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The base-induced ring cleavage of 4-nitro- (Ia), 4-ethoxycarbonyl- (Ib) and 4-acetyl-5-methylisoxazole (Ic) and the conversion of the resulting β -cyanoenolates and β -enaminonitriles into 5-aminoazoles and 4-cyanoazoles was studied.

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In a previous paper we described that 3-unsubstituted isoxazoles bearing electron-accepting groups at C-4 underwent ring cleavage when treated with organic bases leading to stable β -cyanoenolates [2]. As is shown in the present article, the ability of these enolates to be converted into 5-aminoisoxazoles or 5-aminopyrazoles is one of the most interesting features of this work. Much of our recent investigations have been directed to the synthesis of 5-aminoazoles [3] [4] as a result of the interest of these compounds as intermediates for the preparation of derivatives with antihistaminic [5], analgesic [6], antibactericidal [7] and insecticidal [8] activity.

In this paper we report the base-induced ring cleavage of 4-nitro- (Ia), 4-ethoxycarbonyl- (Ib) and 4-acetyl-5-methylisoxazole (Ic) and the conversion of the resulting

open chain products (β -cyanoenolates and β -enaminonitriles) into 5-aminoazoles and 4-cyanoazoles (isoxazoles and pyrazoles). The results are summarized in Figures 1 and 2. Thus, Ia and Ib react with pyridine or sodium hydroxide, primary amines and semicarbazide to give β -cyanoenolates IIa,b; β -enaminonitriles IIIa-c and semicarbazones IVa,b respectively (Figure 1). When IIa,b react with hydroxylamine or hydrazines lead to 4-functionalized-5-aminoisoxazoles Va,b or 4-functionalized-5-aminopyrazoles VIa-c respectively. However the reaction of IIb with phenylhydrazine does not give the expected aminopyrazole; instead of this, VII was isolated. Formation of the 4-cyanopyrazolone VII can be explained if we assume that the cyclization takes place on the ethoxycarbonyl group instead of the cyano group. β -Enaminonitriles IIIa,b behave similarly to β -cyanoenolates leading to the same products Va and VIa-c with different yields. Under analogous reaction conditions IIIc fails to react with hydroxylamine or hydrazines. Cyclization of semicarbazones IVa,b in dilute hydrochloric acid, followed by neutralization, gives the corresponding 5-aminopyrazoles VIa and VIII (Figure 1). Table 1 shows the yields of 5-aminoazoles according to the different method used.

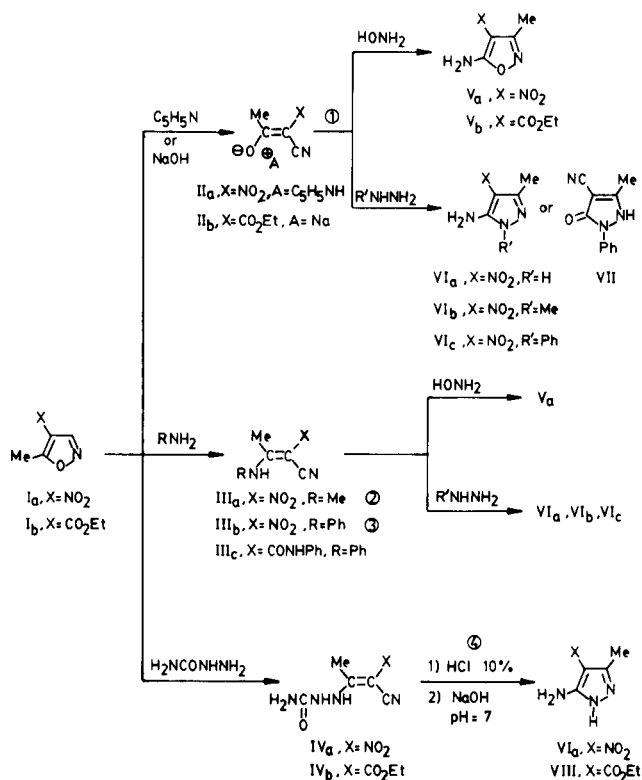


Figure 1

Table 1

5-Aminoisoxazoles and 5-Aminopyrazoles

Product	Method	Yield (%)	mp (°C)
Va	1	72	148-149 [a]
Va	2	50	"
Va	3	57	"
Vb	1	20	152-153 [b]
VIa	1	75	206-207 [c]
VIa	2	55	"
VIa	3	61	"
VIa	4	27	"
VIb	1	43	135-136 [d]
VIb	2	67	"
VIb	3	80	"
VIc	1	86	170-172 [e]
VIc	2	55	"
VIc	3	75	"
VIII	4	82	50 [f]

[a] Lit [13] 149-151°. [b] Lit [14] 133-134°. [c] Lit [16] 205°. [d] Lit [17] 136-138°. [e] Lit [16] 170°. [f] Lit [21] 18-20°.

Table 2
4-Cyanoisoxazoles and 4-Cyanopyrazoles

Product	Method	Yield (%)	mp (°C)
VII	1	43	196-197 [a]
IX	1	67	45-46 [b]
IX	2	68	"
IX	3	66	"
Xa	1	44	107-108 (ethanol)
Xa	2	69	"
Xa	3	63	"
Xa	4	83	"
Xb	1	40	- [c]
Xb	2	92	"
Xb	3	70	"
Xc	1	91	90-91 [d]
Xc	2	96	"
Xc	3	56	"
Xd	1	68	186-187 [e]

[a] Lit [18] 218-220°. [b] Lit [15] 43-44°. [c] bp 70°/15 mm. [d] Lit [19] 89-90°. [e] Lit [20] 180-182°.

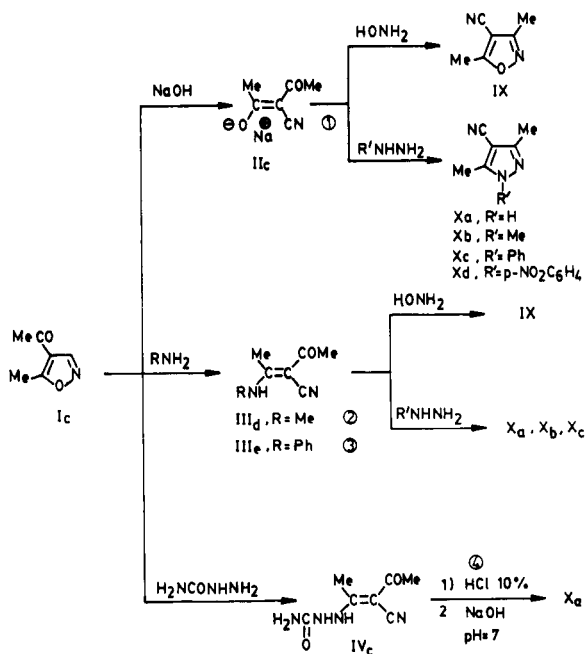


Figure 2

The behaviour of Ic is perceptibly different from that which the analogous Ia,b show. β-Cyanoenolate IIc and β-enaminonitriles IIIc,e react with hydroxylamine or hydrazines to give 4-cyano-3,5-dimethylisoxazole (IX) or 4-cyanopyrazoles Xa-d (Figure 2). Semicarbazone IVc cyclizes to the respective 4-cyanopyrazole Xa. The yields of the 4-cyanoazoles are listed in Table 2. As we discussed before for VII, the formation of 4-cyano derivatives by intramolecular cyclization of the oxime or hydrazone in-

termediates seems to involve addition only on the acetyl group. This chemoselectivity between the acetyl and cyano groups should be noted. Although the course of the reactions seems to proceed with preliminary 1,4-addition of the 1,2-dinucleophile (hydroxylamine, hydrazines) followed by cyclization of the resulting intermediate we defer any definitive statement regarding mechanism.

EXPERIMENTAL

Melting points are uncorrected. 4-Nitro-5-methylisoxazole [9], 4-ethoxycarbonyl-5-methylisoxazole [10] and 4-acetyl-5-methylisoxazole [11] were prepared by established procedures. β-Cyanoenolates IIa-c were prepared according to a literature method [2]. The infrared spectra were recorded in nujol mulls in the case of solids or for thin films in the case of liquids, using a Pye Unicam SP-1100 spectrophotometer. Nuclear magnetic resonance spectra were determined with a Varian T-60A analytical spectrometer with tetramethylsilane as an internal standard. Solvents and reagents were purified by conventional methods.

Preparation of β-Enaminonitriles IIIa-e.

A mixture of 0.1 mole of isoxazole Ia-c and 0.3 mole of aniline or methylamine (40% in water) was refluxed for a few minutes. The cooled solution was added over dilute hydrochloric acid, the solid formed was filtered and recrystallized from ethanol to give IIIa-e. The structures of IIIa-e were elucidated through their physical and spectroscopic characteristics.

3-Methylamino-2-nitro-2-butenenitrile (IIIa).

This compound was obtained as yellow powder (36%) mp 145-146° from ethanol; ir (nujol): 3200, 2200, 1600 cm⁻¹; nmr (dimethylsulphoxide-d₆): δ 2.40 (s, CH₃, 3H), 3.35 (d, CH₂-N, 3H, J = 6 Hz), 10.9 (broad, NH, 1H).

Anal. Calcd. for C₅H₇N₃O₂: C, 42.53; H, 5.01; N, 29.78. Found: C, 42.42; H, 5.09; N, 29.86.

2-Nitro-3-phenylamino-2-butenenitrile (IIIb).

This compound was obtained as brown needles (49%) mp 190-191° from ethanol; ir (nujol): 3200, 2220, 1600, 1480 cm⁻¹; nmr (dimethylsulphoxide-d₆): δ 2.30 (s, CH₃, 3H), 7.50 (s, aromatic protons, 5H), 12.1 (broad, NH, 1H).

Anal. Calcd. for C₁₀H₉N₃O₂: C, 59.10; H, 4.47; N, 20.68. Found: C, 59.03; H, 4.60; N, 20.72.

2-Cyano-N-phenyl-3-phenylamino-2-butenamide (IIIc).

This compound was obtained as colorless plates (26%) mp 179-180° (lit [12] 142° dec).

Anal. Calcd. for C₁₇H₁₅N₃O₂: C, 73.61; H, 5.46; N, 15.15. Found: C, 73.52; H, 5.60; N, 15.29.

2-Acetyl-3-methylamino-2-butenenitrile (IIIc).

This compound was obtained as colorless plates (69%) mp 138-139° from ethanol; ir (nujol): 3100, 2230, 1650 cm⁻¹; nmr (deuteriochloroform): δ 2.30 (s, CH₃, 6H), 3.15 (d, CH₂-N, 3H, J = 6 Hz), 12.0 (broad, NH, 1H).

Anal. Calcd. for C₇H₁₀N₂O: C, 60.84; H, 7.31; N, 20.28. Found: C, 60.78; H, 7.41; N, 20.32.

2-Acetyl-3-phenylamino-2-butenenitrile (IIIe).

This compound was obtained as colorless needles (81%) mp 132-133° from ethanol; ir (nujol): 3200, 2230, 1650 cm⁻¹; nmr (deuteriochloroform): δ 2.30 (s, CH₃, 3H), 2.40 (s, CH₃, 3H), 7.4 (m, aromatic protons, 5H), 13.4 (broad, NH, 1H).

Anal. Calcd. for C₁₂H₁₂N₂O: C, 71.97; H, 6.05; N, 13.94. Found: C, 72.05; H, 6.12; N, 13.84.

Reaction of β-Cyanoenolates IIa-c with Hydroxylamine.

A mixture of 5 mmoles of IIa-c and 5 mmoles of hydroxylamine hydrochloride in 10 ml of water was refluxed for 3 hours. The isoxazoles Va, b and IX were collected from the cooled solution.

5-Amino-3-methyl-4-nitroisoxazole (Va).

This compound was obtained as yellow powder, mp 148-149° (lit [13] 149-151°).

Anal. Calcd. for $C_4H_5N_3O_3$: C, 33.57; H, 3.53; N, 29.37. Found: C, 33.69; H, 3.50; N, 29.42.

5-Amino-3-methyl-4-ethoxycarbonylisoxazole (Vb).

This compound was obtained as colorless plates, mp 152-153° (lit [14] 133-134°).

Anal. Calcd. for $C_7H_{10}N_2O_5$: C, 49.38; H, 5.93; N, 16.46. Found: C, 49.27; H, 5.99; N, 16.42.

4-Cyano-3,5-dimethylisoxazole (IX).

This compound was obtained as white plates, mp 45-46° (lit [15] 43-44°).

Anal. Calcd. for $C_6H_8N_2O$: C, 59.00; H, 4.96; N, 22.94. Found: C, 58.89; H, 5.01; N, 23.00.

Reaction of β -Cyanoenolates IIa-c with Hydrazines.

A mixture of 5 mmoles of IIa-c and 5 mmoles of hydrazine derivative as hydrochloride in 10 ml of water was refluxed for 3 hours. After this time the solution was cooled, the precipitate filtered and dried to give the pyrazoles VIa-c, VII and Xz-d.

5(3)-Amino-3(5)-methyl-4-nitropyrazole (VIa).

This compound was obtained as yellow powder, mp 206-207° (lit [16] 205°).

Anal. Calcd. for $C_8H_8N_4O_2$: C, 33.78; H, 4.26; N, 39.43. Found: C, 33.69; H, 4.35; N, 39.49.

5-Amino-1,3-dimethyl-4-nitropyrazole (VIb).

This compound was obtained as colorless needles, mp 135-136° (lit [17] 136-138°).

Anal. Calcd. for $C_8H_{10}N_4O_2$: C, 38.45; H, 5.17; N, 35.88. Found: C, 38.60; H, 5.15; N, 35.79.

5-Amino-3-methyl-4-nitro-1-phenylpyrazole (VIc).

This compound was obtained as brown powder, mp 170-172° (lit [16] 170°).

Anal. Calcd. for $C_{10}H_{10}N_4O_2$: C, 55.03; H, 4.63; N, 25.68. Found: C, 54.95; H, 4.73; N, 25.57.

4-Cyano-3-methyl-1-phenyl-5-pyrazolone (VII).

This compound was obtained as colorless plates, mp 196-197° (lit [18] 218-220°).

Anal. Calcd. for $C_{11}H_{10}N_3O$: C, 66.31; H, 4.56; N, 21.10. Found: C, 66.40; H, 4.62; N, 21.02.

4-Cyano-3,5-dimethylpyrazole (Xa).

This compound was obtained as colorless needles, mp 107-108° from ethanol; ir (nujol): 3200, 2200, 1600 cm^{-1} ; nmr (dimethylsulphoxide- d_6): δ 2.4 (s, CH_3 , 6H) 9.1 (broad, NH, 1H).

Anal. Calcd. for $C_6H_7N_3$: C, 59.47; H, 5.83; N, 34.69. Found: C, 59.62; H, 5.76; N, 34.62.

4-Cyano-1,3,5-trimethylpyrazole (Xb).

This compound was obtained as colorless liquid, bp 70°/15 mm; ir (thin film): 2200, 1550, 1500 cm^{-1} ; nmr (carbon tetrachloride): δ 2.2 (s, CH_3 , 3H), 2.5 (s, CH_3 , 3H), 3.8 (s, CH_3 -N, 3H).

4-Cyano-3,5-dimethyl-1-phenylpyrazole (Xc).

This compound was obtained as colorless plates, mp 90-91° (lit [19] 89-90°).

Anal. Calcd. for $C_{12}H_{11}N_3$: C, 73.06; H, 5.63; N, 21.31. Found: C, 72.97;

H, 5.72; N, 21.25.

4-Cyano-3,5-dimethyl-1-(*p*)nitrophenylpyrazole (Xd).

This compound was obtained as yellow plates, mp 186° (lit [20] 180-182°).

Anal. Calcd. for $C_{12}H_{10}N_4O_2$: C, 59.49; H, 4.17; N, 23.13. Found: C, 59.60; H, 4.08; N, 23.19.

Reaction of β -Enaminonitriles IIIa-e with Hydroxylamine.

A mixture of 5 mmoles of IIIa-e, 5 mmoles of hydroxylamine hydrochloride and 5 mmoles of sodium hydroxide in 10 ml of ethanol was refluxed for 3 hours. After this time the solution was cooled and the precipitate filtered to give the isoxazoles Va and IX.

Reaction of β -Enaminonitriles IIIa-e with Hydrazines.

A mixture of 5 mmoles of IIIa-e and 5 mmoles of hydrazine derivative in 10 ml of ethanol was refluxed for 3 hours; the solution was cooled and the precipitate filtered to give the pyrazoles VIa-c and Xa-c.

Reaction of Ia-c with Semicarbazide.

One mmole of isoxazole Ia-c was treated with 1 mmole of semicarbazide hydrochloride and 1 mmole of sodium hydroxide in ethanol-water at room temperature until the formation of a precipitate. The solid was collected to give the semicarbazones IVa-c.

Semicarbazone of 2-Nitro-3-oxobutanenitrile (IVa).

This compound was obtained as white plates (50%) mp 180° dec from water; ir (nujol): 3380, 3280, 3150, 2200, 1685, 1610, 1580 cm^{-1} ; nmr (dimethylsulphoxide- d_6): δ 2.4 (s, CH_3 , 3H), 6.6 (broad, NH, 2H), 9.1 (broad, NH, 1H), 12.4 (broad, NH, 1H).

Anal. Calcd. for $C_8H_{10}N_5O_3$: C, 32.43; H, 3.82; N, 37.83. Found: C, 32.40; H, 3.97; N, 37.85.

Semicarbazone of 2-Ethoxycarbonyl-3-oxobutanenitrile (IVb).

This compound was obtained as white plates (15%), mp 185° (lit [10] 185°); ir (nujol): 3430, 3280, 3230, 2180, 1665, 1585 cm^{-1} ; nmr (dimethylsulphoxide- d_6): δ 1.20 (t, CH_3 , 3H), 2.2 (s, CH_3 , 3H), 4.2 (c, CH_2 , 2H), 6.4 (broad, NH, 1H), 8.7 (broad, NH, 1H), 10.8 (broad, NH, 1H).

Anal. Calcd. for $C_9H_{12}N_4O_3$: C, 45.27; H, 5.71; N, 26.40. Found: C, 45.15; H, 5.80; N, 26.52.

Semicarbazone of 2-Acetyl-3-oxobutanenitrile (IVc).

This compound was obtained as white needles (83%), mp 170° from ethanol; ir (nujol): 3400, 3270, 2200, 1680, 1625 cm^{-1} ; nmr (dimethylsulphoxide- d_6): δ 2.1 (s, CH_3 , 6H), 6.4 (broad, NH, 2H), 8.9 (broad, NH, 1H), 11.6 (broad, NH, 1H).

Anal. Calcd. for $C_7H_{10}N_4O_2$: C, 46.14; H, 5.54; N, 30.75. Found: C, 46.21; H, 5.50; N, 30.92.

Cyclization of Semicarbazones IVa-c.

A solution of 1 mmole of IVa-c in 5 ml of 10% hydrochloric acid was heated on a steam bath for 30 minutes. After this time the solution was cooled and neutralized with sodium hydroxide. The solid formed was filtered to give the pyrazoles VIa, VIII and Xa.

5(3)-Amino-4-ethoxycarbonyl-3(5)-methylpyrazole (VIII).

This compound was obtained as colorless needles, mp 50° (lit [21] 18-20°).

Anal. Calcd. for $C_7H_{11}N_3O_2$: C, 49.68; H, 6.57; N, 24.84. Found: C, 49.60; H, 6.60; N, 24.90.

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