Synthesis and Thermolysis of 5-Azido-4-formyloxazoles

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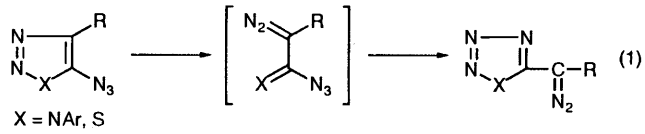
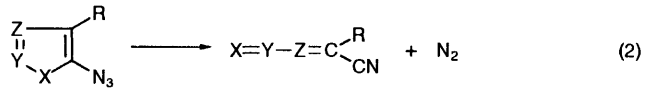
5-Azidooxazole-4-carbaldehydes **5a–c** have been prepared from the corresponding chloro aldehydes and found to be unstable in solution at room temperature. Whereas the phenyl derivative **5a** decomposed with loss of nitrogen and formation of the imine **6** which was trapped with 2,3-dimethylbutadiene, the isopropyl and *tert*-butyl derivatives **5b, c** underwent a Cornforth rearrangement to give 4-azidocarbonyloxazoles **9b, c**. Kinetic measurements revealed the following order of stability: **5a** > **5c** > **5b**.

5-Azido-1*H*-1,2,3-triazoles and 5-azido-1,2,3-thiadiazoles, bearing electron-withdrawing substituents at the 4-position, rearrange thermally by a ring opening–ring closure mechanism and with conservation of all nitrogen atoms [eqn. (1)].[1] All other 5-azidoazoles known so far decompose at relatively low temperature by loss of nitrogen and cleavage of the heterocycle [eqn. (2)].[2]

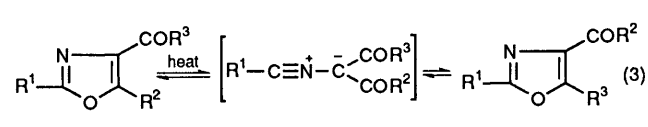


(1)



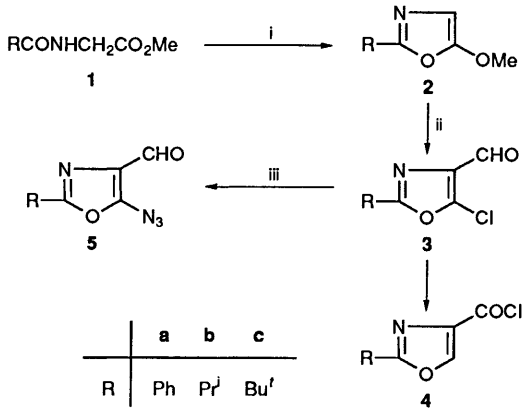
(2)

During our continued search for molecular rearrangements, the Cornforth rearrangement attracted our attention.[3] This reaction comprises the thermal interconversion of 4-carbonyl substituted oxazoles with dicarbonyl ylides as postulated intermediates [eqn. (3)]. Depending on the substituents, the reaction conditions vary from room temperature to heating in xylene. If R^2 is an azide function, the Cornforth rearrangement [cleavage of O–C(2)] offers a possible alternative to the classical decomposition path of eqn. (2) [cleavage of O–C(5)], provided that the reaction temperature is sufficiently low.



(3)

5-Chlorooxazole-4-carbaldehydes **3** are suitable precursors for the azides **5**. Cornforth[3a] had already prepared the phenyl derivative **3a** by a multi-step procedure and reported that this relatively stable compound rearranges on distillation to give the acyl chloride **4a** according to eqn. (3). We have synthesized **3a** by a more convenient and straightforward method shown in Scheme 1. Thus, methyl benzoylaminoacetate **1a** was dehydrated to the 5-methoxyoxazole **2a** by a known procedure[3a] and then treated with Vilsmeier's reagent to afford the chloro aldehyde **3a**. Compounds **3b** and **3c** were similarly prepared from the α-acylamino esters **1b, c** as unstable oils which rearranged slowly when, as solutions in $CDCl_3$, their NMR spectra were recorded. Indeed, the aldehyde protons of **3b, c** at δ 9.9 decreased in intensity in favour of singlets at δ 8.45 for the 5-H of the oxazoles **4b, c**. When the NMR tubes were left overnight, complete rearrangement had occurred and the



Scheme 1 *Reagents:* P_2O_5; ii, $POCl_3$/DMF; iii, NaN_3/DMF

structures of the resulting oxazole-4-carbonyl chlorides **4b, c** were further confirmed by the ^{13}C NMR spectra showing typical resonances at δ 158 for COCl and at δ 148 for C-5 (d, $^1J_{CH}$ 214 Hz) (see Table 1). At 60 °C, the chloro aldehydes **3b, c** rearranged with a half-life of *ca.* 15 min.

The azides **5a–c** were readily obtained from the chloro aldehydes **3a–c** at 0 °C and proved to be unstable in solution at room temperature. Although the freshly prepared chloroform solutions showed evidence of some degree of decomposition in their NMR spectra, complete characterization was possible (see Table 1). Compound **5a** evolved nitrogen only slowly at room temperature and had a half-life of 70 min in $CDCl_3$ at 40 °C. The resulting product was assigned structure **6** on the basis of the newly formed aldehyde proton resonance at δ 9.6 and the characteristic carbon resonances shown on the drawing. Since all attempts at isolation failed, we trapped **6** with 2,3-dimethylbutadiene to afford the Diels–Alder adducts **7** and **8**; deformylation occurred during this reaction.

In contrast to **5a**, the azides **5b** and **5c** both rearranged at room temperature and yielded the isomeric oxazoles **9b, c**. When the reactions were monitored by ^1H NMR spectroscopy in $CDCl_3$ solution, the aldehyde proton resonances of **5b, c** at δ 9.8 were gradually transformed into oxazole 5-H resonances at δ 8.2 with half-lives of 3 and 4.5 h, respectively, at room temperature. The isolated products **9b, c** were readily characterized by spectral methods, particularly by the presence of carbon resonances at δ 166 for CON_3 and at δ 145 (d) for C-5 (Table 1).

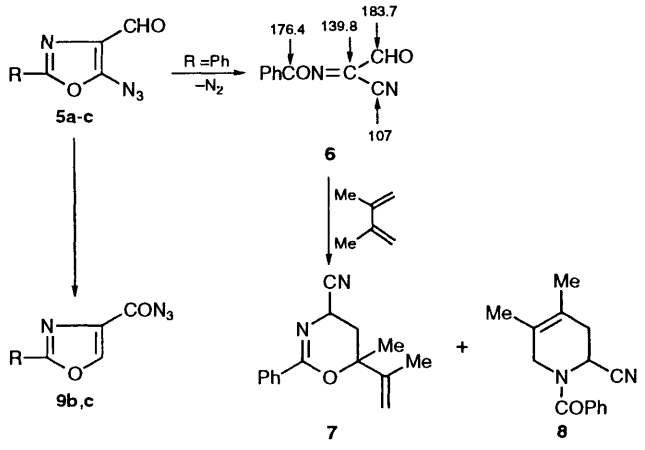
Experimental

IR spectra were recorded on a Perkin–Elmer spectrometer, ^1H and ^{13}C NMR spectra on a Bruker WM-250 or AMX-400

Table 1 Selected ^{13}C chemical shifts of the heterocycles[a]

Compd.	C-2	C-4	C-5	C=O
2a	152.5	99.7	160.7	
2b	159.6	97.5	160.3	
2c	161.7	97.2	160.3	
3a	160.8	133.7	142.5	181.9
3b	168.7	132.5	142.6	181.9
3c	170.9	132.4	142.3	182.0
4a	163.5	136.3	147.8	158.8
4b	171.1	136.9	147.7	158.5
4c	173.2	136.5	148.1	158.2
5a	156.5	125.5	149.1	183.7
5b	163.8	123.9	148.8	183.3
5c	166.1	124.0	148.8	183.5
9b	170.5	134.0	144.55	166.1
9c	172.8	134.1	144.6	166.2

[a] The chemical shifts are given in ppm downfield from TMS in $CDCl_3$ solution. The R substituents resonate at the following positions: Ph C-atoms δ 125–132; Pr^i: δ 20 and 28; Bu^t: δ 28 and 34.



Scheme 2

spectrometer, and mass spectra (EI) on a Hewlett Packard 5989A or Kratos MS50 TC (for high resolution) instrument.

5-Chloro-2-phenyloxazole-4-carbaldehyde **3a**.—Compound **1a** (10 g, 50 mmol) was heated with P_2O_5 (40 g, 280 mmol) in dry chloroform (100 cm^3) overnight after which the reaction mixture was poured into ice-cooled aq. NaOH (10%, 400 cm^3). The chloroform layer was separated and the aqueous layer further extracted with chloroform (3 × 200 cm^3). The combined extracts were washed with water (3 × 200 cm^3), dried ($MgSO_4$) and evaporated. The residue was chromatographed on silica gel with chloroform as the eluent to give the oxazole **2a** (6.65 g, 76%), m.p. 80 °C (from Et_2O). This compound (10 g, 60 mmol) was added to $POCl_3$ (60 cm^3) in DMF (30 cm^3) and the stirred mixture was heated at 90 °C for 2 h. It was then poured cautiously into ice–water (500 cm^3) containing K_2CO_3 (300 g), and extracted with chloroform (3 × 200 cm^3). The combined extracts were washed with water (5 × 200 cm^3), dried and evaporated and the residue was chromatographed on silica gel with chloroform–diethyl ether (1:1) as the eluent to give chloro aldehyde **3a** (8.84 g, 75%), m.p. 94 °C (lit.,[3a] 91–93 °C); ν_{max}(KBr)/cm^{-1} 1705s (CO); δ_H($CDCl_3$) 7.45–7.55 and 8.05 (5 H, m + d, Ph) and 9.96 (1 H, s, CHO); δ_C($CDCl_3$) see Table 1; *m/z* 207 ($M^{\bullet+}$ containing ^{35}Cl isotope, 100%), 179 ($M^{\bullet+}$ − CO, 40), 172 ($M^{\bullet+}$ − Cl, 83), 116 ($M^{\bullet+}$ − 2 CO − Cl, 45) and 89 (52).

5-Chloro-2-isopropyloxazole-4-carbaldehyde **3b**.—P_2O_5 (44 g, 5 equiv.) was added in small portions to a solution of **1b** (10 g, 62 mmol) in chloroform (200 cm^3) and the mixture was refluxed for 16 h. It was then cooled, neutralized with aq. NaOH (10%) and extracted with chloroform (6 × 30 cm^3). The combined extracts were dried ($NaHCO_3$) and evaporated to give the oxazole **2b** (7 g, 77%). This compound (8.5 g, 59 mmol) was added to $POCl_3$ (49 cm^3) in DMF (24 cm^3) and the stirred mixture was heated at 80 °C for 2 h. It was then poured cautiously into ice–water (300 cm^3) containing K_2CO_3 (100 g) and the mixture extracted with chloroform (5 × 50 cm^3). The combined extracts were dried ($NaHCO_3$) and evaporated and the resulting brown residue was dissolved in diethyl ether (50 cm^3) and the solution washed with water (4 × 30 cm^3), dried and evaporated to give chloro aldehyde **3b** as an unstable oil (4.5 g, 43.5%); δ_H($CDCl_3$) 1.3 (6 H, d, 2 Me), 3.05 (1 H, sept., CH) and 9.8 (1 H, s, CHO); δ_C($CDCl_3$) see Table 1.

2-tert-Butyl-5-chlorooxazole-4-carbaldehyde **3c**.—Compound **1c** (10 g, 60 mmol) was heated with P_2O_5 (40 g, 280 mmol) in dry chloroform (100 cm^3) overnight after which the reaction mixture was poured into ice-cooled aq. NaOH (10%; 400 cm^3). The chloroform layer was separated and the aqueous layer further extracted with chloroform (3 × 200 cm^3). The combined extracts were washed with water (3 × 200 cm^3), dried ($MgSO_4$) and evaporated and the residue was chromatographed on silica gel with chloroform as the eluent to give oxazole **2c** as an oil (5.59 g, 62%). This compound (3.2 g, 20 mmol) was added to $POCl_3$ (16 cm^3) in DMF (8 cm^3) and the stirred mixture was heated at 80 °C for 2 h. It was then poured cautiously into ice–water (300 cm^3) containing K_2CO_3 (40 g) and the mixture was extracted with chloroform (7 × 30 cm^3). The combined extracts were dried ($NaHCO_3$) and evaporated and the resulting brown residue was dissolved in diethyl ether (50 cm^3) and the solution washed with water (4 × 30 cm^3), dried ($NaHCO_3$) and evaporated to give the chloro aldehyde **3c** as a dark yellow oil; this was further purified by column chromatography on silica gel with dichloromethane as the eluent (1.7 g, 45%); ν_{max}(neat)/cm^{-1} 1720s (CO); δ_H($CDCl_3$) 1.43 (9 H, s, Bu^t) and 9.9 (1 H, s, CHO); δ_C($CDCl_3$) see Table 1; *m/z* 187 ($M^{\bullet+}$ containing ^{35}Cl isotope, 10%), 152 ($M^{\bullet+}$ − Cl, 65), 136 ($M^{\bullet+}$ − Cl − Me, 22), 96 (17), 69 ($C_5H_9^+$, 23) and 57 ($C_4H_9^+$, 100).

2-Isopropyloxazole-4-carbonyl Chloride **4b**.—A solution of compound **3b** (1 g, 5.4 mmol) in chloroform (30 cm^3) was stirred overnight at room temperature. Chromatography of the mixture on silica gel with chloroform as the eluent gave the acyl chloride **4b** as an oil (0.55 g, 55%), contaminated with traces of the corresponding acid; ν_{max}(neat)/cm^{-1} 1780s (CO); δ_H($CDCl_3$) 1.4 (6 H, d, 2 Me), 3.15 (1 H, sept., CH) and 8.4 (1 H, s, 5-H); δ_C($CDCl_3$) see Table 1.

2-tert-Butyloxazole-4-carbonyl Chloride **4c**.—A solution of compound **3c** (0.5 g, 2.7 mmol) in chloroform (20 cm^3) was stirred at 50 °C for 2 h. Chromatographic purification on silica gel with chloroform as the eluent gave white crystals of the acyl chloride **4c** (0.35 g, 70%), m.p. 54–56 °C ν_{max}(KBr)/cm^{-1} 1780s (CO); δ_H($CDCl_3$) 1.45 (9 H, s, 3 Me) and 8.4 (1 H, s, 5-H); δ_C($CDCl_3$) see Table 1; *m/z* 187 ($M^{\bullet+}$ containing ^{35}Cl isotope, 18%), 172 ($M^{\bullet+}$ − Me, 15), 152 ($M^{\bullet+}$ − Cl, 100), 136 ($M^{\bullet+}$ − Me − HCl, 21), 96 (13), 69 (11) and 57 ($C_4H_9^+$, 54) (Found: $M^{\bullet+}$, 187.0400. $C_8H_{10}ClNO_2$ requires *M*, 187.0400).

5-Azido-2-phenyloxazole-4-carbaldehyde **5a**.—A solution of compound **3a** (1 g, 4.8 mmol) and NaN_3 (0.62 g, 2 equiv.) in DMF (20 cm^3) was stirred at 0 °C for 1 h and then poured into water (50 cm^3) and extracted with diethyl ether (5 × 30 cm^3). The combined extracts were dried ($NaHCO_3$), concentrated and cooled at −20 °C. The crystalline azide **5a** was filtered off and stored at −20 °C (0.76 g, 74.5%), m.p. 98 °C (decomp.);

ν_{max}(KBr)/cm^{-1} 2150s (N_3) and 1680s (CO); δ_H($CDCl_3$) 7.4–7.6 and 8.05 (5 H, m + d, Ph) and 9.9 (1 H, s, CHO); δ_C($CDCl_3$) see Table 1; *m/z* 214 ($M^{\bullet+}$, 2%), 105 ($PhCO^+$, 100), 77 (Ph, 70) and 51 (34) (Found: $M^{\bullet+}$, 214.0489. $C_{10}H_6N_4O_2$ requires *M*, 214.0491).

5-Azido-2-isopropyloxazole-4-carbaldehyde **5b**.—A solution of compound **3b** (2 g, 11.5 mmol) and NaN_3 (1.87 g, 2.5 equiv.) in DMF (30 cm^3) was stirred at 0 °C for 1.5 h and then poured into water (50 cm^3) and extracted with diethyl ether (6 × 30 cm^3). The combined extracts were washed with water (4 × 30 cm^3), dried ($NaHCO_3$) and evaporated to give the azide **5b** as an unstable yellow oil (1.2 g, 58%); ν_{max}(neat)/cm^{-1} 2150s (N_3) and 1693s (CO); δ_H($CDCl_3$) 1.3 (6 H, d, 2 Me), 3.1 (1 H, sept., CH) and 9.8 (1 H, s, CHO); δ_C($CDCl_3$) see Table 1.

5-Azido-2-tert-butyloxazole-4-carbaldehyde **5c**.—A solution of compound **3c** (2 g, 10.6 mmol) and NaN_3 (1.74 g, 2.5 equiv.) in DMF (30 cm^3) was stirred at 0 °C for 1.5 h and then poured into water (50 cm^3) and extracted with diethyl ether (8 × 30 cm^3). The combined extracts were washed with water, dried ($NaHCO_3$), concentrated, diluted with pentane and left overnight at −20 °C. The crystalline azide **5c** was filtered off and stored at −20 °C (1.5 g, 72%), m.p. 48–52 °C (decomp.) ν_{max}(neat)/cm^{-1} 2150s (N_3) and 1690s (CO); δ_H($CDCl_3$) 1.4 (9 H, s, Bu^t) and 9.8 (1 H, s, CHO); δ_C($CDCl_3$) see Table 1.

Thermolysis of the Azide **5a**.—The azide **5a**, freshly prepared from compound **3a** (2 g, 9.6 mmol) and NaN_3 (2 equiv.) as described above, was dissolved in DMF (20 cm^3) and allowed to decompose in the presence of 2,3-dimethylbuta-1,3-diene (10 g, 120 mmol) at room temperature for 30 days. After removal of the solvent, the residue was chromatographed twice on silica gel with chloroform–diethyl ether (15:1) as the eluent to give the two diastereoisomers of the oxazine **7** (370 mg, 16%), the pyridine **8** (231 mg, 10%) and a fraction (64 mg, 2.8%) composed of compounds **7** and **8**.

4-Cyano-5,6-dihydro-*c*-6-methyl-6-(1-methylvinyl)-2-phenyl-4*H*-oxazine **7** (12%); ν_{max}(CCl_4)/cm^{-1} 1651s; δ_H($CDCl_3$) 1.57 and 1.8 (6 H, s + br s, 2 Me), 2.0, 2.52 and 4.41 (3 H, 3 dd, CH_2CH, ^2J 13.7, ^3J 4.5 and 11.9) 4.88 and 4.98 (2 H, 2 s, $=CH_2$) and 7.4, 7.48 and 8.0 (5 H, 2 t + d, Ph); δ_C($CDCl_3$) 18.3 and 26.9 (2 Me), 33.6 (C-5), 43.0 (C-4), 79.7 (C-6), 112.7 and 144.3 (CH_2=C axial), 119.7 (CN), 127.4, 128.2, 131.4 and 132.4 (Ph C-atoms) and 156.8 (C-2); *m/z* 240 ($M^{\bullet+}$, 6%), 135 (11), 105 (100), 82 (20) and 77 (49) (Found: $M^{\bullet+}$, 240.1252. $C_{15}H_{16}N_2O$ requires *M*, 240.1263).

4-Cyano-5,6-dihydro-*t*-6-methyl-6-(1-methylvinyl)-2-phenyl-4*H*-oxazine **7** (4%); ν_{max}(CCl_4)/cm^{-1} 1644s; δ_H($CDCl_3$) 1.5 and 1.9 (6 H, s + br s, 2 Me), 2.2–2.3 and 4.67 (3 H, m + t, CH_2CH, ^2J 13.7, Σ^3J 14.8), 5.01 and 5.11 (2 H, 2 s, $=CH_2$) and 7.4, 7.48 and 8.0 (5 H, 2 t + d, Ph); δ_C($CDCl_3$) 18.5 (Me), 24.7 (Me axial) 33.2 (C-5), 42.7 (C-4), 78.0 (C-6), 111.9 and 145.7 (CH_2=C), 119.2 (CN), 127.4, 128.2, 131.4 and 132.8 (Ph C-atoms) and 157.3 (C-2); *m/z* 240 ($M^{\bullet+}$, 4%), 135 (12), 105 (100), 82 (30) and 77 (36) (Found: $M^{\bullet+}$, 240.1259. $C_{15}H_{16}N_2O$ requires *M*, 240.1263).

1-Benzoyl-2-cyano-1,2,3,6-tetrahydro-4,5-dimethylpyridine **8** (10%); ν_{max}(CCl_4)/cm^{-1} 1656s; δ_H($CDCl_3$ 55 °C) 1.6 and 1.7 (6 H, 2 s, 2 Me), 2.2, 2.65, 3.95 and 4.05 (4 H, 2 d + 2 br d, 2 CH_2), 5.6 (1 H, m, CHCN) and 7.5 (5 H, s, Ph); δ_C($CDCl_3$, 55 °C) 15.9 and 18.4 (2 Me), 33.9 (C-3), 41.4 (br, C-2), 47.4 (br, C-6), 117.5 (CN), 121.8 and 123.2 (C-4 and C-5), 127.1, 128.7, 130.6 and 134.5 (Ph C-atoms) and 170.1 (CO); *m/z* 240 ($M^{\bullet+}$, 11), 105 (100) and 77 (69) (Found: $M^{\bullet+}$ 240.1268. $C_{15}H_{16}N_2O$ requires *M*, 240.1263).

Note: When the azide **5a** was allowed to decompose in $CDCl_3$ without trapping reagent, the NMR spectrum showed the presence of a compound with an aldehyde proton resonance at δ 9.6 and C-resonances (see drawing) consistent with structure **6**.

4-Azidocarbonyl-2-isopropyloxazole **9b**.—Compound **5b** (1 g, 5.5 mmol) was allowed to rearrange in chloroform (50 cm^3) at room temperature for 18 h. The reaction mixture was subjected to column chromatography on silica gel with chloroform as the eluent to give the acyl azide **9b** (0.6 g, 60%), m.p. 37–38 °C; ν_{max}(neat)/cm^{-1} 2150s (N_3) and 1700s, br (CO); δ_H($CDCl_3$) 1.3 (6 H, d, 2 Me), 3.2 (1 H, sept., CH) and 8.2 (1 H, s, 5-H); δ_C($CDCl_3$) see Table 1; *m/z* 180 ($M^{\bullet+}$, 2%), 138 ($M^{\bullet+} - N_3$, 9), 71 ($C_3H_7CO^+$, 32) and 43 ($C_3H_7^+$, 100) (Found: $M^{\bullet+}$ 180.0647. $C_7H_8N_4O_2$ requires *M*, 180.06472).

4-Azidocarbonyl-2-tert-butyloxazole **9c**.—Compound **5c** (1.5 g) was allowed to rearrange in chloroform (50 cm^3) at room temperature for 18h. The reaction mixture was subjected to column chromatography on silica gel with hexane–ethyl acetate (4:1) as the eluent to give the acyl azide **9c** (0.9 g, 60%), m.p. 48 °C; ν_{max}(KBr)/cm^{-1} 2150s (N_3) and 1700s, br (CO); δ_H($CDCl_3$) 1.34 (9 H, s, Bu^t) and 8.2 (1 H, s, 5-H); δ_C($CDCl_3$) see Table 1; *m/z* 194 ($M^{\bullet+}$, 1%) and 57 ($C_4H_9^+$, 100) (Found: C, 49.3; H, 5.2. $C_8H_{10}N_4O_2$ requires C, 49.48; H, 5.15%).

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