Tetrahedron Letters No. 43, pp 4135 - 4136. 0040-4039/78/1022-4135$02.00/0

REARRANGEMENT OF 2-ALKYLPYRIMIDINES TO 2-AMINOPYRIDINES

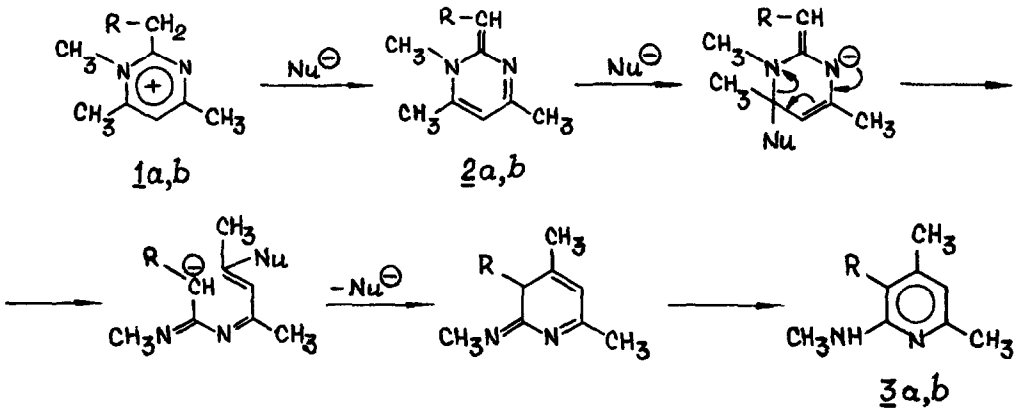
R.S.Sagitullin, A.N.Kost* and G.G.Danagulyan
Department of Chemistry, Moscow State University
Moscow 117234, USSR

A pyrimidine ring, especially in the condensed or quaternized state, readily adds strong nucleophilic agents. For instance, the covalent hydration of pyrimidines[1] is known, and leads to hydrolytic ring opening under more drastic conditions. Similarly, 1-alkylpyridinium salts with ammonia may suffer covalent addition[2,3], ring opening or even elimination of the alkyl group, the reaction sometimes proceeding through a recyclization stage[4]. Hydrazine opens the pyrimidine ring, leading to the corresponding pyrazole[5]. Anions of strong carbon acids, such as cyanoacetic ester, also may open the pyrimidine ring and cyclization now gives 2-aminopyridine derivatives[6]. This process occurs with the insertion of some of the atoms of the reagent into the newly formed ring. At the same time, by analogy with the recently discovered recyclizations of pyrimido 1,2-a indoles[7] and pyrazolo 1,5-a pyrimidines[8] one might expect pyrimidines to isomerise into pyridines on treatment with powerful nucleophiles through a ring opening and ring closure sequence.

We therefore investigated quaternary salts of type 1, which are converted by alkaline reagents into the anhydronium bases 2, where, owing to resonance, the pyrimidine moiety is electron-deficient, and the methene group carries a substantial negative charge. At the same time, as is well known, nucleophiles may attack position 6 of 1-alkylpyrimidinium salts and ring opening followed by recyclization with the participation of the reagent may occur. For instance, liquid ammonia causes dealkylation according to the ANRORC mechanism[4]. In this way the nitrogen atom of ammonia may be incorporated into the pyrimidine ring.

Refluxing the salt 1a in an aqueous solution of sodium hydroxide lead only to hydrolytic cleavage of the pyrimidine ring with the formation of acetylacetone. Similarly, heating with 30% aqueous methylamine afforded the imines $CH_3C(NH_2)=CHCOCH_3$ and $CH_3C(NHCH_3)=CHCOCH_3$.

However, heating the salts 1a or 1b in a sealed tube for 30 hours with an excess of 25% alcoholic methylamine gave the corresponding 2-methylaminopyridines 3a (34%) or 3b (69%) which are isomers of the anhydronium bases 2a,b. The rearrangement also occurs in aqueous-alcoholic solutions of triethylamine.



1a,b 2a,b 3a,b

R = a) C_6H_5; b) $COOC_2H_5$

3a: Oil, M.S. m/e 212 $[M]^+$; NMR (CCl_4), δ: 2.52 and 2.58 (s, 4-CH_3 and 6-CH_3), 3.32 (3H, s, NCH_3), 6.9-7.1 (6H, m, 5-H and C_6H_5); UV λ_{max}^{EtOH} nm ($\log\varepsilon$) 259 (3.59), 310 (3.0).

3b: m.p. 39-40°C; M.S. m/e 208 $[M]^+$; NMR (CCl_4), δ: 1.31 (3H, t, J 8 Hz, CH_2CH_3), 2.27 and 2.31 (6H, s, 4-CH_3 and 6-CH_3), 2.94 (3H, s, NCH_3), 4.18 (2H, q, J 8 Hz, CH_2CH_3), 6.0 (1H, s, 5-H); UV λ_{max}^{EtOH} nm ($\log\varepsilon$) 215 (4.19), 257 (3.89), 341 (3.75).

If the initial pyrimidine has a powerful electron accepting substituent, the isomerization reaction does not require quaternization of the ring. Thus, refluxing 2-methyl-5-nitropyrimidine for 3 hours in 1M aqueous KOH gives 2-amino-5-nitropyridine, m.p. 183-184°C, identical with an authentic sample[9]. The low yield (7%) is due to the competitive formation of resinous products.

It has been noted earlier[10] that 2-methyl-5-nitropyrimidine is both covalently hydrated and unstable in aqueous alkaline solution, but recyclization has not been observed.

REFERENCES

1 A. Albert, Angew. Chem., 1967, 79, 913.
2 J.A. Zoltewicz and L.S. Helmick, J. Am. Chem. Soc., 1972, 94, 682.
3 E.A. Oostveen and H.C. van der Plas, Rec. trav. Chim., 1976, 95, 104.
4 E.A. Oostveen, H.C. van der Plas and H. Jongejen, Rec. trav. Chim., 1974, 93, 114.
5 H.C. van der Plas and H. Jongejen, Tetrahed. Letters, 1967, 4385.
6 E.A. Oostveen and H.C. van der Plas, Rec. trav. Chim., 1974, 93, 233.
7 R.S. Sagitullin, T.V. Mel'nikova and A.N. Kost, Khim. Geterots. Soed., 1974, 1436.
8 A.N. Kost, R.S.Sagitullin and G.G. Danagulyan, Khim. Geterots. Soed., 1977,558.
9 D.J. Collins, J. Chem. Soc., 1963, 1337.
10 M.E.C. Biffin, D.J. Brown and T.C. Lee, J. Chem. Soc. (C), 1967, 573.

(Received in UK 21 August 1978; accepted for publication 4 September 1978)