Chemistry of Heterocyclic Compounds, Vol. 42, No. 3, 2006

RECYCLIZATION OF INTERMEDIATES IN AN ENAMINE REARRANGEMENT OF A PYRIMIDINIUM SALT WHEN TREATED WITH ISONIAZIDE

G. G. Danagulyan and D. A. Tadevosyan

Keywords: 2-hydrazinopyridine, isoniazide, pyrimidinium iodide, rearrangement intermediates, Kost–Sagitullin rearrangement.

In a paper devoted to study of the reaction of 2-(ethoxycarbonylmethyl)-1,4,6-trimethylpyrimidinium iodide (**1**) with carboxylic acid hydrazides, we reported on synthesis of derivatives of 1,2,4-triazolo[4,3-*a*]pyridine [1]. In particular, in that paper we discussed the hypothesis that when salt **1** was treated with isonicotinic acid hydrazide (**2**) (isoniazide), cyclization to form triazolopyridine **4** occurs through a step involving formation of the intermediate 2-hydrazidopyridine **3** (the product of a Kost–Sagitullin rearrangement). However, as shown by later X-ray diffraction studies, during the reaction we do not obtain triazolo[4,3-*a*]pyridines **4** but rather their isomers: derivatives of pyrazolo[1,5-*a*]pyrimidine **5** [2] (Scheme 1).

In studying the reaction of the intermediates for recyclization **6** and **7** with isoniazide **2**, we obtained a compound with a structure matching that of the initially proposed structure for the intermediate product of "rearrangement with transamination" (compound **3**). Probably during the reaction, the pseudobase **6**, by eliminating a water molecule, is converted to the anhydro base **7**, which also undergoes the indicated transformation. Upon recyclization of compounds **6** and **7**, the pyridone **8** and also a slight amount of the demethylation product **9** are formed.

Thus for the first time we have observed a Kost–Sagitullin rearrangement with insertion of a carboxylic acid hydrazide moiety into the molecule of the reaction product.

The ^{1}H and ^{13}C NMR spectra were obtained on a Varian Mercury-300 spectrometer (300 MHz and 76 MHz respectively), internal standard TMS; the mass spectra were recorded on an MK-1321 spectrometer with direct injection of the sample into the ion source with ionization energy 70 eV.

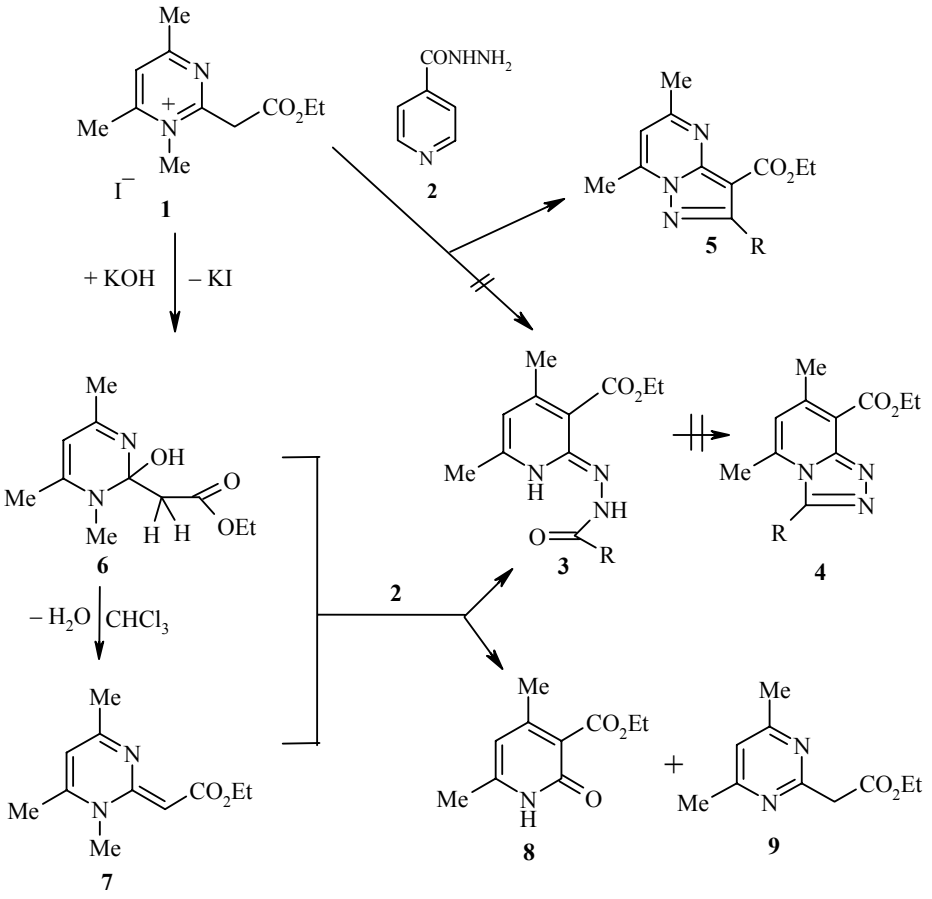
2-(Ethoxycarbonyl)methylidene-1,4,6-trimethyl-1,2-dihydropyrimidine (7). The pseudobase **6** (1.5 g, 6.6 mmol) in $CHCl_3$ (10 ml) was heated for 5 min, the solvent was distilled off, and 1.43 g (96%) of the anhydro base **7** was obtained, R_f 0.62 (*i*-PrOH–ammonia, 1:1). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.28 (3H, t, *J* = 7.1, $\underline{CH_3}CH_2O$); 2.22 (3H, s, 4-CH_3); 2.30 (3H, s, 6-CH_3); 3.19 (3H, s, 1-CH_3); 4.16 (2H, q, *J* = 7.1, $O\underline{CH_2}CH_3$); 4.46 (1H, s, H-2'); 5.76 (1H, s, H-5). Found, %: C 63.56; H 7.35; N 13.78. $C_{11}H_{16}N_2O_2$. Calculated, %: C 63.44; H 7.74; N 13.45.

Reaction of Pseudobase 6 with Isoniazide 2. A mixture of compound **6** (0.9 g, 4 mmol) and hydrazide **2** (1.1 g, 8 mmol) was heated in absolute ethanol (10 ml) for 35 h, the solvent was distilled off, and the following were obtained by preparative fractionation on a column (toluene–acetone, 3:1): 0.21 g (17%) of 3-ethoxycarbonyl-4,6-dimethyl-2-(pyridine-4-carbonyl)hydrazino-1,2-dihydropyridine (**3**); mp 86-87°C, R_f 0.64

Institute of Organic Chemistry, National Academy of Sciences of the Republic of Armenia, Yerevan 375091; e-mail: gdanag@email.com. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 3, pp. 463-465, March, 2006. Original article submitted February 10, 2006.

 0009-3122/06/4203-0414

Scheme 1



3–**5** R = 4-Py

(Silufol, 1:2 toluene–acetone); 0.35 g (45%) of pyridone **8**; and 0.06 g (8%) of compound **9**. ^{1}H NMR spectrum of compound **3** (DMSO-d_6), δ, ppm (*J*, Hz): 1.41 (3H, t, *J* = 7.1, $CH_2\underline{CH_3}$); 2.34 (3H, s, 4-CH_3); 2.45 (3H, s, 6-CH_3); 4.37 (2H, q, *J* = 7.1, OCH_2); 6.50 (H, s, H-5); 7.82 (2H, d, *J* = 6.8, H-2' and -6'); 8.67 (2H, d, *J* = 6.8, H-3' and -5'); 9.27 (H, s, NH); 10.64 (H, br. s, NH). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 13.87 ($CH_2\underline{CH_3}$); 22.08 (4-CH_3); 23.87 (6-CH_3); 60.47 (CH_2); 106.06 ($C_{(3)}$); 117.36 ($C_{(5)}$); 121.21 ($C_{(3')}$ and $C_{(5')}$); 139.69 ($C_{(4')}$); 149.65 ($C_{(2')}$ and $C_{(6')}$); 150.13 ($C_{(4')}$); 157.47 ($C_{(6)}$); 159.38 ($C_{(2)}$); 162.92 (NHC=O); 167.02 (C=O). Mass spectrum, *m*/*z* (I_{rel}, %): 314 (33), 296 (9), 252 (10), 204 (9), 187 (9), 153 (13), 135 (10), 107 (100), 79 (30), 68 (10), 52 (20). Found, %: C 61.43; H 5.29; N 18.19. $C_{16}H_{18}N_4O_3$. Calculated, %: C 61.13; H 5.77; N 17.82.

Reaction of Anhydro Base 7 with Isoniazide 2. Analogously to the procedure given above, the following were obtained from anhydro base **7** (0.62 g, 3 mmol) and isoniazide **2** (0.82 g, 6 mmol): 0.38 g (40%) of compound **3**, 0.07 g (12%) of pyridone **8**, and 0.03 g (5%) of compound **9**.

The synthesis of compound **6** [R_f 0.63 (*i*-PrOH–ammonia, 1:1)] is described in [3], and its melting point and ^{1}H and ^{13}C NMR spectra, as for compounds **8** [R_f 0.52 (toluene–acetone, 1:2)] and **9** [R_f 0.67 (toluene–acetone, 1:1)] [4, 5], are the same as for a known sample.

This research was carried out with the support of the US Civilian Research and Development Foundation (grant US CRDF ARB2-2640-YE-05) and within Topic 0543 of the Ministry of Education and Science of Armenia.

REFERENCES

1. G. G. Danagulyan, L. G. Saakyan, and D. A. Tadevosyan, *Khim. Geterotsikl. Soedin.*, 305 (2003).
2. G. G. Danagulyan, D. A. Tadevosyan, R. A. Tamazyan, and G. A. Panosyan, *Khim. Geterotsikl. Soedin.*, 262 (2006).
3. G. G. Danagulyan, F. S. Kinoyan, and D. A. Tadevosyan, *Khim. Geterotsikl. Soedin.*, 303 (2003).
4. G. G. Danagulyan, L. G. Saakyan, A. R. Katritskii, and S. N. Denisenko, *Khim. Geterotsikl. Soedin.*, 1572 (1999).
5. R. S. Sagitullin, A. N. Kost, and G. G. Danagulyan, *Tetrahedron Lett.*, 4135 (1978).