Studies on Heteroaromaticity. XIX.[1] Direct 1,3-Dipolar Cycloaddition of Hydroxamoyl Chlorides with Enamines

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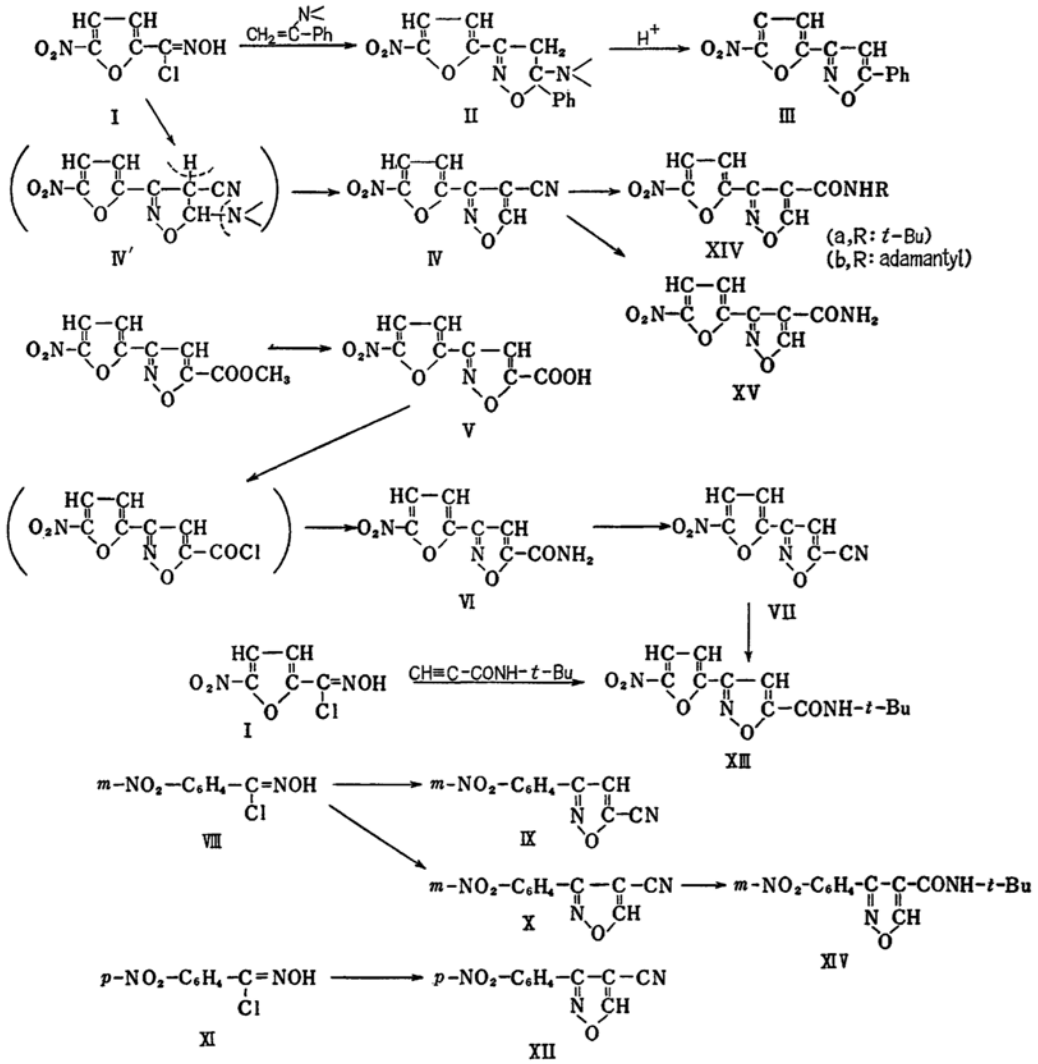
Minami and Matsumoto[2] have reported the 1,3-dipolar cycloaddition of 5-nitro-2-furonitrile oxide with a series of enamines, affording 1 : 1 adducts with a 5-amino-substituted isoxazoline structure and making for facile conversion to the corresponding isoxazoles by subsequent acid treatment. This paper will deal with our finding that the same products can be obtained directly from hydroxyamoyl chloride as from the corresponding nitrile oxide in better yields and by simpler procedures. Furthermore, we will report a novel one-step procedure for preparing isoxazole derivatives using enamines with

1) Part XVIII of this series: T. Sasaki and T. Yoshioka, This Bulletin, **41**, 2211 (1968).
2) S. Minami and J. Matsumoto, *Chem. Pharm. Bull. (Tokyo)*, **15**, 366 (1967).



a specific structure.

5-Nitro-2-furylhydroxamoyl chloride (I)[1] was treated with morpholino-1-phenylethylene in ether at room temperature to afford an adduct (1 : 1), II, in a 80% yield, though the same product was obtained from 5-nitro-2-furonitrile oxide[3] and the same enamine in but a 50% yield. This somewhat lower yield might be caused by the difficult solubility of the nitrile oxide in ether. From the fact that the acid hydrolysis of II supplied a known compound, 3-(5′-nitro-2′-furyl)-5-phenylisoxazole, III, with a mp of 209—210°C,[2] II was concluded to be 3-(5′-nitro-2′-furyl)-5-phenyl-5-morpholinoisoxazoline. When 1-morpholino-2-cyanoethylene[4] was used as a dipolarophilic enamine, one which has a strong electronegative cyano group instead of the electropositive alkyl or alicyclic group in general enamines such as the above-described 1-morpholino-1-phenylethylene, the product, IV, was proved to be 3-(5′-nitro-2′-furyl)-4-cyanoisoxazole as a result of the structural elucidation on the basis of the spectral data; the NMR spectrum in $CDCl_3$ manifested a chemical shift at 0.86 τ (singlet, 1 H, 5-C–H),[5] and the ultraviolet spectrum showed an absorption maximum at 309 mμ (ε=14100)[3] in ethanol.

It is noteworthy that IV has an isoxazole structure instead of the expected isoxazoline (IV′) structure after the spontaneous *cis*-elimination of a morpholine molecule from the latter,[5] presumably

3) T. Sasaki and T. Yoshioka, This Bulletin, **40**, 260 (1967).

4) T. Sasaki, unpublished data.

5) The NMR spectrum of 1-morpholino-2-cyanoethylene showed an AB-quartet about its olefinic protons. This compound was concluded to take a *trans*-configuration, considering that the coupling constant is 14 cps, causing a facile *cis*-elimination of a morpholine molecule. The same thing could be said about 1-pyrrolidino- and 1-piperidino-2-cyanoethylene.

by facile aromatization after removal of hydrogen cyanide on account of the strong tendency toward protonation of a hydrogen atom attached to a carbon bearing a cyano group. All attempts at the direct preparation of an isomer, VII, 3-(5′-nitro-2′-furyl)-5-cyanoisoxazole, were unsuccessful, whether the routine nitrile-oxide method or the direct treatment of I with cyanoacetylene was employed. This compound was finally prepared by the dehydration of 3-(5′-nitro-2′-furyl)-5-carbamidoisoxazole (VI); VI was prepared by the following sequence of reactions starting from a known 5-carbomethoxyisoxazole[3] →V→VI. VII was found to be hardly purified at all even by column chromatography; therefore, it was converted to the corresponding amide (XIII) by a Ritter reaction with *t*-butyl alcohol, which was compared with a product, XIV, derived from IV by the Ritter reaction. XIII and XIV showed similar ultraviolet spectral patterns, but they were quite different in their NMR spectra, as will be shown in the Experimental Section. IV was also prepared from 1-pyrrolidino-,[4,5] and 1-piperidino-2-cyanoethylene[4,5] under similar reaction conditions, indicating that this direct isoxazole-formation is a general characteristic of the above cyano-enamines. Similarly, *m*-nitrophenylhydroxazoyl chloride (VIII) afforded the corresponding 5-cyano- (IX) and 4-cyanoisoxazole (X) by the reactions of the nitrile oxide with cyanoacetylene[6] and of VIII with 1-morpholino-2-cyanoethylene; IX and X were afforded in 30 and 70% yields respectively. On the other hand, from *p*-nitrophenylhydroxamoyl chloride (XI), only the 4-cyanoisoxazole (XII) could be isolated in a 80% yield by a reaction with 1-morpholino-2-cyanoethylene; X underwent a Ritter reaction to afford the corresponding amide (XIV). Acidic hydrolysis of the nitrile in IV was carried out and an almost quantitative yileld of the corresponding amide (XV) was obtained and its infrared spectrum was different from its 5-amide.[3]

Experimental[6]

Reaction of I with 1-Morpholino-1-phenylethylene. A solution of 0.95 g (5 mmol) of I[1] and 1.9 g (10 mmol) of 1-morpholino-1-phenylethylene[7] in 30 m*l* of dry ether was kept standing at room temperature for 1 month. The resulting crystals were collected and recrystallized three times from benzene to afford 1.5 g of II as pale yellow crystals, mp 215—216°C. UV λ_{max}^{EtOH} mμ (ε): 348 (13500), 253 (8600).

Found: C, 59.47; H, 4.88; N, 12.24%. Calcd for $C_{17}H_{17}O_5N_3$: C, 59.47; H, 4.99; N, 12.29%.

The nitrile oxide procedure[3] afforded II, but in only a 50% yield. With hydrochloric acid, II was readily converted to III[2] almost quantitatively.

Reaction of I with 1-Morpholino-2-cyanoethylene. A solution of 0.82 g (4.3 mmol) of I[1] and 1.3 g (10 mmol) of 1-morpholino-2-cyanoethylene[4] in 60 m*l* of dry ether was kept standing at room temperature for 1 month. After the ether had then been removed, the residual oil was digested with 30 m*l* of water; the resulting crystals were collected and recrystallized several times from ethanol to give 0.7 g (80%) of IV as pale yellow crystals, mp 130—132°C. IR (KBr) cm^{-1}: 2300 ($\nu_{C\equiv N}$).

Found: C, 46.90; H, 1.09; N, 20.32%. Cacld for $C_8H_3O_4N_3$: C, 46.87; H, 1.47; N, 20.49%.

The Ritter Reactions of IV. Into a solution of 0.15 g (0.8 mmol) of IV in 7 m*l* of *t*-butanol, there was stirred 0.7 m*l* of concentrated sulfuric acid at room temperature. An exothermic reaction occurred. After the reaction mixture had then been allowed to stand at room temperature for 1 day, it was poured into ice water and the resulting crystals were recrystallized from benzene - petroleum ether to give 0.15 g (70%) of XIVa, mp 169—171°C. IR (KBr) cm^{-1}: 3320 (ν_{NH}), 1665 (ν_{CO}). UV λ_{max}^{EtOH} mμ (ε): 319 (14000). NMR ($CDCl_3$) τ: 1.10 (singlet, 1 H, 5-C-H), 2.55 (singlet, 2 H, nitrofuran ring protons*1), 3.70 (broad, 1 H, NH), 8.51 (singlet, 9 H, t-Bu).

Found: C, 52.15; H, 4.79; N, 14.92%. Calcd for $C_{12}H_{13}O_5N_3$: C, 51.61; H, 4.69; N, 15.05%.

Similarly, from 0.22 g (1.1 mmol) of IV, 0.29 g (1.4 mmol) of adamantly bromide,[9] 10 m*l* of acetic acid and 1 m*l* of 98% sulfuric acid, 0.28 g (70%) of XIVb, mp 174—175°C, was obtined after purification by column chromatography*2 and recrystallization from ethanol-petroleum ether. IR (KBr) cm^{-1}: 3410, 3380 (ν_{NH}), 1665 (ν_{CO}). UV λ_{max}^{MeOH} mμ (ε): 318 (8700).

Found: C, 60.28; H, 5.60; N, 11.05%. Calcd for $C_{18}H_{21}O_5N_3$: C, 60.16; H, 5.89; N, 11.69%.

Acidic Hydrolysis of IV. IV, 0.32 g (1.5 mmol), was dissolved in 4 m*l* of 98% sulfuric acid and this solution was kept standing at room temperature for 1 day and poured into ice water. The resulting crystals were collected and recrystallized from ethanol to give 0.31 g (95%) of XV, mp 271—272°C. IR (KBr) cm^{-1}: 3450, 3360, 3300 (ν_{NH}), 1690 (ν_{CO}). UV λ_{max}^{MeOH} mμ (ε): 315 (12700).

Found: C, 43.03; H, 2.30; N, 18.65%. Calcd for $C_7H_5O_5N_3$: C, 43.06; H, 2.26; N, 18.83%.

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6) Melting points are uncorrected. The ultraviolet absorption spectra were recorded on a Nippon-Bunko optical rotary dispersion recorder, Model ORD/UV-5. The infrared spectra were obtained with a Nippon-Bunko IR-S spectrophotometer. Microanalyses were carried out with a Yanagimoto C. H. N. Corder MT-1 type. The NMR spectra were determined with a Varian A-60 spectrometer, using tetramethylsilane as the internal standard. The chemical shifts are recorded in τ-values.

7) S. Hünig, K. Hübner and E. Benzig, *Chem. Ber.*, **95**, 926 (1962).

8) S. Murahashi, S. Kurioka and S. Maikawa, *Nippon Kagaku Zasshi* (*J. Chem. Soc. Japan, Pure Chem. Sect.*), **77**, 1689 (1956).

*1 This is the first example of the appearance of a singlet of two nitrofuran-ring protons in 2,5-disubstituted furan derivatives. The reason is uncertain at present.

9) T. Sasaki, S. Eguchi and T. Toru, This Bulletin, **41**, 236 (1968).

*2 XIVb was obtained from the second fraction by silica-gel (Mallinckrodt, 100 mesh) chromatography, using chloroform as an eluent. From the third fraction, there was obtained 30 mg (10%) of 3-(5′-nitro-2′-furyl)-isoxazole-4-carbamide, mp 265—257°C, which was identical with XV.

Preparation of an Isomer, XIII. 3-(5′-Nitro-2′-furyl)-5-carbomethoxyisoxazole[3] was quantitatively hydrolyzed with hydrochloric acid to the corresponding acid, V (mp 222°C). IR (KBr) cm^{-1}: 1685 (ν_{CO}).

Found: C, 42.81; H, 1.63; N, 12.52%. Calcd for $C_8H_4O_6N_2$: C, 42.87; H, 1.80; N, 12.50%.

V was treated with thionyl chloride by the routine procedure to afford the corresponding acid chloride, which, without further purification, was then dissolved in benzene. Ammonia gas was introduced into this solution to give VI (mp 246—247°C) in a 92% yield.

Found: C, 43.16; H, 1.88; N, 19.25%. Calcd for $C_8H_5O_5N_3$: C, 43.06; H, 2.26; N, 18.83%.

VI was treated with thionyl chloride or phosphorus pentachloride, and the crude nitrile (its existence was demonstrated by the presence of the 2300 cm^{-1} absorption due to $\nu_{C\equiv N}$ in the IR spectrum) was treated with *t*-butanol in concentrated sulfuric acid, as has been described above, to afford XIII, which was also prepared in a 34% yield from the thermal 1,3-dipolar cycloaddition reaction of I with *N*-*t*-butylpropiolamide.[10] Mp 214—215°C. UV λ_{max}^{EtOH} mμ (ε): 318 (14000). NMR ($CDCl_3$) τ: 2.79 (singlet, 1 H, 4-C–H), 2.60 and 2.87 (each doublet, 1 H, J=3.8 cps, nitrofuran-ring protons), 3.50 (broad, 1 H, NH), 8.50 (singlet, 9 H, *t*-Bu).

Found: C, 51.87; H, 4.70; N, 15.00%. Calcd for $C_{12}H_{13}O_5N_3$: C, 51.61; H, 4.79; N, 15.05%.

3-(*m*-Nitrophenyl)-5-cyanoisoxazole (IX). VIII (0.61 g; 3.0 mmol) was dissolved in 100 m*l* of ether, and into this solution there was stirred an equivalent amount of 1% aqueous sodium hydroxide at room temperature. After 2 min, an ether layer was separated and dried; a solution of 0.3 g (3.0 mmol) of cyanoacetylene[8] was then added. The reaction mixture was kept standing at room temperature for 1 day, and then the residue, obtained after the removal of the ether, was chromatographed on a silica-gel column. From the second fraction there was obtained 0.20 g (30%) of IX, mp 122—123°C from ethanol. IR (KBr) cm^{-1}: 2300 (ν_{CN}). UV λ_{max}^{EtOH} mμ (ε): 248 (13200). NMR ($CDCl_3$) τ: 2.62 (singlet, 1 H, 4-C–H).

Found: C, 55.58; H, 2.01; N, 19.47%. Calcd for $C_{10}H_5O_3N_3$: C, 55.82; H, 2.34; N, 19.53%.

3-(*m*-Nitrophenyl)-4-cyanoisoxazole (X). VIII (0.61 g; 3.0 mmol) and 0.91 g (6.6 mmol) of 1-morpholino-2-cyanoethylene[4] were dissolved in 40 m*l* of ether, and then the reaction mixture was kept standing at room temperature for 1 month. The resulting crystals were recrystallized from ethanol to give 0.52 g (80%) of X, mp 101—103°C. IR (KBr) cm^{-1}: 2300 (ν_{CN}). UV λ_{max}^{EtOH} mμ (ε): 247 (13000). NMR ($CDCl_3$) τ: 0.82 (singlet, 1 H, 5-C–H).

Found: C, 55.99; H, 1.91; N, 19.53%. Calcd for $C_{10}H_5O_3N_3$: C, 55.82; H, 2.34; N, 19.53%.

The Ritter Reaction of X. X (0.2 g; 1 mmol) was dissolved in a mixture of 5 m*l* of *t*-butanol and 1 m*l* of concentrated sulfuric acid. The mixture was kept standing at room temperature for 6 days. It was poured into ice water and the resulting crystals were recrystallized from ethanol - petroleum ether to give 0.21 g (75%) of XIV, mp 141—143°C. IR (KBr) cm^{-1}: 3290 (ν_{NH}), 1650 (ν_{CO}). UV λ_{max}^{MeOH} mμ (ε): 252 (12600).

Found: C, 58.37; H, 5.21; N, 14.39%. Calcd for $C_{14}H_{15}O_4N_3$: C, 58.12; H, 5.23; N, 14.53%.

3-(*p*-Nitrophenyl)-4-cyanoisoxazole (XII). Much as above, XII was prepared from XI and 1-morpholino-2-cyanoethylene[4] in a 80% yield. Mp 165—167°C, from ethanol. IR (KBr) cm^{-1}: 2300 (ν_{CN}). UV λ_{max}^{EtOH} mμ (ε): 265 (14700). NMR ($CDCl_3$) τ: 0.87 (singlet, 1 H, 5-C–H).

Found: C, 55.63; H, 1.84; N, 20.00%. Calcd for $C_{10}H_5O_3N_3$: C, 55.82; H, 2.34; N, 19.53%.

10) T. Sasaki, S. Eguchi and K. Shoji, submitted to *J. Chem. Soc.*