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EFFECT OF THE AMOUNT OF SODIUM ETHOXIDE ON THE DIRECTION OF CYCLIZATION IN REACTIONS OF AMIDINES WITH ETHOXYMETHYLENE ACETOACETATE

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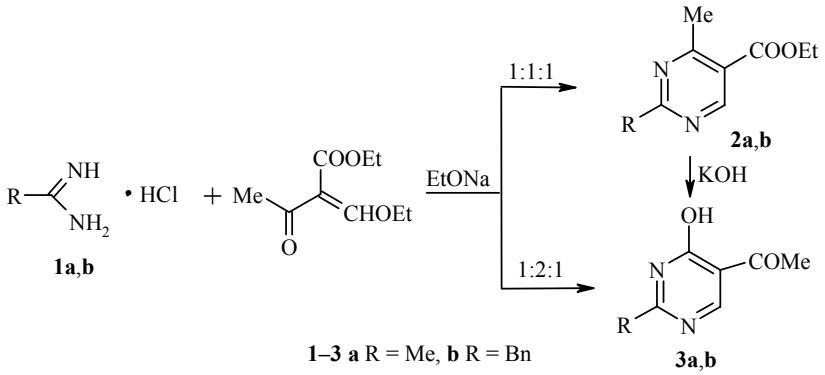
Recyclization of pyrimidines occurring with substitution of the endocyclic carbon atom $C_{(4)}$ by a non-ring carbon atom of the 5-ethoxycarbonyl group was reported earlier in [1, 2]. Such a rearrangement was classified as C–C recyclization of pyrimidines, in contrast to N–N recyclization (the Dimroth rearrangement) [3] and N–C recyclization (the Kost–Sagitullin rearrangement) [4].

In studying the condensation of hydrochlorides of acetamidine (**1a**) and phenylacetamidine (**1b**) with ethoxymethylene acetoacetate in the presence of sodium ethoxide, we noted that the amount of sodium ethoxide has a considerable effect on the direction of heterocyclization. We found that for an equimolar ratio of the amidines, ethoxymethylene acetoacetate, and sodium ethoxide, we obtain 5-ethoxycarbonyl-2-methyl(2-benzyl)-4-methyl-pyrimidines **2a,b** in high yield; while for a two-fold excess of sodium ethoxide relative to the amounts of the reagents used, 5-acetyl-4-hydroxy-2-methyl(2-benzyl)pyrimidines **3a,b** are formed.

We hypothesize that in the case of an excess of sodium ethoxide, as for an equimolar ratio of the reagents, the reaction initially occurs with formation of compounds **2**. However, during treatment, the base formed in the presence of water (for excess sodium ethoxide) leads to recyclization of compounds **2** to form pyrimidines **3**.



1–3 a R = Me, **b** R = Bn

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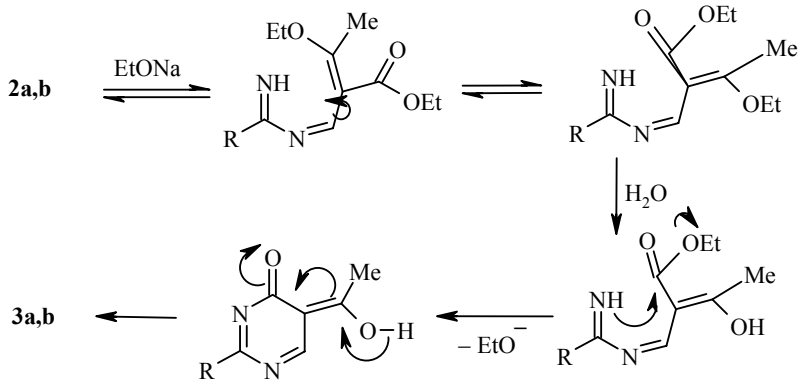
Our experiments showed that in fact, when 5-ethoxycarbonyl derivatives **2** react with KOH in alcohol, 5-acetylpyrimidines **3a,b** are rapidly (within 5-10 min) formed in high yield. By chromatographic monitoring of the reaction mixture, we also found that in a toluene–alcohol solution of sodium ethoxide, compounds **2** are practically unconverted to pyrimidines **3**. However, adding water, i.e. forming OH^- ions in solution, leads to such a transformation. This supports our hypothesis concerning the role of water (more precisely, hydroxide ions) in this rearrangement [2].

As in the previously described examples of the rearrangement under consideration, we did not observe formation of the isomeric pyrimidines **3a,b** of 2-substituted 5-formyl-4-hydroxy-6-methylpyrimidines either during synthesis of compounds **2** and **3** or in recyclization of compounds **2**.



2-Benzyl-5-ethoxycarbonyl-4-methylpyrimidine (2b). Phenylacetamidine hydrochloride (3.4 g, 0.02 mol) was added to a sodium ethoxide solution prepared from sodium (0.46 g, 0.02 mol) in ethanol (30 ml). This was stirred for 30 min at ~20°C. The NaCl precipitate was filtered out and ethyl ethoxymethylene acetoacetate (3.7 g, 0.025 mol) was added to the filtrate, which was then boiled for 6 h. The alcohol was distilled off and the residue was extracted with hexane. The combined extracts were chromatographed on a column with silica gel. Obtained 3.7 g (72%) pyrimidine **2b**, an oil, R_f 0.51 (benzene–acetone, 8:1). ^{1}H NMR spectrum of compound **2b** ($CDCl_3$, 300 MHz), δ, ppm (*J*, Hz): 1.4 (3H, t, *J* = 7.1, $\underline{CH_3}CH_2O$); 2.81 (3H, s, 4-CH_3); 4.29 (2H, s, CH_2); 4.38 (2H, q, *J* = 7.1, OCH_2); 7.19-7.40 (5H, m, Ph); 9.07 (1H, s, H-6). ^{13}C NMR spectrum ($CDCl_3$, 75 MHz), δ, ppm: 14.30 (CH_3); 24.50 (4-CH_3); 46.06 (CH_2); 61.55 (OCH_2); 121.17 ($C_{(5)}$); 126.78 (*p*-Ph); 128.63 (*o*-Ph); 129.31 (*m*-Ph); 137.82 (*ipso*-Ph); 159.22 ($C_{(6)}$); 165.09 ($C_{(4)}$); 169.03 ($C_{(2)}$); 171.65 (CO). Found, %: N 10.58. $C_{15}H_{16}N_2O_2$. Calculated, %: N 10.93.

Rearrangement of 2-Substituted 5-Ethoxycarbonyl-4-methylpyrimidines 2a,b to form 2-Substituted 5-Acetyl-4-hydroxypyrimidines 3a,b when Treated with Alkali. Potassium hydroxide (0.5 g, 9 mmol) and pyrimidine **2a** or **2b** (3 mmol) were dissolved in ethanol (10 ml) and then stirred at 20-25°C. After 10 min, the precipitated crystals of the hydroxypyrimidine salt were filtered out, dissolved in water, and neutralized with a 10% hydrochloric acid solution. The precipitate was filtered out and recrystallized from aqueous alcohol. Obtained 0.35 g (76%) white crystals of 5-acetyl-4-hydroxy-2-methylpyrimidine **3a**; mp 146-148°C, R_f 0.55 (alcohol). After neutralization with hydrochloric acid (during isolation of compound **3b**), it was extracted with benzene. Then the solvent was distilled off. Obtained 0.5 g (73%) of 5-acetyl-2-benzyl-4-hydroxypyrimidine **3b**; mp 160-161°C, R_f 0.59 (benzene–acetone, 4:1). ^{1}H NMR spectrum of compound **3a** (DMSO-d_6, 300 MHz), δ, ppm: 2.53 (3H, s, 2-CH_3); 2.65 (3H, s, $COCH_3$); 8.88 (1H, s, H-6). ^{13}C NMR spectrum (DMSO-d_6, 75 MHz), δ, ppm: 23.68 (CH_3); 25.36 (2-CH_3); 120.77 (5-C); 158.34 ($C_{(6)}$); 165.88 ($C_{(4)}$); 167.49 ($C_{(2)}$); 168.80 (CO). Found, %: N 18.28. $C_7H_8N_2O_2$. Calculated, %: N 18.41.

^{1}H NMR spectrum of compound **3b** ($CDCl_3$, 300 MHz), δ, ppm: 2.95 (3H, s, CH_3); 4.46 (2H, s, CH_2); 7.13-7.43 (5H, m, Ph); 9.16 (1H, s, H-6); 12.25 (1H, br. s, OH). ^{13}C NMR spectrum (DMSO-d_6, 75 MHz), δ, ppm: 24.69 (CH_3); 45.79 (CH_2); 120.52 ($C_{(5)}$); 127.04 (*p*-Ph); 128.79 (*o*-Ph); 129.40 (*m*-Ph); 137.38 (*ipso*-Ph); 159.85 ($C_{(6)}$); 168.69 ($C_{(4)}$); 170.37 ($C_{(2)}$); 172.05 (CO). Mass spectrum (electron impact, 70 eV), *m*/*z* (I_{rel}, %): 228 $[M]^+$ (78), 227 $[M–H]^+$ (100), 226 $[M–H\text{-}1]^+$ (11), 213 $[M–CH_3]^+$ (4), 185 $[M–COCH_3]^+$ (5), 91 $[C_6H_5CH_2]$ (20). Found, %: N 12.48. $C_{13}H_{12}N_2O_2$. Calculated, %: N 12.27.

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