REACTION OF 3-AMINOCROTONAMIDE WITH NITRILES

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Abstract —— The reaction of 3-aminocrotonamide (5) with some nitriles, such as acetonitrile, propiononitrile, *iso*-butyronitrile, and benzonitrile, gave the corresponding 2-substituted 6-methyl-4(3*H*)-pyrimidones (2a - 2d). Phenylacetonitrile reacted with (5) to give 2-benzyl-6-methyl-4(3*H*)-pyrimidone (7) and 6-amino-4-methyl-5-phenyl-2(1*H*)-pyridone (8a). Malononitrile, however, reacted with (5) to afford 6-amino-5-cyano-4-methyl-2(1*H*)-pyridone (8b).

Several methods are available for the preparation of 2-substituted 6-methyl-4(3*H*)-pyrimidone (2). For example, ethyl acetoacetate (1) is allowed to react with amidines in the presence of sodium ethoxide to give the pyrimidone (2).[1] Kano *et al.*[2] also reported the catalytic reduction of 3-methyl-5-acylaminoisoxazole (3) with Raney nickel to give the pyrimidone (2). This reaction might well involve the formation of *N*-acyl-3-aminocrotonamide (4) as an intermediate.

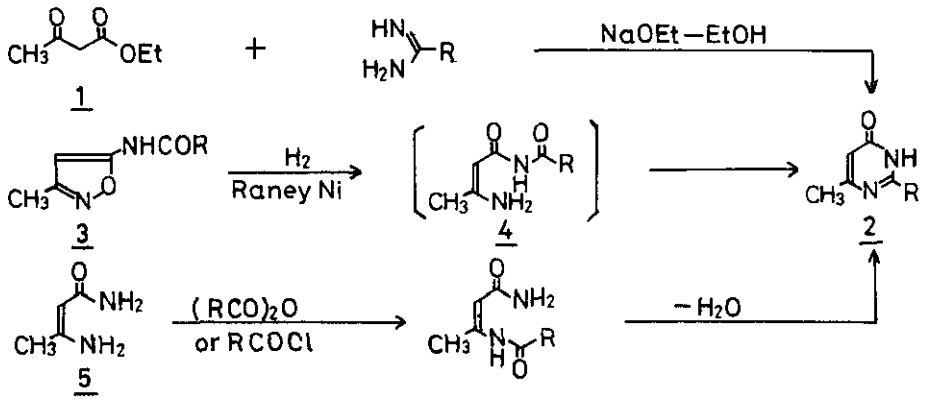
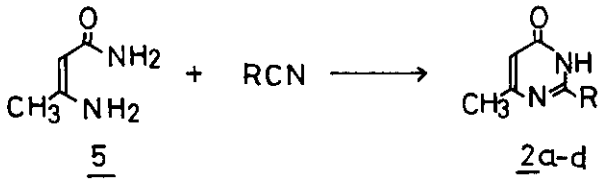


Chart 1

Previously, we have reported a more convenient synthesis of the pyrimidones (2) by the acylation of 3-aminocrotonamide (5)[3] with acid anhydrides,[4a,4b] acid halides,[4a,4b] and esters.[4c,4d] Present paper reports a continuation of this study on preparation of the pyrimidone (2) using nitriles, such as acetonitrile, propiononitrile, *iso*-butyronitrile, and benzonitrile, in place of acylating agents. In addition, some nitriles such as phenylacetonitrile and malononitrile underwent cyclization in a different fashion to give the 6-amino-2-pyridone derivatives (8a and 8b).

3-Aminocrotonamide (5) was allowed to react with three equivalent moles of acetonitrile in methanol in the presence of sodium methoxide prepared freshly from three equivalent gram atoms of sodium in methanol. The reaction mixture was refluxed for 30 hr. Usual work up gave 2,6-dimethyl-4(3*H*)-pyrimidone (2a), mp 194 - 195 °C (lit.[3a] mp 195 - 195.5 °C), in 18% yield. Following the similar procedure, the amide (5) was allowed to react with propiononitrile, *iso*-butyronitrile, and benzonitrile to give 2-ethyl-, 2-isopropyl-, and 2-phenyl-6-methyl-4(3*H*)-pyrimidone (2b, 2c, and 2d), respectively. Results are summarized in Table I.

Table I. Reaction condition and physical properties for product (2a-d)



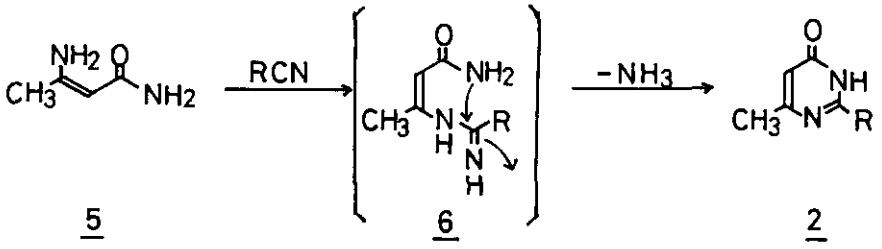
5 2a-d

R	Reaction Condition*				Product
	RCN, g (mmol)	5, g (mmol)	Reaction time (h)	Yield g (%)	mp °C (lit.), Crystal form
CH_3	2.46 (60)	2 (20)	30	2a, 0.45 (18)	194 - 195 (195 - 195.5)[3a] colorless needles
CH_3CH_2	3.3 (60)	2 (20)	26	2b, 1.2 (44)	156 - 157 (156 - 157)[3a] colorless needles
$(CH_3)_2CH$	4.14 (60)	2 (20)	24	2c, 1 (33)	171 - 172 (172 - 173)[3a] colorless needles
C_6H_5	6.18 (60)	2 (20)	2.5	2d, 1.5 (40)	213 - 215 (214 - 215)[3a] colorless needles

* The reaction mixture was refluxed in NaOMe - MeOH (Na (1.38 g, 60 mg atom) - MeOH (20 ml)).

Concerning the formation of the pyrimidone (2), we speculated first that the imidate produced from nitrile might be a probable intermediate, which reacts with (5) to give the product. However, we found that reaction of (5) with methyl benzimidate under the same condition did not proceed smoothly giving a trace of the product (2d). Furthermore, aliphatic nitrile such as acetonitrile was not transformed to the imidate under these conditions.

Reasonable pathway is shown in Chart 2. Namely, the enamino nitrogen of (5) adds to the nitrile carbon directly to give the amidine intermediate like (6), which cyclizes to give the pyrimidone (2).



5 6 2

Chart 2

Next, similar reactions of phenylacetonitrile and malononitrile were carried out. Thus, phenylacetonitrile was allowed to react with (5) in methanol in the presence of sodium methoxide under reflux. Usual work up gave crystalline product, which was dissolved in benzene. Benzene insoluble substance was recrystallized from ethyl acetate to give compound (8a) (25%), mp 234 - 235 °C (dec.). (Found: C, 72.0; H, 6.05; N, 14.0. $C_{12}H_{12}N_2O$ requires C, 71.85; H, 6.0; N, 14.1%), $\nu_{max.}$ (Nujol) 3 400, 3 320, and 1 660 cm^{-1}; δ (DMSO-d_6) 1.77 (3H, s, CH_3), 4.83 - 5.40 (2H, br, NH_2), 5.50 (1H, s, 2-H), 6.93 - 7.63 (6H, m, benzene ring protons and NH). Benzene soluble fraction was purified by silica gel column chromatography. Elution with ethyl acetate gave a 19% yield of compound (7), as needles, mp 172 - 173 °C, (lit.[5] mp 175 °C).

Lastly, malononitrile was allowed to react with (5) in a similar fashion to give compound (8b) (81%), mp 288 - 290 °C (dec.). (Found: C, 56.35; H, 4.75; N, 28.2. $C_7H_7N_3O$ requires C, 56.55; H, 4.75; N, 28.5%). $\nu_{max.}$ (Nujol) 3 380, 3 300, 3 200, and 1 680 cm^{-1}; δ (DMSO-d_6) 2.15 (3H, s, CH_3), 5.43 (1H, s, 2-H), 6.48 - 7.00 (2H, br, NH_2), 10.35 - 10.96 (1H, br, NH).

A likely mechanism is shown in Chart 3. Namely, carbanion of active methylene of nitrile attacks to the enamino-carbon of (5) to give the intermediate (9), which cyclized to give (8) with the elimination of ammonia.

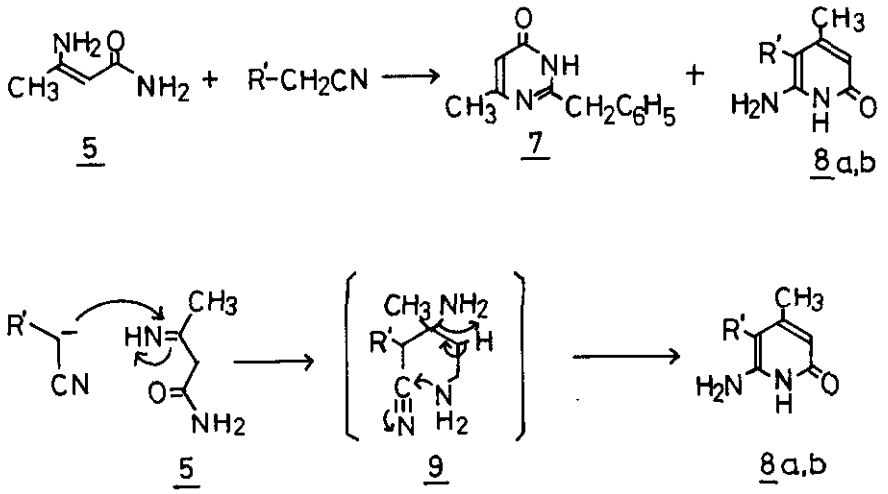


Chart 3

ACKNOWLEDGEMENTS

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