Chemistry of Heterocyclic Compounds, Vol. 36, No. 5, 2000

ACTIVATION OF THE KOST–SAGITULLIN REARRANGEMENT IN A SERIES OF 2-BENZYLPYRIMIDINE DERIVATIVES

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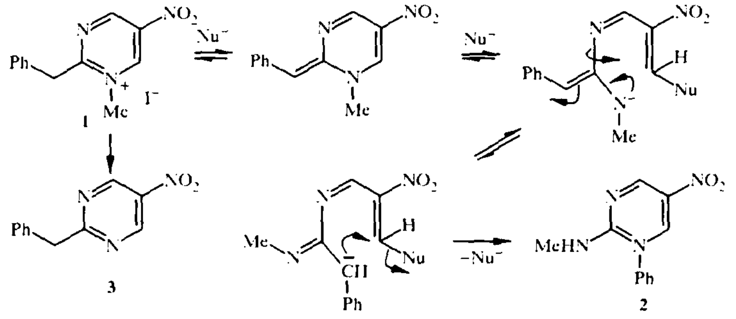
Keywords: 2-benzylpyrimidine, methylamine, pyrimidinium salts, pyridine, enamine rearrangement.

We previously accomplished rearrangement of 2-benzyl-1,4,6-trimethylpyrimidinium iodide to 4,6-dimethyl-2-methylamino-3-phenylpyridine [1,2]. We recently described similar transformations occurring according to the Kost–Sagitullin enamine rearrangement scheme for a series of 2-pyrimidylacetic acid derivatives [3,4].

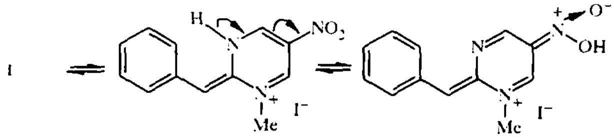
Continuing an investigation of the effect of substituents at the pyrimidine ring on the course of the reaction, we studied the possibility of rearrangement of the salt we synthesized: 2-benzyl-1-methyl-5-nitropyrimidinium iodide (**1**). We found that introduction of a nitro group to the heterocycle promoted recyclization: iodide **1** in alcoholic solution of methylamine converted with 65% yield to 2-methylamino-5-nitro-3-phenylpyridine (**2**); and when treated with sodium ethoxide, the reaction occurred even at room temperature.



As a byproduct, we isolated 2-benzyl-6-nitropyrimidine (**3**). Probably an alternative orientation for attack by the nucleophile is attack at the N-methyl group, which leads to formation of the demethylation product.

The structure of the rearrangement product was confirmed by the ^{1}H NMR and mass spectra.

We should note the anomalous position (8.95 ppm) and broadening of the signal from protons of the methylene group in the ^{1}H NMR spectrum of salt **1**, which suggests high CH-acidity of the carbon atom and the presence of pronounced prototropic tautomerism, due to the effect of the nitro group. The latter also explains the facile recyclization.



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0009-3122/00/3605-0613$25.00©2000 KluwerAcademic/Plenum Publishers

2-Benzyl-5-nitropyrimidine Methyl Iodide (1). A mixture of 2-benzyl-5-nitropyrimidine (0.3 g, 1.4 mmol) [5] and of methyl iodide (6 ml) was heated for 15 h at 90-100°C in a sealed ampoule. The precipitating crystals were filtered off, washed with hexane, and dried. Yield of salt **1** 0.35 g (70%); mp 216-217°C. ^{1}H NMR spectrum (DMSO-d$_6$): 4.07 (3H, s, N–CH$_3$); 7.55 (5H, m, Ph); 8.18 (1H, d, *J* = 2.1 Hz, 4-H); 8.95 (2H, br. s, CH$_2$); 9.53 ppm (1H, d, *J* = 2.1 Hz, 6-H). Found, %: C 40.09; H 3.10; N 11.48. $C_{11}H_9N_3O_2 \cdot CH_3I$. Calculated, %: C 40.37; H 3.39; N 11.77.

Rearrangement of 2-Benzyl-1-methyl-5-nitropyrimidinium Iodide 1 to 2-Methylamino-5-nitro-3-phenylpyridine (2). A solution of methyl iodide **1** (0.18 g, 0.5 mmol) in 13% ethanol solution of methylamine (5 ml) was heated in a sealed ampoule for 20 h at 90-100°C. The solvent was distilled off and the residue was washed with hot hexane (20 ml). After removal of hexane, we obtained 0.06 g (54%) of pyridine **2**; mp 104-105°C, *R$_f$* 0.73 (benzene–acetone, 3:1). The residue of the reaction mixture was treated with benzene. The solvent was distilled off and the residue was separated on a column (Silica gel 5/40) in a 3:1 benzene–acetone system. We obtained an additional 0.012 g (11%) of compound **2** and 0.01 g (10%) of 2-benzyl-5-nitropyrimidine (**3**). ^{1}H NMR spectrum of compound **2** (CDCl$_3$): 3.08 (3H, d, *J* = 4.8 Hz, $NH\underline{CH_3}$); 5.37 (1H, br. s, $\underline{NH}CH_3$); 7.4-7.55 (5H, m, Ph); 8.05 (1H, d, *J* = 2.5 Hz, 6-H); 9.11 ppm (1H, d, *J* = 2.5 Hz, 4-H). Mass spectrum, *m/z* (I_{rel}): 229 (48), 228 (100), 182 (29), 168 (13), 154 (12), 140 (12), 127 (16), 115 (20), 77 (9). Found, %: C 63.09; H 4.71; N 18.09. $C_{12}H_{11}N_3O_2$. Calculated, %: C 62.87; H 4.84; N 18.33.

This research was part of a joint project with the financial support of the National Foundation for Science and Advanced Technology of Armenia and the US Civilian Research and Development Foundation (NFSAT RA-US CRDF, grant ACH 006-98/AC1-955), and also grant 96-559 from State Centralized Financing of the Republic of Armenia.

We would like to thank Professor Alan R. Katritzky (University of Florida, USA) for support and cooperation.

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