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

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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 of the cycloadduct.

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

4-Unsubstituted-5-aminoimidazoles are useful synthetic intermediates. Early workers claimed that these simple amines are very unstable and, although they were implicated in the anaerobic antibacterial activity of 5-nitroimidazoles such as metronidazole (2) (R1 = Me, R2 = CH2CH2OH), their chemistry remained largely unexplored. We have subsequently shown that 5-nitroimidazoles are readily reduced to 5-aminoimidazoles (Figure 1), which can be isolated or trapped by soft electrophiles 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. 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 of selected N-vinyl derivatives of both 4- and 5-nitroimidazoles and now report our findings. Because of the ready availability of metronidazole (2) (R1 = Me, R2 = CH2CH2OH) 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 co-workers. 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 occurred when the alkene 9 was reacted with freshly prepared cyclopentadiene, even in the presence of acid catalysts (AlCl3, TiCl4, aq HCl). Similarly, no cycloaddition products were identified using phenyl azide or the four 1,3-dipoles RHC=(Me)N+X– (X = O or CH2, 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≡N+O–), generated in situ by treatment of a mixture of 1-nitropropane and phenyl isocyanate with a catalytic amount of Et3N, 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-
nent 10. In particular the isoxazoline ring protons were observed at $\delta = 3.53$ ($J = 5, 18.5$ Hz, CHCH$_2$(trans)), 4.08 ($J = 10, 18.5$ Hz, CHCH$_2$(cis)) and 7.33 ($J = 5, 10$ Hz, CH$_2$. 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, 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$_3$N.$^{11}$ 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 $\delta = 3.53$ 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 anemic proton (1') appears at low field (\(\delta = 7.33\)) as a doublet of doublets ($\delta = 5, 10$ Hz). The imidazole proton at position 4 and the methyl substituent at position 2 appear as singlets at $\delta = 7.91$ and $\delta = 2.49$. 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 oxy-gen, and the anomic 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$_4$O$_3$ 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$_3$N 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 $\delta = 1.35$. This is at too high field to be a simple 2-methyl-5-nitroimidazole signal (ca $\delta = 2.5$) and suggests a methyl group attached to a saturated carbon atom. A singlet at $\delta = 8.30$, 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 $\delta = 2.16$ (ddd, $J = 14, 4, 1$ Hz), $\delta = 3.70$ (dd, $J = 14, 6$ Hz) and $\delta = 7.71$ (dd, $J = 6, 4$ Hz). A DEPT spectrum confirmed that the protons at $\delta = 2.16$ and $\delta = 3.70$ are associated with a methylene group ($J_{AB} = 14$ Hz, CH$_2$H$_2$). One of these protons ($\delta = 2.16$) 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 $\delta = 8.30$ 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 $\delta = 135.5$, 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$_4$O$_3$. 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.
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%). 1H 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 OCH2 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. (Tetrahydrofuranyloxy)acetonyltrile oxide [THP-OCH2CNO]15 was formed by reaction of 2-(2-nitroethoxy)tetrahydropyran with PhNCO–Et3N 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 CH2OH 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) 1H 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–HCO2H)
followed by chromatography gave a low yield (7%) of a yellow oil. This was identified as the product 28 by 1H 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. 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 nitroene [H2C=(THP)N+O–] generated in situ from N-(tetrahydropyran-2-yl)hydroxylamine and para-formaldehyde. 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 1H 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 1H NMR it could not be isolated in pure form. Deprotection of the crude mixture (MeOH–conc 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 1H NMR it could not be isolated in pure form. Deprotection of the crude mixture (MeOH–HCO2H) 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.

![Figure 2](image-url)

The 1H and 13C NMR spectra were recorded on a Bruker Avance DPX300 NMR spectrometer at 300 MHz and 50 MHz, respectively, in CDCl3 (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 PF254 containing CaSO4.

5-Nitro-1-(2-tosyloxyethyl)imidazole (15) p-TsCl (11.4 g, 60 mmol) was added to 1-(2-hydroxyethyl)-5-nitroimidazole17 (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.

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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. 49–50 °C).

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

\(^1\)H NMR (CDCl\(_3\)—TMS): \(\delta = 2.51 (s, 3 \text{ H}, \text{CH}_3), 5.41 \text{ (dd, } J = 1.3 \text{, } 15.6 \text{ Hz, } 1 \text{ H, CH} = \text{CH}_2\text{(trans)}), 5.64 \text{ (dd, } J = 1.3 \text{, } 8.2 \text{ Hz, } 1 \text{ H, CH} = \text{CH}_2\text{(cis)}\), 7.06 (dd, \(J = 8.2\), 15.6 Hz, 1 H, NCH=CH\(_2\)), 7.93 \text{ (s, } 1 \text{ H, imidazole C(4)H)\).}

\(^1^C\) NMR (CDCl\(_3\)—TMS): \(\delta = 15.13 \text{ (2-CH}_3\text{), 116.40 (C(3)), 119.59 (C(2)), 132.10 (C(5)H), 135.83 (C(4)H), 147.67 \text{ (C(4)C), 157.69 C(3))\).}

MS (EI): \(m/z = 153 (61) \text{ [M]}^+, 67, 54, 43, 39, 29 (100), 27\). Anal. Calcd for C\(_{13}\)H\(_{12}\)N\(_4\)O\(_3\) (272.26): C, 57.35; H, 4.44; N, 20.58. Found: C, 57.34; H, 4.51; N, 20.31.

1,3-Dipolar Cycloaddition Reactions of 4- and 5-Nitro-1-vinylimidazoles
(a) With Benzonitrile Oxide

2-Methyl-5-nitrovinylimidazole (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\(_3\)N (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\(_3\)N (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): 937, 975, 1095, 1164, 1203, 1245, 1342, 1412, 1455, 1607, 1723, 2893 cm\(^{-1}\).

\(^1\)H NMR (CDCl\(_3\)—TMS): \(\delta = 2.49 \text{ (s, } 3 \text{ H, CH}_3\), 3.53 (dd, \(J = 4.8\), 18.4 Hz, 1 H, CH\(_2\)C\(_{=\text{CH}}\)\(\text{trans}\)), 4.08 (d, \(J = 10.1\), 18.4 Hz, 1 H, CH\(_2\)C\(_{=\text{CH}}\)\(\text{cis}\)), 7.33 (dd, \(J = 4.8\), 10.1 Hz, 1 H, NCH=CH\(_2\)), 7.37–7.66 (m, 5 H, arom-H), 7.91 (s, 1 H, imidazole C(4)H)\). Anal. Calcd for C\(_{13}\)H\(_{12}\)N\(_4\)O\(_3\) (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\(_3\)N (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\(^{-1}\).

\(^1\)H NMR (CDCl\(_3\)—TMS): \(\delta = 1.36 \text{ (d, } J = 1.0 \text{ Hz, } 3 \text{ H, CH}_3\), 2.20 (dd, \(J = 4.0\), 14.1 Hz, 1 H, CH\(_2\)C\(_{=\text{CH}}\)\(\text{trans}\)), 3.70 (dd, \(J = 5.9\), 14.1 Hz, 1 H, CH\(_2\)C\(_{=\text{CH}}\)\(\text{cis}\)), 7.51–7.63 (m, 5 H, arom-H), 7.71 (dd, \(J = 4.1\), 5.8 Hz, 1 H, NCH=CH\(_2\)), 8.30 (s, 1 H, imidazole C(4)H)\). MS (EI): \(m/z = 272 (1) \text{ [M]}^+, 226, 184, 160, 149, 119, 83, 84, 76, 51, 49 (100)\). HRMS: \(m/z = 274.1066 \text{ cale}d \text{ for C}_{13}\text{H}_{14}\text{N}_{4}\text{O}_{3}\). Found: 274.1062.

| (b) With N-Methylbenzaldehyde Nitrone |

2-Methyl-5-(5-nitroimidazol-1-yl)-3-phenyl-4,5-dihydroisoxazole (18)

N-Methylbenzaldehyde nitrore 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, 0.72 mmol) was added to the filtered nitrore 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; EtOAc as eluent) yielded the isoxazolidine 18 (42 mg, 21%).

IR (film): 649, 699, 826, 1064, 1119, 1207, 1466, 1526, 2875 cm\(^{-1}\).

\(^1\)H NMR (CDCl\(_3\)—TMS): \(\delta = 2.42 \text{ (ddd, } J = 3.3\), 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, CH\(_2\)C\(_{=\text{CH}}\)), 3.77 (dd, \(J = 9.6\), 8.2 Hz, 1 H, CH\(_2\)C\(_{=\text{CH}}\)), 6.59 (dd, \(J = 7.3\), 3.3 Hz, 1 H, OCH), 7.21–7.35 (m, 5 H, arom-H), 8.02 (dd, \(J = 1.0 \text{ Hz, 1 H, imidazole C(4)H}, 8.30 \text{ (s, } 1 \text{ H, imidazole C(2)H)}\). MS (EI): \(m/z = 274 (22) \text{ [M]}^+, 135, 134 (100), 118, 115, 105, 104, 103, 91, 78, 77, 52, 42, 28\). HRMS: \(m/z = 272.1263 \text{ cale}d \text{ for C}_{13}\text{H}_{14}\text{N}_{4}\text{O}_{3}\). Found: 272.1269.
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%).

1H NMR (CDCl3-TMS): δ = 2.58 (ddd, J = 3.7, 9.7, 13.7 Hz, 1 H, CH(C(5)H2)), 2.69 (s, 3 H, NCH3), 3.41 (dt, J = 7.9, 13.8 Hz, 1 H, CH(C(5)H2)), 3.74 (dd, J = 9.7, 7.9 Hz, 1 H, NCHPh), 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 = 5.0 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 C18H17N3O3: 299.1349; found: 299.1350.

(c) With O-(Tetrahydropran-2-yl)oxyacetone
3-Hydroxymethyl-5-(4-nitroimidazo-1-yl)isoxazoline (24)
2-(2-Nitroethoxy)tetrahydropran (0.52 g, 3 mmol), phenyl isocy-
mate (1.0 g, 8 mmol) and Et3N (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, 1:2 as eluent)
gave an oil that was dissolved in MeOH (30 mL) and concd HCl (1
drop). The mixture was stirred overnight at 0 °C and was identified as the isoxazoline
(25; 0.27 g, 1 mmol) was dissolved in MeOH (20
mL). To the solution was added concd HCl (2 drops) and the result-

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