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

Angel Alberola*, Luis F. Antolín , Ana M. González , Miguel A. Laguna , and Francisco J. Pulido
Departamento de Química Orgánica de la Universidad de Valladolid
Valladolid , Spain

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.

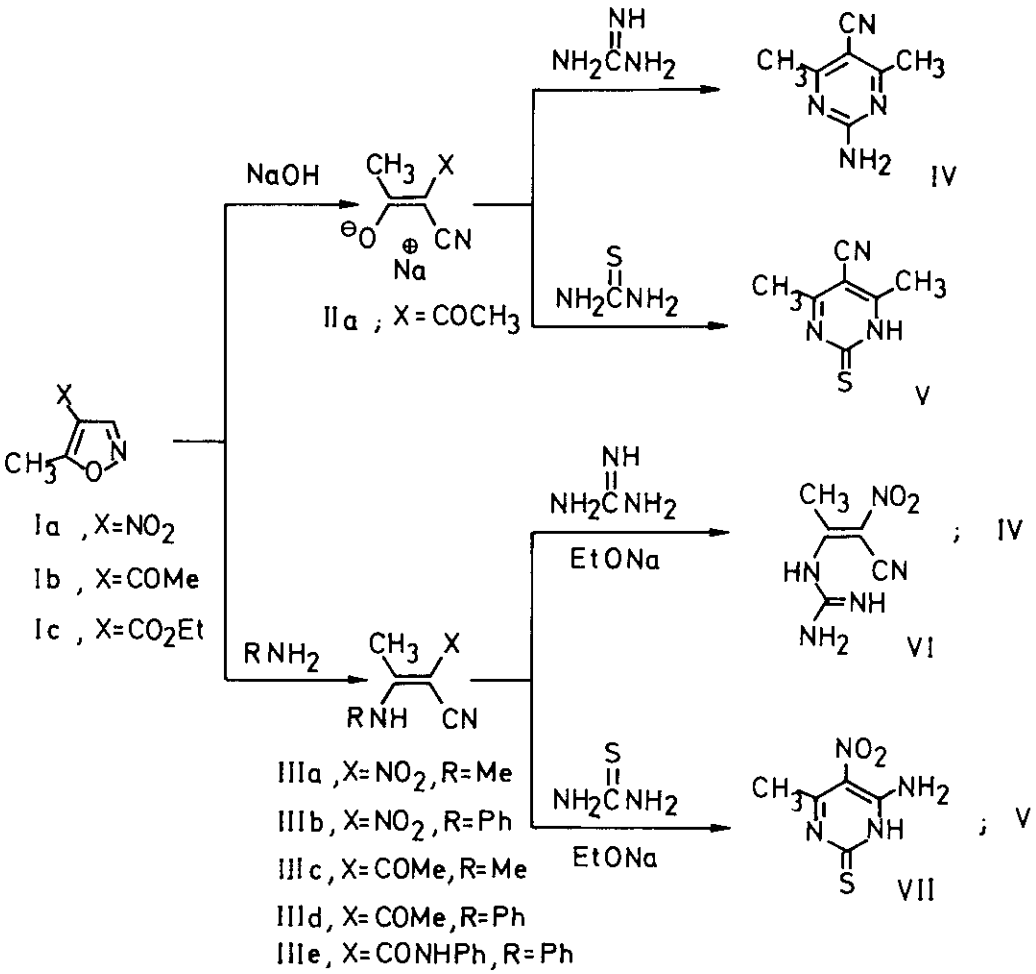
INTRODUCTION

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- cyanoenolates[1]. More recently we have noted the ability of these enolates to be converted in 5-aminoisoxazoles or 5-aminopyrazoles by reaction with 1,2-dinucleophiles[2]. 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 similary 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

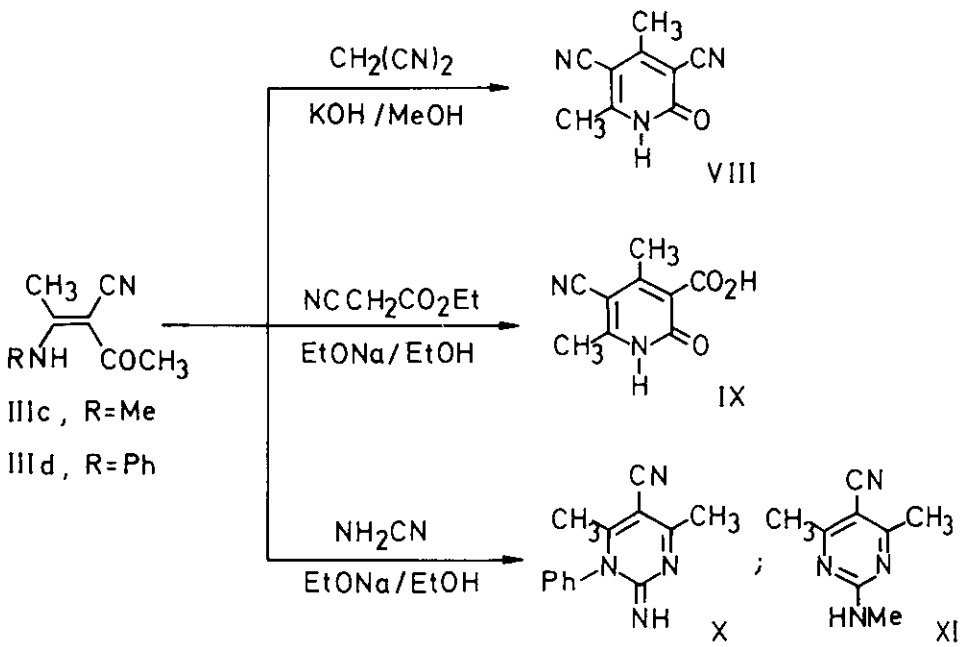
Figure 1



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 X [5].

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-dinucleophiles[2], 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-methylisoxazole[6],4-acetyl-5-methylisoxazole[7] and 4-ethoxycarbonyl-5-methylisoxazole[8] were prepared by established procedures. The cyanoenolate IIa and the β-enaminonitriles IIIa-e were prepared according to a previous work[2]. ^{1}H-NMR spectra were determined using $(CD_3)_2SO$ 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 IIId, 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}. ^{1}H-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 C H N O : 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}H-NMR ($(CD_3)_2SO$): 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 $C_5H_6N_4O_2S$: 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 $C_9H_7N_3O$: 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}H-NMR($(CD_3)_2SO$): 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)carboxilic acid (IX) : colorless needles from water, mp 260°C dec. Anal. Calcd. for $C_9H_8N_2O_3$: 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}H-NMR($(CD_3)_2SO$): 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 $C_{13}H_{12}N_4$: 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}H-NMR($(CD_3)_2SO$): 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 $C_8H_{10}N_4$: C, 59.26; H, 6.17; N, 34.57. Found: C, 59.30; H, 6.20; N, 34.49.

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