

BASE-INDUCED RING CLEAVAGE OF 4-FUNCTIONALIZED 3-UNSUBSTITUTED
ISOXAZOLES. SYNTHESIS OF 2-AMINOPYRIMIDINES AND PYRIMIDINE-2(3H)-
THIONES

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Abstract- 4-Functionalized 3-unsubstituted isoxazoles undergo
ring cleavage when treated with bases. The resulting open chain
products (β -cyanoenolates , β -enaminonitriles) were converted
into pyrimidines, pyrimidinethiones and pyridinones by reaction
with 1,3-dinucleophiles (guanidine, thiourea) and compounds
having activated methylene groups.

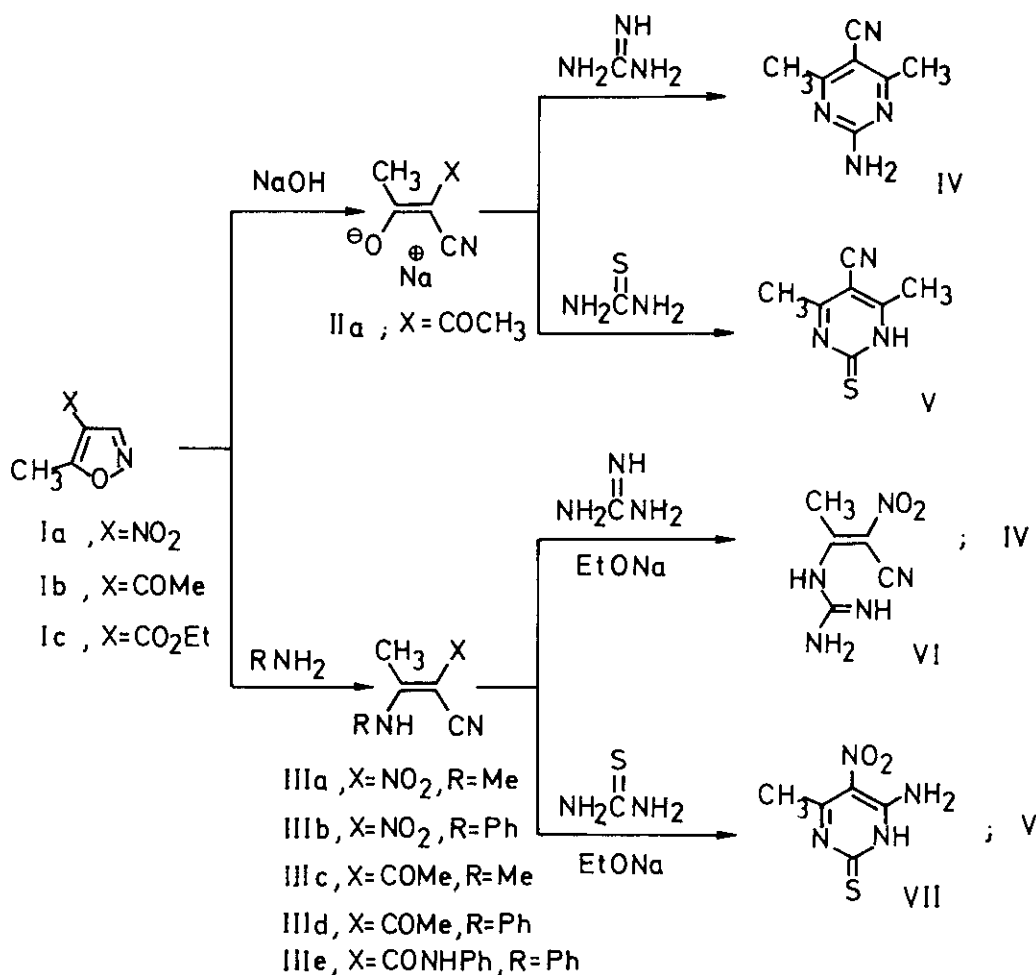
INTRODUCTION

We have previously reported that 3-unsubstituted isoxazoles bearing electron-
withdrawing groups at C-4 underwent ring cleavage when treated with organic bases
leading to stable β -cyanoenolates¹. More recently we have noted the ability of
these enolates to be converted in 5-aminoisoxazoles or 5-aminopyrazoles by
reaction with 1,2-dinucleophiles². Some of our recent efforts have been directed
to the synthesis of pyrimidine derivatives as a result of the interest of these
compounds as intermediates for the preparation of derivatives with pharmacological
activity^{3,4}.

RESULTS AND DISCUSSION

4-Functionalized 5-methylisoxazoles (Ia-c) react with sodium hydroxide and primary
amines to give the β -cyanoenolate IIa and β -enaminonitriles IIIa-e respectively
(figure 1). When IIa reacts with guanidine or thiourea it leads to the 2-amino-5-
cyanopyrimidine IV or the 5-cyanopyrimidine-2(3H)-thione V. β -Enaminonitriles
IIIc,d behave similar to IIa leading to the same products IV and V with different
yields. On the other hand, β -enaminonitriles IIIa,b react with thiourea to give
the 4-amino-5-nitropyrimidine-2(3H)-thione VII. However the reaction of IIIa,b
with guanidine leads to the guanidine derivative VI and the attempts to cyclize
this intermediate resulted in recovery of unchanged VI. Under analogous reaction

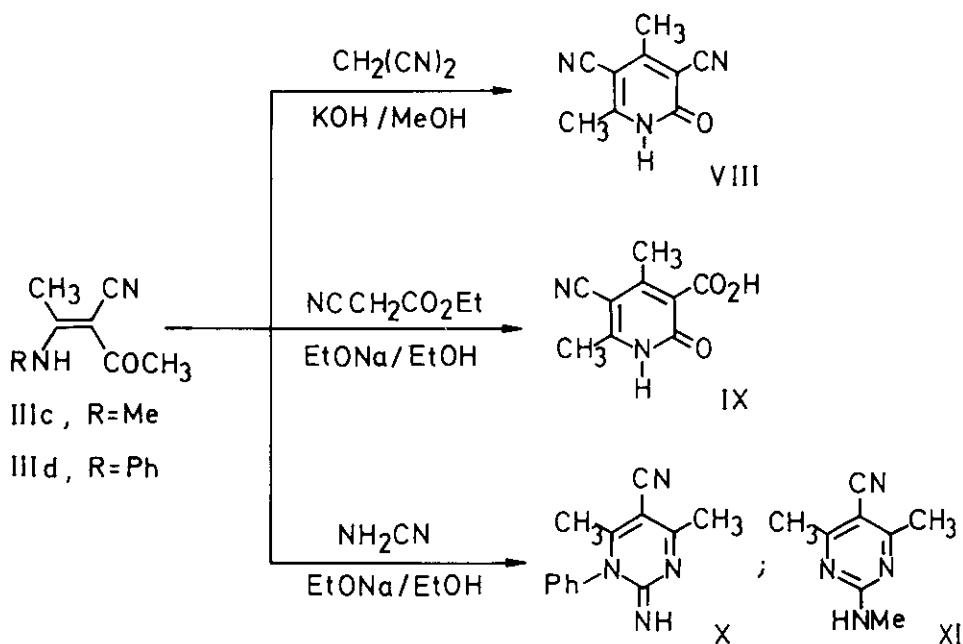
Figure 1



conditions, IIIc fails to react with guanidine and thiourea. Urea was proven to be totally inactive toward β -enaminonitriles IIIa-e in all possible conditions. Although the mechanism of the reaction is not yet clear, it may proceed by 1,4-addition of the 1,3-dinucleophile (guanidine, thiourea) and subsequently cyclization of the resulting intermediate. β -Enaminonitriles also undergo base-induced cyclizations when treated with cyanamide and compounds having activated methylene groups (ethyl cyanacetate and malonitrile) (figure 2). Thus, the preparation of pyrimidinones VIII and IX and pyrimidines X and XI may be cited as an illustration of the effectiveness of these intermediates in heterocyclic synthesis. Formation of XI involves base-induced rearrangement of the methyl analogous of X⁵.

We conclude that β -enaminonitriles and β -cyanoenolates, readily available from 3-unsubstituted isoxazoles, are intermediates of some importance and wide

Figure 2



applicability which react with 1,2-dinucleophiles², 1,3-dinucleophiles and compounds having activated methylene groups, thus providing new routes to pyridine and pyrimidine synthesis.

EXPERIMENTAL

All mp are uncorrected. 4-Nitro-5-methylisoxazole⁶, 4-acetyl-5-methylisoxazole⁷ and 4-ethoxycarbonyl-5-methylisoxazole⁸ were prepared by established procedures. The cyanoenolate IIa and the β -enaminonitriles IIIa-e were prepared according to a previous work². ¹H-NMR spectra were determined using $(\text{CD}_3)_2\text{SO}$ solutions and TMS as standard reference.

Reaction of IIa with thiourea and guanidine. A mixture of IIa (0.02 M) and 0.02 M of the 1,3-dinucleophile (thiourea or guanidine) in 25 ml of ethanol was refluxed for 5 h. After cooling the precipitate was filtered off and recrystallized from ethanol to give IV or V (Table 1).

Reaction of IIIa-e with thiourea and guanidine. A mixture of 5 mM of IIIa-e, 5 mM of sodium ethoxide and 5 mM of thiourea or guanidine in 10 ml of ethanol was refluxed for 8 h. The solution was cooled and acidified with dilute acetic acid. The precipitate was filtered off and recrystallized from ethanol to give IV-VII.

Reaction of IIIc,d with malonitrile. A mixture of 5 mM of IIIc or IIIId, 5 mM of malonitrile and 5 mM of KOH in 20 ml of methanol was refluxed for 4 h. The

solution was cooled and acidified with dilute acetic acid. The precipitate was filtered off and recrystallized from acetic acid to give VIII.

Reaction of IIIc,d with ethyl cyanoacetate . IIIc or IIId (5 mM) was treated with 5 mM of the sodium salt of ethyl cyanoacetate in 10 ml of ethanol. The mixture was refluxed for 7 h , then cooled and acidified with dilute acetic acid. The precipitate was recrystallized from water to give IX .

Reaction of IIIc,d with cyanamide . To a solution of 5 mM of IIIc or IIId and 5 mM of sodium ethoxide in 10 ml of ethanol, was added 5 mM of cyanamide. The solution was refluxed for 10 h , then cooled and acidified with dilute acetic acid. The precipitate was filtered off and recrystallized from ethanol to give X and XI .

Table 1
Yields of Pyridine and Pyrimidine Derivatives

Substrate	t/h	Product	Yield (%)
IIa	4	IV	17
IIa	5	V	9
IIIa	20	VI	87
IIIb	20	VI	69
IIIa	5	VII	12
IIIb	7	VII	35
IIIc	10	IV	47
IIId	10	IV	51
IIIc	5	V	15
IIId	7	V	53
IIIc	8	VIII	35
IIId	5	VIII	65
IIIc	7	IX	43
IIId	7	IX	52
IIId	10	X	78
IIIc	10	XI	36

2-Amino-5-cyano-4,6-dimethylpyrimidine (IV) : yellow powder from ethanol, mp 247-248° C. (lit.⁵ 250° C). Anal. Calcd. for $C_7H_8N_4$: C, 56.76; H, 5.40; N, 37.84. Found: C, 56.80; H, 5.35; N, 37.82.

5-Cyano-4,6-dimethyl-3(H)-2-thiopyrimidinone (V) : yellow powder from ethanol, mp 204-205°C . Anal. Calcd. for $C_7H_7N_3S$: C, 50.91; H, 4.24; N, 25.45. Found: C, 50.86; H, 4.30; N, 25.38. IR(nujol): 3300, 2220, 1620, 1600 cm^{-1} . 1H -NMR($(CD_3)_2SO$)

2.55(6H, s, 4- and 6- CH_3), 8.1 (1H, broad, NH).

3-(2-Nitro-2-butenenitrile)guanidine (VI) : yellow powder from ethanol, mp 200°C dec. Anal. Calcd. for $\text{C}_5\text{H}_6\text{N}_4\text{O}_2$: C, 35.50; H, 4.14; N, 41.42. Found: C, 35.57; H, 4.20; N, 41.35. IR(nujol) : 3400, 3300, 3150, 2185, 1650, 1550 cm^{-1} . $^1\text{H-NMR}$ ($(\text{CD}_3)_2\text{SO}$) : 2.3 (3H, s, CH_3), 7.0 (4H, broad, NH).

4-Amino-6-methyl-5-nitro-3(H)-2-thiopyrimidinone (VII) : yellow powder from ethanol, mp 250°C dec. (lit.⁹ 250° dec.). Anal. Calcd. for $\text{C}_5\text{H}_6\text{N}_4\text{O}_2\text{S}$: C, 32.26; H, 3.23; N, 30.11. Found: C, 32.18; H, 3.27; N, 30.03.

3,5-Dicyano-4,6-dimethyl-1(H)-2-pyridinone (VIII) : white powder from acetic acid mp 230°C dec. Anal. Calcd. for $\text{C}_9\text{H}_7\text{N}_3\text{O}$: C, 62.43; H, 4.05; N, 24.28. Found : C, 62.50; H, 4.10; N, 24.25. IR(nujol): 3100, 2200, 1650, 1600 cm^{-1} . $^1\text{H-NMR}$ ($(\text{CD}_3)_2\text{SO}$) : 2.55(6H, s, 4- and 6- CH_3), 7.5 (1H, broad, NH).

3-(5-Cyano-4,6-dimethyl-1(H)-2-oxo-pyridin)carboxylic acid (IX) : colorless needles from water, mp 260°C dec. Anal. Calcd. for $\text{C}_9\text{H}_8\text{N}_2\text{O}_3$: C, 56.25; H, 4.17; N, 14.58. Found: C, 56.31; H, 4.13; N, 14.63. IR(nujol): 3500-3100, 2200, 1680, 1640, 1570 cm^{-1} . $^1\text{H-NMR}$ ($(\text{CD}_3)_2\text{SO}$) : 2.4 (6H, s, 4- and 6- CH_3), 8.2 (2H, broad, NH and OH).

5-Cyano-4,6-dimethyl-1-phenyl-2-iminopyrimidinone (X) : white needles from ethanol, mp 195-196°C dec. Anal. Calcd. for $\text{C}_{13}\text{H}_{12}\text{N}_4$: C, 69.64; H, 5.36; N, 25.00. Found: C, 69.70; H, 5.32; N, 24.96. IR(nujol): 3250, 2190, 1720, 1600, 1550 cm^{-1} . $^1\text{H-NMR}$ ($(\text{CD}_3)_2\text{SO}$) : 2.15(3H, s, CH_3 -4), 2.55(3H, s, CH_3 -6), 4.0 (1H, broad, NH), 7.4 (5H, m, aromatic protons).

5-Cyano-4,6-dimethyl-2-methylaminopyrimidine (XI) : yellowish powder from ethanol mp 195-196°C (lit.⁵ 198°). Anal. Calcd. for $\text{C}_8\text{H}_{10}\text{N}_4$: C, 59.26; H, 6.17; N, 34.57. Found: C, 59.30; H, 6.20; N, 34.49.

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