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ON THE PYRIMIDINE SYNTHESIS FROM ETHYL ETHOXYMETHYLENECYANOACETATE AND AMIDINES

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The syntheses of pyrimidines by condensation of ethyl ethoxymethylenecyanoacetate (I) (1) with amidines have been the subject of several studies (2-5) since old times, where the intermediates ethyl 3-amidino-2-cyanoacrylates are capable of cyclization by attack of the terminal nucleophilic amino group to an electrophilic center, either cyano or carbethoxy group. The reaction leads, in general, to a mixture and there is difficulty in predicting a predominance of the two directions of this intramolecular cyclization.

Todd and Bergel (3) reported that condensation of compound I with acetamidine gave an intermediate, probably ethyl 3-acetamidino-2-cyanoacrylate, which on heating with alkali yielded 5-cyano-4-hydroxy-2-methylpyrimidine in low yield (15%). Accordingly their efforts were made to cause direct production of the pyrimidine so as to avoid the losses involved in the cyclization of the intermediate ester with sodium hydroxide; for this purpose condensations were made at various temperatures with various amounts of sodium ethoxide but without satisfactory results.

During a reinvestigation of the direct pyrimidine synthesis described above, we have found that the proportion of reacting components has a drastic effect upon the results of the reaction, especially yields of products. Treatment of 1 equiv of I with 3 equiv of acetamidine in ethanol under cooling and maintaining the mixture overnight in an icebox gave 5-cyano-4-hydroxy-2-methylpyrimidine acetamidinate (II) (m.p. 184-188°, colorless needles from ethyl acetate, Anal. Calcd. for $C_8H_{11}N_5O$: C, 49.73; H, 5.74; N, 36.25. Found: C, 49.36; H, 5.98; N, 36.39) in 85.5% yield, while the use of 2 or 1 equiv of acetamidine caused

the decrease of the yields (see TABLE I). In every case, a small amount of ethyl 4-amino-2-methylpyrimidine-5-carboxylate was accompanied, which could be isolated by extraction with ether from the reaction mixture.

TABLE I

Reaction of Ethyl Ethoxymethylenecyanoacetate (I) and Acetamidine

Mole Ratio of Acetamidine to Compound I	Reaction Condition	Yield of Products (%) Compound II	Ethyl 4-Amino-2-methyl-pyrimidine-5-carboxylate
1 : 1	Icebox, 15 hr	20.3	trace
2 : 1	Icebox, 15 hr	69.0	trace
3 : 1	Icebox, 15 hr	85.5	8.3

The possibility of compound II to be 3-acetamidino-2-cyanoacryloyl acetamidine (III) is eliminated from following facts: (1) Compound II is converted quantitatively to 5-cyano-4-hydroxy-2-methylpyrimidine (3) by neutralization with acetic acid. (2) Compound II is prepared quantitatively by mixing equimolar 5-cyano-4-hydroxy-2-methylpyrimidine and acetamidine in ethanol. (3) The mass spectrum of compound II reveals the respective strong parent ions (m/e 135 and 58), which correspond to those of 5-cyano-4-hydroxy-2-methylpyrimidine and acetamidine, but no molecular ion (m/e 193) of compound III.

The reaction between I and 2-ethyl-2-thiopseudourea was also examined and the remarkable contrast of the products was observed according to the difference of the mole ratios of reactants (see TABLE II). Separation of the products was easy; ethyl 3-{[amino(ethylthio)methylene]amino}-2-cyanoacrylate (IV) (2,5) began to separate after a few minutes. The filtrate was kept in an icebox overnight and concentrated to give a mixture of the other two, from which ethyl 4-amino-2-ethylthiopyrimidine-5-carboxylate was isolated by extraction using ether.

5-Cyano-2-ethylthio-4-hydroxypyrimidine 2-ethyl-2-thiopseudoureate (V) (m.p. 175-177°, colorless needles from ethyl acetate, Anal. Calcd. for $C_{10}H_{15}N_5OS_2$: C, 42.08; H, 5.31; N, 22.47. Found: C, 42.23; H, 5.47; N, 22.39) has been regarded as 3-{3-{[amino(ethylthio)methylene]amino}-2-cyanoacryloyl}-2-ethyl-2-thiopseudourea (VI) (2,5) for a long time. Now compound VI has proved to be V, based on the quantitative decomposition to 5-cyano-2-ethylthio-4-hydroxypyrimidine

(VII) (2,5) with acetic acid, the formation of V from VII and 2-ethyl-2-thiopseudourea, and the analysis by mass spectroscopy (no molecular ion (m/e 285) of VI).

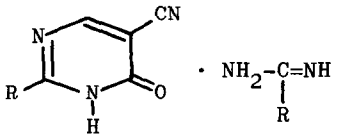
TABLE II

Reaction of Ethyl Ethoxymethylenecyanoacetate (I) and 2-Ethyl-2-thiopseudourea

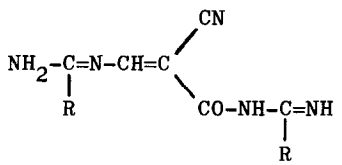
Mole Ratio of 2-Ethyl-2-thiopseudourea to Compound I	Reaction Condition (Solvent)	Yield of Products (%) Compound IV	Compound V	Ethyl 4-Amino-2-ethylthiopyrimidine-5-carboxylate
1 : 1	a) (methanol)	45.4	13.1	trace
2 : 1	a) (ethanol)	43.7	18.0	trace
2 : 1	a) (methanol)	65.5	26.0	trace
3 : 1	Icebox, 15 hr (methanol)	-	53.0	5.0
4 : 1	Icebox, 15 hr (methanol)	-	56.1	trace

a) After filtration of IV, the filtrate was allowed to stand in an icebox for 15 hr.

The reaction of I with guanidine in ethanol under the same conditions gave predominantly ethyl 2,4-diaminopyrimidine-5-carboxylate (VIII) (6,7) (m.p. 215-217°, colorless needles from ethanol, Anal. Calcd. for $C_7H_{10}N_4O_2$: C, 46.15; H, 5.52; N, 30.76. Found: C, 46.48; H, 5.64; N, 30.82) along with a trace of 2-amino-5-cyano-4-hydroxypyrimidine guanidinate (IX) (m.p.>300°, colorless prisms from methanol, Anal. Calcd. for $C_6H_9N_7O$: C, 36.97; H, 4.66; N, 50.24. Found: C, 36.94; H, 4.74; N, 50.36), which could be easily separated by fractional crystallization from ethanol. The latter was converted to 2-amino-5-cyano-4-hydroxypyrimidine (m.p.>300°, colorless needles from acetic acid, Anal. Calcd. for $C_5H_4N_4O$: C, 44.12; H, 2.96; N, 41.17. Found: C, 44.09; H, 3.20; N, 40.85) by treating with acetic acid.



R=CH_3- (II)
C_2H_5S- (V)
NH_2- (IX)



R=CH_3- (III)
C_2H_5S- (VI)

As can be seen from TABLE III, this reaction is also significantly influenced by the proportion of reacting components and the use of great excess of guanidine brings about an excellent result.

TABLE III

Reaction of Ethyl Ethoxymethylenecyanoacetate (I) and Guanidine

Mole Ratio of Guanidine to Compound I	Reaction Condition	Yield of Products (%) Compound VIII	Compound IX
1 : 1	R. T., 15 hr	37.5	5.8
2 : 1	Icebox, 15 hr	55.0	trace
2 : 1	R. T., 15 hr	70.0	trace
4 : 1	Icebox, 15 hr	85.0	-
4 : 1	R. T., 15 hr	95.0	-

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