Synthesis of 3-Imidazolylazole Derivatives from a New Nitrile Oxide [1]

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The synthesis of a series of 3-Imidazolylazole derivatives using cycloaddition reactions of a useful new nitrile oxide is described.

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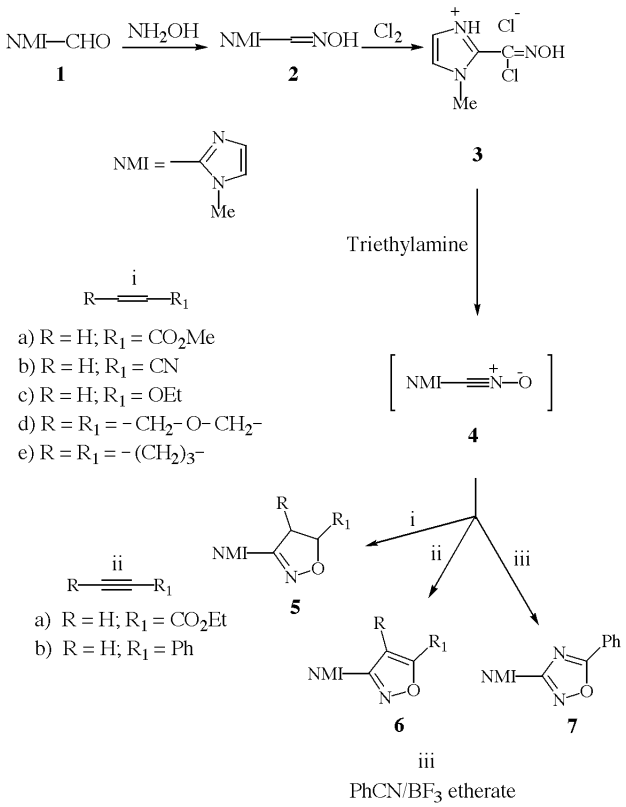
Imidazole chemistry continues to be an intense investigative area since a large number of natural and synthetic compounds are associated with this class of heterocycle. For example, many naturally occurring imidazoles have remarkable biological activity, and a large number of synthesised compounds are widely used as antibacterial drugs and in cancer therapy [2].

The idea of employing an isoxazole or an oxazole substrate, which are widely used by pharmaceutical and agricultural industries, combined with an imidazole ring to obtain more complex heterocycle compounds, led us to design and synthesise the *N*-methyl-2-imidazolyl nitrile oxide **4**. The new nitrile oxide allowed us to prepare, *via* a 1,3 dipolar cycloaddition with selected substrates, 3-imidazolyl, 5-membered *N*,*O*-heterocycles.



The 1,3-dipole was synthesised starting from the aldehyde **1** [3] using a three-step procedure (70% overall yield): oxime **2** formation followed by chlorination to **3** and subsequent *in situ* generation of **4** by dehydrohalogenation with triethylamine.

Cycloaddition reactions were performed on selected electron-rich or electron-poor dipolarophiles using diethyl ether as solvent. As expected, the cycloaddition with monosubstituted dipolarophiles showed high regioselectivity, giving only the 5-substituted derivatives **5** and **6** where the oxygen atom is bound to the more hindered terminus of the dipolarophilic site [4]. The relative yields, which are not optimized are in the range of 30-57%.

Attempted cycloaddition of the nitrile oxide with non-conjugated nitriles such as acetonitrile and phenylacetonitrile was unsuccessful. However, reaction with benzonitrile in the presence of the appropriate catalyst [5] afforded oxadiazolyl-imidazole **7** in moderate yield.

Attempts to oxidise the isoxazoline rings to the isoxazole derivatives, using literature methods employing MnO_2 and NiO_2 [6], were unsuccessful and the required products were not isolated.

EXPERIMENTAL

Melting points were determined with Reichert-Kofler hot stage apparatus and are uncorrected. IR spectra were obtained on Nicolet FT-IR Impact 400D spectrometer, mass spectra were acquired using a Finnigan Mat 90 spectrometer and the microanalyses for C, H, and N on a Carlo Erba 1102. ^{1}H NMR spectra were recorded on a Bruker ARX 300 spectrometer, in the solvent indicated. Chemical shifts (δ) are relative to TMS, which was used as an internal reference. Column chromatography was performed on Merck silica gel 70-270 mesh. All solvents and reagents were obtained from commercial sources and purified before use if necessary.

Preparation of 2-Imidazolyloxime (**2**).

A solution of 20.85 g of NH_2OH·HCl in 30 ml of water and 60 ml of a 20% NaOH were added to 5.5 g, 0.05 mol of *N*-methyl-2-formylimidazole in 150 ml of ethanol. The mixture was heated to boiling for a few minutes, and subsequently the alcohol was evaporated under reduced pressure. The remaining solution was cooled to room temperature, and 150 ml of iced water was added. The oxime precipitated from the solution and

was collected by filtration. (mp 170 °C, 5.0 g, 80%). EIMS m/z 125 (M^+); IR(nujol): 2800-2400 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.8 (s, 3H), 6.97 (s, 1H), 7.25 (s, 1H), 8,04 (s, 1H), 11.47 (s, 1H).

Anal. Calcd. for $C_5H_7N_3O$: C, 48.0; H, 5.6; N, 33.6. Found: C, 48.2; H, 5.7; N, 33.5.

Preparation of the Hydroxamoyl Chloride Hydrochloride (**3**).

A mixture of 1.25 g, 10 mmol of **2** in 250 ml of $CHCl_3$, was added in small portions to a vigorously stirred solution of 0.78 g, 11 mmol of Cl_2 in 250 ml $CHCl_3$ at 5 °C. The mixture was left stirring overnight at room temperature, then the product was collected by filtration, and washed with acetone; **3** (m.p. 187 °C dec., 1.76g, 90%). FABMS m/z 160 (M^+-Cl); IR(nujol): 2800-2400, 1594 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.88 (s, 3H), 4.43 (br, 2H), 7.52 (s, 1H), 7.72 (s, 1H).

Anal. Calcd. for $C_5H_7N_3OCl_2$: C 30.6, H 3.6, N 21.4. Found: C 30. 8, H 3.5, N 21.6.

General Procedure for Synthesis Compounds (**5**) and (**6**).

The appropriate dipolarophile (10 mmol) was added to 0.39 g (2.0 mmol) of **3** suspended in 50 ml of diethyl ether. A solution containing 4 mmol of triethylamine (TEA) in 30 ml of diethyl ether was added dropwise with stirring. The mixture was left stirring overnight at room temperature, washed with 50 ml of water, dried over anhydrous sodium sulphate, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel packing, diethyl ether eluent).

Methyl 3-(1-Methyl-1*H*-imidazol-2-yl)-4,5-dihydroisoxazole-5-carboxylate (**5a**).

This compound was obtained in a yield of 34% (0.142 g), mp 60 °C; EIMS m/z 209 (M^+); IR(nujol): 1731, 1602 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.81 (s, 3H), 3.84 (d, 2H, J = 9 Hz), 3.95 (s, 3H), 5.13 (t, 1H, J = 9 Hz), 7.01 (s, 1H), 7.13 (s, 1H).

Anal. Calcd. for $C_9H_{11}N_3O_3$: C, 51.7; H, 5.3; N, 20.1. Found: C, 51.8; H, 5.5; N, 19.9.

3-(1-Methyl-1*H*-imidazol-2-yl)-4,5-dihydro-isoxazole-5-carbonitrile (**5b**).

This compound was obtained in a yield of 32% (0.113 g), mp 84 °C; EIMS m/z 176 (M^+); IR(nujol): 1610 cm^{-1}[7]; ^1H NMR ($CDCl_3$) δ 3.90 (m, 2H), 3.95 (s, 3H), 5.28 (m, 1H), 7.07 (s, 1H), 7.18 (s, 1H).

Anal. Calcd. for $C_8H_8N_4O$: C, 54.5; H, 4.6; N, 31.8. Found: C, 54.8; H, 4.7; N, 31.6.

5-Ethoxy-3-(1-methyl-1*H*-imidazol-2-yl)-4,5-dihydroisoxazole (**5c**).

This compound was obtained in a yield of 33% (0.129 g), mp 45 °C; EIMS m/z 195 (M^+); IR(nujol): 1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.22 (t, 3H, J = 7 Hz), 3.5 (q, 2H, J = 7 Hz), 3.60 (m, 1H), 3.91 (m, 1H), 3.95 (s, 3H), 5.62 (m, 1H), 6.98 (s, 1H), 7.11 (s, 1H).

Anal. Calcd. for $C_9H_{13}N_3O_2$: C, 55.4; H, 6.7; N, 21.5. Found: C, 55.6; H, 6.9; N, 21.3.

3-(1-Methyl-1*H*-imidazol-2-yl)-3a,4,6,6a-tetrahydrofuro[3,4-*d*]-isoxazole (**5d**).

This compound was obtained in a yield of 52% (0.200 g), mp 62 °C; EIMS m/z 193 (M^+); IR(nujol): 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.79 (dd, 1H, J_{32} = 4 Hz, J_{34} = 11 Hz), 3.92 (s, 3H), 4.31 (d, 2H, J_{43} = 11 Hz), 4.42 (d, 2H, J_{12} = 10 Hz), 5.28 (dd, 1H, J_{23} = 4 Hz, J_{21} = 10 Hz), 6.99 (s, 1H), 7.11 (s, 1H).

Anal. Calcd. for $C_9H_{11}N_3O_2$: C, 55.9; H, 5.7; N, 21.7. Found: C, 56.1; H, 5.9; N, 21.6.

3-(1-Methyl-1*H*-imidazol-2-yl)-4,5,6,6a-tetrahydro-3a*H*-cyclopenta[*d*]isoxazole (**5e**).

This compound was obtained in a yield of 53 % (0.202 g), bp 105 °C/15 mmHg; EIMS m/z 191 (M^+); IR(nujol): 1610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.41-2.22 (m, 6H), 3.9 (s, 3H), 4.23 (m, 1H), 5.13 (m, 1H), 6.95 (s, 1H), 7.11 (s, 1H).

Anal. Calcd. for $C_{10}H_{13}N_3O$: C, 62.8; H, 6.8; N, 22,0. Found: C, 62.9; H, 6.9; N, 21.8.

Ethyl 3-(1-Methyl-1*H*-imidazol-2-yl)-isoxazole-5-carboxylate (**6a**).

This compound was obtained in a yield of 30% (0.132 g), mp 46 °C; EIMS m/z 221 (M^+); IR(nujol): 1725, 1590 cm^{-1}; δ 1.43 (t, 3H, J = 7.5 Hz), 4.06 (s, 3H), 4.46 (q, 2H, J = 7.5 Hz), 7.05 (s, 1H), 7.19 (s, 1H), 7.50 (s, 1H).

Anal. Calcd. for $C_{10}H_{11}N_3O_3$: C, 54.3; H, 5.0; N, 19.00. Found: C, 54.5; H, 5.1; N, 18.7.

3-(1-Methyl-1*H*-imidazol-2-yl)-5-phenyl-isoxazole (**6b**).

This compound was obtained in a yield of 39% (0.175 g), mp 72 °C; EIMS m/z 225 (M^+); IR(nujol): 1617 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.08 (s, 3H), 7.02 (s, 1H), 7.14 (s, 1H), 7.19 (s, 1H), 7.49 (m, 3H), 7.84 (m, 2H).

Anal. Calcd. for $C_{13}H_{11}N_3O$: C, 69.3; H, 4.9; N, 18.6. Found: C, 69.4; H, 4.8; N, 18.4.

Preparation of 3-(1-Methyl-1*H*-imidazol-2-yl)-5-phenyl-[1,2,4]oxadiazole (**7**).

A BF_3 etherate solution (0.568 g, 4 mmol) and later an ether solution of imidazolylnitrile oxide, obtained from 0.585 g (3 mmol) of chlorooxime hydrochloride and triethylammine 0.6 g (6 mmol), were added in a flask containing benzonitrile (2 ml); after removing ether by heating, the reaction mixture was refluxed for about 2 hours. The solution was evaporated to dryness under reduced pressure and the residue was purified by column chromatography (silica gel packing, chloroform eluent) to afford **7**, 0.203 g (45%), mp 143 °C; EIMS m/z 226 (M^+); IR(nujol): 1611 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.12 (s, 3H), 7.12 (s, 1H), 7.33 (s, 1H), 7.55 (m, 3H), 8.29 (m, 2H).

Anal. Calcd. for $C_{12}H_{10}N_4O$: C, 63.7; H, 4.4; N, 24.8. Found: C, 63.9; H, 4.6; N, 24.6.

REFERENCES AND NOTES

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