A NOVEL SYNTHESIS OF PYRIMIDINES. III. CYCLIZATION OF ALKYL N-CYANO-CYANOACETIMIDATES

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Cyclization reaction of N-cyano-cyanoacetimidates (III) with hydrogen halides has been found to give a mixture of 4-alkoxy-6-amino-2-halogenopyrimidines(IV) and 4-alkoxy-2-amino-6-halogenopyrimidines(V). In the presence of a Lewis acid with hydrogen chloride, this reaction proceeded in one specific direction to give IV.

In our preceding paper of this series[1] we reported the new synthesis of pyrimidine rings by cyclization of cyanoacetyl-cyanamides and N-cyano-cyanoacetamidines with hydrogen halides.

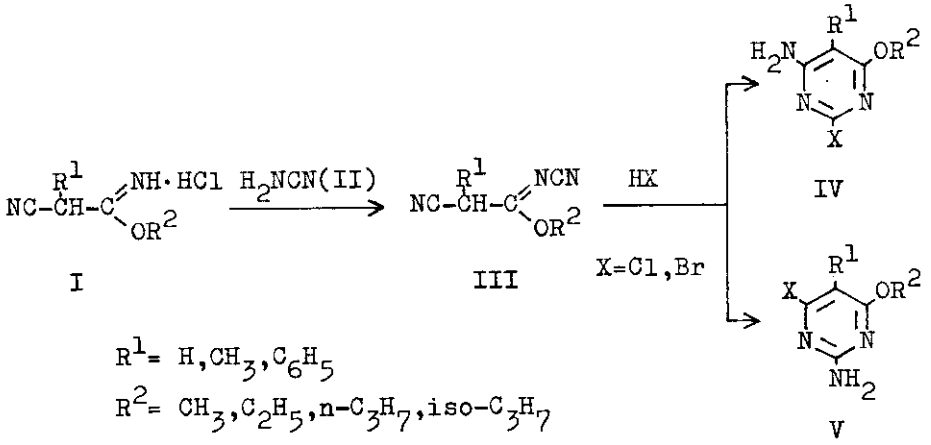
We now report further extension of these reactions to the synthesis of pyrimidines by the reaction of alkyl N-cyano-cyano-acetimidates(III) with hydrogen halides as shown in Chart.

Alkyl N-cyano-cyanoacetimidates(III), which were not obtained by known method[2], could be successfully prepared by the

reaction of alkyl cyanoacetimidate hydrochlorides(I)[3] with cyanamide(II) in nonpolar solvents in the presence of some selected dispersing agents(Molecular sieves, Al_2O_3, etc.) in good yields(Table I). In this reaction, solvent and dispersing agent appeared to play an important role. The general method for the preparation of III was as follows.

Cyanamide(II, 0.02 M) was added to a suspension of I(0.02 M) and Molecular sieves-4A(1.5 g, fine powders) with vigorous stirring in benzene(30 ml) at 20-25°C for 4-6 h, then the reaction mixture was filtered and the filtrate was evaporated under reduced pressure below 30°C to give crude product(III, purity 90-95 %).

The cyclization reaction of III with hydrogen halides in a nonpolar solvent such as ether and benzene gave a mixture of two isomers of pyrimidines viz. 4-alkoxy-6-amino-2-halogenopyrimidines(IV) and 4-alkoxy-2-amino-6-halogenopyrimidines(V). When this reaction was carried out in the presence of a Lewis acid or in acetic acid with hydrogen chloride, the cyclization has been found to proceed preferentially in one specific direction to form IV in excellent yields (Table II). On the other hand, treatment of IIIa with hydrogen bromide in acetic acid did not lead to formation an expected 6-amino-2-bromo-4-methoxypyrimidine(IVg) but instead 2-amino-6-bromo-4-methoxypyrimidine(Vg) was obtained, which was subsequently converted under the similar reaction condition to 2-amino-6-bromo-4-hydroxypyrimidine (VIg). However, IIIa gave a mixture of IVg and Vg (1:2) in 54 % yield in the presence of a Lewis acid in a nonpolar solvent.



Chart

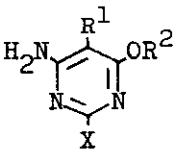
Table I Alkyl N-cyano-cyanoacetimidates(III)

compd.	R^1	R^2	mp(°C)	yield(%)	recrystn. solvent
IIIa	H	CH_3	45.5	91	benzene-ether
IIIb	CH_3	CH_3	68-69	74	$CHCl_3$
IIIc	C_6H_5	CH_3	oil*	81	-
IIId	H	C_2H_5	64-65	87	$CHCl_3$
IIIe	H	n-C_3H_7	oil*	92	-
IIIf	H	iso-C_3H_7	65.5-66.5	98	$CHCl_3$

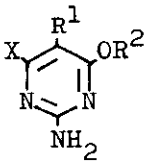
* mass spectra: IIIc, 199(M^+) ; IIIe, 151(M^+)

All crystalline compounds gave satisfactory elemental analyses.

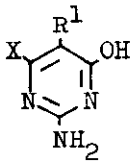
Table II



IV



V



VI

compd.	R^1	R^2	X	mp(°C)	yield(%)
IVa[6]	H	CH_3	Cl	184-185	93
IVb	CH_3	CH_3	Cl	168-169	75
IVc	C_6H_5	CH_3	Cl	174-175	95
IVd[6]	H	C_2H_5	Cl	132-133	95
IVe	H	n-C_3H_7	Cl	104-105	81
IVf	H	iso-C_3H_7	Cl	119-120	97
IVg	H	CH_3	Br	186-188(d)	19*
Vg	H	CH_3	Br	161-163	35*
VIg	H	-	Br	233-234(d)	92

* A mixture of IVg and Vg was determined by nmr spectrum respectively.

Satisfactory analytical data were obtained for all the pyrimidines.

The general procedure for the preparation of IV was as follows.

A solution of hydrogen chloride(0.06 M) in ether(15 ml) was added dropwise to a solution of III(0.01 M) and BF_3-Ether complex(0.001-0.01 M) in benzene-ether(1:2, 15 ml) at 20-25°C. After 6 h, the precipitates were collected, followed by treatment of water and neutralization with aq. $NaHCO_3$ to yield IV.

The structures of III were confirmed by analyses and ir, nmr, mass spectra and their cyclization with hydrogen halides to the pyrimidines(IV,V). The pyrimidines(IVa,b,g, Vg) were identified by methoxylation to known compounds such as 6-amino-2,4-dimethoxypyrimidines[4] and 2-amino-4,6-dimethoxypyrimidine[5], and the other pyrimidines(IVc-f,VIg) were characterized by comparison of their spectra(uv,ir,nmr) with those of the chemically assigned pyrimidines.

This method represents a one-step synthesis of a type of 4-alkoxy-6-amino-2-halogenopyrimidines(IV) which have not been practically available previously[6] and provides an economical means for preparation of the useful pyrimidines from inexpensive and readily available starting materials.

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