole (**9**; 1.00 g, 6.3 mmol) was dissolved in anhyd THF (50 mL) at 0 °C and benzohydroximinoyl chloride (1.00 g, 6.4 mmol) was added. The solution was stirred rapidly and $Et_3N$ (0.65 g, 6.4 mmol) was added. Stirring was maintained at r.t. (20 h), after which time TLC showed that starting material was still present. Further portions of benzohydroximinoyl chloride (0.50 g, 3.22 mmol) and $Et_3N$ (0.33 g, 3.22 mmol) were added and stirring was continued (24 h). The precipitate was removed and the filtrate was concentrated (ca. 10 mL). Column chromatography (silica gel; EtOAc as eluent) gave cycloadduct **11** (500 mg, 31%); light yellow solid; mp 118 °C.

IR (KBr): 693, 762, 860, 1045, 1140, 1166, 1203, 1245, 1362, 1412, 1480, 1535, 1732, 2983 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$–TMS): δ = 2.49 (s, 3 H, $CH_3$), 3.53 [dd, *J* = 4.8, 18.4 Hz, 1 H, CHC$H_2$(*trans*)], 4.08 [*J* = 10.1, 18.4 Hz, 1 H, CHC$H_2$(*cis*)], 7.33 (dd, *J* = 4.8, 10.1 Hz, 1 H, NC*H*$CH_2$), 7.37–7.66 (m, 5 H, arom-H), 7.91 [s, 1 H, imidazole C(4)H].

$^{13}C$ NMR ($CDCl_3$–TMS): δ = 16.51 [C(2′)*C*$H_3$], 43.74 [C(4)$H_2$], 87.47 [C(5)H], 127.02 (arom-CH), 127.40 (arom-C), 129.10 (arom-CH), 131.37 (arom-CH), 133.43 [C(4′)H], 138.76 [C(5′)], 150.44 [C(2′)], 157.50 [C(3)].

MS (EI): *m*/*z* (%) = 272 (1) [$M^+$], 146, 145, 127 (100), 81, 77, 54, 53, 52, 43, 42, 40, 27, 26.

Anal. Calcd for $C_{13}H_{12}N_4O_3$ (272.26): C, 57.35; H, 4.44; N, 20.58. Found: C, 57.34; H, 4.51; N, 20.31.

In a separate experiment the solution was stirred rapidly and $Et_3N$ (2 drops) and $NaHCO_3$ (2.0 g) were added. Stirring was then maintained at r.t. for 20 h. The precipitate was removed and the filtrate concentrated (ca. 10 mL). Column chromatography (silica gel; EtOAc as eluent) gave the adduct **11** (27%) together with a second product that was identified as **12** (50 mg, 3%); light yellow solid; mp 113 °C.

IR (KBr): 659, 699, 775, 804, 879, 1026, 1051, 1098, 1261, 1298, 1365, 1413, 1448, 1509, 1571, 1601 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$–TMS): δ = 1.36 (d, *J* = 1.0 Hz, 3 H, $CH_3$), 2.20 [dd, *J* = 4.0, 14.1 Hz, 1 H, CHC$H_2$(*trans*)], 3.70 [dd, *J* = 5.9, 14.1 Hz, 1 H, CHC$H_2$(*cis*)], 7.51–7.63 (m, 5 H, arom-H), 7.71 (dd, *J* = 4.1, 5.8 Hz, 1 H, NC*H*$CH_2$), 8.30 [s, 1 H, imidazole C(4)H].

$^{13}C$ NMR ($CDCl_3$–TMS): δ = 27.67 [C(2′)*C*$H_3$], 45.34 [C(4)$H_2$], 87.47 [C(5)H], 98.68 (arom-C), 119.94 (arom-CH), 121.58 [C(5′)], 128.75 (arom-CH), 129.89 (arom-CH), 132.56 [C(4′)H], 135.83 [C(2′)], 152.55 [C(3)], 153.51 [C(4)H].

MS (EI): *m*/*z* (%) = 272 (1) [$M^+$], 226, 184, 160, 149, 119, 103, 86, 84, 76, 51, 49 (100).

HRMS: *m*/*z* calcd for $C_{13}H_{13}N_4O_3$ [M + H]: 273.0982; found: 273.0983.

#### 5-(5-Nitroimidazol-1-yl)-3-phenyl-4,5-dihydroisoxazole (16)

Following the method described for compound **11**, the title compound was obtained from 5-nitro-1-vinylimidazole (**17**; 100 mg, 0.72 mmol); yield: 66 mg (36%); pale yellow solid; mp 119 °C.

IR (KBr): 690, 772, 858, 954, 1120, 1214, 1257, 1370, 1467, 1535, 3077 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$–TMS): δ = 3.55 [dd, *J* = 2.1, 18.2 Hz, 1 H, CHC$H_2$(*trans*)], 4.14 [dd, *J* = 8.1, 18.2 Hz, 1 H, CHC$H_2$(*cis*)], 7.09 (dd, *J* = 2.1, 8.1 Hz, 1 H, NC*H*$CH_2$), 7.26–7.51 (m, 3 H, arom-H), 7.64–7.69 (m, 2 H, arom-H), 7.88 [s, 1 H, imidazole C(4)H], 8.01 [s, 1 H, imidazole C(2)H].

MS (EI): *m*/*z* (%) = 258 (7) [$M^+$], 163, 146, 145 (100), 144, 118, 117, 105, 103 (75), 91, 77, 51, 40, 39.

Anal. Calcd for $C_{12}H_{10}N_4O_3$ (258.24): C, 55.81; H, 3.90; N, 21.70. Found: C, 55.76; H, 3.88; N, 21.93.

#### 5-(4-Nitroimidazol-1-yl)-3-phenyl-4,5-dihydroisoxazole (20)

Following the method described for compound **11**, the title compound was obtained from 4-nitro-1-vinylimidazole (**21**; 1.00 g, 7.19 mmol); yield: 766 mg, (41%); flat almost colourless crystals from toluene; mp 136 °C.

IR (KBr): 692, 794, 938, 1286, 1346, 1507, 1539, 1653, 3093 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$–TMS): δ = 3.57 [dd, *J* = 2.5, 17.9 Hz, 1 H, CHC$H_2$(*trans*)], 4.00 [dd, *J* = 9.0, 17.9 Hz, 1 H, CHC$H_2$(*cis*)], 6.51 (dd, *J* = 2.5, 8.9 Hz, 1 H, NC*H*$CH_2$), 7.39–7.50 (m, 3 H, arom-H), 7.58 [d, *J* = 1.5 Hz, 1 H, imidazole C(5)H], 7.64–7.67 (m, 2 H, arom-*H*), 7.76 [d, *J* = 1.5 Hz, 1 H, imidazole C(2)H].

$^{13}C$ NMR (DMSO-$d_6$–TMS): δ = 40.99 [C(4′)$H_2$], 86.33 [C(5′)H], 119.03 (arom-CH), 127.27 (arom-CH), 127.84 (arom-C), 128.77 (arom-CH), 130.83 [C(5)H], 135.94 [C(2)H], 147.67 [C(4)], 157.69 [C(3)].

MS (EI): *m*/*z* (%) = 258 (4) [M], 146 (100), 145, 144, 118, 91, 77, 51, 40, 28.

Anal. Calcd for $C_{12}H_{10}N_4O_3$ (258.24): C, 55.81; H, 3.90; N, 21.70. Found: C, 55.72; H, 3.86; N, 21.45.

#### (b) With *N*-Methylbenzaldehyde Nitrone

#### 2-Methyl-5-(5-nitroimidazol-1-yl)-3-phenylisoxazolidine (18)

*N*-Methylbenzaldehyde nitrone was prepared from benzaldehyde (0.5 g, 4.7 mmol) and kept as the crude product in toluene solution. 5-Nitro-1-vinylimidazole (**17**; 100 mg, 0.7 mmol) was added to the filtered nitrone solution and the mixture was heated under reflux and a $N_2$ atmosphere until TLC showed that no starting imidazole remained (72 h). Evaporation and column chromatography (silica gel; $Et_2O$ as eluent) yielded the isoxazolidine **18** (42 mg, 21%).

IR (film): 649, 699, 826, 1064, 1119, 1209, 1371, 1466, 1526, 2875 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$–TMS): δ = 2.42 (ddd, *J* = 3.3, 9.6, 13.7 Hz, 1 H, ArCH), 2.74 (s, 3 H, $NCH_3$), 3.54 (dt, *J* = 7.7, 14.1 Hz, 1 H, CHC$H_2$CH), 3.77 (dd, *J* = 9.6, 8.2 Hz, 1 H, CHC$H_2$CH), 6.59 (dd, *J* = 7.3, 3.3 Hz, 1 H, OCH), 7.21–7.35 (m, 5 H, arom-H), 8.02 [d, *J* = 1.0 Hz, 1 H, imidazole C(4)H], 8.30 [s, 1 H, imidazole C(2)H].

MS (EI): *m*/*z* (%) = 274 (22) [$M^+$], 135, 134 (100), 118, 115, 105, 104, 103, 91, 78, 77, 52, 42, 28.

HRMS: *m*/*z* calcd for $C_{13}H_{14}N_4O_3$: 274.1066; found: 274.1061.

**2-Methyl-5-(4-nitroimidazol-1-yl)-3-phenylisoxazolidine (22)**
Following the method described for compound **18**, the title compound was obtained from 4-nitro-1-vinylimidazole (100 mg, 0.719 mmol); yield: 53 mg (27%).

$^1$H NMR ($CDCl_3$–TMS): δ = 2.58 (ddd, *J* = 3.7, 9.7, 13.7 Hz, 1 H, CHC*H*$_2$CH)), 2.69 (s, 3 H, $NCH_3$), 3.41 (dt, *J* = 7.9, 13.8 Hz, 1 H, CHC*H*$_2$CH), 3.74 (dd, *J* = 9.7, 7.9 Hz, 1 H, NC*H*Ph), 6.03 (dd, *J* = 3.7, 7.9 Hz, 1 H, OCH), 7.32–7.41 (m, 5 H, arom-H), 7.79 [d, *J* = 1.5 Hz, 1 H, imidazole C(5)H], 8.16 [d, *J* = 1.5 Hz, 1 H, imidazole C(2)H].

HRMS: *m*/*z* calcd for $C_{13}H_{14}N_4O_3$: 274.1066; found: 274.1054

**(c) With *O*-(Tetrahydropyran-2-yl)oxyacetonitrile**
**3-Hydroxymethyl-5-(4-nitroimidazo-1-yl)isoxazoline (24)**
2-(2-Nitroethoxy)tetrahydropyran (0.52 g, 3 mmol), phenyl isocyanate (1.0 g, 8 mmol) and $Et_3N$ (2 drops) were placed in benzene (15 mL) and stirred (1 h). 4-Nitro-1-vinylimidazole (**21**; 0.28 g, 2 mmol) was dissolved in THF (15 mL) and this solution was added to the reaction mixture and the resultant solution was stirred (24 h). Column chromatography (silica gel: EtOAc–hexane 1:1 as eluent) separated the fraction below the 4-nitro-1-vinylimidazole as an orange oil that was dissolved in MeOH (30 mL) and concd HCl (1 mL) and stirred (1 h). The acidity was adjusted to pH 7 using aq $NaHCO_3$ and the solvent was removed. Column chromatography (silica gel: EtOAc as eluent) yielded a yellow oil which crystallised overnight at 0 °C and was identified as the isoxazoline **24** (0.26 g, 61%); yellow crystals; mp 119 °C.

IR (KBr): 3331, 3155, 3124, 1553, 1503, 1294, 1034, 8489, 676 $cm^{-1}$.

$^1$H NMR (DMSO-$d_6$–TMS): δ = 3.57 (dd, *J* = 18.9, 2.6 Hz, 1 H, 4-CH), 3.82 (dd, *J* = 18.9, 9.1 Hz, 1 H, 4-CH), 4.39 (m, 2 H, C*H*$_2$OH), 5.56 (t, *J* = 5.9, 6.3 Hz, 1 H, OH), 6.75 (dd, *J* = 9.1, 2.7 Hz, 1 H, 5-CH), 8.05 [d, *J* = 1.4 Hz, 1 H, imidazole C(5)H], 8.47 [d, *J* = 1.4 Hz, 1 H, imidazole C(2)H].

$^{13}$C NMR (DMSO-$d_6$–TMS): δ = 41.90 [C(4′)H$_2$], 55.72 ($CH_2OH$), 85.36 [C(5′)H], 118.82 [imidazole C(5)H], 135.91 [imidazole C(2)H], 147.65 [imidazole C(4)], 160.77 [C(3′)].

MS (EI): *m*/*z* (%) = 212 (3) [M$^+$], 113, 99, 69, 43, 31 (100).

HRMS: *m*/*z* [M$^+$] calcd for $C_7H_8N_4O_4$: 212.0546; found: 212.0548

**(c) With *N*-(tetrahydropyran-2-yl)formaldehyde Nitrone**
**5-(4-Nitroimidazo-1-yl)isoxazolidine (26)**
1-Vinyl-4-nitroimidazole (**21**; 0.28 g, 2 mmol), 5-hydroxypentanal oxime (0.35 g, 3 mmol) and *p*-formaldehyde (0.12 g, 4 mmol) were placed in THF (25 mL) and the mixture was stirred under reflux (24 h). Column chromatography (silica gel, EtOAc–hexane, 1:2 as eluent) separated the fraction just above the 1-vinyl-4-nitroimidazole starting material. This was identified as the isoxazolidine **25** (0.33 g, 62%; mp 98 °C), which was used without further characterization.

$^1$H NMR (DMSO-$d_6$–TMS): δ = 1.31–1.78 (m, 6 H, 3 × THP-C*H*$_2$), 2.57 (m, 1 H, 4-CH), 2.77 (m, 1 H, 4-CH), 3.15 [m, 1 H, THP(2)-CH], 3.25–3.46 [m, 2 H, THP(6)-C*H*$_2$], 3.86 (m, 1 H, 3-CH), 4.10–4.28 (dd, *J* = 8.8, 2.6 Hz, 1 H, 3-CH), 6.22 (ddd, *J* = 10.0, 7.7, 2.8 Hz, 1 H, 5-CH), 8.03 [t, *J* = 1.2 Hz, 1 H, imidazole C(5)H], 8.48 [t, *J* = 1.6 Hz, 1 H, imidazole C(2)H].

The isoxazolidine **25** (0.27 g, 1 mmol) was dissolved in MeOH (20 mL). To the solution was added concd HCl (2 drops) and the resultant solution was stirred under a $N_2$ atmosphere (1 h). The pH was adjusted to 7 using 1 M aq $K_2CO_3$ and the solvent was removed under reduced pressure. Column chromatography (silica gel: EtOAc as eluent) gave an oil that was identified as the isoxazolidine **26** (0.13 g, 71%); colourless oil.

$^1$H NMR (DMSO-$d_6$–TMS): δ = 2.57 (m, 1 H, 4-CH), 2.74 (br s, 1 H, 4-CH), 3.07 (br s, 1 H, 3-CH), 3.37 (br s, 1 H, 3-CH), 6.22 (dd, *J* = 6.9, 3.2 Hz, 1 H, 5-CH), 7.08 (br s, 1 H, 2-NH), 8.08 [s, 1 H, imidazole C(5)H], 8.62 [s, 1 H, imidazole C(2)H].

$^{13}$C NMR (DMSO-$d_6$–TMS): δ = 37.05 [C(4′)H$_2$], 47.31 [C(3′)H$_2$], 87.10 [C(5′)H], 119.65 [imidazole C(5)H], 136.40 [imidazole C(2)H], 147.50 [imidazole C(4)].

MS (EI): *m*/*z* (%) = 184 (9) [M$^+$], 113, 69 (100), 43, 31.

HRMS: *m*/*z* [M$^+$] calcd for $C_6H_8N_4O_3$: 184.0597; found: 184.0592

## Acknowledgment

We thank Scotia Pharmaceuticals for financial support and the EPSRC National Mass Spectrometry Service for mass spectra.

## References

(1) Lythgoe, D. J.; Ramsden, C. A. In *Advances in Heterocyclic Chemistry*, Vol. 61; Katritzky, A. R., Ed.; Academic Press: San Diego, **1994**, 1.
(2) Boyer, J. H. *Organic Nitro Chemistry Series 1: Nitroazoles. The C-Nitro Derivatives of Five Membered N- and N,O-Heterocycles*; VCH Publishers: Deerfield Beach, Florida, **1986**, 147.
(3) McFadzean, J. A. *Flagyl: The Story of a Pharmaceutical Discovery*; Parthenon Publishing Group Ltd.: Lancaster, **1986**.
(4) Al-Shaar, A. H. M.; Gilmour, D. W.; Lythgoe, D. J.; McClenaghan, I.; Ramsden, C. A. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2779.
(5) Jones, R. H.; Lothian, A. P.; Ramsden, C. A. *Acta Crystallogr., Sect. C* **1996**, *52*, 982.
(6) Al-Shaar, A. H. M.; Chamber, R. K.; Gilmour, D. W.; Lythgoe, D. J.; McClenaghan, I.; Ramsden, C. A. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2789.
(7) (a) Clayton, R.; Davis, M. L.; Fraser, W.; Li, W.; Ramsden, C. A. *Synlett* **2002**, 1483. (b) Curtis, A. D. M.; Humphries, M. J.; Ramsden, C. A. *Arkivoc* **2000**, *iii*, 218. (c) Humphries, M. J.; Ramsden, C. A. *Synthesis* **1999**, 985. (d) Humphries, M. J.; Ramsden, C. A. *Synlett* **1995**, 203. (e) Ramsden, C. A. *Chem. Heterocycl. Compd. (Engl. Transl.)* **1995**, 1323. (f) Al-Shaar, A. H. M.; Gilmour, D. W.; Lythgoe, D. J.; McClenaghan, I.; Ramsden, C. A. *J. Chem. Soc., Chem. Commun.* **1989**, 551.
(8) Ross, W. J.; Jamieson, W. B.; McCowen, M. C. *J. Med. Chem.* **1972**, *15*, 1035.
(9) Mukaiyama, T.; Hoshino, T. *J. Am. Chem. Soc.* **1960**, *82*, 5339.
(10) Barrow, S. J.; Easton, C. J.; Savage, G. P.; Simpson, G. W. *Tetrahedron Lett.* **1997**, *38*, 2175.
(11) Liu, K.-C.; Shelton, B. R.; Howe, R. K. *J. Org. Chem.* **1980**, *45*, 3916.
(12) McKillop, A.; Wright, D. E.; Podmore, M. L.; Chambers, R. K. *Tetrahedron* **1983**, *39*, 3797.
(13) Clayton, R.; Ramsden, C. A. *J. Heterocycl. Chem.* **2004**, *41*, 701.
(14) DeShong, P.; Leginus, J. M. *J. Org. Chem.* **1984**, *49*, 3421.
(15) Xiang, Y.; Chen, J.; Schinazi, R. F.; Zhao, K. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1051.
(16) Mzengeza, S.; Whitney, R. A. *J. Chem. Soc., Chem. Commun.* **1984**, 606.
(17) Rhone-Poulenc, S. Eur. Patent, 0324691A1, **1989**.