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Condensation Reactions of Ethyl Ethoxymethylenecyanoacetate with Amidines[1]

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The pyrimidine synthesis from ethyl ethoxymethylenecyanoacetate (EMCE) and amidines is significantly influenced by the mole ratios of reacting components. In general the use of excess amidine gives better yields. Condensation of EMCE with excess acetamidine gives 4-hydroxy-2-methyl-5-pyrimidinecarbonitrile acetamidinate as the main product in good yield. Reaction between EMCE and excess 2-ethyl-2-thiopseudourea gives 2-ethylthio-4-hydroxy-5-pyrimidinecarbonitrile 2-ethyl-2-thiopseudoureate rather than 3-{3-{[amino(ethylthio)methylene]amino}-2-cyanoacryloyl}-2-ethyl-2-thiopseudourea originally claimed. The condensation reactions of EMCE with other amidines such as guanidine and benzamidine have been studied.

4-Hydroxy-5-pyrimidinecarbonitriles have considerable practical importance as synthetic intermediates. The usual method to prepare these substances is the condensation of ethyl ethoxymethylenecyanoacetate (referred to hereafter as EMCE) with amidines, which leads, in general, to a mixture of 4-hydroxy-5-pyrimidinecarbonitrile and ethyl 4-amino-5-pyrimidinecarboxylate. 4-Hydroxy-2-methyl-5-pyrimidinecarbonitrile has been prepared by this method by Todd and Bergel,[3] however the yield was recorded as unsatisfactory (15%). We have repeated Todd's work with slight modifications in some detail and found that the mole ratios of reacting components have a remarkable effect upon the yields of products. This result prompted us to look more closely into the reactions between EMCE and some other amidines such as benzamidine, 2-ethyl-2-thiopseudourea or guanidine. The present paper describes the outcome of these studies.

Reaction between EMCE and Acetamidine

Treatment of 1 equiv. of EMCE with 3 equiv. of acetamidine in ethanol under cooling and maintaining the mixture overnight in an icebox gave 4-hydroxy-2-methyl-5-pyrimidinecarbonitrile acetamidinate (I) in 85.5% yield, while the use of 2 or 1 equiv. of acetamidine caused a decrease of the yields as seen in Table I. In every case, a small amount of ethyl 4-amino-2-methyl-5-pyrimidinecarboxylate (II)[3] was present, which could be isolated from the reac-

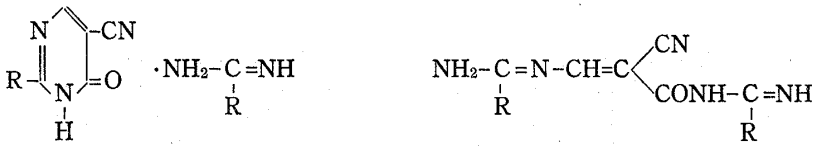
Table I. Reaction of EMCE and Acetamidine

Mole ratio of acetamidine to EMCE	Reaction condition	Yield of products (%)	
		Compound I	Compound II
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

1) Previous communication: S. Nishigaki, K. Aida, K. Senga and F. Yoneda, *Tetrahedron Letters*, **1969**, 247.
2) Location: *35, Shinanomachi, Shinjuku-ku, Tokyo.*
3) A.R. Todd and F. Bergel, *J. Chem. Soc.*, **1937**, 364.

tion mixture by extraction with ether. When the condensation was made at room temperature, the yields of I and II were not as good.

The possibility of compound I to be 3-acetamidino-2-cyanoacryloylacetamidine (III) is eliminated from following facts. Compound I is converted quantitatively to 4-hydroxy-2-methyl-5-pyrimidinecarbonitrile by treatment with acetic acid. Compound I is prepared quantitatively by mixing equimolar 4-hydroxy-2-methyl-5-pyrimidinecarbonitrile and acetamidine in ethanol. The mass spectrum of compound I reveals the respective strong parent ions at *m/e* 135 and 58, which are attributed to 4-hydroxy-2-methyl-5-pyrimidinecarbonitrile and acetamidine, but no molecular ion (*m/e* 193) of compound III.



I : R=CH_3–
V : R=C_2H_5S–
IX: R=NH_2–

III: R=CH_3–
VI : R=C_2H_5S–

Chart 1

Reaction between EMCE and 2-Ethyl-2-thiopseudourea

The condensation of EMCE with 2-ethyl-2-thiopseudourea similarly showed the remarkable contrast of the products according to the difference of the mole ratios of reactants as seen in Table II. On using 1 or 2 equiv. of 2-ethyl-2-thiopseudourea, the intermediate ethyl 3-{[amino(ethylthio)methylene]amino}-2-cyanoacrylate (IV)[4,5] was obtained, however the use of more than 3 equiv. of 2-ethyl-2-thiopseudourea afforded only 2-ethylthio-4-hydroxy-5-pyrimidinecarbonitrile 2-ethyl-2-thiopseudoureate (V) as the main product. Compound V has been regarded as 3-{3-{[amino(ethylthio)methylene]amino}-2-cyanoacryloyl}-2-ethyl-2-thiopseudourea (VI)[4,5] for a long time. Now it has been shown that VI has in fact structure V based on the quantitative decomposition to 2-ethylthio-4-hydroxy-5-pyrimidinecarbonitrile (VII)[4,5] with acetic acid, and the formation of V from VII and 2-ethyl-2-thiopseudourea. The mass spectrum shows no molecular ion for VI at *m/e* 285 but shows those for VII and 2-ethyl-2-thiopseudourea at *m/e* 181 and 104. The minor product, ethyl 4-amino-2-ethylthio-5-pyrimidinecarboxylate,[4,5] was easily isolated from the reaction mixture by extraction using ether.

Table II. Reaction between EMCE and 2-Ethyl-2-thiopseudourea

Mole ratio of 2-ethyl-2-thiopseudourea to EMCE	Reaction condition (solvent)	Yield of products (%)		
		Compound IV	Compound V	Ethyl 4-amino-2-ethylthio-5-pyrimidine carboxylate
1:1	A (MeOH)	45.4	13.1	trace
2:1	A (MeOH)	43.7	18.0	trace
2:1	A (MeOH)	65.5	26.0	trace
3:1	icebox, 15 hr (MeOH)	—	53.0	5.0
4:1	icebox, 15 hr (MeOH)	—	56.1	trace

A : After filtration of IV, the filtrate was allowed to stannd in an icebox for 15 hr.

4) T.B. Johnson and H.L. Wheeler, *Am. Chem. J.*, **42**, 505 (1909).
5) A. Dornow and G. Petsch, *Ann.*, **588**, 45 (1954).

Reaction between EMCE and Guanidine

The reaction of EMCE with guanidine in ethanol under the same conditions gave predominantly ethyl 2,4-diamino-5-pyrimidinecarboxylate (VIII)[6,7] along with a trace of 2-amino-4-hydroxy-5-pyrimidinecarbonitrile guanidinate (IX), which was converted to 2-amino-4-hydroxy-5-pyrimidinecarbonitrile treatment with acetic acid. This reaction is also significantly influenced by the mole ratios of reacting components and in fact the use of 4 equiv. of guanidine in room temperature brings about the formation of VIII in 95% yield. This method offers a more convenient method than that described earlier for the synthesis of VIII. Compound VIII is readily hydrolyzed into 2,4-diamino-5-pyrimidinecarboxylic acid with aqueous sodium hydroxide.

Table III. Reaction between EMCE and Guanidine

Mole ratio of guanidine to EMCE	Reaction condition	Yield of products (%)	
		Compound VIII	Compound IX
1:1	room temp., 15 hr	37.5	5.8
2:1	icebox, 15 hr	55.0	trace
2:1	room temp., 15 hr	70.0	trace
4:1	icebox, 15 hr	85.0	trace
4:1	room temp., 15 hr	95.0	trace

Reaction between EMCE and Benzamidine

The reaction of EMCE with less basic benzamidine is a little different from the other reactions described above. In this case, the intermediate, ethyl 3-benzamidino-2-cyanoacrylate (X), is the usual main product and the formation of 4-hydroxy-2-phenyl-5-pyrimidinecarbonitrile (XI) is very small as seen from Table IV. However, on heating in acetic acid, aqueous sodium hydroxide, DMF or benzene, compound X yielded XI in good yield, accompanied by ethyl 4-amino-2-phenyl-5-pyrimidinecarboxylate (XII). It is noteworthy that the moderate yield of XII was observed on using excess benzamidine at room temperature.

Table IV. Reaction between EMCE and Benzamidine

Mole ratio of benzamidine to EMCE	Reaction condition	Yield of products (%)			
		Compound X	Compound XI	Compound XII	Total
1:1	icebox, 15 hr	50.6	5.7	—	56.3
2:1	icebox, 15 hr	73.3	—	trace	73.3
3:1	icebox, 15 hr	76.7	2.6	trace	79.3
1:1	room temp., 15 hr	55.9	1.6	—	57.5
2:1	room temp., 15 hr	31.4	—	41.8	73.2
3:1	room temp., 15 hr	48.9	—	28.8	77.7

6) F. Eiden, *Archiv der Pharmazie*, **295**, 516 (1962). He synthesized compound VIII by heating 2-dimethylaminomethylenecyanoacetate with guanidine in ethanol.

7) R.S. Shadbolt and T.L.V. Ulbricht, *J. Chem. Soc.*(C), **1967**, 1172. Compound VIII was obtained from both ethyl 2-amino-4-cyano-5-pyrimidinecarboxylate and ethyl 4-amino-2-cyano-5-pyrimidinecarboxylate by treatment with ammonia in methanol at room temperature.

Experimental[8]

Reaction of EMCE and Acetamidine——To an ice-cold solution of 1.38 g (0.06 g atom) of Na in 30 ml of absolute EtOH was added 5.68 g (0.06 mole) of acetamidine-HCl, shaken for a few min and quickly filtered from precipitated NaCl. To the cooled filtrate (2—5°) was added 3.38 g (0.02 mole) of EMCE in portions under shaking to give an orange yellow solution. After standing overnight (*ca.* 15 hr) in an icebox, the crystals which separated were collected by filtration to yield crude 4-hydroxy-2-methyl-5-pyrimidinecarbonitrile acetamidinate (I). The filtrate was evaporated under reduced pressure to dryness to give a mixture of I and ethyl 4-amino-2-methyl-5-pyrimidinecarboxylate (II), from which 0.3 g (8.3%) of the latter was isolated by extraction using ether. The combined I was recrystallized from EtOAc to give 3.3 g (85.5%) of colorless needles, mp 184—188°. *Anal.* Calcd. for $C_8H_{11}ON_5$: C, 49.73; H, 5.74; N, 36.25. Found: C, 49.46; H, 5.98; N, 36.39.

4-Hydroxy-2-methyl-5-pyrimidinecarbonitrile[3]——Two grams (0.01 mole) of I was added in 20 ml of AcOH and warmed on a water bath for 30 min. After cooling, the pale yellow precipitates were collected by filtration and recrystallized from H_2O several times to give 1.25 g (93%) of colorless needles, mp 243—245° (decomp.). *Anal.* Calcd. for $C_6H_5ON_3$: C, 53.33; H, 3.73; N, 31.10. Found: C, 53.23; H, 4.02; N, 31.26.

Formation of I from 4-Hydroxy-2-methyl-5-pyrimidinecarbonitrile and Acetamidine——In 3 ml of absolute EtOH was dissolved 0.05 g (0.0022 g atom) of Na and then added 0.2 g (0.0022 mole) of acetamidine-HCl. After shaking for a few min, the precipitated NaCl was filtered off. To the filtrate was added 0.3 g (0.0022 mole) of 4-hydroxy-2-methyl-5-pyrimidinecarbonitrile and the mixture was allowed to stand overnight in an icebox to precipitate I in quantitative yield.

Reaction of EMCE and 2 Equiv. of 2-Ethyl-2-thiopseudourea——To an ice-cold solution of 2.63 g (0.04 mole) of 85% KOH in 13 ml of MeOH was added an ice-cold solution of 7.40 g (0.04 mole) of 2-ethyl-2-thiopseudourea-HBr in 10 ml of MeOH and after a few min the precipitated NaBr was filtered off. To the cooled filtrate (8—10°) was added 2.38 g (0.02 mole) of EMCE in portions under shaking. After 5 min crystals which separated were collected by filtration to give 3.0 g (65.5%) of ethyl 3-{[amino(ethylthio) methylene]-amino}-2-cyanoacrylate (IV) in high state of purity, mp 130—135°.[6,7]

After the mother liquid was allowed to stand overnight in an icebox, the crystals were filtered to give 1.5 g (26%) of crude 2-ethylthio-4-hydroxy-5-pyrimidinecarbonitrile 2-ethyl-2-thiopseudoureate (V) from which a trace of ethyl 4-amino-2-ethylthio-5-pyrimidinecarboxylate[6,7] was isolated by extraction with ether. Recrystallization of crude V from EtOAc gave colorless needles, mp 175—177°. *Anal.* Calcd. for $C_{10}H_{15}ON_5S_2$: C, 42.08; H, 5.31; N, 22.47. Found: C, 42.23; H, 5.47; N, 22.39.

Reaction of EMCE and 4 Equiv. of 2-Ethyl-2-thiopseudourea——To an ice-cold solution of 2.63 g (0.04 mole) of 85% KOH in 23 ml of MeOH was added 7.40 g (0.04 mole) of 2-ethyl-2-thiopseudourea-HBr and shaked for a few min. After the precipitated NaBr was filtered off, 1.69 g (0.01 mole) of EMCE was added in portions under cooling and shaking to give a yellow solution. After standing overnight (*ca.* 15 hr) in an icebox, the reaction mixture was condensed under reduced pressure to separate crystals, which were collected by filtration and extracted with ether with warming to remain 1.6 g (56.1%) of 2-ethylthio-4-hydroxy-5-pyrimidinecarbonitrile 2-ethyl-2-thiopseudoureate (V). Evaporation of the ether extracts gave a trace of ethyl 4-amino-2-ethylthio-5-pyrimidinecarboxylate, mp 102—105°.

Cyclization of IV——To 0.4 ml of 12% aqueous NaOH was added 0.1 g of IV and warmed at 40—50° for 10 min. After cooling, the reaction mixture was acidified with 10% HCl to precipitate crystals, which were filtered off, washed with H_2O and dried giving 0.06 g (76%) of 2-ethylthio-4-hydroxy-5-pyrimidinecarbonitrile (VII),[6,7] mp 220°. This compound was identical with the product which was obtained by acidification of V with AcOH.

Reaction of EMCE and Guanidine——In 120 ml of EtOH including 4.1 g (0.176 g atom) of Na was added 15.8 g (0.088 mole) of guanidine carbonate and refluxed for 1 hr. After cooling, the precipitated Na_2CO_3 was filtered off and to the filtrate was added 7.5 g (0.044 mole) of EMCE, shaked well and allowed to stand overnight. The crystals which separated were collected by filtration and recrystallized from EtOH to give 7.6 g (95%) of ethyl 2,4-diamino-5-pyrimidinecarboxylate (VIII), mp 215—217°.[6,7] *Anal.* Calcd. for $C_7H_{10}O_2N_4$: C, 46.15; H, 5.52; N, 30.76. Found: C, 46.48; H, 5.64; N, 30.82.

The less soluble compound which remained insoluble on recrystallization from EtOH, was recrystallized from MeOH to give a trace of 2-amino-4-hydroxy-5-pyrimidinecarbonitrile guanidinate (IX) as colorless prisms, mp>300°. *Anal.* Calcd. for $C_6H_9ON_7$: C, 36.97; H, 4.66; N, 50.24. Found: C, 36.94; H, 4.74; N, 50.36.

8) Infrared spectra were determined on a Japan Spectroscopic Co., Ltd. Spectrophotometer, Model IR-E, from samples mulled in Nujol. NMR spectra were taken on a Japan Electron Optics Lab. Model JNM-C-60-H instrument in DMSO-d_6 using tetramethylsilane (TMS) as an internal reference. Melting points are uncorrected.

Recrystallization of IX from AcOH gave the free base, 2-amino-4-hydroxy-5-pyrimidinecarbonitrile as colorless needles, mp>300°. *Anal.* Calcd. for $C_5H_4ON_4$: C, 44.12; H, 2.96; N, 41.17. Found: C, 44.09; H, 3.20; N, 40.85.

2,4-Diamino-5-pyrimidinecarboxylic Acid——A mixture of 0.5 g (0.0027 mole) of VIII in 5.0 ml of 10% alcoholic NaOH was refluxed for 10 min to precipitate the Na salt, which was collected by filtration, dissolved in H_2O and acidified with AcOH to give 0.3 g (71.4%) of colorless crystals, mp>300°. Recrystallization from EtOH gave colorless needles. *Anal.* Calcd. for $C_5H_6O_2N_4$: C, 38.96; H, 3.92; N, 36.35. Found: C, 39.04; H, 3.97; N, 36.25.

Reaction of EMCE and Benzamidine under Cooling——To an ice-cold solution of 0.8 g (0.036 g atom) of Na in 20 ml of absolute EtOH was added 5.6 g (0.036 mole) of benzamidine-HCl, shaked for a few min and filtered from precipitated NaCl. To the cooled filtrate (0—2°) was added 2.0 g (0.012 mole) of EMCE in portions under shaking to give an orange yellow solution. After maintaining the mixture overnight in an icebox, the crystals which separated were collected by filtration to give 2.2 g (76.7%) of yellow powder of ethyl 3-benzamidino-2-cyanoacrylate (X). Its NMR spectrum showed a broad singlet at 9.06 ppm (NH_2), a sharp singlet at 8.55 ppm (vinyl H), an aromatic multiplet between 8.0 and 7.6 ppm, a quartet at 4.20 ppm (J=7 cps) (CH_3 of ethyl) (ratio 2:1:5:2:3). The infrared spectrum of X showed a nitrile band at 2250 cm^{-1}. This compound showed no definite melting point and could not be recrystallized because of instability.

The mother liquid was concentrated *in vacuo* and the precipitated crystals were filtered off. This procedure was repeated three times and 0.06 g (2.6%) of 4-hydroxy-2-phenyl-5-pyrimidinecarbonitrile (XI), mp>300° and a trace of ethyl 4-amino-2-phenyl-5-pyrimidinecarboxylate (XII), mp 110—115°, were obtained.

Reaction of EMCE and Benzamidine at Room Temperature——To an ice-cold solution of 0.55 g (0.024 g atom) of Na in 20 ml of absolute EtOH was added 3.8 g (0.024 mole) of benzamidine-HCl, shaked for a few min and filtered from precipitated NaCl. To the filtrate was added 2.0 g (0.012 mole) of EMCE in portions and allowed to stand overnight at room temperature. The crystals which separated were collected by filtration, dried and recrystallized from benzene to give 1.2 g (41.8%) of ethyl 4-amino-2-phenyl-5-pyrimidinecarboxylate (XII) as colorless plates, mp 115°. *Anal.* Calcd. for $C_{13}H_{13}O_2N_3$: C, 64.18; H, 5.39; N, 17.28. Found: C, 64.56; H, 5.24; N, 17.67.

The mother liquid was concentrated *in vacuo* to remain 0.9 g (31.4%) of X.

Cyclization of X——One gram (0.0041 mole) of X was added in 10 ml of AcOH and refluxed for 1 hr at 140° and allowed to stand overnight. The crystals were collected by filtration, dried and recrystallized from DMF to give 0.45 g (55.6%) of XI as colorless needles. *Anal.* Calcd. for $C_{11}H_7ON_3$: C, 67.00; H, 4.58; N, 21.31. Found: C, 66.89; H, 3.49; N, 21.07.

The mother liquor was evaporated *in vacuo* to remain 0.3 g (30%) of XII.