Synthesis and hydroxydeamination in the series of 6-aryl- and 6-benzoimidazolyl-7-aminoazolo[5,1-*c*]-1,2,4-triazines

E. N. Ulomskii,[a] S. L. Deev,[b] T. S. Shestakova,[a] V. L. Rusinov,[a]★ and O. N. Chupakhin[b]

[a]*Ural State Technical University,*
19 ul. Mira, 620002 Ekaterinburg, Russian Federation.
Fax: +7 (343 2) 74 0458. E-mail: rusinov@htf.ustu.ru
[b]*Institute of Organic Synthesis, Ural Branch of the Russian Academy of Sciences,*
20 ul. S. Kovalevskoi, 620219 Ekaterinburg, Russian Federation.
Fax: +7 (343 2) 74 1189. E-mail: chupakhin@ios.uran.ru

The replacement of the amino group with the hydroxy group was examined in the series of 6-aryl- and 6-benzoimidazolyl-7-aminoazolo[5,1-*c*]-1,2,4-triazines. These reactions provide a convenient synthetic procedure for the preparation of fused azolo[5,1-*c*]-1,2,4-triazin-7-ones.

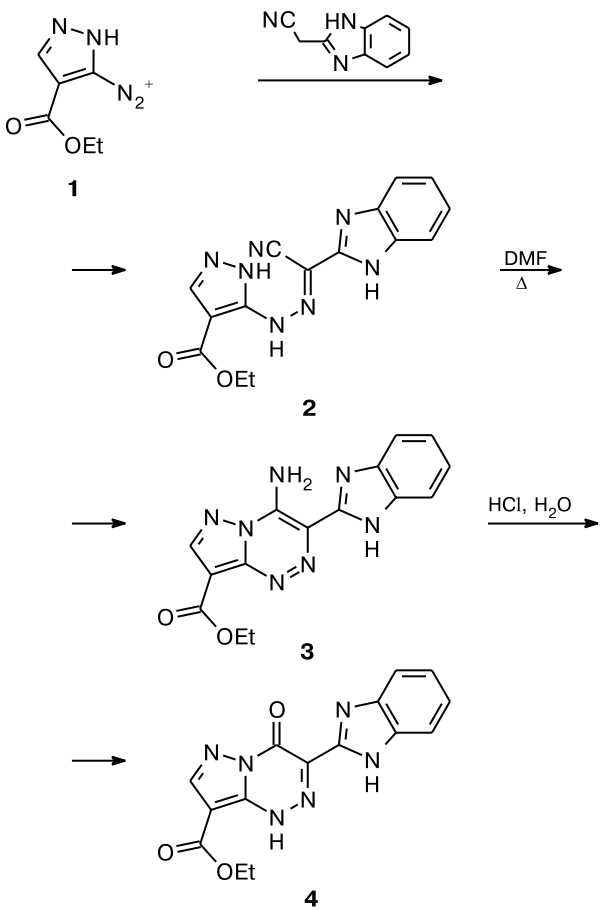
Key words: hydroxydeamination, hetarylamine, azo coupling, alkylation, cyclocondensation.

Fused azoloazines attract continuing interest of chemists primarily because of their structural similarity to purines.[1] Due to this structural feature, fused azoloazines can serve as antimetabolites being efficient antiviral and antitumor drugs.[2—5] One line of investigation in this field of chemistry of heterocyclic compounds involves the synthesis of 6-substituted azolo[5,1-*c*]-1,2,4-triazines and examination of their properties. In the present study, we synthesized 6-aryl- and 6-benzoimidazolyl-7-aminoazolo[5,1-*c*]-1,2,4-triazines and examined their hydroxydeamination with the aim of preparing 7-oxo derivatives of azolo[5,1-*c*]-1,2,4-triazines. Some compounds of the latter series proved to possess antiviral activity.[3]

Results and Discussion

It is known[6,7] that the reactions of azolyldiazonium salts (**1**) with 2-cyanomethylbenzoimidazole afforded 6-benzoimidazolyl-7-aminoazolo[5,1-*c*]-1,2,4-triazines. We applied procedures described previously[6] in the synthesis of hydrazone **2** and benzoimidazolylpyrazolotriazine (**3**) starting from 4-ethoxycarbonylpyrazol-3-yldiazonium (Scheme 1).

Scheme 1



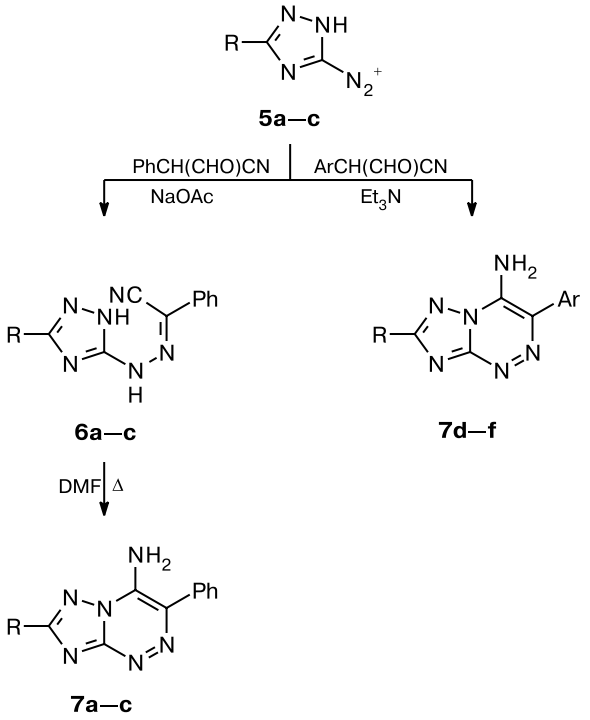
However, an attempt to perform azo coupling of compounds **5a—c** with arylacetonitrile derivatives failed. We found that the preparation of 6-phenyl-1,2,4-triazolo[5,1-*c*]-1,2,4-triazines required the use of aryl(formyl)acetonitriles activated with respect to the electrophilic attack. Thus the reactions of phenyl(formyl)acetonitrile with triazolyldiazonium salts **5a—c** in the presence of sodium acetate afforded hydrazones **6a—c**. At-

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 9, pp. 1594—1600, September, 2002.

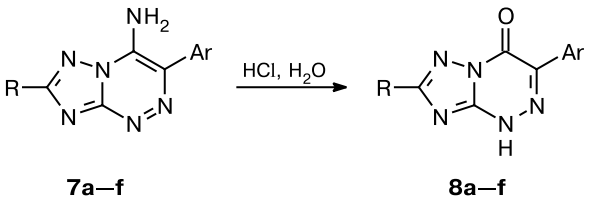
1066-5285/02/5109-1737 $27.00 © 2002 Plenum Publishing Corporation

tempts to purify compounds **6a—c** by crystallization led to cyclization giving rise to compounds **7a—c** even upon heating for a short period, which did not allow us to characterize hydrazones **6a—c** by elemental analysis. A more convenient procedure for the synthesis of 7-amino-6-aryl-1,2,4-triazolo[5,1-*c*]-1,2,4-triazines **7a—c** involves refluxing of hydrazones **6a—c** in DMF. The use of triethylamine instead of sodium acetate in the azo coupling reactions made it possible to directly prepare 7-amino-6-aryl-1,2,4-triazolo[5,1-*c*]-1,2,4-triazines. This procedure was used for the synthesis of compounds **7d—f** (Scheme 2).

Scheme 2



5: R = H (**a**), Me (**b**), SMe (**c**)



6—8	R	Ar	7, 8	R	Ar
a	H	Ph	**d**	H	3,5-$(CF_3)_2C_6H_3$
b	Me	Ph	**e**	Me	3,5-$(CF_3)_2C_6H_3$
c	SMe	Ph	**f**	SMe	3,5-$(CF_3)_2C_6H_3$

The IR spectra of hydrazones **2** and **6a—c** have a strong absorption band in the region of 2210—2215 cm^{-1} corresponding to stretching vibrations of the nitrile group.

Table 1. Yields, melting points, IR spectroscopic data, and molecular weights (according to the results of mass spectrometry) of compounds **2—4**, **6—9**, and **10a**

Compound	M.p.[a] /°C	Yield (%)[b]	M^+, *m/z*	IR spectrum, ν/cm^{-1}
2	276	76	323	2215 (CN), 3320, 3390, 3400 (NH)
3	278	63	323	3120, 3150, 3460 (NH)
4	>300	70 (*A*), 50 (*B*)	324	1650 (C=O), 1695 (C=O) (1615, 1640)[c]
6a	280—282	81	212	2210 (CN), 3450 (NH)
6b	297	72	226	2210 (CN), 3460 (NH)
6c	271	85	258	2215(CN), 3450 (NH)
7a	283—286	60	212	3290, 3230 (NH)
7b	293	65	226	3400, 3270 (NH)
7c	297	55	258	3280, 3190 (NH)
7d	220[d]	40	348	3310, 3200 (NH)
7e	230[d]	71	362	3210, 3100 (NH)
7f	240—242[d]	52	394	3330, 3090 (NH)
8a	232	90	213	1720 (C=O), 3300 (NH)
8b	245	74	227	1700 (C=O), 3270 (NH)
8c	220	75	259	1730(C=O), 3300 (NH)
8d	221	69	349	1705 (C=O), 3250 (NH)
8e	210	65	363	1690 (C=O), 3200 (NH)
8f	232	53	395	1690 (C=O), 3120 (NH)
9a	130[d]	51 (*A*), 70 (*B*)	241	1720 (C=O)
9b	137[d]	39	255	1710 (C=O)
9c	140[d]	35	287	1710 (C=O)
10a[e]	207—210	40		3190, 3300 (NH)

[a] After recrystallization from DMF.
[b] A synthesis procedure is indicated in parentheses.
[c] See Ref. 8.
[d] After recrystallization from EtOH.
[e] X = BF_4.

In the IR spectra of compounds **3** and **7a—f**, the amino group is manifested as a broad band in the region of 3200—3400 cm^{-1} (Table 1). The ^1H NMR spectra of azolo[5,1-*c*]-1,2,4-triazines **3** and **7a—f** show resonances assigned to the protons of the aryl and azole substituents. The presence of the equivalent trifluoromethyl substituents in compounds **7d—f** is confirmed by the presence of singlets in their ^{19}F NMR spectra (δ 100.29—100.46) (Table 2).

The [5,1-*c*]-fusion of the rings is confirmed by the presence of a singlet in the ^{13}C NMR spectrum of compound **7a** recorded without suppression of $^{13}C—^1H$ spin-spin coupling (Table 3).

We found that 7-aminoazolo[5,1-*c*]-1,2,4-triazines **3** and **7a—f** underwent hydroxydeamination in dilute hydrochloric acid to give azolo[5,1-*c*]-1,2,4-triazin-7-ones **4** and **8a—f**, respectively, as evidenced by the fact that the IR spectra of compounds **4** and **8a—f** have absorption bands in the region of 1690—1730 cm^{-1} corresponding to the carbonyl group (see Table 1). It is worthy of note

Table 2. Data from ^{1}H and ^{19}F NMR spectroscopy for compounds **2—4**, **6—9**, and **10a** (Bruker WM-250)

Compound	δ	
	^{1}H	^{19}F
2	1.48 (t, 3 H, $OCH_2\underline{Me}$); 4.59 (q, 2 H, $OC\underline{H}_2Me$); 7.40—7.70, 7.80—8.20 (both m, 2 H each, C_6H_4); 8.76 (s, 1 H, H(2)); 10.76, 13.15, 14.50 (all br.s, 1 H each, NH)	—
3	1.36 (t, 3 H, $OCH_2\underline{Me}$); 4.35 (q, 2 H, $OC\underline{H}_2Me$); 7.20—7.37, 7.60—7.78 (both m, 2 H each, C_6H_4); 8.73 (s, 1 H, H(2)); 9.76, 10.15, 13.50 (all br.s, 1 H each, NH)	—
4	1.34 (1.37)[a] (t, 3 H, $OCH_2\underline{Me}$); 4.35 (4.35)[a] (q, 2 H, $OC\underline{H}_2Me$); 7.41—7.57 (7.10—7.45)[a], 7.73—7.89 (7.57—7.83)[a] (both m, 2 H each, C_6H_4); 8.39 (8.70)[a] (s, 1 H, H(2))	—
6a	7.30—7.52, 7.70—7.86 (both m, 2 H each, Ph); 7.88 (s, 0.7 H, H(2)); 8.51 (s, 0.3 H, H(2)); 5.50—7.00 (br.s, 2 H, NH)	—
6b	2.25 (s, 3 H, CMe); 7.25—7.39 (m, 3 H, Ph); 7.72—7.83 (m, 2 H, Ph); 4.50—6.50 (br.s, 2 H, NH)	—
6c	2.59 (s, 3 H, SMe); 7.35—7.39 (m, 3 H, Ph); 7.86—7.90 (m, 2 H, Ph); 5.70—7.00 (br.s, 2 H, NH)	—
7a	7.49—7.59 (m, 3 H, Ph); 7.70—7.74 (m, 2 H, Ph); 8.67 (s, 1 H, H(2)); 8.50 (br.s, 2 H, NH_2)	—
7b	2.54 (s, 3 H, CMe); 7.46—7.58 (m, 3 H, Ph); 7.64—7.80 (m, 2 H, Ph); 8.44 (br.s, 2 H, NH_2)	—
7c	2.72 (s, 3 H, SMe); 7.47—7.59 (m, 3 H, Ph); 7.63—7.80 (m, 2 H, Ph); 8.50 (br.s, 2 H, NH_2)	—
7d	7.99 (s, 1 H, $C_6H_3(CF_3)_2$); 8.25 (s, 2 H, $C_6H_3(CF_3)_2$); 8.55 (s, 1 H, H(2)); 8.90 (br.s, 2 H, NH_2)	100.46 (s, CF_3)
7e	2.58 (s, 3 H, CMe); 7.98 (s, 1 H, $C_6H_3(CF_3)_2$); 8.25 (s, 2 H, $C_6H_3(CF_3)_2$); 8.73 (br.s, 2 H, NH_2)	100.46 (s, CF_3)
7f	2.73 (s, 3 H, SMe); 8.19 (s, 1 H, $C_6H_3(CF_3)_2$); 8.30 (s, 2 H, $C_6H_3(CF_3)_2$); 8.79 (br.s, 2 H, NH_2)	100.44 (s, CF_3)
8a	7.40—7.52 (m, 3 H, Ph); 8.02—8.07 (m, 2 H, Ph); 8.29 (s, 1 H, H(2)); 13.00—14.00 (br.s, 1 H, NH)	—
8b	2.48 (s, 3 H, CMe); 7.44—7.52 (m, 3 H, Ph); 7.95—8.07 (m, 2 H, Ph); 13.00—14.00 (br.s, 1 H, NH)	—
8c	2.66 (s, 3 H, SMe); 7.41—7.49 (m, 3 H, Ph); 7.96—8.05 (m, 2 H, Ph); 13.00—14.00 (br.s, 1 H, NH)	—
8d	8.03 (s, 1 H, $C_6H_3(CF_3)_2$); 8.30 (s, 1 H, H(2)); 8.63 (s, 2 H, $C_6H_3(CF_3)_2$); 14.50 (br.s, 1 H, NH)	100.29 (s, CF_3)
8e	2.61 (s, 3 H, CMe); 8.04 (s, 1 H, $C_6H_3(CF_3)_2$); 8.25 (s, 2 H, $C_6H_3(CF_3)_2$)	100.44 (s, CF_3)
8f	2.75 (s, 3 H, SMe); 8.02 (s, 1 H, $C_6H_3(CF_3)_2$); 8.24 (s, 2 H, $C_6H_3(CF_3)_2$)	100.41 (s, CF_3)
9a	1.48 (t, 3 H, $NCH_2\underline{Me}$); 4.44 (q, 2 H, $N\underline{CH}_2Me$); 7.46—7.52 (m, 3 H, Ph); 8.00—8.10 (m, 2 H, Ph); 8.42 (s, 1 H, H(2))	—
9b	1.46 (t, 3 H, $NCH_2\underline{Me}$); 2.44 (s, 3 H, CMe); 4.37 (q, 2 H, $N\underline{CH}_2Me$); 7.44—7.50 (m, 3 H, Ph); 7.99—8.02 (m, 2 H, Ph)	—
9c	1.46 (t, 3 H, $NCH_2\underline{Me}$); 2.65 (s, 3 H, SMe); 4.37 (q, 2 H, $N\underline{CH}_2Me$); 7.47—7.50 (m, 3 H, Ph); 8.00—8.03 (m, 2 H, Ph)	—
10a[b]	1.53 (t, 3 H, $NCH_2\underline{Me}$); 4.48 (q, 2 H, $N\underline{CH}_2Me$); 7.56—7.59 (m, 3 H, Ph); 7.66—7.70 (m, 2 H, Ph); 8.76 (s, 1 H, H(2))	—

[a] See Ref. 8.
[b] X = BF_4.

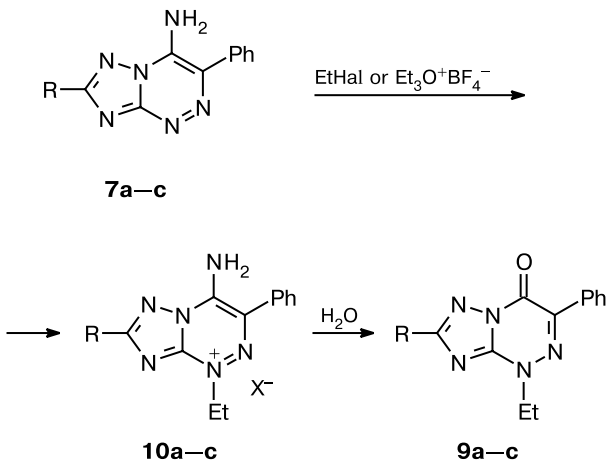
Table 3. Data from ^{13}C NMR spectroscopy for compounds **7a**, **8a**, and **9a—c** (Bruker DRX-400)

Compound	δ ($J_{C,H}$/Hz)							
	R	C(2)	C(3a)	C(6)	C(7)	NCH_2	CMe	Ph
7a	—	155.88 d (^{1}J = 209)	155.25 d (^{3}J = 5.7)	133.89 t (^{3}J = 7.2)	139.94 s	—	—	128.50; 128.55; 128.90; 133.41
8a	—	153.53 d (^{1}J = 210)	151.22 d (^{3}J = 9.3)	139.14 t (^{3}J = 3.7)	149.47 s	—	—	128.08; 128.36 129.34; 132.55
9a	—	153.24 d (^{1}J = 210.6)	150.73 dt (^{3}J = 9.3, ^{3}J = 2.7)	138.64 t (^{3}J = 3.7)	149.03 s	49.40 tq (^{1}J = 143.0, ^{3}J = 4.6)	13.0 qt (^{1}J = 128.4, ^{3}J = 3.3)	132.42 (C(1′)); 128.13 (C(2′), C(6′)); 128.40 (C(3′), C(5′)); 129.45 (C(4′))
9b	13.59 q (^{1}J = 122.7)	162.79 q (^{2}J = 7.2)	150.93 t (^{3}J = 2.7)	138.60 t (^{3}J = 3.6)	148.50 s	49.24 tq (^{1}J = 143.0, ^{3}J = 4.6)	14.2 qt (^{1}J = 128.8, ^{3}J = 3.9)	132.32 (C(1′)); 128.31 (C(2′), C(6′)); 128.50 (C(3′), C(5′)); 129.45 (C(4′))
9c	13.43 q (^{1}J = 142.5)	151.22 q (^{3}J = 4.7)	151.22 t (^{3}J = 2.6)	139.02 t (^{3}J = 3.6)	147.63 s	49.24 tq (^{1}J = 143.3, ^{3}J = 4.5)	12.86 qt (^{1}J = 128.5, ^{3}J = 3.24)	132.23 (C(1′)); 128.13 (C(2′), C(6′)); 128.45 (C(3′), C(5′)); 129.44 (C(4′))

that the aromatic protons in the ^{1}H NMR spectrum of benzoimidazole **4** are manifested as an AA´XX´ system consisting of two symmetrical two-proton multiplets.

The reactions of 7-amino-6-phenyl-1,2,4-triazolo[5,1-*c*]-1,2,4-triazines (**7a—c**) with EtI or EtBr in DMF followed by treatment of the reaction mixture with water afforded 4-ethyl-1,2,4-triazolo[5,1-*c*]-1,2,4-triazin-7-ones (**9a—c**), which represent simultaneously alkylation and hydroxydeamination products (Scheme 3).

Scheme 3



R = H (**a**), Me (**b**), SMe (**c**); X = Hal, BF_4

The position of the *N*-ethyl group in compounds **9a—c** was established by ^{13}C NMR spectroscopy. The assignment of the signals in the spectra was made based on the chemical shifts in the spectra measured with full ^{13}C—^{1}H decoupling and taking into account the hyperfine structure of the signals in the spectra measured with retention of ^{13}C—^{1}H spin-spin coupling. In the spectrum of compound **9a**, the C(2) atom gives a doublet with a large spin-spin coupling constant ($^1J_{C,H}$ = 210.6 Hz) without additional splitting, which excludes the presence of the Et substituent in the azole fragment of the molecule. This conclusion was confirmed by the structure of the resonance for the bridgehead C(3a) atom, which is manifested as a doublet of triplets with small spin-spin coupling constants ($^3J_{C(3a),H(2)}$ = 9.3 Hz and $^3J_{C(3a),H(NCH_2)}$ = 2.7 Hz). In the spectra of compounds **9b,c**, the signals for the C(2) atom are observed as quartets with small spin-spin coupling constants ($^2J_{C,H}$ = 7.2 Hz and $^3J_{C,H}$ = 4.7 Hz, respectively) and the signal for the bridgehead C(3a) atom degenerates into a triplet (see Table 3). In the spectra of compounds **9a—c**, the low-field singlet (δ 147.5—149.1) was assigned to the C(7) atom and the triplet at δ 138—139 was attributed to the resonance for the C(6) atom. The remaining low-field multiplets belong to the Ph group. The high-field region of the spectra has signals of the Et group. In the spectra of compounds **9b,c**, resonances of the substituent R are also observed (see Table 3).

The ^{1}H NMR spectra of compounds **9a—c** have signals for the protons of both the azole and aryl substituents (δ 7.0—8.0). The signals of the Et groups are observed at δ 1.30—4.40 (see Table 2).

The mechanisms *A*, *B*, and *C* can be proposed for the reactions of hetarylamines **7a—c** with EtI or EtBr (Scheme 4).

The mechanism *A* involves hydroxydeamination as the first step giving rise to triazolotriazines **8a—c**, which are strong NH-acids.[9] These acids form salts **11a—c** with ammonia that liberated. Then, compounds **11a—c** are alkylated under standard conditions.[10] The mechanism *B* involves the formation of quaternary ammonium salts **12a—c**. In this case, the triethylammonium group is readily replaced giving rise to compounds **8a—c**. The latter react with triethylammonium hydrohalide and ethyl halide. The mechanism *C* involves the formation of triazinium cations **10a—c**, which are readily transformed into triazolo[5,1-*c*]-1,2,4-trazinones **9a—c**.

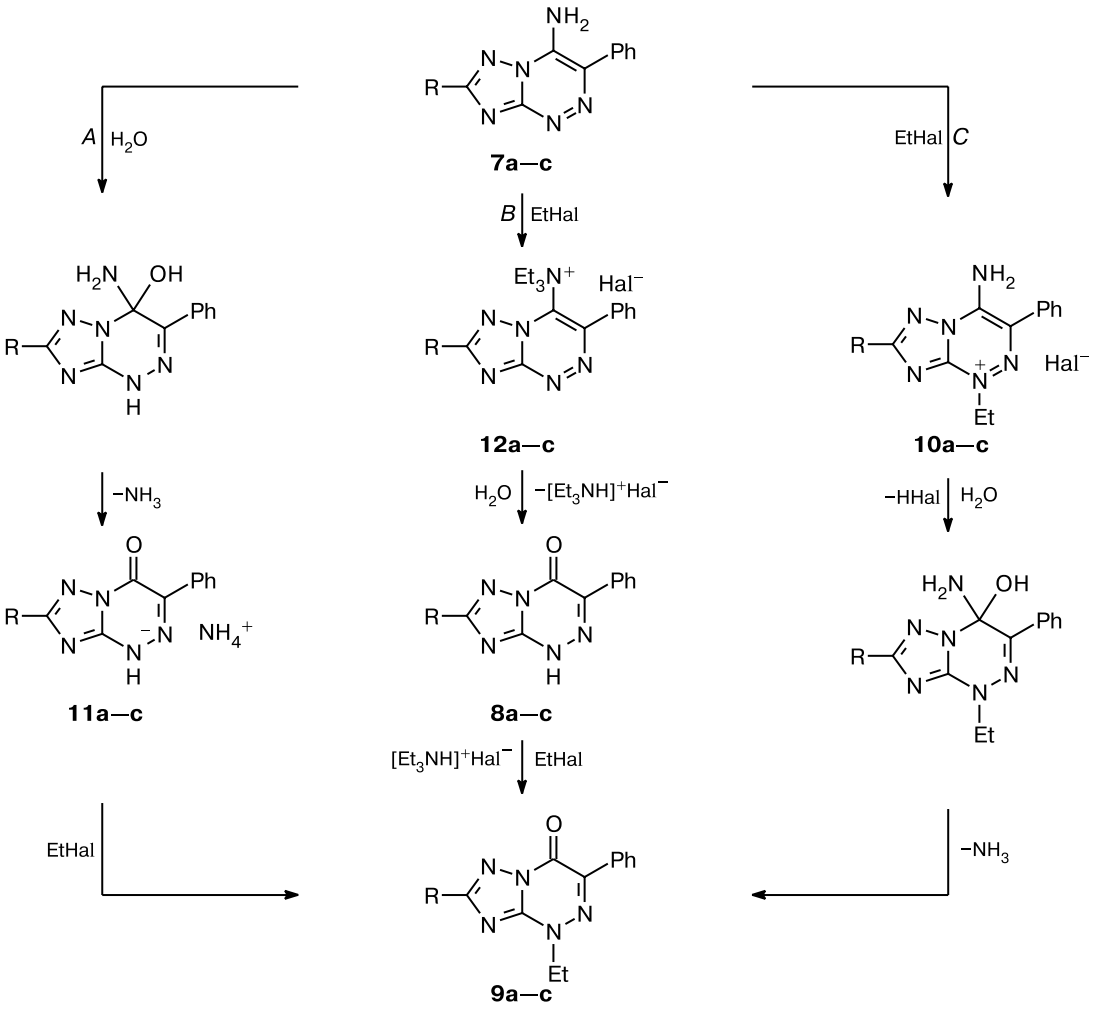
To establish the reaction pathway, we carried out additional experiments. We found that compound **8a** did not react with triethylammonium hydrobromide and EtBr in DMF. The starting compound **8a** was isolated from the reaction mixture, which allowed us to exclude the path *B*. Further examination of the resistance of hetarylamine **7a** to hydrolysis demonstrated that prolonged refluxing of compound **7a** in water or aqueous DMF did not afford triazolo[5,1-*c*]-1,2,4-triazin-7-one **8a**. This indicates that the reaction cannot follow the path *A*. Hence, the reaction most probably proceeds through the mechanism *C*.

The ^{1}H NMR spectrum of the reaction mixture which was obtained by the reaction of hetarylamine **7a** with EtBr shows signals for the protons of the azole ring at δ 8.1—8.9 corresponding to amine **7a**, triazolotriazine **9a**, and an unidentified alkyl derivative. The latter is, apparently, salt **10a** (X = Br). In addition, the spectrum has overlapping signals of the Et groups, multiplets of the Ph substituents of all the above-mentioned compounds, and a triplet corresponding to the ammonium ion (δ 7.1, ^1J = 49.95 Hz). The absence of the signals of alkylammonium salts is additional evidence that the path *B* is impossible.

With the aim of studying the reactions of hetarylamines **7a—c** with alkyl halides, triazolotriazinium **10a** was synthesized from triazolo[5,1-*c*]-1,2,4-triazine **7a** (X = BF_4) under the action of the Meerwein reagent and the spectroscopic characteristics of this salt were determined. Thus the chemical shift of the H(2) atom (δ 8.76) corresponds to the signal of the unidentified compound observed in the ^{1}H NMR spectrum of the reaction mixture.

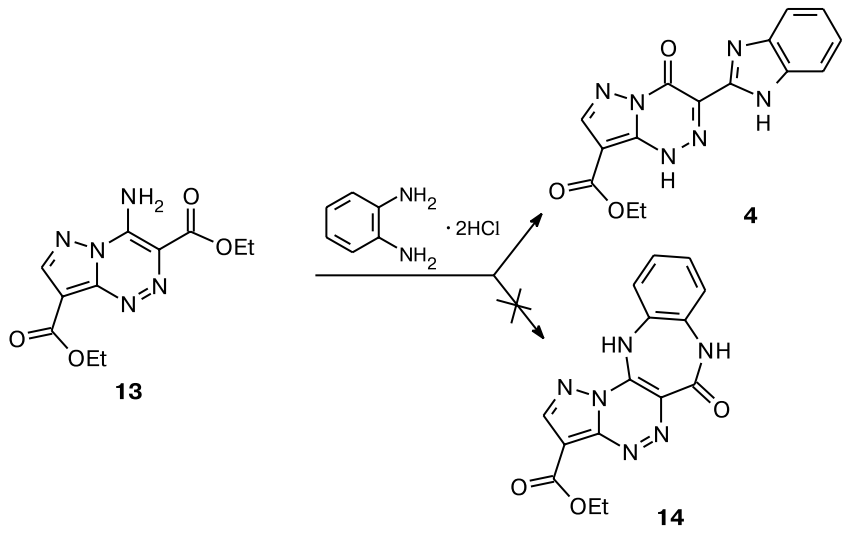
In addition, brief refluxing of salt **10a** (X = BF_4) in water afforded a compound whose physicochemical char-

Scheme 4



R = H (**a**), Me (**b**), SMe (**c**); Hal = Br, I

Scheme 5



acteristics are identical with those of 6-phenyl-1,2,4-triazolo[5,1-*c*]-1,2,4-triazin-7-one (**9a**) prepared by the reaction of amine **7a** with EtI or EtBr in DMF. These experiments demonstrate that the formation of triazolo[5,1-*c*]-1,2,4-trazinones **9a—c** proceeds most likely *via* the pathway *C*.

Compound **4** can also be prepared by the reaction of diethyl 7-aminopyrazolo[5,1-*c*]-1,2,4-triazino-3,6-dicarboxylate (**13**) with *ortho*-phenylenediamine dihydrochloride in acetic acid (Scheme 5). Aminoheterocycle **3** generated in the first step of the reaction readily underwent hydroxydeamination under the action of hydrogen chloride that has been liberated and water.

The results of our study are in contradiction with the results of an earlier investigation[8] in which the tetracyclic structure (**14**) was assigned to the reaction product. The authors established the structure of benzodiazepine **14** based on the data from IR spectroscopy, mass spectrometry, elemental analysis, and ^{1}H NMR spectroscopy, which is insufficient because compounds **4** and **14** are isomers.

We performed the independent synthesis of heterocycle **4** and demonstrated that tetracyclic structure **14** assigned to the condensation product[8] is in error and that benzoimidazole derivative **4** is in fact the reaction product.

Hence, hydroxydeamination is a typical reaction of 7-aminoazolo[5,1-*c*]-1,2,4-triazines and provides a convenient procedure for the synthesis of azolotriazinones.

Experimental

The IR spectra were recorded on a Specord IR-75 spectrometer (KBr pellets). The ^{1}H, ^{13}C, and ^{19}F NMR spectra were measured on Bruker WM-250 (250 MHz) and Bruker DRX-400 (400 MHz) spectrometers in DMSO-d_6 with Me_4Si, DMSO-d_6, and C_6F_6 as the internal standards for the ^{1}H, ^{13}C, and ^{19}F NMR spectra, respectively. The mass spectra were obtained on a Varian-MAT-311A instrument with direct inlet of the sample into the ion source (energy of ionizing electrons was 70 eV, temperature of the ionization chamber was 100—300 °C). The melting points were determined on a Boetius stage. The TLC analysis was carried out on Silufol UV-254 plates in ethyl acetate; spots were visualized with UV light or iodine vapor.

3-R-5-Amino-1,2,4-triazoles were prepared according to known procedures.[11—13] Triethyloxonium tetrafluoroborate was synthesized according to a procedure described previously.[14] Phenyl(formyl)acetonitrile and its bis(trifluoromethyl) derivative, which were synthesized according to a known procedure,[15] were kindly provided by P. V. Podsevalov (Scientific Development Firm "Okta," Perm, Russia). Ethyl 3-aminopyrazole-4-carboxylate and benzoimidazol-2-ylacetonitrile were purchased from Aldrich. All other reagents and solvents were domestically produced and used without additional purification.

The yields of the reaction products and solvents used for their crystallization are listed in Table 1. The results of elemental analysis are given in Table 4.

Table 4. Data from elemental analysis of compounds **3**, **4**, **7—9**, and **10a**

Compound	Found / Calculated (%)			Molecular formula
	C	H	N	
3	55.49	4.00	30.22	$C_{15}H_{13}N_7O_2$
	55.73	4.02	30.34	
4	55.30	3.81	25.45	$C_{15}H_{12}N_6O_3$
	55.55	3.70	25.91	
7a	56.60	3.92	39.41	$C_{10}H_8N_6$
	56.60	3.80	39.60	
7b	58.61	4.42	37.60	$C_{11}H_{10}N_6$
	58.41	4.46	37.15	
7c	51.26	4.01	32.09	$C_{11}H_{10}N_6S$
	51.15	3.90	32.54	
7d	41.21	1.89	23.86	$C_{12}H_6F_6N_6$
	41.38	1.72	24.14	
7e	43.00	2.11	23.24	$C_{13}H_8F_6N_6$
	43.09	2.21	23.20	
7f	39.63	2.05	21.26	$C_{13}H_8SF_6N_6$
	39.59	2.03	21.32	
8a	56.33	3.10	32.96	$C_{10}H_7N_5O$
	56.34	3.31	32.85	
8b	58.30	3.91	30.35	$C_{11}H_9N_5O$
	58.15	3.99	30.82	
8c	50.90	3.33	27.07	$C_{11}H_9N_5OS$
	50.96	3.50	27.01	
8d	41.36	1.47	20.01	$C_{12}H_5F_6N_5O$
	41.26	1.43	20.06	
8e	42.68	2.02	18.85	$C_{13}H_7F_6N_5O$
	42.98	1.93	19.28	
8f	39.75	1.77	17.29	$C_{13}H_7F_6N_5OS$
	39.49	1.77	17.72	
9a	59.55	4.60	28.95	$C_{12}H_{11}N_5O$
	59.74	4.60	29.03	
9b	61.04	5.21	26.98	$C_{13}H_{13}N_5O$
	61.17	5.13	27.43	
9c	54.34	4.55	24.66	$C_{13}H_{13}N_5OS$
	54.34	4.56	24.37	
10a*	44.24	4.03	26.10	$C_{12}H_{13}BF_4N_6$
	44.04	3.97	25.69	

* X = BF_4.

7-Amino-6-benzoimidazolylpyrazolo[5,1-*c*]-1,2,4-triazine (3) was synthesized according to a procedure described previously.[6]

Azolylhydrazones 2, 6a—c. Nitric acid (d = 1.4 g mL^{-1}, 7 mL, 0.1 mol) or concentrated HCl (11 mL, 0.1 mol) was added to a solution of 5-amino-1,2,4-triazole or ethyl 3-aminopyrazole-4-carboxylate (0.05 mol), respectively, in water (20 mL). The reaction mixture was cooled to 0 °C and then a solution of $NaNO_2$ (3.45 g, 0.05 mol) in water (5 mL) was added at 0 °C. The reaction mixture was kept at 0 °C for 15 min and added to a solution of phenyl(formyl)acetonitrile (7.25 g, 0.05 mol) or benzoimidazol-2-ylacetonitrile (7.9 g, 0.05 mol) and NaOAc (10 g) in 50% aqueous EtOH (40 mL) cooled to 5 °C. Then the reaction mixture was kept at ~20 °C for 2 h. The precipitate of hydrazone **2** or **6** that formed was filtered off, washed with water and EtOH, and dried.

R-7-Amino-6-phenyl-1,2,4-triazolo[5,1-*c*]-1,2,4-triazines (7a—c). A solution of hydrazone **6a—c** (0.01 mol) in DMF (5 mL) was refluxed for 10 min and cooled. The precipitate that formed was filtered off and recrysallized.

R-7-Amino-6-[3,5-bis(trifluoromethyl)phenyl]-1,2,4-triazolo[5,1-*c*]-1,2,4-triazines (7d—f). Diazotization of 3-R-5-amino-1,2,4-triazoles was carried out as described above. The reaction mixture was kept at 0 °C for 15 min and then added to a solution of formyl[3,5-bis(trifluoromethyl)]acetonitrile (14.05 g, 0.05 mol) and Et_3N (10 mL) in 50% aqueous EtOH (40 mL) cooled to 5 °C. Then reaction mixture was kept at ~20 °C for 2 h. The precipitate of hetarylamine **7** that formed was filtered off, washed with water, and recrystallized.

6-Benzoimidazolylpyrazolo[5,1-*c*]-1,2,4-triazin-7-one (4). Method *A*. A suspension of hetarylamine **3** (0.32 g, 1 mmol) in 23% HCl (d = 1.115 g mL^{-1}; 5 mL) was refluxed for 0.5 h. After cooling of the reaction mixture, the precipitate that formed was filtered off and recrystallized.

Method *B*. Compound **4** was synthesized from pyrazolo[5,1-*c*]-1,2,4-triazine (**13**) according to a procedure described previously.[8]

6-Aryl-4,7-dihydro-1,2,4-triazolo[5,1-*c*]-1,2,4-triazin-7-ones (8a—f). A suspension of hetarylamine (**7a—f**) (1 mmol) in 23% HCl (d = 1.115 g mL^{-1}; 5 mL) was refluxed for 0.5 h. After cooling of the reaction mixture, the precipitate that formed was filtered off and recrystallized.

2-R-4-Ethyl-6-phenyl-4,7-dihydro-1,2,4-triazolo[5,1-*c*]-1,2,4-triazin-7-ones (9a—c). Ethyl bromide or iodide (0.012 mol) was added to a solution of hetarylamine **7a—c** (0.01 mol) in DMF (10 mL), the reaction mixture was heated for 2 h at 100 °C, and water (20 mL) was added to the cooled reaction mixture. The precipitate that formed was filtered off and recrystallized.

4-Ethyl-6-phenyl-4,7-dihydro-1,2,4-triazolo[5,1-*c*]-1,2,4-triazin-7-one (9a). Method *B*. A suspension of compound **10a** (1 g, 3 mmol) in water (5 mL) was refluxed for 20 min. After cooling of the reaction mixture, the precipitate that formed was filtered off and recrystallized.

7-Amino-4-ethyl-6-phenyl-1,2,4-triazolo[5,1-*c*]-1,2,4-triazinium tetrafluoroborate (10a) (X = BF_4). Triethyloxonium tetrafluoroborate (3.4 g, 1.8 mmol) was added to a suspension of amine **6a** (2 g, 1 mmol) in dichloroethane (15 mL). The reaction mixture was kept at ~20 °C for 24 h. The precipitate that formed was filtered off.

This study was financially supported by the Russian Foundation for Basic Research (Project Nos. 00-15-97390 and 99-03-32923) and the US Civilian Research and Development Foundation (CRDF, Grant REC-005).

References

1. R. K. Robins, G. R. Ravenkar, D. E. O´Brien, R. H. Springer, T. Novinson, A. Albert, K. Senga, J. P. Miller, and D. G. Streeter, *J. Heterocycl. Chem*., 1985, **22**, 601.
2. *Selective Toxicity, The Physico-Chemical Basis of Therapy*, Ed. A. Albert, Chapman and Hall, London—New York, 1987, **1**.
3. V. L. Rusinov, E. N. Ulomskii, O. N. Chupakhin, M. M. Zubairov, A. B. Kapustin, N. I. Mitin, M. I. Zhiravetskii, and I. A. Vinograd, *Khim.-farm. Zh*., 1990, **41**, 24 [*Pharm. Chem. J*., 1990, **41** (Engl. Transl.)].
4. K. L. Horspool, M. F. G. Stevens, G. G. Newton, E. Lunt, R. J. A. Walsh, B. L. Pedgrift, G. U. Baig, F. Lavelle, and C. Fizames, *J. Med. Chem*., 1990, **33**, 1393.
5. M. J. Wanner, J. K. F. D. Künzel, A. P. Ijzerman, and G.-J. Koomen, *Bioorgan. Med. Chem. Lett*., 2000, **10**, 2141.
6. E. N. Ulomskii, S. L. Deev, V. L. Rusinov, and O. N. Chupakhin, *Zh. Org. Khim*., 1999, **35**, 1384 [*Russ. J. Org. Chem*., 1999, **35** (Engl. Transl.)].
7. J. Slouka and V. Bekarek, *Collect. Czech. Chem. Commun*., 1984, **49**, 275.
8. Y. Kurasawa, Y. Okamoto, and A. Takada, *J. Heterocycl. Chem*.,1987, **24**,1799.
9. L. G. Egorova, A. Yu. Petrov, and V. L. Rusinov, *Khim. Geterotsikl. Soedin*., 1984, 697 [*Chem. Heterocycl. Compd*., 1984, **20** (Engl. Transl.)].
10. E. N. Ulomskii, V. L. Rusinov, O. N. Chupakhin, G. L. Rusinov, A. V. Chernyshev, and G. G. Aleksandrov, *Khim. Geterotsikl. Soedin*., 1987, 1543 [*Chem. Heterocycl. Compd*., 1987, **23** (Engl. Transl.)].
11. *Organic Synthesis*, J. Wiley and Sons, New York; Chapman and Hall, London, 1946, **26**.
12. *Beilsteins Handbuch der Organischen Chemie*, Springer, Berlin, 1936, **26**, 145.
13. S. M. Desenko and V. D. Orlov, *Azageterotsikly na osnove aromaticheskikh nepredel´nykh ketonov* [*Azaheterocycles Based on Aromatic Unsaturated Ketones*], Folio, Kharkov, 1998, 148 pp. (in Russian).
14. L. E. Fieser and M. Fieser, *Reagents for Organic Synthesis*, Wiley-Interscience, New York—London—Sydney—Toronto, 1968, **3**.
15. US Pat. 2,989,539, 20.06.1961.

Received July 20, 2001;
in revised form May 16, 2002