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1,3-Dipolar Cycloaddition Reactions of Nitrile Oxides with 4,5-Dihydrooxazole and 4,5-Dihydrothiazole Derivatives

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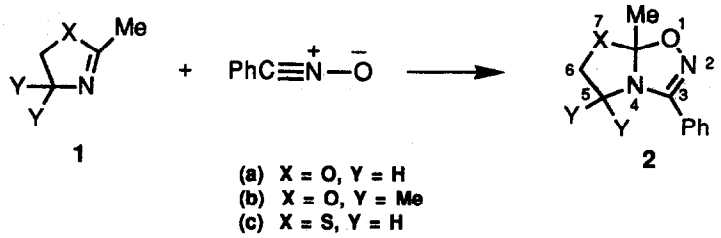
Abstract: 4,5-Dihydro-2-methyloxazole **1a** and 4,5-dihydro-2,4,4-trimethyloxazole **1b**, which are examples of cyclic imidate esters, undergo 1,3-dipolar cycloaddition reactions with benzonitrile *N*-oxide, to give the appropriate 5,6-dihydro-7a-methyl-3-phenyl-7a*H*-oxazolo[3,2-*d*]-1,2,4-oxadiazole (**2a** and **2b** respectively). 4,5-Dihydro-2-methylthiazole **1c** gives the thia analogue **2c**.
With alkanoyl and aroyl cyanide *N*-oxides (RCOCNO), 4,5-dihydro-2-methyloxazole **1a** and 4,5-dihydro-2-methylthiazole **1c** give the open-chain compounds, $RCOXCH_2CH_2N(CN)COMe$ (X = O and S respectively).

Professor Charles Rees has concluded that "of all the artillery added in recent years to the armoury of the heterocyclic chemist, the most powerful must surely be that which is based on the use of cycloaddition reactions".[1] More specifically, 1,3-dipolar cycloaddition reactions have provided a vast range of 5-membered heterocycles of varying degrees of complexity. We have continued to tread the path which was so elegantly laid in this area by the Huisgen Group,[2] and here describe some of our studies on 1,3-dipolar cycloadditions to imidate esters.

Relatively little attention has been paid to this aspect of imidate chemistry. Huisgen[3] and his co-workers showed that ethyl acetamidate will react with nitrile imines to produce the fully aromatic heterocycle by the loss of ethanol from the proposed cycloadduct. Other workers[4,5] have similarly obtained fully aromatised 1,2,4-oxadiazoles by reaction of a range of open-chain imidates with nitrile oxides. We (P.D.K. and R.W.) have carried out cycloaddition reactions on 2-ethoxy- or 2-(ethylthio)-1-azetines, which may be regarded as imidate esters of the type -C(XEt)=N- (X = O or S), in which the C=N moiety is constrained within a 4-membered ring.[6,7]

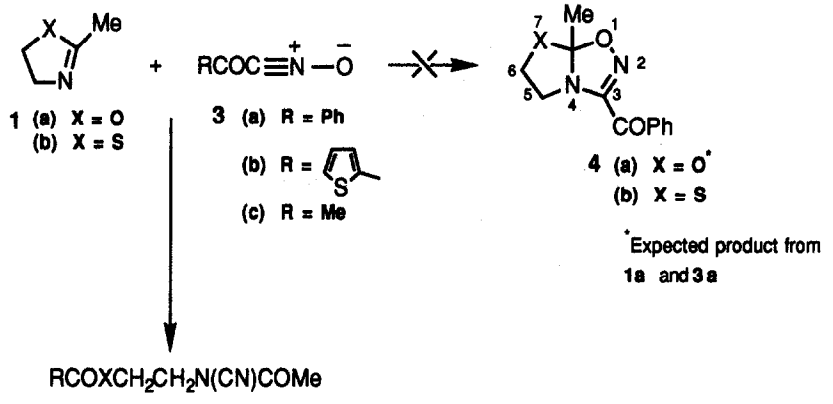
We have now studied some cycloaddition reactions of the 4,5-dihydrooxazoles **1a** and **1b** and the sulfur analogue **1c** (Scheme 1); such compounds **1** may be regarded as cyclic imidate esters. In 1971 German workers showed that 4,5-dihydro-2-methyloxazole **1a** reacted with benzonitrile *N*-oxide, to give the expected adduct **2a** (87%).[8] Since no proof of the structure of the adduct was presented, we repeated this work (our yield was 59%) and confirmed the structure spectroscopically.



(a) X = O, Y = H
(b) X = O, Y = Me
(c) X = S, Y = H

Scheme 1

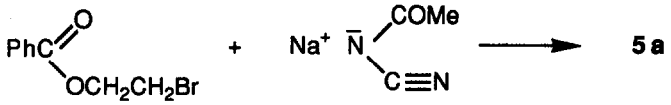
We showed also that 4,5-dihydro-2,4,4-trimethyloxazole **1b** and 4,5-dihydro- 2-methylthiazole **1c** reacted similarly with benzonitrile *N*-oxide, to give the bicyclic adducts **2b** (28%) and **2c** (30%) respectively. We were unable to confirm the regiochemistry of the reaction, but there is ample precedent[9] to show that, in accordance with the principle of maximum gain in σ-bond energy, the electronegative end of a heterodipolarophile becomes joined to the carbon atom of the nitrile oxide. Spectroscopic details of the adducts **2a-2c** are cited in the Experimental Section. However, two points are worthy of comment. In the ^{1}H NMR spectrum, the two protons in the 6-position and the two protons in the 5-position (in **2a** and **2c**), have well separated chemical shifts, and the expected couplings are observed. In the mass spectrum, the adducts show a base peak at *m/z* 119, corresponding to the starting nitrile oxide, formed presumably *via* a cycloreversion reaction. Similar behaviour has been observed in the mass spectra of pyrrolo[2,1-*b*]-1,2,4-oxadiazoles, obtained by cycloaddition of benzonitrile *N*-oxide to 3,4-dihydro-2,2-dimethyl-2*H*-pyrrole.[10]



5 (a) X = O, R = Ph
(b) X = S, R = Ph
(c) X = O, R = 2-thienyl
(d) X = S, R = 2-thienyl
(e) X = O, R = Me
(f) X = S, R = Me

Scheme 2

We next investigated the reactions of **1a** with benzoyl cyanide *N*-oxide **3a**, which is easily prepared and is known[11] to undergo 1,3-dipolar cycloaddition reactions with a range of ethylenic and acetylenic dipolarophiles. It was immediately obvious that the product (57%) from this reaction was not the expected cycloadduct **4a** (Scheme 2). Surprisingly, the unknown product showed characteristic nitrile absorption ($\nu_{max.}$ 2235 cm^{-1}) and *two* carbonyl absorptions ($\nu_{max.}$ 1720 and 1735 cm^{-1}) in the IR spectrum. Alkaline hydrolysis gave benzoic acid, so that at least one of the carbonyl groups formed part of the ester function, PhCOO-. In the ^1H NMR spectrum, the methylene groups in the OCH_2CH_2N unit now appeared as a pair of triplets (in contrast to the complex coupling observed for the oxazoline protons in the cycloadducts **2**) showing that they were likely to form part of an open chain structure. All analytical and spectral data were in accord with the *N*-cyano structure **5a**, which was then prepared unambiguously by reaction of the sodium salt of *N*-cyanoacetamide[12] with (2-bromoethyl) benzoate (Scheme 3).

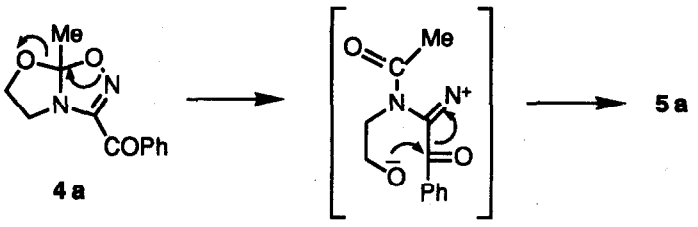


Scheme 3

In an earlier, unsuccessful approach to **5a**, we treated (2-aminoethyl) benzoate hydrochloride[13] with cyanogen bromide in alkaline solution to obtain the *N*-cyano compound, $PhCOOCH_2CH_2NHCN$. Attempted acetylation of the latter with acetic anhydride undoubtedly gave some of the required **5a** (prep. TLC and ^1H NMR) but, surprisingly, this underwent decomposition during the work-up procedure.

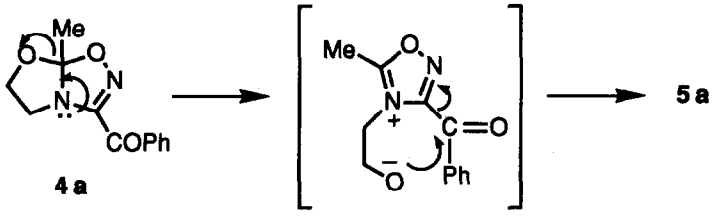
The mode of genesis of the ring-opened product **5a** is open to speculation. Whilst it is known[14] that the *C*-terminus of the 1,3-dipole in benzoyl cyanide *N*-oxide **3a** can act as an electrophile towards an electron-rich carbon-carbon double bond, and thus give rise directly to an open-chain structure, such a reaction would be unlikely to lead to compound **5a**. In view of the fact that the cycloadducts **2** were formed successfully from nitrile oxides, we consider that the expected cycloadduct **4** is formed initially, and that this undergoes subsequent ring opening. Since the adduct **4a** is a "bicyclic amide acetal",[15] and since such compounds would be expected to be labile towards acids, we first considered that **4a** had been hydrolysed by the HCl produced during the generation of benzoyl cyanide *N*-oxide by the thermal decomposition of 2-oxo-2-phenylethanohydroximoyl chloride [PhCOC(=NOH)Cl] (*cf.* ref.16). However, we found that the ring-opened compound **5a** was also formed (64%) when the nitrile oxide was generated under basic conditions from its chloro-oxime precursor by the use of triethylamine. Moreover, the ring opening reaction also occurred (79%) when pre-formed nitrile oxide **3a** was allowed to react with **1a**.

We have considered two mechanisms for the conversion of **4a** into **5a**. In the first (Scheme 4), cleavage of the weak N-O bond of the oxadiazole ring would generate the required *N*-acetyl carbonyl group and provide an alkoxide ion for attack on the phenacyl carbonyl group. Subsequent



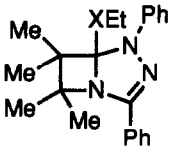
Scheme 4

generation of the cyano group is attained by cleavage of the C-C bond α- to the newly generated ester carbonyl group. Clearly the proposed adduct **4a** bears a formal resemblance to an α-oxoketoxime; the latter type of compound is known to undergo ready fragmentation to a nitrile.[17] However, the involvement of an unstable nitrenium intermediate (if only implicit) must cast some doubt upon this suggested mechanism.



Scheme 5

Alternatively (Scheme 5), the generation of the alkoxide ion may be promoted by the donation of the lone pair of electrons from the bridgehead nitrogen atom into the ring. The ensuing positive charge would then be carried by an iminium ion and the oxadiazolium intermediate would attain some degree of aromatic stabilisation. Fragmentation could then occur as before. We have invoked a similar iminium ion to explain the instability of the cycloadduct **6**, in which case the bridgehead substituent EtX is expelled as EtX^- (X = O or S);[7] other workers have used parallel reasoning to explain the instability of adducts formed from thiazolium *N*-ylides and substituted alkynes.[18]



6 (X = O or S)

If our reasoning is correct, a similar reaction should occur when benzoyl cyanide *N*-oxide **3a** reacts with **1b**. The ring fission of the resulting cycloadduct **4b** would then proceed with the generation of a thiolate anion and the subsequent formation of *S*-(*N*-cyano-2-acetamidoethyl) thiobenzoate **5b**. We showed that **5b** was indeed formed in this reaction (61%), and confirmed its structure both spectroscopically and chemically, by hydrolysis to benzoic acid.

Reactions similar to those just described also occur when **1a** is treated with 2-thenoyl cyanide *N*-oxide **3b** and ethanoyl cyanide *N*-oxide **3c**. Structures of the products **5c** and **5e** were established spectroscopically; that of **5e** was confirmed by synthesis from the sodio *N*-cyanoacetamide [NaN(CN)COMe] and (2-chloroethyl) acetate ($MeCOOCH_2CH_2Cl$).[19] The sulfur analogue **1b** gave the expected product **5f** with the nitrile oxide **3c**; surprisingly, it failed to react with nitrile oxide **3b**.

Work is now in progress to extend and amplify the above reactions.

EXPERIMENTAL

General Experimental Details.

^1H and ^{13}C NMR spectra were determined in deuteriochloroform solution (unless stated otherwise) at 270 and 68 MHz respectively on a JEOL JNM-GX-FT-NMR spectrometer. Chemical shifts are recorded in parts per million (ppm) downfield from tetramethylsilane. IR spectra were determined for KCl discs or liquid films on a Perkin-Elmer PE 783 spectrometer. Mass spectra were determined on a Finnigan-MAT 1020 automated GC/MS instrument.

Ether refers to diethyl ether and light petroleum refers to the fraction of b.p. 40-60 °C. Toluene, benzene and ether were dried over sodium wire, then redistilled. *N,N*-Dimethylformamide (DMF) was dried over molecular sieves.

Starting Materials.

4,5-Dihydro-2-methyloxazole **1a**, 4,5-dihydro-2,4,4-trimethyloxazole **1b**, and 4,5-dihydro-2-methylthiazole **1c** were available commercially.

Precursors of Nitrile N-oxides. α-Chlorobenzaldoxime (PhCCl=NOH), was best obtained by the chlorination of benzaldoxime with t-butyl hypochlorite.[20] Nitrosation of phenacyl chloride with isopropyl nitrite in the presence of hydrogen chloride gave *N*-hydroxy-α-oxobenzeneethanimidoyl chloride [PhCOCCl(=NOH)].[21] 1-Chloro-1-hydroximinopropanal, MeCOCCl(=NOH), was prepared similarly from 2-chloroacetone.[22] 2-Thenoyl bromide [$ThCOCH_2Br$ (Th = 2-thienyl)][23] reacted with dimethyl sulfide in boiling methanol, to give the sulfonium salt, $ThCOCH_2SMe_2^+$ Br^- (35%), m.p. 143-144 °C, δ_H (DMSO-d_6) 2.17, 2.11 (each 3H, s, 2 x Me), and 5.82 (2H, s, CH_2); nitrosation of the sulfonium salt with sodium nitrite and hydrochloric acid gave *N*-hydroxy-α-oxo-2-thiophene-ethanimidoyl chloride, ThCOCCl(=NOH).[24]

*5,6-Dihydro-7a-methyl-3-phenyl-7a*H*-thiazolo[3,2-d]-1,2,4-oxadiazole* **2c**.

A mixture of triethylamine (0.51 g, 5 mmol), α-chlorobenzaldoxime (0.78 g, 5 mmol), and cold (-10 °C) ether (50 cm^3) was swirled gently for 15 min, then filtered.The filtrate was added directly

to a vigorously stirred solution of 4,5-dihydro-2-methylthiazole **1c** (0.51 g, 5 mmol) in dry ether (25 cm^3) at -10 °C. Stirring was continued at this temperature for 2 h, then the mixture was filtered and the filtrate was evaporated to dryness *in vacuo*. The oily residue, which crystallised slowly at -10 °C, was then recrystallised from ethanol-water, to give the product **2c** (0.33 g, 30%) as needles, m.p. 75-76 °C (Found: C, 59.9; H, 5.3; N, 12.5. $C_{11}H_{12}N_2OS$ requires C, 59.95; H, 5.5; N, 12.7%); δ_H 2.14 (s, 7a-Me), 2.66 (ddd, H_c, J_{cd} 10.5, J_{bc} 12.2, J_{ac} 5.7Hz), 2.81 (dd, H_d, J_{cd} 10.5, J_{bd} 5.8, J_{ad} 0 Hz), 3.26 (ddd, H_b, J_{ab} 12.9, J_{bc} 12.2, J_{bd} 5.8 Hz), 4.19 (dd, H_a, J_{ab} 12.9, J_{ac} 5.7, J_{ad} 0 Hz), 7.4-7.7 (m, 5 x arom. H) (The signals H_a, H_b, H_c, and H_d relate to the protons, S-CH_aH_b-CH_cH_d-N, *i.e.* protons attached to C-6 and C-5 in the reduced thiazole ring; the asssignments of chemical shifts to H_a and H_b may, of course, be reversed, as may those to H_c and H_d); δ_C 29.7 (7a-Me), 32.2 (C-6), 53.4 (C-5), 119.7 (C-7a), 125-131 (6 x arom. C), 159.2 (C-3); *m/z* 220 (M^+), 160 (M - CH_2CH_2S), and 119 (base peak, PhCNO).

*5,6-Dihydro-5,5,7a-trimethyl-3-phenyl-7a*H*-oxazolo[3,2-d]-1,2,4-oxadiazole* **2b**.

This was prepared from 4,5-dihydro-2,4,4-trimethyloxazole **1b** by the method just described. The oily product was crystallised at -10 °C, then the crystals were washed with light petroleum until they were colourless. A 28% yield of **2b** was obtained; m.p. 58-59 °C (from ethanol-water) (Found: C, 67.3; H, 6.9; N, 11.9. $C_{13}H_{16}N_2O_2$ requires C, 67.2; H, 6.95; N, 12.05%); δ_H, 0.96, 1.37 (2 x 5-Me), 1.78 (s, 7a-Me), 3.58 (dq, H_a, J_{ab} 8.5, $J_{a,5\text{-Me}}$ 0.8 Hz), 3.78 (d, H_b, J_{ab} 8.5 Hz) (The signals H_a and H_b relate to the 6-CH_2 protons; the assignments may, of course, be reversed); δ_C 23.4, 25.2, 27.4 (3 x Me), 65.5 (C-5), 76.6 (C-6), 127.0 (C-7a), 127.5-130.6 (6 x arom. C), and 157.9 (C-3); *m/z* 232 (M^+) and 119 (PhCNO).

*5,6-Dihydro-7a-methyl-3-phenyl-7a*H*-oxazolo[3,2-d]-1,2,4-oxadiazole* **2a**.

Prepared (59%) by the method used for **2c** and using the work-up procedure described for **2b**, this had m.p. 63-64 °C (lit.,[8] m.p. 64 °C; yield 87%); δ_H 1.80 (s, 7a-Me), 3.37 (ddd, H_c, J_{cd} 11.0, J_{bc} 11.5, J_{ac} 6.0 Hz), 3.53 (ddd, H_b, J_{ab} 8.0, J_{bc} 11.5, J_{bd} 5.0 Hz), 3.65 (ddd, H_d, J_{cd} 11.0, J_{bd} 5.0, J_{ad} 1.0 Hz), 3.91 (ddd, H_a, J_{ab} 8.0, J_{ac} 6.0, J_{ad} 1.0 Hz) (The signals H_a, H_b, H_c, and H_d relate to the protons, O-CH_aH_b-CH_cH_d-N, *i.e.* protons attached to C-6 and C-5 in the reduced oxazole ring; the asssignments of chemical shifts to H_a and H_b may, of course, be reversed, as may those to H_c and H_d), 7.4-7.8 (m, 5 x arom. H) ; *m/z* 204 (M^+) and 119 (base peak, PhCNO).

(N-Cyano-2-acetamidoethyl) Benzoate **5a** via *Cycloaddition*.

Method A. A mixture of *N*-hydroxy-α-oxobenzeneethanimidoyl chloride (0.45 g, 2.5 mmol), 4,5-dihydro-2-methyloxazole **1a** (0.21 g, 2.5 mmol), and dry toluene (25 cm^3) was heated under reflux for 2 h, then the solvent was removed under reduced pressure and the residue was purified by flash column chromatography (silica gel). Elution with chloroform gave crystals (0.33 g, 57%) of **5a**, m.p. 67-68 °C (from ethanol) (Found: C, 62.05; H, 5.0; N, 11.85. $C_{12}H_{12}N_2O_3$ requires C, 62.05; H, 5.2; N, 12.05%); $\nu_{max.}$ 2235 (C≡N), 1735 (ester CO), and 1720 (amide CO) cm^{-1};

δ_H 2.50 (3H, s, COMe), 4.04 (2H, t, OCH_2CH_2N, *J* 5.5 Hz), 4.56 (2H, t, OCH_2CH_2N), 7.5-7.8 (m, 3 x arom. H), and 8.15 (m, 2 x arom. H); δ_C 22.1 (Me), 45.7 (NCH_2), 61.8 (OCH_2), 111.0 (C≡N), 128.6, 129.3, 129.9, 130.0, 133.5 (arom. C), 166.2 and 169.3 (CO); *m/z* 172 (*M* - HCN - MeCO) and 105 (base peak, PhCO) [No M^+ in EI spectrum; in CI spectrum (NH_3 carrier gas), *m/z* 250 ($M + NH_4^+$)].

Method B. A solution of *N*-hydroxy-α-oxobenzeneethanimidoyl chloride (0.45 g, 2.5 mmol) in benzene (50 cm^3) was added slowly to a stirred mixture of 4,5-dihydro-2-methyloxazole **1a** (0.21 g, 2.5 mmol), triethylamine (0.51 g, 5 mmol), and dry benzene (25 cm^3) at 0 °C. The mixture was stirred for a further 2 h, then the triethylamine hydrochloride was filtered off, and the solvent was removed *in vacuo* from the filtrate. Chromatography on silica and elution with dichloromethane - ethyl acetate (10:1) gave crystals (0.37 g, 64%), m.p. 67-68 °C, identical with those obtained by Method A.

Method C. Use of the procedure already described for the preparation of **2a**, followed by work up as in Method B, gave **5a** (79%), m.p. 67-68 °C.

Heating **5a** under reflux for 3 h with aqueous 2% sodium hydroxide, followed by isolation of acidic material, gave benzoic acid (60%), m.p. and mixed m.p. 121-122 °C

Independent Synthesis of (N-Cyano-2-acetamidoethyl) Benzoate **5a**.

A solution of (2-bromoethyl) benzoate (commercially available; 1.15 g, 5 mmol) in dry DMF (10 cm^3) was added dropwise during 1h to a stirred solution of the sodium salt of *N*-cyanoacetamide[12] (0.53 g, 5 mmol) in hot (70 °C), dry DMF (10 cm^3). The temperature was then raised to 100 °C and stirring was continued for a further 4 h. An excess of acetone was added, then the precipitated sodium bromide was filtered off (Hyflo) and the solvent was removed. The resulting oil crystallised when kept at -20 °C, to yield **5a** as colourless needles (0.45 g, 39%), m.p. 67-68 °C, identical (IR spectrum) with the product obtained from the cycloaddition reaction.

2-(N-Cyanoamino)ethyl Benzoate.

A solution of sodium hydrogen carbonate (2.1 g, 26 mmol) in water (20 cm^3) was added to a stirred, cooled (-10 °C) suspension of (2-aminothyl) benzoate hydrochloride[13] (4.0 g, 20 mmol) in ether (50 cm^3). After the evolution of carbon dioxide had ceased, a solution of cyanogen bromide (2.12 g, 20 mmol) was added and the mixture was stirred vigorously for 0.5 h. The organic layer was separated, dried, and evaporated, to yield a residue, which on crystallisation from ethanol gave needles (0.85 g, 22%), m.p. 71-72 °C (Found: C, 63.0; H, 5.2; N,. 14.6. $C_{10}H_{10}N_2O_2$ requires C, 63.15; H, 5.3; N, 17.75%); $\nu_{max.}$ 2215 (C≡N) and 1715 (ester CO) cm^{-1}; δ_H 3.50 [t, (with broadening: coupling with NH), OCH_2CH_2N, *J* 6.0 Hz], 4.44 (t, OCH_2CH_2N), 4.0 (br s, NH), 7.5 (m, 3 x arom. H) and 8.1 (m, 2 x arom. H); *m/z* 190 (M^+), 189 (*M* - H) and 105 (PhCO, base peak).

Attempted acetylation by treatment overnight with acetic anhydride gave material which contained some of the expected **5a** (preparative TLC, followed by ^{1}H NMR spectroscopy), but which decomposed on attempted purification.

S-(N-*Cyano-2-acetamidoethyl) Thiobenzoate* **5b**.

This was prepared from 4,5-dihydro-2-methylthiazole and *N*-hydroxy-α-oxobenzeneethanimidoyl chloride by the method used to prepare **5a** (Procedure A). The crude product was purified by chromatography on silica. Elution with chloroform gave needles (72%), m.p. 50-51 °C (Found: C, 57.9; H, 4.8; N, 11.5; S, 13.05. $C_{12}H_{12}N_2O_2S$ requires C, 58.05; H, 4.85; N, 11.3; S, 12.9%); $\nu_{max.}$ 2240 (C≡N), 1730, and 1720 (CO) cm^{-1}; δ_H 2.46 (3H, s, COMe), 3.40 (2H, t, SCH_2CH_2N, *J* 5.0 Hz), 3.88 (2H, t, SCH_2CH_2N), 7.4-7.7 (m, 3 x arom. H), and 8.0 (m, 2 x arom. H); δ_C 22.15 (Me), 26.9 (NCH_2), 46.1 (SCH_2), 111.0 (C≡N), 127.5, 129.3, 128.8, 133.95, 136.4 (arom. C), 169.3 and 190.7 (CO); *m/z* 105 (base peak, PhCO) [No M^+ in EI spectrum; in CI spectrum (NH_3 carrier gas), *m/z* 266 ($M + NH_4^+$)].

Alkaline hydrolysis as for **5a** gave benzoic acid (45%).

(N-Cyano-2-acetamidoethyl) Acetate **5e**.

This was prepared from 1-chloro-1-hydroximinopropanal and 4,5-dihydro-2-methyloxazole by the method (Procedure A) used for **5a**. Elution in chloroform from a silica column, followed by distillation at 125 °C and 2.5 mmHg (Kugelrohr) and cooling of the distillate, gave the product as a solid, m.p. 27-28 °C (30%) (Found: C, 49.4; H, 5.9; N, 16.45. $C_7H_{10}N_2O_3$ requires C, 49.4; H, 5.9; N, 16.45%); $\nu_{max.}$ 2235 (C≡N), 1740, and 1730 (CO) cm^{-1}; δ_H 2.12, 2.44 (each 3H, s, COMe), 3.83 (2H, t, OCH_2CH_2N, *J* 5.5 Hz), and 4.29 (2H, t, OCH_2CH_2N); δ_C; 20.7, 22.1 ($COCH_3$), 45.6 (NCH_2), 61.0 (OCH_2), 110.8 (C≡N), 169.3, and 170.8 (2 x CO); *m/z* 110 (base peak, *M* - COMe - HCN) [No M^+ in EI spectrum].

Authentic (N-Cyano-2-acetamidoethyl) Acetate **5e** was obtained (42%) from the sodium salt of *N*-cyanoacetamide[12] and (2-chloroethyl) acetate[19] by the method used for **5a**. It was purified by chromatography on silica [eluant: light petroleum - chloroform (1:3)], followed by distillation (Kugelrohr) at 110 °C and 0.5 mmHg. It was identical with the product isolated from the ring-opening reaction.

S-(N-*Cyano-2-acetamidoethyl) Thiobenzoate* **5f**.

Prepared from 4,5-dihydro-2-methylthiazole and 1-chloro-1-hydroximinopropanal by the method (Procedure A) used for **5a**, this was purified by column chromatography on silica (eluant: chloroform), then by distillation (Kugelrohr). It was obtained as a pale yellow oil (90%), b.p. 225 °C at 0.4 mmHg (Found: C, 45.15; H, 5.4; N, 14.8; S, 17.0. $C_7H_{10}N_2O_2S$ requires C, 45.15; H, 5.4; N, 15.05; S, 17.2%); $\nu_{max.}$ 2215 (C≡N), 1765, and 1730 (CO) cm^{-1}; δ_H 2.39, 2.42 (each 3H, s, COMe), 3.15 (2H, t, SCH_2CH_2N, *J* 4.5 Hz), and 3.77 (2H, t, SCH_2CH_2N); δ_C 22.2, 27.2 ($COCH_3$), 30.6 (SCH_2), 46.0 (NCH_2), 110.8 (C≡N), 169.3, and 194.8 (CO); *m/z* 158, 144, and 129 (base peak) [No M^+ in EI spectrum].

(N-Cyano-2-acetamidoethyl) Thiophene-2-carboxylate **5c**

This was prepared from N-hydroxy-α-oxo-2-thiopheneethanimidoyl chloride[24] and the oxazole **1a**. Heating in toluene solution (*cf.* Method A for **5a**) caused extensive charring, so the nitrile oxide was generated by the addition of triethylamine (*cf.* Method B for **5a**) at -10 °C. The resulting oil was purified by chromatography on silica and elution with chloroform, then by distillation (Kugelrohr).

The *N*-cyanoamide **5c** (29%) had b.p.170 °C at 0.5 mmHg (Found: C, 50.65; H,4.2; N, 11.65; S, 13.2. $C_{10}H_{10}N_2O_3S$ requires C, 50.4; H, 4.2; N, 11.75; S, 13.45%); $\nu_{max.}$ 2235 (C≡N), 1730, and 1705 (CO) cm^{-1}; δ_H 2.46 (s, Me), 3.96 (t, NCH_2, *J* 5.0 Hz), 4.48 (t, OCH_2), 7.13 (1H, dd, 4-H, $J_{3,4}$ 4.0, $J_{4,5}$ 5.0 Hz), and 7.61 (1H, dd, 5-H, $J_{3,5}$ 1.5 Hz); δ_C 22.1 ($COCH_3$), 45.6 (NCH_2), 61.8 (OCH_2), 110.8 (C≡N), 128.1, 132.6, 133.4, 134.4 (thiophene ring C), 161.7, and 169.3 (CO); *m/z* 238 (M^+) and 111 (2-$ThCO^+$; base peak).

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