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Regioselective and Regiospecific Reactions of Ethyl *ortho*-(Dimethylaminovinylazoloazinylcarboxylates with Hydrazine

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Abstract—Selectivity of reactions of ethyl 4-[(*E*)-2(dimethylamino)vinyl]pyrazolo[5,1-*c*]-[1,2,4]triazino-3-ylcarboxylates and ethyl 7-[(*E*)-2-(dimethylamino)vinyl][1,2,4]triazolo[1,5]pyrimidine-6-ylcarboxylates with hydrazine in various solvents was studied. The formation of a pyridone cycle proceeds regiospecifically in dimethyl formamide or dimethyl acetamide. A regioselective cyclization resulting in fused 1,2-diazepines occurs in acetic or propionic acid.

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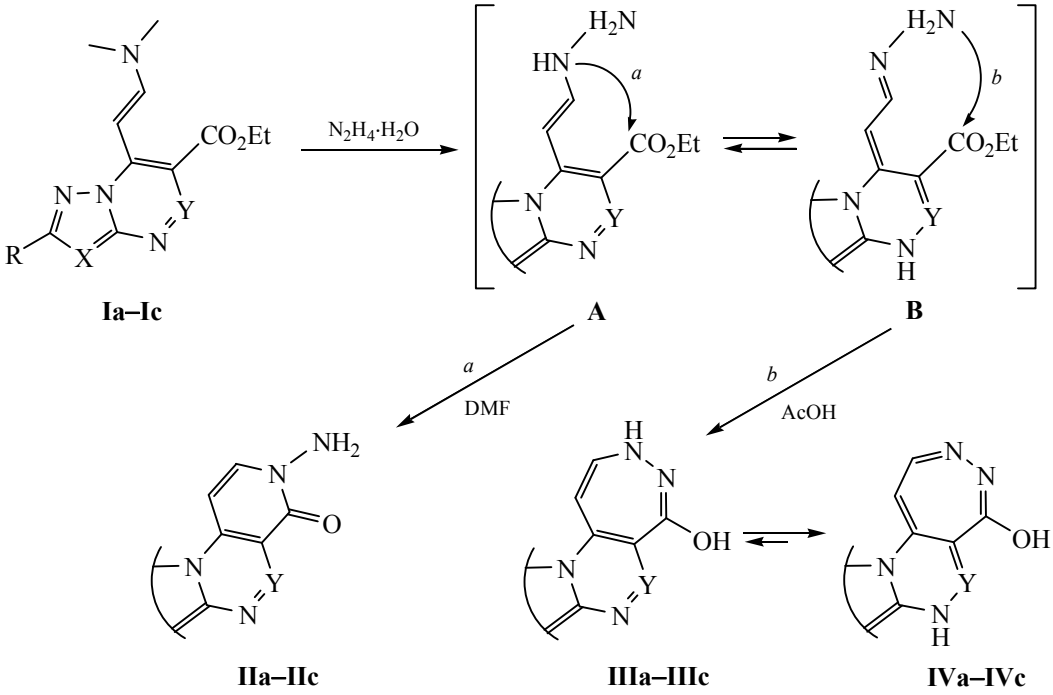
Derivatives of pyrazolo[5,1-*c*][1,2,4]triazine and [1,2,4]triazolo[1,5]pyrimidine are of great interest for researchers. Being isosteres of biogenic purine bases, these compounds exhibit a wide spectrum of pharmacological activity and are applied as pesticides, antineoplastic and antiviral drugs [1–4]. Preparatively accessible methods of the synthesis of azoloazines make it possible to obtain compounds with versatile substituents in both fragments [5–10]. In this connection further modification of the specified systems with the purpose of obtaining new polyheterocycles and studying their biological activity is actual.

It is known that the CH_3 group in a vicinal position to the nodal nitrogen atom of pyrazolo[5,1-*c*][1,2,4]-triazines and also of pyrazolo- and *symm*-triazolo[1,5]-pyrimidines undergoes the aminomethyleneation upon short-term heating with dimethylacetal in DMF. Enamines having an ester group in the *ortho*-position are capable to close the pyridine cycle on interacting with primary amines [11–13]. To continue our investigations [12, 13], we have studied special features of the reactions of the third cycle fusion with participation of ethyl *ortho*-(dimethylaminovinyl)azoloazinyl-carboxylates and hydrazine in protic (AcOH and propionic acid) and aprotic (DMF and dimethylacetamide) solvents.

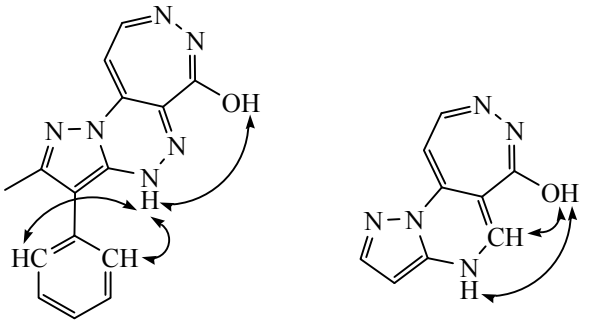
Boiling of enamines **Ia–Ic** with hydrazine in DMF or dimethyl acetamide leads exclusively to derivatives of 7-aminopyrazolo[5,1-*c*]pyrido[4,3-*e*][1,2,4]triazino-6(7*H*)-one (**IIa**) and 7-aminopyrido[3,4-*e*][1,2,4]-triazolo[1,5-*a*]pyrimidin-6(7*H*)-one (**IIb, IIc**) through the stage of the formation of presumed intermediate **A** [14]. In the ^{1}H NMR spectra of the obtained compounds signals of vinyl protons in the region of 7.50 and 9.50 ppm and also signals of two methyl groups at the nitrogen atom disappear. Instead of them doublets of aromatic pyridine protons (δ 7.05–7.10 and 8.20–8.30 ppm) and a singlet of the *N*-amino group are observed.

The application of acetic or propionic acid as a solvent in essence changes the cyclization direction. Analysis of the mixture of reaction products has shown that compounds **IIa–IIc** are present as minor products (5–10%). Previously unknown 8*H*-pyrazolo[5',1':3,4]-[1,2,4]triazino[6,5-*d*][1,2]diazepine (**IIIa**) and 8*H*-[1,2,4]-triazolo[5',1':2,3]pyrimido[5,4-*d*][1,2]diazepines (**IIIb, IIIc**) were isolated as dominating compounds, which can also exist in the corresponding 4*H* tautomeric forms **IVa–IVc**. In the ^{1}H NMR spectra of the obtained substances there are doublets of CH protons of a seven-membered cycle in the region of 6.88–7.00 and 7.70–7.78 ppm, and also broadened signals of two "acid" protons at 13.15–13.40 and 14.12–14.20 ppm belonging to the OH and NH groups.



I–IV, R = Me, X = C–Ph, Y = N (**a**); R = H (**b**); R = CF_3 (**c**); X = N, Y = CH (**b, c**).

The NOESY experiment has allowed us to determine strictly that tricyclic diazepines exist in DMSO-d_6 in the tautomeric form **IVa–IVc**. Correlation peaks between the NH proton of the triazine cycle (δ 14.11 ppm) and *ortho*-protons of the phenyl group (7.52 ppm) are observed in the two-dimensional spectrum of compound **IVa**. Furthermore the NH proton gives intensive cross-peaks with the hydroxy group at 13.15/14.11 ppm. The 2D ^{1}H NMR spectrum of compound **IVb** also points to the presence of the lactim hydrogen atom (13.30 ppm) interacting with protons of the pyrimidine CH (8.47 ppm) and NH groups (14.15 ppm).



IVa **IVb**

Thus our experimental data testify that the direction of the heterocyclization reaction of ethyl *ortho*-(dimethylaminovinyl)azoloazinylcarboxylates with hydrazine depends on the solvent nature. In an aprotic medium the cyclization occurs regiospecifically along path *a* with the participation of the second amino group of enhydrazine **A** and with the fusion into a less stressed pyridine ring. The path *b* implemented in the medium of carboxylic acids involves a regioselective cyclocondensation with the participation of the free amino group of intermediate **B** and the closure of a seven-membered cycle. The reaction of enamines **Ia–Ic** with hydrazine hydrate in AcOH or propionic acid can be considered as a new method of the synthesis of fused 1,2-diazepines, as thus far such transformations were not described in the literature [15].

EXPERIMENTAL

Monitoring of the individuality of reagents and products and qualitative analysis of reaction mixtures were carried out by the TLC on Merk Silufol UV-254 plates with chloroform and ethyl acetate as eluents. The ^{1}H NMR spectra were recorded on a Bruker AM-300 spectrometer (300 MHz) at 20°C in DMSO-d_6, internal reference TMS. The 2D ^{1}H NMR spectra were obtained on a Bruker DRX-500 spectrometer (500 MHz) in similar conditions. Mass spectra were recorded on an LKB-9000 instrument with direct sample injection in an ionic source; energy of ionizing electrons 70 eV. The elemental analysis was carried out on a Carlo Erba NA 1500 analyzer.

Initial enamines **Ia–Ic** were obtained by the procedure described earlier [12, 13].

Pyrazolo[5,1-*c*]pyrido[4,3-*e*][1,2,4]triazine-6(7*H*)-on (IIa) and pyrido[3,4-*e*][1,2,4]triazolo[1,5-*a*]pyrimidine-6(7*H*)-ones (IIb, IIc). A mixture of 4 mmol of enamine **Ia–Ic**, 4 ml of hydrazine hydrate, and 3–4 ml of DMF (or dimethyl acetamide) was boiled for 0.5 h. The precipitate formed on cooling was filtered off, washed with isopropanol, and recrystallized.

7-Amino-2-methyl-3-phenylpyrazolo[5,1-*c*]pyrido-[4,3-*e*][1,2,4]triazine-6(7*H*)-one (IIa). Yield 0.70 g (50%), mp 227–229°C (DMF), orange powder. ^{1}H NMR spectrum, δ, ppm: 2.72 s (3H, Me), 6.20 br.s (2H, NH_2), 7.03 d (1H, $CH_{pyridine}$, J = 8.0 Hz), 7.40 t (1H, CH_{arom}, J = 7.5 Hz), 7.52 t (2H, CH_{arom}, J = = 7.6 Hz), 7.83 d (2H, CH_{arom}, J = 7.6 Hz), 8.25 d (1H, $CH_{pyridine}$, J = 8.0 Hz). Mass spectrum, *m/z* (I_{rel}, %): 292 $[M]^+$ (100). Found, %: C 61.51; H 4.24; N 28.85. $C_{15}H_{12}N_6O$. Calculated, %: C 61.64; H 4.14; N 28.75. *M* 292.30.

7-Aminopyrido[3,4-*e*][1,2,4]triazolo[1,5-*a*]pyrimidine-6(7*H*)-one (IIb). Yield 0.61 g (77%), mp 274–276°C (DMF). ^{1}H NMR spectrum, δ, ppm: 6.25 s (2H, NH_2), 7.05 d (1H, $CH_{pyridine}$, J = 7.7 Hz), 8.32 d (1H, $CH_{pyridine}$, J = 7.7 Hz), 8.72 s (1H, $CH_{triazole}$), 9.37 s (1H, $CH_{pyrimidine}$). Mass spectrum, *m/z* (I_{rel}, %): 202 $[M]^+$ (100). Found, %: C 47.44; H 3.11; N 41.65. $C_8H_6N_6O$. Calculated, %: C 47.53; H 2.99; N 41.57. *M* 202.17.

7-Amino-2-(trifluoromethyl)pyrido[3,4-*e*][1,2,4]-triazolo[1,5-*a*]pyrimidine-6(7*H*)-one (IIc). Yield 0.76 g (71%), mp 231–233°C (DMF). ^{1}H NMR spectrum, δ, ppm: 6.40 s (2H, NH_2), 7.12 d (1H, $CH_{pyridine}$, J = 8.0 Hz), 8.40 d (1H, $CH_{pyridine}$, J = 8.0 Hz), 9.50 s (1H, $CH_{pyrimidine}$). Mass spectrum, *m/z* (I_{rel}, %): 270 $[M]^+$ (100). Found, %: C 40.17; H 1.80; N 31.01. $C_9H_4F_3N_6O$. Calculated, %: C 40.01; H 1.87; N 31.11. *M* 270.17.

4*H*-Pyrazolo[5',1':3,4][1,2,4]triazino[6,5-*d*][1,2]-diazepine (IVa) and 4*H*-[1,2,4]triazolo-[5',1':2,3]-pyrimidine[5,4-*d*] [1,2]diazepines (IVb, IVc). A mixture of 4 mmol of enamine **Ia–Ic**, 4 ml of hydrazine hydrate, and 5 ml of AcOH (or propionic acid) was boiled for 30–60 min. A precipitate of the compound **IVa–IVc** with an admixture of *N*-amine **IIa–IIc** was filtered off, washed with isopropanol, and recrystallized twice.

2-Methyl-3-phenyl-4*H*-pyrazolo[5',1':3,4][1,2,4]-triazino[6,5-*d*][1,2]diazepin-6-ol (IVa). Yield 0.59 g (42%), mp 290°C with decomposition (AcOH–DMF, 2:1), yellow crystals. ^{1}H NMR spectrum, δ, ppm: 2.41 s (3H, Me), 6.99 d (1H, $CH_{diazepine}$, J = 2.0 Hz), 7.39 m (1H, CH_{arom}), 7.52 d (4H, CH_{arom}, J = 1.5 Hz), 7.70 d (1H, $CH_{diazepine}$, J = 2.0 Hz), 13.15 br.s (1H, OH), 14.12 br.s (1H, NH). Mass spectrum, *m/z* (I_{rel}, %): 292 $[M]^+$ (55). Found, %: C 61.58; H 4.20; N 28.69. $C_{15}H_{12}N_6O$. Calculated, %: C 61.64; H 4.14; N 28.75. *M* 292.30.

4*H*-[1,2,4]Triazolo[5',1':2,3]pyrimidino[5,4-*d*][1,2]-diazepin-6-ol (IVb). Yield 0.53 g (65%), mp 199–201°C (AcOH–DMF, 2:1). ^{1}H NMR spectrum, δ, ppm: 6.90 d (1H, $CH_{diazepine}$, J = 3.0 Hz), 7.76 d (1H, $CH_{diazepine}$, J = 3.0 Hz), 8.31 s (1H, $CH_{triazole}$), 8.47 s (1H, $CH_{pyrimidine}$), 13.30 br.s (1H, OH), 14.15 br.s (1H, NH). Mass spectrum, *m/z* (I_{rel}, %): 202 $[M]^+$ (40). Found, %: C 47.60; H 2.92; N 41.49. $C_8H_6N_6O$. Calculated, %: C 47.53; H 2.99; N 41.57. *M* 202.17.

2-(Trifluoromethyl)-4*H*-[1,2,4]triazolo[5',1':2,3]-pyrimidino[5,4-*d*][1,2]diazepin-6-ol (IVc). Yield 0.65 g (60%), mp 171–173°C (AcOH–DMF, 2:1). ^{1}H NMR spectrum, δ, ppm: 6.88 d (1H, $CH_{diazepine}$, J = 3.0 Hz), 7.78 d (1H, $CH_{diazepine}$, J = 3.0 Hz), 8.59 s (1H, $CH_{pyrimidine}$), 13.40 br.s (1H, OH), 14.20 br.s (1H, NH). Mass spectrum, *m/z* (I_{rel}, %): 270 $[M]^+$ (26). Found, %: C 40.17; H 1.80; N 31.03. $C_9H_4F_3N_6O$. Calculated, %: C 40.01; H 1.87; N 31.11. *M* 270.17.

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