Synthesis of 6-mono- and 5,6-disubstituted 1,2,3-triazolo[4,5-*d*]pyrimidin-7-ones

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The reactions of N-substituted 4-amino-3-benzyl-1,2,3-triazole-5-carboxamides with phosphorus oxochloride and dimethylformamide at 80 °C or with triethyl orthoacetate and acetic anhydride at 160 °C afforded 6-mono- or 5,6-disubstituted 1,2,3-triazolo[4.5-*d*]pyrimidin-7-ones in 30—85% and 65—90% yields, respectively.

Key words: 4-amino-3-benzyl-1,2,3-triazole-5-carboxylic acid, 1,2,3-triazolo[4,5-*d*]pyrimidin-7-ones.

1,2,3-Triazolo[4,5-*d*]pyrimidines (TP) belonging to 8-azapurines[1] attract attention because some of these compounds exhibit antiviral,[2] antitumor,[2—4] or herbicide activities[5] or can be used in photomaterials.[6] Earlier, analogs of nucleosides, *viz.*, compounds bearing a carbohydrate residue in the triazole ring and unsubstituted in the pyrimidine ring, have aroused particular interest.[1] In recent years, TPs containing substituents in the pyrimidine ring have also attracted attention. The aim of the present study was to synthesize 5- and(or) 6-substituted 1,2,3-triazolo[4,5-*d*]pyrimidin-7-ones (**1**) starting from N-substituted 4-amino-3-benzyl-1,2,3-triazole-5-carboxamides **2**. The latter were planned to prepare from the corresponding acid **3** (synthesis of **3** has been described earlier[7]). However, refluxing of a mixture of acid **3**, aniline, and dicyclohexylcarbodiimide (DCC) in acetonitrile for 2 h afforded only compound **4**, which is a product of addition of acid **3** to DCC (Scheme 1).

The synthesis of amides from acids using DCC is widely used, in particular, in peptide chemistry. Adducts **4** were sometimes isolated from the reactions of acids with DCC in the absence of amines.[8] However, to our knowledge, compounds of type **4** never remained unchanged after refluxing with aniline in acetonitrile. Ester of acid **3** is also poorly reactive.[7] Thus, heating with a solution of ammonia in ethylene glycol at 100 °C for 24 h was required for the preparation of the corresponding amide. The reaction of acid **3** with $POCl_3$ also did not give rise to identified compounds.

We synthesized amides **2** from cyanoacetamides **5** in high yields (Scheme 2, Table 1).

Scheme 1

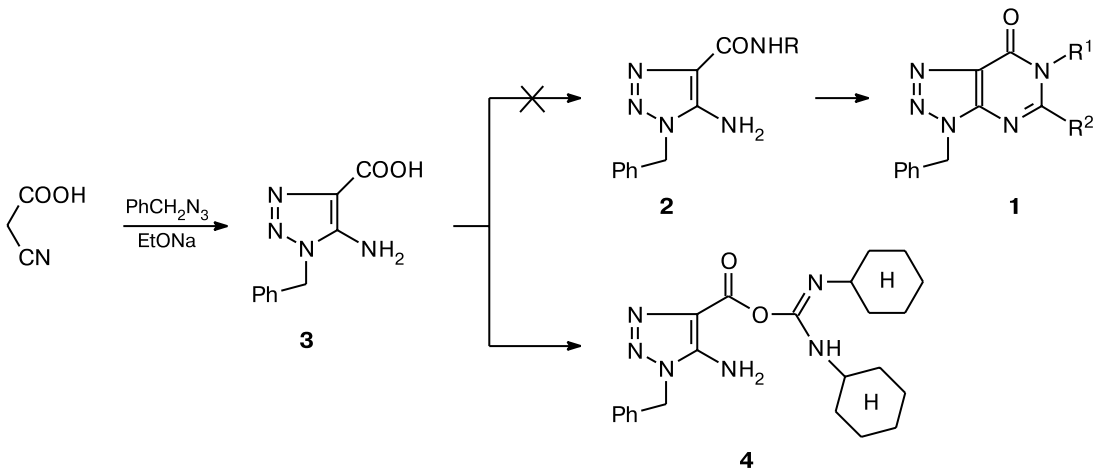

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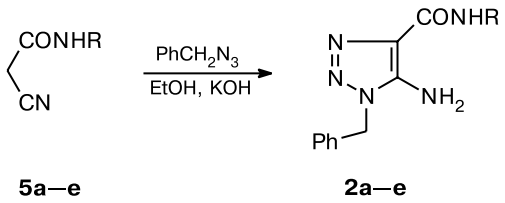
Table 1. Yields, melting points, and data from elemental analysis and ^{1}H NMR spectroscopy of 4-amino-3-benzyl-1,2,3-triazole-5-carboxamides (**2a—e**)

Compound	Yield (%)	M.p. /°C	Found / Calculated (%) C	H	N	Molecular formula	^{1}H NMR (δ, *J*/Hz) NH_2 (s, 2 H)	CH_2 (s, 2 H)	Ph (m)	Other signals
2a	85	233—234	55.2 55.3	5.4 5.1	32.3 32.3	$C_{10}H_{11}N_5O$	6.30	5.40	7.20—7.40 (5 H)	6.95, 7.20 (both br.s, 1 H each, $CONH_2$)
2b	75	150—152	57.6 57.1	5.2 5.6	30.4 30.4	$C_{11}H_{13}N_5O$	6.20	5.39	7.20—7.40 (5 H)	2.80 (d, 3 H, MeNHCO, *J* = 4.6); 7.70 (br.s, 1 H, MeNHCO)
2c	86	182—186	66.0 65.5	5.7 5.1	22.8 22.8	$C_{17}H_{17}N_5O$	6.18	5.40	7.20—7.35 (10 H)	4.47 (d, 2 H, $PhCH_2NHCO$, *J* = 6.2); 8.10 (br.s, 1 H, $PhCH_2NHCO$)
2d	79	205—207	65.9 66.4	5.3 5.5	23.2 22.8	$C_{16}H_{15}N_5O$	6.50	5.48	7.00—7.80 (10 H)	9.90 (br.s, 1 H, NHCO)
2e	91	180—182	63.2 63.1	5.5 5.3	22.0 21.7	$C_{17}H_{17}N_5O$	6.45	5.45	7.20—7.40 (5 H)	3.95 (s, 3 H, CH_3O); 6.90—7.05 (m, 3 H) + 8.35 (d, 1 H, *J* = 8.9) (2-$MeOC_6H_4$); 9.05 (br.s, 1 H, NH)

Scheme 2



5a—e **2a—e**

R = H (**a**), Me (**b**), CH_2Ph (**c**), Ph (**d**), 2-$MeOC_6H_4$ (**e**)

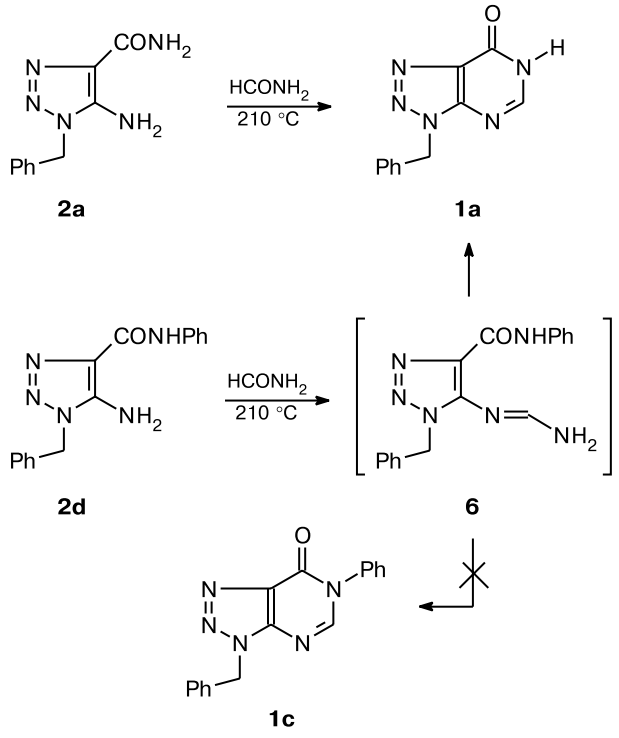
5-Unsubstituted TPs were synthesized by heating 4-amino-3-phenyl-1,2,3-triazole-5-carboxamide with $HCONH_2$ at 180—200 °C.[9] We extended this procedure to amide **2a** and prepared triazolopyrimidine **1a** as the reaction product. The reaction with the use of amide **2d** also gave **1a** in low yield (Scheme 3). Apparently, this is attributable to the fact that the attack of the amidine amino group in the assumed intermediate **6** at the amide group is more preferable than the attack of the amide NH group at the amidine carbon atom.

At the same time, the reaction with $POCl_3$ and DMF (80 °C, 0.5 h) afforded a mixture of amidine **7d** and TP **1d** (Scheme 4).

By varying the reaction conditions, it is possible to selectively prepare either amidine **7d** (40 °C, 0.5 h) or TP **1d** (80 °C, 4 h). The experimental conditions thus found were used in the synthesis of amidines **7c,d** and TP **1b—e** (Table 2).

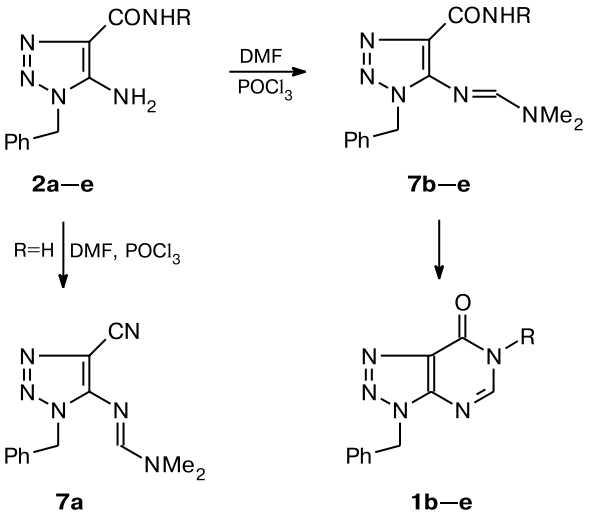
It should be noted that the Vilsmeier reaction of amide **2a** afforded only amidine **7a**, whereas the synthesis of TP **1e** was accompanied by substantial resinification.

Scheme 3

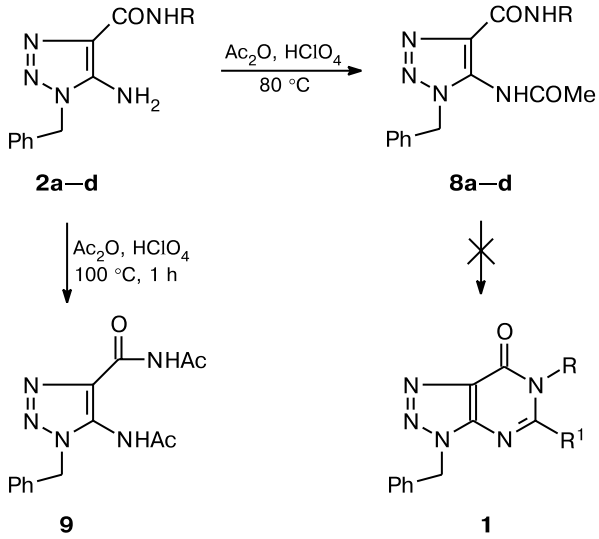


It is common practice to synthesize various fused pyrimidines from heterocycles bearing the amino group and the carboxamide group in the *ortho* position by heating in acetic anhydride (or in any other anhydride).[10] However, amides **2** remained unconsumed upon refluxing in acetic anhydride for 4 h, whereas the reactions in acetonitrile in

Scheme 4



Scheme 5



the presence of mineral acids (H_2SO_4, $HClO_4$) afforded *N*-acylated derivatives **8a—d** in high yields (Scheme 5, Table 3).

The reactions in the presence of strong mineral acid but at higher temperature (100 °C, acetic anhydride, $HClO_4$, 1 h) gave compound **9**.

This behavior of the $CONH_2$-substituted product is anomalous. Thus, either cyclization to form pyrimidine or dehydration to give nitrile generally takes place in the series of other heterocycles.

Under all the conditions used, attempts at subjecting products **8a—d** to cyclization giving rise to TP failed. An attempt to use a mixture of $POCl_3$ and DMF as a dehydrating agent led to the generation of only 5-unsubstituted amide **2c** from **8c** (elimination of the $COCH_3$

Table 2. Yields, melting points, and data from elemental analysis and ^{1}H NMR spectroscopy of Vilsmeier reaction products **1a—e** and **7a,c,d**

Compound	Yield (%)	M.p. /°C	Found / Calculated (%)			Molecular formula	^{1}H NMR (δ, *J*/Hz)			
			C	H	N		CH* (s, 1 H)	CH_2 (s, 2 H)	Ph (m)	Other signals
1b	71	215—220	59.4 59.7	4.9 4.6	28.6 29.0	$C_{12}H_{11}N_5O$	8.55	5.75	7.30—7.40 (5 H)	3.53 (s, 3 H, CH_3N)
1c	74	146—148	67.5 68.1	4.5 4.7	22.4 22.1	$C_{18}H_{15}N_5O$	8.65	5.80	7.25—7.35 (10 H)	5.25 (s, 2 H, NCH_2Ph)
1d	85	195—197	67.8 67.3	4.0 4.3	23.7 23.1	$C_{17}H_{13}N_5O$	8.37	5.78	7.20—7.60 (10 H)	—
1e	30	110—115	64.3 64.9	4.7 4.5	21.5 21.0	$C_{18}H_{15}N_5O_2$	8.17	5.85	7.10—7.55 (5 H)	3.85 (s, 3 H, MeO)
7a	72	118—120	61.2 61.4	5.4 5.5	33.6 33.1	$C_{13}H_{14}N_6$	8.25	5.38	7.30—7.40 (5 H)	3.05, 3.15 (both s, 3 H each, Me_2N)
7c	49	132—134	66.1 66.3	6.4 6.1	23.4 23.2	$C_{20}H_{22}N_6O$	9.30	5.40	7.15—7.35 (10 H)	4.50 (d, 2 H, $N\underline{CH_2}Ph$, *J* = 6.21); 8.30 (br.s, 1 H, CONH); 3.05, 3.15 (both s, 3 H each, Me_2N)
7d	55	142—144	65.0 65.5	5.4 5.7	24.0 24.1	$C_{19}H_{20}N_6O$	9.15	5.42	7.15—7.30 (10 H)	3.05, 3.15 (both s, 3 H each, Me_2N); 8.30 (br.s, 1 H, CONH)

* CH is the N=CH—NMe_2 fragment for **7a,c,d** or C(5) for **1b—e**.

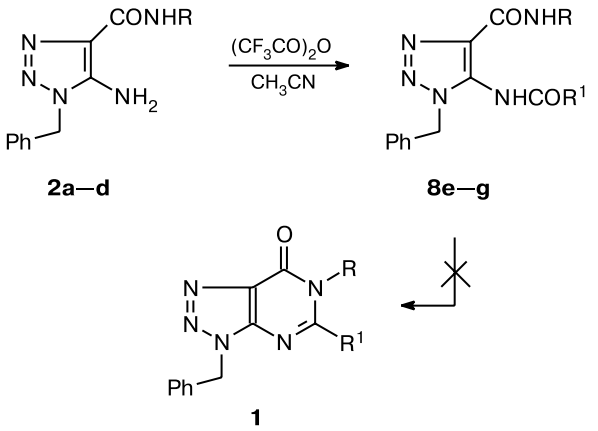
Table 3. Yields, melting points, and data from elemental analysis and ^{1}H NMR spectroscopy of acylated products **8b—g** and **9**

Compound	Yield (%)	M.p. /°C	Found / Calculated (%) C	H	N	Molecular formula	^{1}H NMR (δ, *J*/Hz) 4-CH_3CONH (br.s)	CH_2 (s, 2 H)	Ph (m)	Other signals
8b	80	183—184	56.8 57.1	5.5 5.5	25.2 25.6	$C_{13}H_{15}N_5O_2$	2.1 (3 H, Me); 9.95 (1 H, NH)	5.42	7.20—7.35 (5 H)	2.8 (d, 3 H, *J* = 4.63); 8.2 (br.s, 1 H, MeNHCO)
8c	78	178—180	65.1 65.3	5.5 5.4	20.5 20.0	$C_{19}H_{19}N_5O_2$	2.1 (3 H, Me); 10.1 (1 H, NH)	5.45	7.20—7.40 (10 H)	4.44 (d, 2 H, $PhC\underline{H}_2NHCO$, *J* = 6.2); 8.8 (br.s, 1 H, $PhCH_2N\underline{H}CO$)
8d	85	156—158	64.4 64.5	5.4 5.0	23.7 23.2	$C_{18}H_{17}N_5O_2$	2.15 (3 H, Me); 10.15 (1 H, NH)	5.50	7.05—7.80 (10 H)	10.05 (s, 1 H, PhNHCO)
8e	85	215—220	47.3 47.7	3.7 3.7	21.7 21.4	$C_{13}H_{12}F_3N_5O_2$	11.5 (1 H, NH)	5.45	7.20—7.35 (5 H)	2.82 (d, 3 H, $\underline{Me}NHCO$, *J* = 4.49); 8.2 (br.s, 1 H, $MeN\underline{H}CO$)
8f	90	170—173	56.2 56.6	4.2 4.0	17.0 17.4	$C_{19}H_{16}F_3N_5O_2$	11.6 (1 H, NH)	5.50	7.15—7.40 (10 H)	4.45 (d, 2 H, $PhC\underline{H}_2NHCO$, *J* = 5.74); 8.80 (br.s, 1 H, $PhCH_2N\underline{H}CO$)
8g	87	165—170	55.0 55.5	3.9 3.6	18.5 18.0	$C_{18}H_{14}F_3N_5O_2$	11.65 (1 H, NH)	5.55	7.05—7.8 (10 H)	10.1 (br.s, 1 H, $\underline{NH}CO$)
9	75	155—157	55.7 55.8	5.4 5.0	23.7 23.2	$C_{14}H_{15}N_5O_3$	2.1 (3 H, Me); 10.25 (1 H, NH)	5.50	7.20—7.35 (5 H)	2.4 (s, 3 H, $\underline{Me}CONHCO$); 9.95 (br.s, 1 H, $MeCON\underline{H}CO$)

group occurred), whereas attempts to perform cyclization under alternative conditions (heating in acetonitrile with P_2O_5 or $POCl_3$, refluxing in toluene in the presence of TsOH with a water trap, heating in $Si(OEt)_4$ and TsOH, refluxing in pure $SOCl_2$) led only to gradual accumulation of the starting nonacylated triazoles **2**.

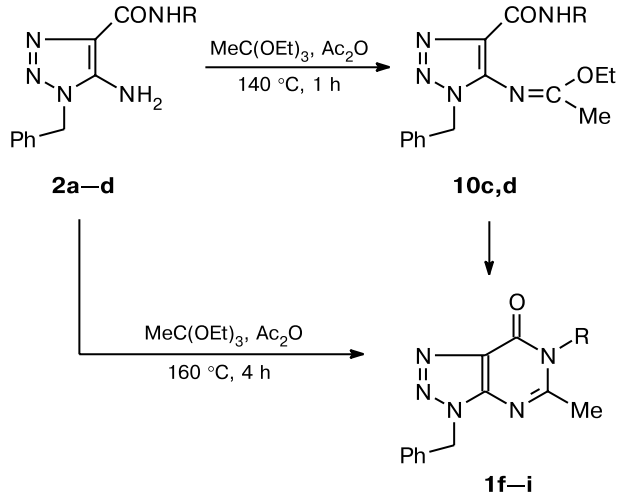
The reactions with trifluoroacetic anhydride afforded *N*-trifluoroacetyl derivatives **8e—g**, which we also failed to subject to cyclization with the formation of TP under all the conditions used (Scheme 6).

Scheme 6



R = Me (**2b**, **8e**), CH_2Ph (**2c**, **8f**), Ph (**2d**, **8g**)

Scheme 7

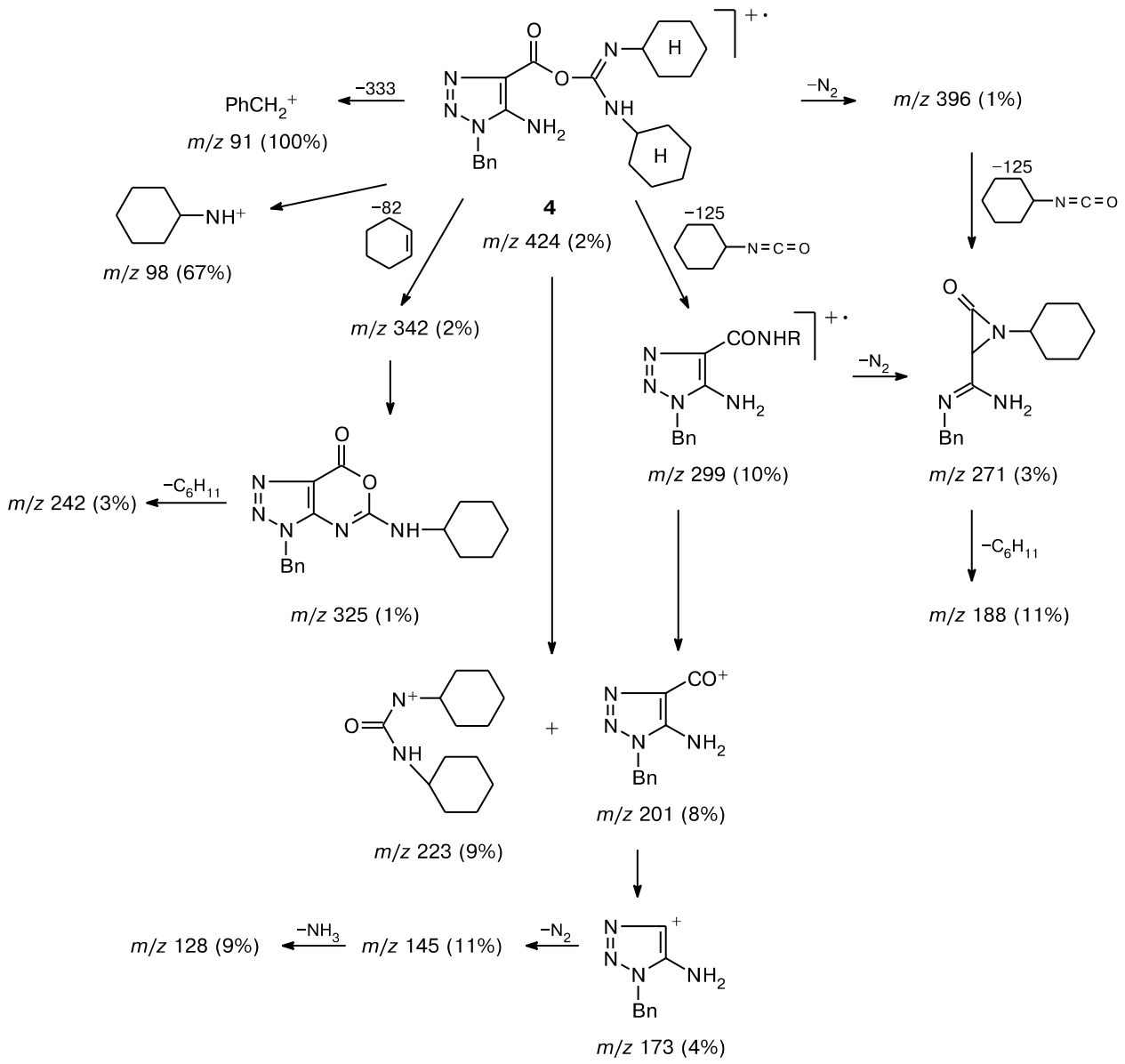


R = H (**1f**, **2a**), Me (**1g**, **2b**), CH_2Ph (**1h**, **2c**, **10c**), Ph (**1i**, **2d**, **10d**)

Triazolopyrimidines **1f—i** were prepared by heating amides **2a—d** with $MeC(OEt)_3$ in the presence of acetic anhydride (160 °C, 4 h). When the reactions were performed at low temperature (130—140 °C, 1 h), compounds **10c,d** were isolated in pure form, the latter being, presumably, intermediates of these reactions (Scheme 7).

The structures of the compounds synthesized were confirmed by ^1H NMR spectroscopy, mass spectrometry, and IR spectroscopy. The CH_2Ph fragment is a common structural element of all the compounds synthesized. The chemical shift of the CH_2 unit for the monocyclic compounds varies within a narrow range (5.30—5.48 ppm), whereas this shift for TP is in the range of 5.68—5.85 ppm, which allows one to readily distinguish between bicyclic and monocyclic structures. The characteristic feature of compounds **8a—d** containing the CH_3CONH fragment is an unusually strong broadening of the signal of the methyl group at δ 2.1—2.15 (up to 40 Hz). The fact that the CN group was formed from the $CONH_2$ fragment in **7a** was confirmed by the IR spectrum in which the CN group is observed at 2240 cm^{-1}. The mass spectrometric study of acids **2** and TPs is rather efficient because all these compounds, including even **4** ($[M]^+$ (424)), give a pronounced molecular ion. Scheme 8 shows the fragmentation of compound **4**. Due to the presence of numerous parallel fragmentation channels, all peaks, except for the peak of $PhCH_2^+$ (100%) and the peak of *cyclo*-$C_6H_{11}NH^+$ (67%),

Scheme 8



as well as the molecular ion by itself have low intensities (<10%).

Experimental

The ^{1}H NMR spectra were recorded on a Bruker WM-250 instrument operating at 250 MHz in DMSO-d_6. The IR spectra were measured on a Specord M80 instrument in KBr. Cyanoacetamides were prepared either by the reactions of cyanoacetic ester with amines at ~20 °C in alcohol or by heating a mixture of cyanoacetic ester and anilines without a solvent at 180—200 °C with distillation of the alcohol formed. Commercial dicyclohexylcarbodiimide (DCC) was used without additional purification.

Reaction of acid 3 with dicyclohexylcarbodiimide. Synthesis of cyclohexylamino(cyclohexylimino)methyl 5-amino-1-benzyl-1,2,3-triazole-4-carboxylate (4). A mixture of acid **3** (0.5 g, 2.3 mmol), DCC (0.5 g, 2.4 mmol), aniline (0.4 g, 4.3 mmol), and acetonitrile (10 mL) was refluxed for 2 h, after which the starting compounds were completely dissolved. The reaction mixture was cooled and kept for some time. Then the precipitate was filtered off. Compound **4** was obtained in a yield of 0.8 g (79%), m.p. 182 °C. MS: M 424 (calculated for $C_{23}H_{32}N_6O_2$: M 424). ^{1}H NMR, δ: 4.4 (t, 1 H, NH—<u>CH</u>$(CH_2)_2$, ^3J = 10.5 Hz); 3.55 (m, 1 H, N—<u>CH</u>$(CH_2)_2$); 2.00—1.10 (m, 10 H, two cyclohexyl rings); 5.51 (s, 2 H, CH_2Ph); 7.30—7.50 (m, 5 H, Ph); 6.60 (br.s, 2 H, NH_2); 7.90 (br.s, 1 H, NH of cyclohexyl). Found (%): C, 65.5; H, 7.9; N, 20.0. $C_{23}H_{32}N_6O_2$. Calculated (%): C, 65.09; H, 7.55; N, 19.81.

Synthesis of 5-amino-1-benzyl-1,2,3-triazole-4-carboxamides (2a—e) (general procedure). Cyanoacetamide (45 mmol) was added with stirring to a solution of KOH (2.8 g, 50 mmol) in alcohol (30 mL) (weak cooling of the solution was observed). After 15 min, a solution of benzyl azide (8.9 g, 67 mmol) in alcohol (20 mL) was added to a suspension (the reaction mixture immediately turned yellow). The reaction mixture was refluxed for 1 h (the precipitate was completely dissolved and then formed in the process of refluxing). The reaction mixture was cooled to ~20 °C. The precipitate was filtered off on a Schott filter and reprecipitated from methanol by adding water (1 : 1, v/v).

The yields, melting points, and ^{1}H NMR spectroscopic data are given in Table 1.

Synthesis of triazolopyrimidin-7-ones (1b—e) under the conditions of the Vilsmeier reaction (general procedure). A suspension of amide **2b—e** (5 mmol) in DMF (5 mL) was cooled to 0—2 °C and then $POCl_3$ (0.85 mL, 1.42 g; 9.3 mmol) was added dropwise with stirring. The resulting solution was stirred at 0 °C for 5 min, at 25 °C for 10 min, and at 80±1 °C for 3 h. Then the reaction solution was cooled to ~20 °C and poured onto ice (~50 g). The precipitate that formed was filtered off and reprecipitated from methanol by adding water (in the course of dissolution in methanol, the mixture was neutralized by a 2 *N* ammonia solution to pH 7).

The yields, melting points, and ^{1}H NMR spectroscopic data are given in Table 2.

Synthesis of 1-benzyl-5-(dimethylaminomethyleneamino)-1,2,3-triazole-4-carboxamides (7c,d) (general procedure). A suspension of amide **2c,d** (5 mmol) in DMF (5 mL) was cooled to 0—2 °C. Then $POCl_3$ (0.85 mL, 1.42 g, 9.3 mmol) was added dropwise with stirring. The resulting solution was stirred at 0 °C for 5 min, at 25 °C for 10 min, and at 80±1 °C for 0.5 h. Then the solution was cooled to ~20 °C and poured onto ice (~50 g). The precipitate that formed was filtered off and reprecipitated from methanol by adding water (in the course of dissolution in methanol, the mixture was neutralized by a 2 *N* ammonia solution to pH 7).

Table 4. Yields, melting points, and data from elemental analysis and ^{1}H NMR spectroscopy of products of condensation with triethyl orthoacetate **3f—i** and **10c,d**

Compound	Yield (%)	M.p. /°C	Found / Calculated (%)			Molecular formula	^{1}H NMR (δ, *J*/Hz)				
			C	H	N		C—CH_3 (s, 3 H)	OCH_2CH_3	CH_2 (s, 2 H)	Ph (m)	Other signals
1f	90	185—187	<u>59.2</u> 59.7	<u>4.9</u> 4.6	<u>28.7</u> 29.0	$C_{12}H_{11}N_5O$	2.45	—	5.75	7.25—7.35 (5 H)	12.5 (br.s, 1 H, <u>NH</u>CO)
1g	40	135—138	<u>60.8</u> 61.2	<u>4.9</u> 5.1	<u>27.8</u> 27.4	$C_{13}H_{13}N_5O$	2.68	—	5.78	7.20—7.30 (5 H)	3.6 (s, 3 H, <u>Me</u>NHCO)
1h	65	170—175	<u>68.7</u> 68.9	<u>5.0</u> 5.1	<u>20.8</u> 21.1	$C_{19}H_{17}N_5O$	2.58	—	5.68	7.15—7.40 (10 H)	5.4 (s, 2 H, <u>CH_2</u>NCO)
1i	72	152—156	<u>69.0</u> 68.1	<u>4.8</u> 4.7	<u>21.8</u> 22.1	$C_{18}H_{15}N_5O$	2.25	—	5.73	7.20—7.60 (10 H)	—
10b	62	160—165	<u>59.5</u> 59.8	<u>6.0</u> 6.3	<u>23.5</u> 23.3	$C_{15}H_{19}N_5O_2$	1.65	1.35 (t, 3 H); 4.30 (d, 2 H, *J* = 7.0)	5.30	7.20—7.40 (5 H)	2.80 (d, 3 H, <u>Me</u>NHCO, *J* = 4.1); 7.90 (br.s, 1 H, MeN<u>H</u>CO)
10c	48	115—117	<u>66.4</u> 66.8	<u>6.2</u> 6.1	<u>18.7</u> 18.6	$C_{21}H_{23}N_5O_2$	1.65	1.35 (t, 3 H); 4.30 (d, 2 H, *J* = 7.0)	5.33	7.15—7.35 (10 H)	4.45 (d, 2 H, PhC<u>H_2</u>NHCO, *J* = 6.2); 8.4 (br.s, 1 H, $PhCH_2N$<u>H</u>CO)

The yields, melting points, and ^{1}H NMR spectroscopic data are given in Table 2.

Acetylation of 5-acetylamino-1-benzyl-1,2,3-triazole-4-carboxamides. Synthesis of 5-acetylamino-1-benzyl-1,2,3-triazole-4-(*N*-R)-carboxamides (8a—d) (general procedure). Amides **2b—d** (3.6 mmol) were suspended in acetonitrile (5 mL). Then acetic anhydride (1.1 g, 11 mmol) and two drops of 57% perchloric acid were added. The suspension was heated to 60 °C and kept at this temperature for 30 min. Then the reaction mixture was cooled. The precipitate that formed was filtered off and recrystallized from ethanol (in the course of heating, the solution was neutralized with an aqueous solution of ammonia to pH 7).

The yields, melting points, and ^{1}H NMR spectroscopic data are given in Table 3.

Synthesis of *N*-substituted acetylamide of 1-benzyl-5-trifluoroacetylamino-1,2,3-triazole-4-carboxylic acid (9). A 57% perchloric acid solution (0.3 mL) was added to a suspension of 4-amino-3-benzyl-1,2,3-triazole-5-carboxamide (**2a**) (1 g, 4.6 mmol), which was preliminarily recrystallized from acetic acid, in acetic anhydride (8 mL). The reaction mixture was heated to 100 °C. After 1 h, the mixture was cooled. The precipitate was filtered off and recrystallized from ethanol (in the course of heating, the solution was neutralized with aqueous ammonia to pH 7). The yield was 0.6 g (43%). The melting points and ^{1}H NMR spectroscopic data are given in Table 3.

Trifluoroacetylation of amides 2b—d. Synthesis of 1-benzyl-5-trifluoroacetylamino-1,2,3-triazole-4-(*N*-R)-carboxamides (8e—h) (general procedure). Trifluoroacetic anhydride (1.95 g, 9.3 mmol) was added to a suspension of amides **2b—d** (3 mmol) in acetonitrile (4 mL). The suspension was heated to 45—50 °C and kept at this temperature for 60 min. The resulting solution was concentrated on a rotary evaporator and the residue was recrystallized from ethanol (in the course of heating, the solution was neutralized with aqueous ammonia to pH 7).

The yields, melting points, and ^{1}H NMR spectroscopic data are given in Table 3.

Synthesis of 5-methyl-substituted 1,2,3-triazolo[4,5-d]pyrimidin-7-ones (1f—i) (general procedure). Aminotriazoles **2** (4.4 mmol) were mixted with acetic anhydride (1 g, 9.8 mmol) and $MeC(OEt)_3$ (0.89 g, 7.4 mmol) in a flask equipped with a thermometer. The reaction mixture was heated to 160 °C and kept at this temperature for 4 h, 1 mL of the solution being distilled from the reaction mixture. After cooling, the reaction mixture that solidified was dissolved in hot ethanol and again cooled. The precipitate that formed was filtered off on a Schott filter. The yields, melting points, and ^{1}H NMR spectroscopic data are given in Table 4.

Synthesis of *N*-substituted 1-benzyl-5-(1-ethoxyethyleneamino)-1,2,3-triazole-4-carboxamides (10) (general procedure). Acid **2** (4.4 mmol) was mixed with acetic anhydride (1 g, 9.8 mmol) and $MeC(OEt)_3$ (0.89 g, 7.4 mmol) in a flask equipped with a thermometer. The reaction mixture was heated to 140 °C and kept at this temperature for 2 h. The reaction mixture was cooled, poured into water, and neutralized with aqueous ammonia to pH 7. The precipitate that formed was filtered off on a Schott filter and recrystallized from toluene. The yields, melting points, and ^{1}H NMR spectroscopic data are given in Table 4.

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