Chemistry of Heterocyclic Compounds, Vol. 43, No. 8, 2007

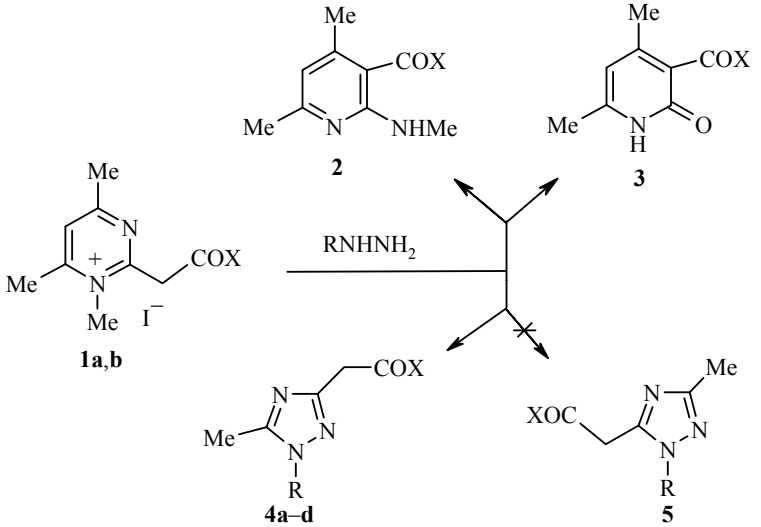
RECYCLIZATION OF PYRIMIDINIUM SALTS INTO 1,2,4-TRIAZOLE DERIVATIVES

G. G. Danagulyan[1], G. A. Panosyan[2], and L. G. Sahakyan[1]

The interaction of the iodomethylates of pyrimidinyl-2-acetic acid derivatives with monosubstituted hydrazines, in addition to the products of a Kost–Sagitullin rearrangement, leads also to N-substituted triazoles. The structure of the triazoles was demonstrated by NOESY NMR experiments. The structure of the reaction products was determined on the basis of the response observed in the spectra between the methyl group protons of the triazole ring and the spatially close proton of the substituent in position 1 and a conclusion was drawn on the direction of the primary attack of nucleophile in the recyclization process of the pyrimidinium salts into a 1,2,4-triazole.

Keywords: arylhydrazines, pyrimidinium salts, 1,2,4-triazole, 2-methylaminonicotinic acid ester, NOESY method, rearrangement, recyclization, NMR spectroscopy.

The recyclization of pyrimidines into other heterocycles is a vast class of reactions, discovered and investigated in recent decades [1, 2]. Among them is a distinct group consisting of conversions accompanied by a reduction of the number of atoms in the ring, in particular the conversion of pyrimidines into derivatives of pyrazole [3, 4] and 1,2,4-triazole [5, 6].



X = OEt, NH_2; R = Ph, *p*-$HO_2CC_6H_4$, 2-benzyl-6-methyl-4-pyrimidinyl

[1]Institute of Organic Chemistry, National Academy of Sciences of the Republic of Armenia, Erevan 375091; e-mail: gdanag@email.com. [2]Molecular Structure Research Center, National Academy of Sciences of the Republic of Armenia, Erevan 375014. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 8, pp. 1175-1179, August, 2007. Original article submitted March 17, 2006.

 0009-3122/07/4308-0996©2007 Springer Science+Business Media, Inc.

On studying the interaction of pyrimidinium iodomethylates **1a,b** with monosubstituted hydrazines it turned out that the conversion may proceed both in the direction of forming products of a Kost–Sagitullin rearrangement (derivatives of 2-methylaminonicotinic acid **2** or pyridone **3**) and is also accompanied by the formation of derivatives of 1,2,4-triazole.

Only two reports are known concerning the preparation of 1,2,4-triazole derivatives from compounds of the pyrimidine series. It has been shown that 4,6-dichloro(or diethoxy, dimethylthio, dihydrazino)pyrimidines are converted on reaction with hydrazine hydrate into 3-methyl-1,2,4-triazole in 30-60% yield [3], while the corresponding 4-substituted and 2,4-disubstituted derivatives of pyrimidine are mainly rearranged into 3-aminopyrazole, and 3-methyl-1,2,4-triazole is obtained in only 3-5% yield [4].

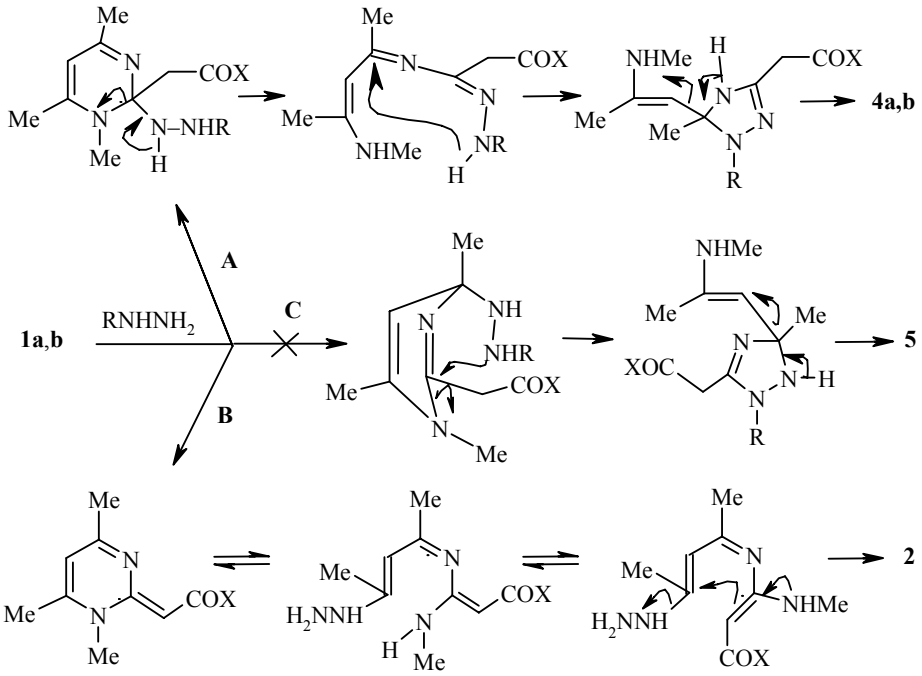
In our case ^{1}H and ^{13}C NMR spectra of the isolated compounds and also the peaks of the molecular ions and the character of the breakdown in the mass spectra of all the compounds indicate the formation of triazole derivatives, containing a methyl group, a fragment of an acetic acid derivative, and the aromatic or hetaryl substituent at the nitrogen atom. Nonetheless the methods mentioned do not give an unequivocal answer on the structure of the compounds obtained since the recyclization of pyrimidines **1a** and **1b** into derivatives of 1,2,4-triazole may proceed by two routes. The reaction products may be either compounds **4** or **5** depending on the direction of the initial nucleophile attack (at position 2 or 4 of the heterocycle).

Assignment of the signals in the NMR spectra and confirmation of the structure of the obtained compounds was made by us on the basis of NOESY NMR spectroscopic data. In the spectra of all the substances a response was observed between the methyl group of the triazole ring and a spatially close proton of the substituent in position 1. If the substituent in position 1 of the triazole ring is a phenyl group (compound **4a**) or its *para*-substituted analog (compound **4b**), then a cross peak is observed between the signals of the methyl group and the *ortho* protons of the benzene ring, which indicates unequivocally the occurrence of the methyl group at position 5, i.e. the position neighboring the substituted $N_{(1)}$ atom of the triazole. Analogously, in the spectra of the products of interacting salts **1a,b** with 2-benzyl-4-hydrazino-6-methylpyrimidine (compounds **4c** and **4d**) a clear cross peak is observed between the protons of the methyl group of the triazole ring and the H-5 proton of the pyrimidine fragment. Not in a single spectrum did we observe interaction between the protons of the substituent at the $N_{(1)}$ atom and the methylene group of the acetic acid fragment, which might indicate the formation of compound **5**.

The formation of triazoles **4** and the absence of the isomeric compounds **5** indicates, in our opinion, that the direction of primary attack of the nuclephile is at position 2, and not 4, of the salt, which might lead to the isomeric recyclization products.

An important result of these investigations is also the fact that we have recorded for the first time the Kost-Sagitullin rearrangement (recyclization of 1,2-dialkylpyrimidinium salts into pyridine derivatives **2** and **3**), proceeding under the action of 1,2-dinucleophiles which are hydrazine derivatives. The truth in this case is that we were unsuccessful in establishing the formation of the rearrangement product including a fragment of the nucleophile in position 2 of the resulting pyridine ring as has been observed under the action of other nucleophilic reagents [7, 8]. In fact here the role of nucleophile is limited by the opening of the pyrimidine ring, i.e. by initiation of the isomerization recyclization into pyridine derivatives. We note that in a series of examples we also isolated products of demethylation of the initial salts.

Probably the initial attack, a nucleophilic attack, may proceed both at position 2 of the pyrimidine, which, as a result of subsequent participation of the second nitrogen atom of hydrazine and its involvement in the heterocyclization process, leads to closing of the 1,2,4-triazole ring (route **A**), and as a result of nucleophilic attack at position 6, which leads the process along the route of isomerization recyclization to pyridine derivatives (route **B**). Route **C**, attack at position 4 and conversion into the isomeric thiazoles **5** does not occur.



EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra (300 and 75 MHz respectively) were obtained on a Varian Mercury-300 instrument at the Center for the Investigation of Molecular Structure of the National Academy of Sciences of Armenia (US CRDF RESC 17-5 program), internal standard was TMS. Sample temperature was 303 K.

The mass spectra were recorded on a chromato-mass spectrometer (HP 6890 Series Gas Chromatograph, HP 5973 Mass Selective Detector), obtained on Grant AR1-991 US CRDF, and also on a MK-1321 spectrometer with direct insertion of samples into the ion source, ionization energy was 70 eV.

The TLC was carried out on Silufol UV-254 plates in the system benzene–acetone, 3:1, visualization was with iodine vapor and Ehrlich reagent. Preparative separation was effected by column chromatography on silica gel (L 5/40 μm).

Interaction of 2-Ethoxycarbonyl-1,4,6-trimethylpyrimidinium Iodide (1a) with Phenylhydrazine. An alcohol solution of phenylhydrazine, prepared by neutralizing phenylhydrazine hydrochloride (0.72 g, 5 mmol) with an alcoholic solution of sodium ethylate (sodium (0.1 g) in absolute ethanol (5 ml)), was added to an alcoholic solution of iodide **1a** (0.67 g, 2 mmol) in absolute ethanol (5 ml). The reaction mixture was boiled for 4 h, the solvent removed, and the residue was treated sequentially with hot hexane and benzene. On cooling the benzene solution phenylhydrazine hydroiodide (0.1 g) mp 285-286°C was precipitated. The hexane and benzene solutions were combined and evaporated to dryness, and the residue was separated on a column of silica gel in the system benzene–acetone, 4:1. 3-(Ethoxycarbonyl)methyl-5-methyl-1-phenyl-1,2,4-triazole (**4a**) (0.2 g, 41%) was obtained as an oil, R_f 0.33 (benzene–acetone, 3:1). Pyridone **3** (30 mg, 8%) was also isolated. ^{1}H NMR spectrum of compound **4a** ($CDCl_3$), δ, ppm (*J*, Hz): 1.27 (3H, t, *J* = 7.1, CH_3); 2.49 (3H, s, CH_3); 3.75 (2H, s, $COCH_2$); 4.19 (2H, q, *J* = 7.1, OCH_2); 7.36-7.49 (5H, m, C_6H_5). ^{13}C NMR spectrum of compound **4a**, δ, ppm: 13.2 (CH_3); 14.2 (CH_3); 34.5 (CH_2); 61.2 (OCH_2); 124.6 and 129.4 (*o*- and *m*-C_6H_5); 128.7 (*p*-C_6H_5); 137.7 (*ipso*-C_6H_5); 152.6 (C=N); 157.1 (C=N); 169.2 (CO). Mass spectrum (EI), *m/z* (I_{rel}, %): 246 (12) $[M+1]^+$, 245 (90) $[M]^+$, 204 (52.4) $[M–CH_3CN]^+$, 174 (11.7) $[M+1–CO_2–C_2H_4]^+$, 173 (90.5) $[M–CO_2–C_2H_4]^+$, 172 (74.7)

$[M–COOC_2H_5]^+$, 132 (12) $[M–CO_2–C_2H_4–CH_3CN]^+$, 131 (39) $[M–CH_3CN–COOC_2H_5]^+$, 103 (51), 92 (17) $[C_6H_5CH_3]$, 91 (100) $[C_6H_5N]$, 77 (42.8) $[C_6H_5]$, 64 (26). Found, %: C 63.51; H 6.41; N 17.31. $C_{13}H_{15}N_3O_2$. Calculated, %: C 63.66; H 6.16; N 17.13.

Interaction of 2-Ethoxycarbonyl-1,4,6-trimethylpyrimidinium Iodide (1a) with *p*-Hydrazinobenzoic Acid. A mixture of iodide **1a** (1 g, 3 mmol) and *p*-hydrazinobenzoic acid (0.91 g, 6 mmol) in absolute ethanol (15 ml) was heated in a sealed ampule on a water bath for 15 h. The alcohol was distilled off and the residue was treated with hot benzene. The crystals precipitated from the benzene solution on cooling were filtered off, washed with hexane, and dried. 1-(*p*-Carboxyphenyl)-3-(ethoxycarbonyl)methyl-5-methyl-1,2,4-triazole (**4b**) (0.25 g, 29%) was obtained of mp 196-197°C, R_f 0.51 (benzene–acetone, 2:1). The residue from the benzene solution was separated preparatively in benzene–acetone, 8:1, and 3-ethoxycarbonyl-4,6-dimethylpyrid-2-one (**3**) (0.2 g, 36%) and 2-ethoxycarbonylmethyl-4,6-dimethylpyrimidine (0.2 g, 34%), identical with known specimens, were isolated. ^{1}H NMR spectrum of compound **4b** (DMSO–d_6–CCl_4, 1:3), δ, ppm (*J*, Hz): 1.25 (3H, t, *J* = 7.1, CH_3); 2.54 (3H, s, CH_3); 3.70 (2H, s, CH_2); 4.14 (2H, q, *J* = 7.1, OCH_2); 7.70 (2H, d, *J* = 8.6, H-3,5$_{Ar}$); 8.10 (2H, d, *J* = 8.6, H-2,6$_{Ar}$); 13.0 (1H, br. s, COOH). ^{13}C NMR spectrum of compound **4b**, δ, ppm: 13.0 (CH_3); 13.8 (CH_3); 33.8 (CH_2); 60.1 (OCH_2); 123.1 and 130.3 (2,3,5,6-C_{Ar}); 130.5 (4-C_{Ar}); 140.2 1-C_{Ar}); 152.3 (C=N); 156.8 (C=N); 166.1 (CO); 168.1 (CO). Found, %: C 57.80; H 5.01; N 14.31. $C_{14}H_{15}N_3O_4$. Calculated, %: C 58.13; H 5.23; N 14.53.

Interaction of 2-Ethoxycarbonyl-1,4,6-trimethylpyrimidinium Iodide (1a) with 2-Benzyl-4-hydrazino-6-methylpyrimidine. A mixture of iodide **1a** (0.34 g, 1 mmol) and 2-benzyl-4-hydrazino-6-methylpyrimidine (0.42 g, 2 mmol) in absolute ethanol (7 ml) was heated in a sealed ampule on a water bath for 20 h. The alcohol was distilled, the residue was washed sequentially with hexane, benzene, and acetone, all being hot. From the benzene solution 1-(2-benzyl-4-methyl-6-pyrimidinyl)-3-(ethoxycarbonyl)methyl-5-methyl-1,2,4-triazole (**4c**) (150 mg, 43%) was obtained with mp 85-86°C, R_f 0.72 (benzene–acetone, 5:1). The crystals precipitated on cooling the acetone solution were filtered off and the hydroiodide of the initial hydrazinopyrimidine (150 mg) was obtained having mp 275-277°C. From the hexane solution the ethyl ester of 4,6-dimethyl-2-methylaminonicotinic acid (20 mg, 10%) was obtained and corresponded in TLC and ^{1}H NMR spectrum with a authentic sample. ^{1}H NMR spectrum of compound **4c** (DMSO-d_6–CCl_4, 1:3), δ, ppm (*J*, Hz): 1.28 (3H, t, *J* = 7.1, CH_3); 2.56 (3H, s, CH_3); 3.63 (2H, s, CH_2); 4.14 (2H, q, *J* = 7.1, OCH_2); 4.18 (2H, s, $CH_2C_6H_5$); 7.14-7.32 (5H, m, C_6H_5); 7.56 (1H, s, H-5$_{Pyr}$). Mass spectrum (EI), *m/z,* (I_{rel}, %): 352 (24.9) $[M+H]^+$, 351 (100) $[M]^+$, 350 (23.2) $[M–H]^+$, 278 (16.7) $[M–COOC_2H_5]^+$, 277 (14.8) $[M–H–COOC_2H_5]^+$, 238 (17.2) $[M–CO_2–C_2H_4–CH_3CN]^+$, 237 (25.5) $[M–COOC_2H_5–CH_3CN]^+$, 197 (35.1) $[M–CO_2–C_2H_4–CH_3CN–CH_3CN]^+$, 91 (38.7) $[C_7H_7]$. Found, %: C 65.21; H 5.80; N 19.59. $C_{19}H_{21}N_5O_2$. Calculated, %: C 64.94; H 6.02; N 19.93.

Interaction of 2-Carbamoylmethyl-1,4,6-trimethylpyrimidinium Iodide (1b) with 2-Benzyl-4-hydrazino-6-methylpyrimidine. A mixture of iodide **1b** (0.31 g, 1 mmol) and 2-benzyl-4-hydrazino-6-methylpyrimidine (0.42 g, 2 mmol) in absolute ethanol (7 ml) was heated in a sealed ampule on a water bath for 25 h. The solid was filtered off. On cooling the alcohol solution 1-(2-benzyl-4-methyl-6-pyrimidinyl)-3-carbamoylmethyl-5-methyl-1,2,4-triazole (**4d**) (0.1 g, 31%) was precipitated, mp 171-172°C, R_f 0.44 (acetone). 2-Carbamoylmethyl-4,6-dimethylpyrimidine (0.1 g, 55%), identical by TLC with an authentic sample, was isolated from the filtrate by a preparative separation on a column of silica gel. ^{1}H NMR spectrum of compound **4d** ($CDCl_3$), δ, ppm: 2.60 (3H, s, CH_3); 2.70 (3H, s, CH_3); 3.72 (2H, s, CH_2); 4.28 (2H, s, $CH_2C_6H_5$); 5.65 (1H, br. s, NH_2); 6.95 (1H, br. s, NH_2); 7.22-7.37 (5H, m, C_6H_5); 7.56 (1H, s, H-5$_{Pyr}$). ^{13}C NMR spectrum of compound **4d**, δ, ppm: 16.6 (CH_3); 23.5 (CH_3); 35.7 (CH_2); 44.5 ($CH_2C_6H_5$); 108.2 (5-C_{Pyr}); 127.3 (*p*-C_6H_5); 128.9 and 129.8 (*o*- and *m*-C_6H_5); 136.8 (*ipso*-C); 156.8, 157.8, 158.6, 169.0, 169.1, and 169.4 (C=N and C=O). Mass spectrum (EI), m/z (I_{rel}, %): 323 (23) $[M+H]^+$, 322 (95) $[M]^+$, 321 (13.5) $[M–H]^+$, 280 (22) $[M–H–CH_3CN]^+$, 279 (100) $[M–H–CONH_2]^+$, 278 (14) $[M–CONH_2]^+$, 238 (19) $[M–HNCO–CH_3CN]^+$, 237 (15) $[M–CONH_2–CH_3CN]^+$, 197 (21) $[M–HNCO–CH_3CN–CH_3CN]^+$, 184 (14), 91 (67) $[C_7H_7]$. Found, %: C 63.61; H 5.38; N 25.78. $C_{17}H_{18}N_6O$. Calculated, %: C 63.34; H 5.63; N 26.07.

The authors are grateful to Prof. Alan Katritzky (University of Florida, USA) for support and collaboration.

The work was carried out with the financial support of the National Fund for Science and Advanced Technology of Armenia and the Fund for Civil Investigations and Development of the USA (NFSAT RA-US CRDF, grant NCH 090-02/12040), and also, within the framework of scientific topics 0471 and 0543, of the Ministry of Science and Education of the Armenian Republic.

REFERENCES

1. D. J. Brown, *Mechanisms of Molecular Migrations*, Vol. 1, J. Wiley, New York (1968), p. 209.
2. H. C. Van der Plas, *Ring Transformations of Heterocycles*, Vol. 1, 2, Academic Press, London, New York (1973).
3. H. C. Van der Plas and H. Jongejan, *Tetrahedron Lett.*, **44**, 4385 (1967).
4. A. N. Kost, R. S. Sagitullin, and G. G. Danagulyan, *Khim. Geterotsikl. Soedin.*, 1400 (1978). [*Chem. Heterocycl. Comp.*, **14**, 1139 (1978)].
5. H. C. Van der Plas and H. Jongejan, *Rec. Trav. Chim. Pays-Bas*, **89**, 680 (1970).
6. H. C. Van der Plas and H. Jongejan, *Rec. Trav. Chim. Pays-Bas*, **91**, 336 (1972).
7. G. G. Danagulyan, L. G. Sahakyan, A. R. Katritzky, and S. N. Denisenko, *Heterocycles*, **53**, 419 (2000).
8. G. G. Danagulyan and L. G. Sahakyan, *Khim. Geterotsikl. Soedin.*, 395 (2004). [*Chem. Heterocycl. Comp.*, **40**, 320 (2004)].