Nucleophilic substitution in the series of (1,2,3-triazol-1-yl)-1,2,5-oxadiazoles. Reactions with N-, O-, and S-nucleophiles

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Methods for the synthesis of amino(1,2,3-triazol-1-yl)-1,2,5-oxadiazoles (aminotriazolylfurazans) with CH_2Cl and $COCH_2Br$ substituents in the triazole ring were developed and nucleophilic substitution for their halogen atom in reactions with N-, O-, and S-nucleophiles were studied. The possibility of displacing the NO_2 group from the furazan and triazole rings in triazolylfurazans by an azido group was investigated. Novel compounds of this series were synthesized; the reaction rate and pathway were found to depend on the nature of the substrate and the reagent and the position of the substituent in isomers.

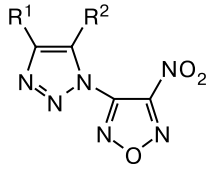
Key words: (1,2,3-triazol-1-yl)-1,2,5-oxadiazoles; nucleophilic substitution; chloromethyl, bromoacetyl, and nitro derivatives; aminoazidofurazan; amines; thiols; thiourea; thioacetamide.

The chemistry of 1,2,3-triazoles and 1,2,5-oxadiazoles (furazans) have been much investigated. Derivatives of these heterocycles attract the attention of researchers as possible starting material for preparation of novel energy-rich and biologically active compounds.[1—4] A possible route to compounds of these series with desired substituents is provided by nucleophilic substitution reactions. For instance, reactions of nitrofurazans with O- and S-nucleophiles have been studied[5,6] and substitution of the N_3 group for chlorine in the CH_2Cl substituent in the 1,2,3-triazole ring has been reported.[7]

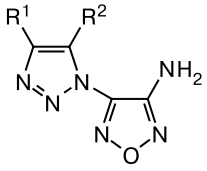
Earlier,[8—11] we have developed methods for the synthesis of (1,2,3-triazol-1-yl)-1,2,5-oxadiazoles, in which the triazole and furazan rings are linked by the N(1′)—C bond. Some reactions of these compounds (*e.g.*, oxidation of the NH_2 group at the furazan ring into NO_2, NO, and N=N groups and transformation of the NH_2 group into an N_3 group *via* diazotization) were investigated.[12] The first example of nucleophilic substitution in triazolylfurazans was displacement of the nitro group at the furazan ring in 4-nitro-3-(4-phenyl-1*H*-1,2,3-triazol-1-yl)-1,2,5-oxadiazole by an amino group in a reaction with morpholine.[12]

Recently,[13] new representatives of triazolylfurazans have been obtained by reactions of aminoazidofurazan with ethyl chloroacetoacetate, also with the use of N-nucleophiles such as hydrazine and secondary amines (dimethylamine, diethylamine, isobutylamine, pyrrolidine, and piperidine). Information on the preparation of the starting chloromethyl substrate in the individual state and its physicochemical characteristics are lacking. A study[13] of the biological activity of the compounds obtained revealed that some of them are promising as selective inhibitors of kinase-3 of glycogen synthase (GSK-3).

The present study was devoted to nucleophilic substitution for some functional substituents in both rings of triazolylfurazans. Substitution for the NO_2 groups in the nitrofurazan and nitrotriazole fragments of triazolylfurazans **1a,b** and for the chlorine and bromine atoms in the CH_2Cl and $BrCH_2CO$ substituents at the triazole ring in compounds **2**—**4** was studied in the presence of various nucleophiles. Additional goals were to substantially extend the range of substituted triazolylfurazans and elucidate the effects of both heterocycles and the nature and position of the substituents on the reactivities of the corresponding functional groups.



1a,b



2a—c, **3a—c**, **4**

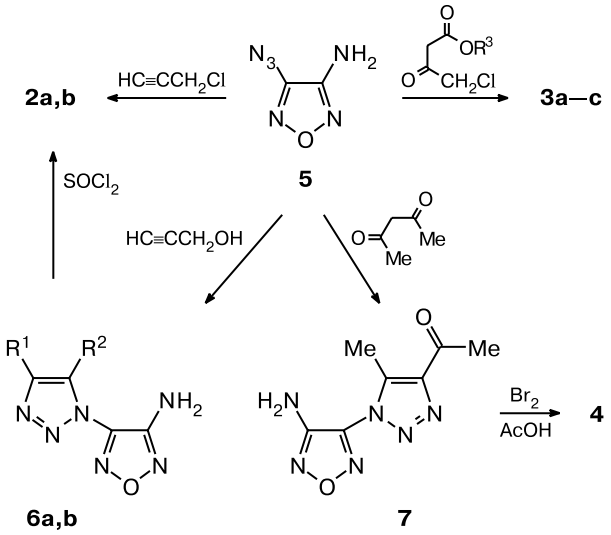
Compound	R^1	R^2	Compound	R^1	R^2
1a	H	CH_2OH	**3a**	CO_2Et	CH_2Cl
1b	NO_2	H	**3b**	CO_2Me	CH_2Cl
2a	CH_2Cl	H	**3c**	CO_2Pr^i	CH_2Cl
2b	H	CH_2Cl	**4**	$C(O)CH_2Br$	Me
2c	NO_2	H			

Nitro compounds **1a,b** and **2c** and chloromethyl derivatives **2a,b** have been synthesized earlier.[8,9,12] Triazolylfurazans **3a—c** and **4** have not been described. The

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 8, pp. 1866—1876, August, 2005.

1066-5285/05/5408-1923

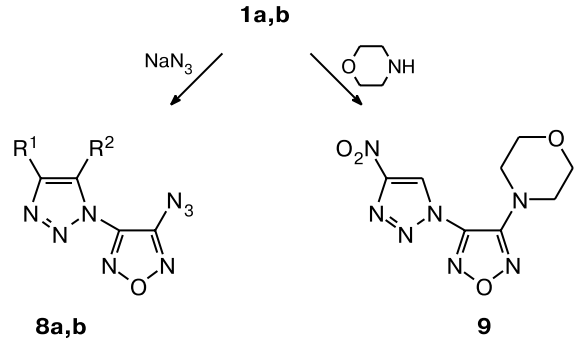
Scheme 1



6: $R^1 = CH_2OH$, $R^2 = H$ (**a**); $R^1 = H$, $R^2 = CH_2OH$ (**b**)

synthesis of chlorides **2a,b** by cycloaddition of 4-amino-3-azidofurazan (**5**) to propargyl chloride[8] allowed only one isomer (**2a**) to be isolated in good yield; for this reason, we employed here an alternative method of preparing compound **2b**. A reaction of the corresponding 5-hydroxymethyl derivative **6b** (obtained from azide **5** and propargyl alcohol) with $SOCl_2$ in $CHCl_3$ in the presence of pyridine (the conditions used for similar transformations in 1,2,3-triazoles[14]) gave isomer **2b** in high yield (Scheme 1). Chlorination of 4-hydroxymethyl derivative **6a** (see Ref. 8) under the same conditions was also efficient. Compounds **3a—c** were synthesized by reactions of 4-amino-3-azidofurazan[15] (**5**) with the corresponding alkyl chloroacetoacetates as described earlier[10] (see Scheme 1). Compound **4** was obtained by the action

Scheme 2



8: $R^1 = H$, $R^2 = CH_2OH$ (**a**); $R^1 = NO_2$, $R^2 = H$ (**b**)

of bromine in AcOH on product **7** prepared by cycloaddition of azide **5** to acetylacetone[10] (see Scheme 1).

The structures of halo derivatives **3a—c** and **4** were proved by ^1H and ^{13}C NMR and IR spectroscopy, mass spectrometry, and elemental analysis (Tables 1—3).

To obtain azides from nitro compounds **1a** and **1b** and chloro derivatives **3a—c**, we studied their reactions with NaN_3. The reactions of compounds **1a** and **1b** with NaN_3 were carried out in MeCN and AcOH (**1a**). It turned out that the reaction in AcOH virtually does not occur; in MeCN, the nitro group at the furazan ring was successfully replaced by an azido group to give the corresponding azides **8a** and **8b** (Scheme 2). The nitro group in the triazole ring of compound **1b** remained intact. Azide **8b** was identified from R_f and the IR spectrum with an authentic sample synthesized[12] by diazotization of the corresponding amine followed by treatment of the diazonium ion with NaN_3. The structure of azide **8a** was proved by elemental analysis and spectroscopic studies (see Tables 1—3). Refluxing of compound **2c** containing, in contrast to dinitro derivative **1b**, the NO_2 group only in

Table 1. Selected physicochemical characteristics of the compounds obtained

Compound	Yield (%) (method)	M.p./°C (solvent)	R_f (eluent)	Found / Calculated (%) C	H	N	Hal	S	Molecular formula
3a	83 (*A*) 90 (*B*)	125—126 (EtOH)	0.39 (PhH—AcOEt, 5 : 1)	35.48 35.24	3.18 3.33	30.51 30.82	13.29 13.00	—	$C_8H_9ClN_6O_3$
3b	76	134—135 (MeOH)	0.38 (PhH—AcOEt, 5 : 1)	33.04 32.51	2.83 2.73	31.99 32.50	14.29 13.71	—	$C_7H_7ClN_6O_3$
3c	81	91—92 (Pr^iOH)	0.44 (PhH—AcOEt, 5 : 1)	38.01 37.71	4.03 3.87	29.04 29.32	12.11 12.37	—	$C_9H_{11}ClN_6O_3$
4	86	170—171 (MeOH)	0.68 (PhH—AcOEt, 5 : 1)	29.52 29.29	2.53 2.46	29.59 29.27	27.64 27.83	—	$C_7H_7BrN_6O_2$
8a	79	59—62 (α) 79—81 (β)	0.36 (CH_2Cl_2—AcOEt, 3 : 1)	29.10 28.86	1.85 1.92	54.03 53.84	—	—	$C_5H_4N_8O_2$

(*to be continued*)

Table 1 (*continued*)

Compound	Yield (%) (method)	M.p./°C (solvent)	R_f (eluent)	Found / Calculated (%)					Molecular formula
				C	H	N	Hal	S	
9	68	210—211 (acetone)	0.60 (PhH—AcOEt, 3 : 1)	35.87 35.96	3.45 3.40	36.50 36.69	—	—	$C_8H_9N_7O_4$
10a	90	90—94 (EtOH)	0.76 (CH_2Cl_2—AcOEt, 3 : 1)	28.78 28.99	2.60 2.41	61.10 60.86	—	—	$C_5H_5N_9O$
10b	97	105—106	0.66 (CH_2Cl_2—AcOEt, 3 : 1)	28.83 28.99	2.30 2.41	61.25 60.86	—	—	$C_5H_5N_9O$
11a	80	81—82 (EtOH)	0.39 (PhH—AcOEt, 5 : 1)	34.59 34.41	3.18 3.25	45.48 45.15	—	—	$C_8H_9N_9O_3$
11b	86	115—116 (MeOH)	0.33 (PhH—AcOEt, 5 : 1)	31.46 31.70	2.58 2.66	47.93 47.54	—	—	$C_7H_7N_9O_3$
11c	83	117—118 (acetone—H_2O, 1 : 1)	0.60 (PhH—AcOEt, 5 : 1)	36.98 36.86	3.91 3.78	43.32 42.99	—	—	$C_9H_{11}N_9O_3$
12a	96	161—162 (EtOH)	0.12 (PhH—AcOEt, 5 : 1)	44.81 44.58	5.41 5.30	30.67 30.33	—	—	$C_{12}H_{17}N_7O_4$
12b	87	156—157 (EtOH)	0.36 (PhH—AcOEt, 5 : 1)	50.37 50.14	6.42 6.31	29.67 29.24	—	—	$C_{14}H_{21}N_7O_3$
12c	94	115—116 (EtOH)	0.30 (PhH—AcOEt, 5 : 1)	48.54 48.85	5.98 5.89	24.55 24.92	—	—	$C_{16}H_{23}N_7O_5$
12d	88	122—123 (EtOH)	0.16 (PhH—AcOEt, 5 : 1)	49.03 48.85	5.74 5.89	24.61 24.92	—	—	$C_{16}H_{23}N_7O_5$
12e	89	140—141 (EtOH)	—	42.41 42.47	5.11 5.05	28.61 28.89	9.29 9.45	—	$C_{12}H_{17}N_7O_3S$
12f	97	161—162	0.43 (PhH—AcOEt, 5 : 1)	53.97 54.08	4.74 4.82	27.40 27.59	—	—	$C_{16}H_{17}N_7O_3$
12g	75	207—208 (EtOH)	0.27 (PhH—AcOEt, 5 : 1)	54.31 54.26	5.52 5.57	28.31 28.12	—	—	$C_{18}H_{22}N_8O_3$
12h	90	139—140	0.53 (PhH—AcOEt, 1 : 1)	48.78 48.59	6.14 5.96	30.18 30.51	—	—	$C_{13}H_{19}N_7O_3$
14	85	183—184 (decomp.)	0.58 (MeOH)	29.53 29.46	2.14 2.06	34.57 34.36	14.57 14.49	—	$C_6H_5ClN_6O_3$
15	68	101—102 (EtOH)	0.56 (PhH—AcOEt, 5 : 1)	50.78 50.91	4.36 4.27	25.69 25.44	—	—	$C_{14}H_{14}N_6O_4$
18a	93.5	211—212 (EtOH)	—	38.05 38.16	4.02 3.91	29.96 29.67	—	11.24 11.32	$C_{18}H_{22}N_{12}O_6S_2$
18b	83	232—233 (EtOH)	0.16 (PhH—AcOEt, 5 : 1)	46.54 46.63	3.74 3.65	29.35 29.00	—	8.21 8.30	$C_{15}H_{14}N_8O_3S$
18c	82	127—128 (EtOH)	0.52 (PhH—AcOEt, 5 : 1)	46.64 46.51	3.29 3.38	25.19 25.31	—	8.36 8.28	$C_{15}H_{13}N_7O_4S$
18d	83	149—150 (EtOH)	0.58 (PhH—AcOEt, 5 : 1)	44.78 44.66	3,34 3.25	24.69 24.30	—	16.01 15.83	$C_{15}H_{13}N_7O_3S_2$
18e	97	145—146 (EtOH)	0.40 (PhH—AcOEt, 5 : 1)	45.07 44.95	3.87 3.77	28.44 28.23	—	9.40 9.23	$C_{13}H_{13}N_7O_3S$
18f	95	143—144 (EtOH)	0.39 (PhH—AcOEt, 5 : 1)	36.53 36.61	3.03 3.07	33.47 33.21	—	10.94 10.86	$C_9H_9N_7O_3S$
18g	87	191—192	0.20 (PhH—AcOEt, 3 : 1)	37.83 37.94	3.51 3.58	33.02 33.19	—	6.04 6.33	$C_{16}H_{18}N_{12}O_6S$
18h	76	170—171 (MeOH)	0.31 (PhH—AcOEt, 5 : 1)	43.37 43.24	3.21 3.33	29.68 29.41	—	9.48 9.62	$C_{12}H_{11}N_7O_3S$
20	87	266—267 (decomp.) (acetone)	0.79 (AcOEt)	36.21 36.36	3.18 3.05	42.57 42.40	—	11.97 12.13	$C_8H_8N_8OS$
21	98	193—194	0.35 (AcOEt)	45.16 45.05	5.23 5.15	33.87 33.43	—	—	$C_{11}H_{15}N_7O_3$

Table 2. ^{1}H and ^{13}C NMR spectra of the compounds obtained

Compound	NMR, δ (*J*/Hz)	
	^{1}H	^{13}C
3a	1.44 (t, 3 H, Me, *J* = 7.4); 4.02 (s, 2 H, CH_2Cl); 4.50 (q, 2 H, CH_2O, *J* = 7.4); 6.41 (s, 2 H, NH_2)	13.91 (Me); 31.50 (CH_2Cl); 61.59 (CH_2O); 138.82 (C(3)); 139.90 (C(5′)); 141.83 (C(4′)); 152.40 (CNH_2); 159.52 (CO)
3b	3.96 (s, 3 H, MeO); 5.17 (s, 2 H, CH_2); 6.75 (s, 2 H, NH_2)	31.52 (Me); 52.73 (CH_2Cl); 136.69; 140.15; 141.95; 152.47 (CNH_2); 160.16 (CO)
3c	1.44 (d, 6 H, 2 Me, *J* = 6.6); 5.14 (s, 2 H, CH_2); 5.30 (sept, 1 H, CH, *J* = 5.3); 6.60 (s, 2 H, NH_2)	21.45 (Me); 31.47 (CH_2Cl); 69.56 (CH); 137.10; 139.79; 141.85; 152.38 (CNH_2); 158.99 (CO)
4	2.68 (s, 3 H, Me); 4.87 (s, 2 H, CH_2); 6.67 (s, 2 H, NH_2)	9.49 (Me); 65.80 (CH_2); 140.25; 140.60; 140.66; 142.23; 152.49 (CNH_2); 194.04 (CO)
8a	4.76 (s, 2 H, CH_2); 5.90 (s, 1 H, OH); 7.90 (s, 1 H, CH)	52.96 (CH_2); 132.98; 141.45; 144.73; 149.73
9	3.10 (br.s, 4 H, $(CH_2)_2O$); 3.60 (br.s, 4 H, $(CH_2)_2N$); 9.90 (s, 1 H, C(5′)H)	47.46 (CH_2N); 65.05 (CH_2O); 128.04; 142.67; 153.69 (CNO_2); 154.56
10a	4.52 (s, 2 H, CH_2); 5.69 (s, 2 H, NH_2); 8.45 (s, 1 H, CH)	44.13 (CH_2); 124.36 (C(5′)H); 143.19 (C(4′)); 144.71 (C(3)); 151.15 (CNH_2)
10b	4.82 (s, 2 H, CH_2); 5.69 (s, 2 H, NH_2); 7.85 (s, 1 H, CH)	42.77 (CH_2); 134.12 (C(4′)H); 135.30 (C(5′)); 142.50 (C(3)); 151.75 (CNH_2)
11a	1.38 (t, 3 H, Me, *J* = 7.1); 4.45 (q, 2 H, CH_2O, *J* = 7.1); 4.99 (s, 2 H, CH_2); 6.69 (s, 2 H, NH_2)	13.99 (Me); 41.65 (CH_2); 61.50 (CH_2O); 137.18 (C(4′)); 138.86 (C(5′)); 142.05 (C(3)); 152.51(CNH_2); 159.67 (CO)
11b	3.96 (s, 3 H, OMe); 5.00 (s, 2 H, CH_2N_3); 6.70 (s, 2 H, NH_2)	41.60 (CH_2N_3); 52.36 (MeO); 137.00 (C(4′)); 138.89 (C(5′)); 142.03 (C(3)); 152.41 (CNH_2); 160.14 (CO)
11c	1.34 (d, 6 H, 2 Me, *J* = 6.6); 4.94 (s, 2 H, C(5′)CH_2); 5.25 (sept, 1 H, CH, *J* = 5.3); 6.71 (s, 2 H, NH_2)	21.43 (Me); 41.65 (CH_2N_3); 69.52 ($\underline{C}Me_2$); 137.53 (C(4′)); 138.58 (C(3)); 142.09 (C(5′)); 152.54 (CNH_2); 159.24 (CO)
12a	1.37 (t, 3 H, Me, *J* = 7.2); 2.30 (s, 4 H, CH_2OCH_2); 3.34 (s, 4 H, (CH_2NCH_2)); 4.00 (s, 2 H, C(5′)CH_2); 4.41 (q, 2 H, Me$C\underline{H}_2O$, *J* = 7.2); 6.54 (s, 2 H, NH_2)	14.10 (Me); 49.91 (C(5′)$\underline{C}H_2$); 52.73 (CH_2N); 61.07 (Me$\underline{C}H_2O$); 65.78 (CH_2O); 136.90 (C(4′)); 142.54 (C(5′)); 143.54 (C(3)); 153.54 (CNH_2); 160.26 (CO)
12b	0.75 (m, 2 H, CH_2); 0.80 (d, 3 H, Me, *J* = 6.4); 1.23 (m, 1 H, CH); 1.35 (q, 3 H, Me, *J* = 7.1); 1.42 (m, 2 H, CH_2); 1.98 (t, 2 H, CH_2, *J* = 10.9); 2.52 (m, 2 H, CH_2); 3.99 (s, 2 H, CH_2); 4.40 (q, 2 H, CH_2, *J* = 7.1); 6.58 (s, 2 H, NH_2)	14.10 ($\underline{Me}CH_2O$); 21.57 (Me); 29.44 (CH); 33.44 (CH_2); 39.51 (CH_2N); 50.15; 52.95; 60.94 (CH_2O); 136.45 (C(4′)); 143.24 (C(5′)); 143.52 (C(3)); 153.37 (CNH_2); 160.20 (CO)
12c	1.17, 1.36 (both t, 3 H each, Me, *J* = 7.0); 1.24, 2.12 (both m, 2 H each, CH_2); 1.52, 1.77, 2.02, 2.52, 2.78 (all m, 1 H each, CH); 4.04 (m, 4 H, 2 CH_2); 4.40 (q, 2 H, CH_2, *J* = 7.0); 6.60 (s, 2 H, NH_2)	13.99, 14.10 (Me); 23.77; 26.11; 39.81; 40.81 (CH); 49.87; 52.72; 54.45; 59.84 (CH_2O); 61.03 (CH_2O); 136.69 (C(4′)); 142.80 (C(5′)); 143.38 (C(3)); 153.35 (CNH_2); 160.18 (C(4′)$\underline{C}O$); 172.75 (CO)
12d	1.19, 1.38 (both t, 3 H each, Me, *J* = 7.1); 1.25, 1.64, 2.07, 2.55 (all m, 2 H each, CH_2); 2.17 (m, 1 H, CH); 3.98 (s, 2 H, CH_2); 4.04, 4.40 (both q, 2 H each, CH_2, *J* = 7.1); 6.56 (s, 2 H, NH_2)	13.81, 13.86 (Me); 27.23; 39.40 (CH); 49.68; 51.79; 59.50 (CH_2O); 60.77 (CH_2O); 136.55 (C(4′)); 142.64 (C(5′)); 143.27 (C(3)); 153.14 (CNH_2); 160.05 (C(4′)$\underline{C}O$); 173.71 (CO)
12e	1.35 (t, 3 H, Me, *J* = 7.1); 2.34, 2.55 (both m, 4 H each, 4 CH_2); 4.00 (s, 2 H, C(5′)CH_2); 4.40 (q, 2 H, CH_2O, *J* = 7.1); 6.50 (s, 2 H, NH_2)	14.00 (Me); 26.70 (CH_2S); 50.40 (C(5′)$\underline{C}H_2$); 54.20 (CH_2N); 61.00 (CH_2O); 136.90 (C(5′)); 142.70 (C(4′)); 143.50 (C(3)); 153.40 (CNH_2);160.20 (CO)
12f	1.37 (t, 3 H, Me, *J* = 7.1); 2.73, 3.13 (both t, 2 H each, CH_2, *J* = 6.1); 4.45 (q, 2 H, CH_2O, *J* = 7.1); 4.77 (s, 2 H, C(5′)CH_2); 6.43 (d, 1 H, Ph, *J* = 8.0); 6.53 (s, 2 H, NH_2); 6.68 (t, 1 H, Ph, *J* = 8.0); 6.95 (m, 2 H, Ph)	14.10 (Me); 27.90 (C(3″)); 42.40 (C(5′)$\underline{C}H_2$); 53.70 (C(2″)); 61.20 (CH_2O); 107.10 (C(7″)); 118.00 (C(4″)); 124.20 (C(5″)); 127.00 (C(6″)); 129.20 (C(3″a)); 136.60 (C(4′)); 142.60 (C(3)); 142.90 (C(5′)); 150.70 (C(7″a)); 153.00 (CNH_2); 160.20 (CO)
12g	1.35 (t, 3 H, Me, *J* = 7.2); 2.50, 2.85 (both s, 4 H each, 4 CH_2); 4.10 (s, 2 H, C(5′)CH_2); 4.45 (q, 2 H, CH_2O, *J* = 7.2); 6.50 (s, 2 H, NH_2); 6.70 (t, 1 H, *p*-Ph, *J* = 7.1); 6.85 (d, 2 H, *o*-Ph, *J* = 7.1); 7.20 (t, 2 H, *m*-PhH, *J* = 7.1)	14.00 (Me); 47.70 (PhN$\underline{C}H_2$); 49.50 (C(5′)$\underline{C}H_2$); 52.10 ($CH_2\underline{C}H_2N$); 60.90 (CH_2O); 115.20 (*o*-Ph); 118.80 (*p*-Ph); 128.70 (*m*-Ph); 136.70 (C(5′)); 142.60(C(3)); 143.40 (C(4′)); 150.60 (CNH_2); 153.40 (*ipso*-Ph); 160.20 (CO)

(*to be continued*)

Table 2 (*continued*)

Compound	NMR, δ (*J*/Hz)	
	^{1}H	^{13}C
12h	1.30 (br.s, 6 H, 2 Me); 1.55, 2.40 (both m, 4 H each, 4 CH_2); 4.20 (s, 2 H, C(5′)CH_2); 5.25 (br.s, 1 H, CH); 6.60 (s, 2 H, NH_2)	21.60 (Me); 23.18 ($NCH_2\underline{C}H_2$); 46.50 (C(5′)$\underline{C}H_2$); 52.90 (NCH_2); 68.70 (CH); 136.40 (C(4′)); 143.20 (C(3)); 143.50 (C(5′)); 153.20 (CNH_2); 159,70 (CO)
14	5.17 (s, 2 H, CH_2); 6.77 (s, 2 H, NH_2)	31.44 (CH_2Cl); 137.49 (C(4′)); 139.60 (C(5′)); 141.83 (C(3)); 152.30 (CNH_2); 160.93 (CO)
15	1.33 (t, 3 H, Me, *J* = 7.1); 4.44 (q, 2 H, CH_2O, *J* = 7.1); 5.59 (s, 2 H, C(5′)CH_2); 6.60 (s, 2 H, NH_2); 6.89 (d, 2 H, Ph, *J* = 8.1); 6.98 (t, 1 H, Ph, *J* = 7.2); 7.30 (t, 2 H, Ph, *J* = 7.8)	14.00 (Me); 58.51 (C(5′)$\underline{C}H_2$); 61.44 (CH_2O); 114.39 (*o*-Ph); 121.86 (*p*-Ph); 129.68 (*m*-Ph); 136.90 (C(4′)); 140.08 (C(5′)); 142.76 (C(3)); 152.92 (CNH_2); 157.01 (*ipso*-Ph); 159.85 (CO)
18a	1.35 (t, 6 H, 2 Me, *J* = 7.0); 2.65 (s, 4 H, CH_2CH_2); 4.28 (s, 4 H, 2 C(5′)CH_2); 4.38 (q, 4 H, 2 CH_2O, *J* = 7.0); 6.62 (s, 4 H, 2 NH_2)	13.81 (Me); 22.13 (C(5′)$\underline{C}H_2$); 30.93 ($S\underline{C}H_2\underline{C}H_2S$); 61.08 ($CH_2O$); 136.05 (C(4′)); 141.89 (C(3)); 142.10 (C(5′)); 152.21 (CNH_2); 159.93 (CO)
18b	1.36 (t, 3 H, Me, *J* = 7.4); 4.36 (q, 2 H, CH_2O, *J* = 7.4); 4.97 (s, 2 H, CH_2S); 6.62 (s, 2 H, NH_2); 7.10, 7.35 (both m, 2 H each, Ph); 12.50 (s, 1 H, NH)	13.92 (Me), 23.42 (CH_2S); 61.22 (CH_2O); 110.42, 117.67 (C_{Ph}—N); 121.28, 121.96 (C_{Ph}); 137.06 (C(4′)); 141.70 (C(5′)); 142.50 (C(3)); 147.62 (C_{Ar}—S); 152.55 (CNH_2); 159.80 (CO)
18c	1.35 (t, 3 H, Me, *J* = 7.4); 4.45 (q, 2 H, CH_2O, *J* = 7.4); 5.05 (s, 2 H, CH_2S); 6.70 (br.s, 2 H, NH_2); 7.30, 7.55 (both m, 2 H each, Ar)	13.97 (Me); 23.70 (CH_2S); 61.39 (CH_2O); 110.10, 118.40, 124.57, 124.69 (C_{Ph}); 137.32 (C(4′)); 140.85 (C(5′)); 142.50 (C(3)); 146.64, 151.46 (C_{Ph}); 152.70 (CNH_2); 159.79 (CO); 162.25 (C_{Ar}—S)
18d	1.30 (t, 3 H, Me, *J* = 7.4); 4.40 (q, 2 H, CH_2O, *J* = 7.4); 5.10 (s, 2 H, CH_2S); 6.70 (br.s, 2 H, NH_2); 7.38, 7.45 (both t, 1 H each, Ph, *J* = 8.4); 7.70, 7.95 (both d, 1 H each, Ph, *J* = 9.1)	13.83 (Me); 24.22 (CH_2S); 61.26 (CH_2O); 121.06, 121.66, 124.77, 126.27 (Ph); 134.95 (C_{Ph}—S); 137.21 (C(4′)); 140.96 (C(5′)); 142.23 (C(3)); 151.91 (C_{Ph}—N); 152.45 (CNH_2); 159.72 (CO); 163.76 (C_{Ar}—S)
18e	1.35 (t, 3 H, Me, *J* = 7.4); 4.40 (q, 2 H, CH_2O, *J* = 7.4); 4.90 (s, 2 H, CH_2S); 6.70 (br.s, 2 H, NH_2); 7.10, 7.20, 7.60, 8.12 (all br.s, 1 H each, Py)	13.90 (Me); 21.00 (CH_2S); 61.00 (CH_2O); 120.30, 121.80 (Py); 136.70 (C(4′)); 142.30 (C(3)); 142.40 (C(5′)); 148.80 (Py); 152.50 (CNH_2); 155.30 (C_{Py}—S); 159.80 (CO)
18f	1.35 (t, 3 H, Me, *J* = 7.4); 4.40 (q, 2 H, CH_2O, *J* = 7.4); 4.90 (s, 2 H, CH_2S); 6.70 (s, 2 H, NH_2)	13.80 (Me); 24.60 (CH_2S); 61.50 (CH_2O); 111.11 (CN); 137.20 (C(4′)); 138.70 (C(5′)); 141.80 (C(3)); 152.00 (CNH_2); 159.40 (CO)
18g	1.32 (br.s, 6 H, 2 Me); 4.35 (br.s, 8 H, 2 CH_2; 2 CH_2O); 6.69 (br.s, 4 H, 2 NH_2)	13.87 (Me); 23.40 (CH_2S); 61.18 (CH_2O); 136.34 (C(4′)); 141.01 (C(5′)); 141.95 (C(3)); 152.19 (CNH_2); 159.83 (CO)
18h	3.96 (s, 3 H, MeO); 4.90 (s, 2 H, CH_2S); 6.67 (s, 2 H, NH_2); 7.06 (t, 1 H, C(5″)H, *J* = 6.1); 7.20 (d, 1 H, C(3″)H, *J* = 8.0); 7.60 (t, 1 H, C(4″)H, *J* = 7.5); 8.16 (d, 1 H, C(6″)H, *J* = 4.0)	21.16 (C(5′)$\underline{C}H_2$); 52.41 (MeO); 120.50 (C(4″)); 122.00 (C(5″)); 136.80 (C(4′)); 137.00 (C(3″)); 142.60 (C(3)); 142.90 (C(5′)); 149.00 (C(6″)); 152.80 (CNH_2); 155.70 (C(2″)S); 160.60 (CO)
20	2.75 (s, 3 H, Me); 6.63 (s, 2 H, NH_2 furazan.); 7.05 (s, 1 H, CH); 7.13 (s, 2 H, NH_2 thiazole.)	9.57 (Me); 103.60 (CH); 132,05; 140.39; 141.40; 142.73; 152.16 (CNH_2, furazan.); 168.94 (CNH_2, thiazole.)
21	2.57 (br.s, 4 H, CH_2OCH_2); 2.68 (s, 3 H, Me); 3.61 (br.s, 4 H, $(CH_2)_2N$); 3.98 (s, 2 H, CH_2CO); 6.65 (s, 2 H, NH_2)	9.52 (Me); 53.11; 63.91; 66.16; 140.42; 141.75; 142.17; 152.34 (CNH_2); 191.42 (CO)

the triazole ring with NaN_3 in MeCN recovered the starting compound.

It should be noted that azide **8a**, like previously reported amino(triazolyl)furazans[8,9] with the NO_2 (**2c**) and CH_2OH groups (**6a**) in position 4 of the triazole ring, yields two interconvertible forms arbitrarily denoted as α (lower-melting, m.p. 59—62 °C) and β (higher-melting, m.p. 79—81 °C), depending on the solvent nature. Also, the IR spectra of their crystalline samples are different. Azide **8a** obtained as the α-form was converted into the β-form upon refluxing in CCl_4, MeCN, or cyclohexane; in turn, the β-form was completely (or partially in benzene) converted into the α-form upon refluxing in hexane or heptane. The distinguishing absorption bands in the IR spectra of the β-form appear at 1370, 1350, 1320, 980, 970, and 840 cm^{-1}, while those for the α-form appear at 1450, 1430, 1305, 1280, and 1165 cm^{-1}. The ability of 1,2,3-triazoles to exist in two forms was discovered[16] for methyl 5-chloro-1-phenyl-1*H*-1,2,3-triazole-4-carboxylate.

As noted earlier,[12] the nitro group in 4-nitro-3-(4-phenyl-1*H*-1,2,3-triazol-1-yl)-1,2,5-oxadiazole is success-

Table 3. IR and mass spectra of the compounds obtained

Compound	IR, ν/cm^{-1}	MS, m/z (I_{rel} (%))
3a	3440, 3345, 3060, 3000, 1750 (CO), 1650, 1570, 1540, 1480, 1460, 1390, 1355, 1310, 1280, 1260, 1180, 1100, 1060, 1020, 920, 880, 850, 820, 770, 730, 710	272 $[M]^+$ (23), 254 (9), 209 $[M - N_2 - Cl]^+$, 168 $[M + 1 - EtO - N_2 - NO]^+$ (34), 54 (100)
3b	3400, 3300, 3000, 1752 (CO), 1632, 1572, 1452, 1260, 1160, 1112, 1032, 996, 872, 820, 728, 712	258 $[M]^+$ (15), 228 (6), 200 (2), 194 (15), 49(100)
3c	3430, 3335, 3055, 2985, 2935, 1740 (CO), 1635, 1580, 1565, 1450, 1385, 1300, 1270, 1150, 1100, 1030, 990, 872, 848, 728, 712	286 $[M]^+$ (8), 227 $[M- N_2H - NO]^+$ (15), 181 (20), 150 (22), 43(100)
4	3408, 3312, 2944, 1704 (CO), 1644, 1600, 1553, 1408, 1384 1304, 1192, 1100, 972, 864, 736	286 $[M - 1]^+$ (21), 258 $[M - 1 - N_2]^+$ (16), 228 $[258 - N_2 - NO]^+$ (11), 201 (38), 165 (73), 149 (87), 67 (100)
8a	α-form: 3365, 3140, 2155 (N_3), 1600, 1580, 1545, 1450, 1430, 1390, 1340, 1305, 1280, 1230, 1165, 1100, 1080, 1063, 1050, 985, 880, 790 β-form: 3340, 2165 (N_3), 1600, 1580, 1545, 1440, 1400, 1370, 1350, 1320, 1185, 1120, 1090, 1075, 1060, 1035, 980, 970, 880, 840	—
9	3112 (CH triazole.), 2992, 2936, 2868, 1588, 1552, 1524, 1460, 1444, 1400, 1380, 1344, 1308, 1296, 1260, 1204, 1104, 1064, 1028, 980, 940, 832	267 $[M]^+$ (10), 239 $[M - N_2]^+$ (29), 100 (100)
10a	3450, 3350, 3110, 2115 (N_3), 1650, 1600, 1580, 1345, 1270, 1260, 1250, 1190, 1070, 1050, 985, 840, 780	—
10b	3464, 3332, 3148, 2124 (N_3), 1636, 1584, 1356, 1308, 1280, 1088, 1060, 976, 868, 856	—
11a	3408, 3316, 2984, 2140 (N_3), 2104 (N_3), 2072, 1720 (CO), 1640, 1624, 1568, 1448, 1240, 1132, 1096, 1040, 968, 848	—
11b	3416, 3316, 3020, 2964, 2880, 2144 (N_3), 2112 (N_3), 1724 (CO), 1636, 1584, 1452, 1248, 1132, 1040, 996, 972, 876, 800, 748	—
11c	3460, 3324, 2988, 2176 (N_3), 2140 (N_3), 2112 (N_3), 2080, 1736 (CO), 1628, 1588, 1568, 1452, 1388, 1288, 1248, 1220, 1184, 1096, 1040, 992, 964, 916, 848, 796, 756, 728	—
12a	3452, 3272, 3228, 2980, 2960, 2944, 2872, 2832, 1728 (CO), 1632, 1588, 1568, 1454, 1360, 1280, 1260, 1228, 1216, 1132, 1104, 1072, 1040, 1004, 972, 916, 868, 812, 784	323 $[M]^+$ (1), 278 (1), 100 (100), 86 (8), 56 (21)
12b	3452, 3272, 3104, 2978, 2932, 2856, 2784, 1728 (CO), 1628, 1592, 1568, 1452, 1308, 1264, 1248, 1228, 1216, 1128, 1104, 1044, 988, 860, 772	335 $[M]^+$ (1), 290 $[M - EtO]^+$ (1), 134 (7), 112 (100)
12c	3452, 3092, 2984, 2952, 2868, 2815, 1732 (CO), 1628, 1452, 1372, 1300, 1272, 1232, 1184, 1116, 1052, 1028, 988, 860, 812, 788	393 $[M]^+$ (1), 365 $[M - N_2]^+$ (1), 348 (3), 171 (11), 170 (100), 156 (24)
12d	3452, 3090, 2984, 2948, 2820,1732 (CO), 1628, 1588, 1568, 1452, 1304, 1260, 1248, 1208, 1168, 1124, 1096, 1052, 1040, 988, 860, 776	393 $[M]^+$ (1), 348 $[M - EtO]^+$ (7), 171 (13), 170 (100), 156 (24)
12e	3448, 3180, 2976, 2820, 1724 (CO), 1628, 1584, 1568, 1452, 1380, 1292, 1240, 1196, 1132, 1104, 1036, 988, 952, 912, 848, 776	—
12f	3464, 3336, 2972, 2936, 2864, 1732 (CO), 1628, 1584, 1564, 1484, 1444, 1376, 1300, 1252, 1208, 1128, 1092, 1040, 1016, 988, 868, 776, 752, 716	355 $[M]^+$ (2), 168 (5), 167 (14), 132 (100), 118 (26)
12g	3456, 3272, 3100, 2944, 2832, 1724 (CO), 1632, 1600, 1588, 1564, 1504, 1448, 1350, 1292, 1268, 1244, 1224, 1180, 1124, 1100, 1036, 984, 920, 856, 792, 756, 692	—
12h	3468, 2976, 2844, 2804, 1716 (CO), 1632, 1568, 1444, 1376, 1308, 1248, 1232, 1132, 1096, 1036, 988, 912, 848	321 $[M]^+$ (3), 293 $[M - N_2]^+$ (1), 262 $[M - N_2H - NO]^+$ (5), 236 (1), 203 (4), 84 (100)
14	3424, 3300, 2867, 2760, 2534, 1716 (CO), 1640, 1588, 1568, 1432, 1260, 1220, 1184, 1104 1032, 996, 892, 768	244 $[M]^+$ (50), 227 $[M - OH]^+$ (4), 200 $[M - CO_2]^+$ (62), 44 (CO) (100)

(*to be continued*)

Table 3 (*continued*)

Compound	IR, ν/cm^{-1}	MS, m/z (I_{rel} (%))
15	3468, 3444, 2988, 1736 (CO), 1628, 1600, 1588, 1572, 1496, 1448, 1376, 1268, 1240, 1212, 1036, 984, 860, 844, 788, 752, 688	330 $[M]^+$ (22.6), 301 $[M - N_2H]^+$ (1), 226 (45), 163 (53), 138 (52), 107 (91), 93 (14), 77 (Ph) (100)
18a	3408, 3312, 2984, 1708 (CO), 1640, 1628, 1592, 1564, 1444, 1416, 1372, 1304, 1272, 1164, 1132, 1032, 988, 868, 848, 796, 716	566 $[M]^+$ (1), 329 (47), 301(52), 269 (48), 133 (100)
18b	3448, 3268, 3232, 2984, 1736 (CO), 1636, 1560, 1472, 1452, 1408, 1384, 1356, 1268, 1260, 1220, 1184, 1112, 1100, 1036, 1008, 992, 864, 848, 772, 756, 708	—
18c	3476, 3428, 3328, 2984, 1732 (CO), 1632, 1584, 1560, 1500, 1380, 1300, 1256, 1236, 1220, 1176, 1136, 1096, 1032, 988, 740	387 $[M]^+$ (40), 359 $[M - N_2]^+$ (19), 329 $[M - NO - N_2]^+$ (12), 283 (12), 179 (10), 164 (35), 150 (73), 122 (100)
18d	3480, 3436, 2996, 1740 (CO), 1632, 1584, 1560, 1452, 1276, 1240, 1184, 1136, 1096, 1032, 988, 868, 848, 740	403 $[M]^+$ (5), 375 (2), 302 (17), 167 (93), 148 (9), 134 (16), 108 (100)
18e	3412, 3312, 3040, 2992, 1740 (CO), 1624, 1556, 1456, 1416, 1384, 1268, 1240, 1224, 1188, 1128, 1088, 1032, 988, 872, 844, 796, 776, 724	—
18f	3440, 3328, 3024, 3000, 2972, 2168 (CN), 1700 (CO), 1636, 1596, 1560, 1452, 1352, 1280, 1180, 1112, 1032, 984, 868, 848, 796, 716	295 $[M]^+$ (35), 250 $[M - EtO]^+$ (7), 238 (2), 150 (100)
18g	3460, 3348, 2984, 1720 (CO), 1632, 1568, 1448, 1272, 1028, 988	506 $[M]^+$ (10), 269 (18), 238 (100), 210 (15), 163 (30), 98 (28)
18h	3484, 3324, 2956, 1728 (CO), 1628, 1580, 1560, 1452, 1416, 1388, 1260, 1220, 1124, 1096, 1032, 988, 872, 788, 764, 716	—
20	3472, 3408, 3364, 3248, 3115, 1628, 1580, 1528, 1304, 1128, 976, 840	264 $[M]^+$ (19), 206 (50), 179 (80), 151 (70), 109 (81), 69 (100)
21	3440, 3284, 3240, 3196, 2972, 2932, 2864, 2808, 1700 (CO), 1632, 1588, 1556, 1452, 1408, 1388, 1296, 1212, 1176, 1112, 1088, 1036, 964, 920, 864, 776	—

fully replaced by the morpholine fragment. We demonstrated here that a reaction of dinitro compound **1b** with morpholine yields 4-morpholinofurazan (**9**) (see Scheme 2, Tables 1—3).

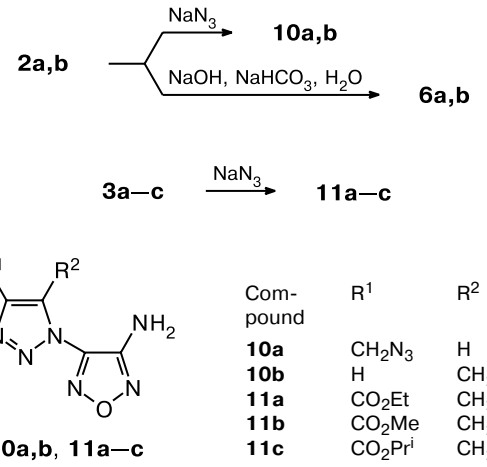
We tried to convert isomeric compounds **2a** and **2b** containing the CH_2Cl group in positions 4 and 5, respectively, into azides **10a** and **10b** by a reaction with NaN_3 in boiling MeCN (Scheme 3). Monitoring of the reaction by TLC was impossible because the retention factors (R_f) of the reaction products and the starting chlorides were equal. The course of the reaction was monitored by ^1H NMR spectroscopy. It was found that both isomers afford the corresponding azido derivatives **10a** and **10b** in high yields; the 4-isomer **2a** is more reactive than the 5-isomer **2b**, which is evident from the times of the reaction completion.

Reactions of 5-chloromethyl derivatives **3a—c** with NaN_3 in boiling aqueous solutions of ethanol or acetone gave the corresponding azides **11a—c** (see Scheme 3, Tables 1—3).

With the aim of obtaining 5-aminomethyl derivatives **12** from compounds **3a—c**, we studied reactions of the latter with various heterocyclic amines **13**.

Reactions of amines **13a—g** (morpholine (**13a**), 4-methylpiperidine (**13b**), ethyl piperidine-3- (**13c**) and -4-carboxylates (**13d**), thiomorpholine (**13e**), indoline (**13f**), and *N*-phenylpiperazine (**13g**)) with compound **3a** as an example were carried out with a slight excess of the amine (1 : 1.3) in the presence of $NaHCO_3$ (1 : 1.4) or with a double excess of the amine (1 : 2.2) in the absence of $NaHCO_3$. Substitution products **12a—g** were obtained

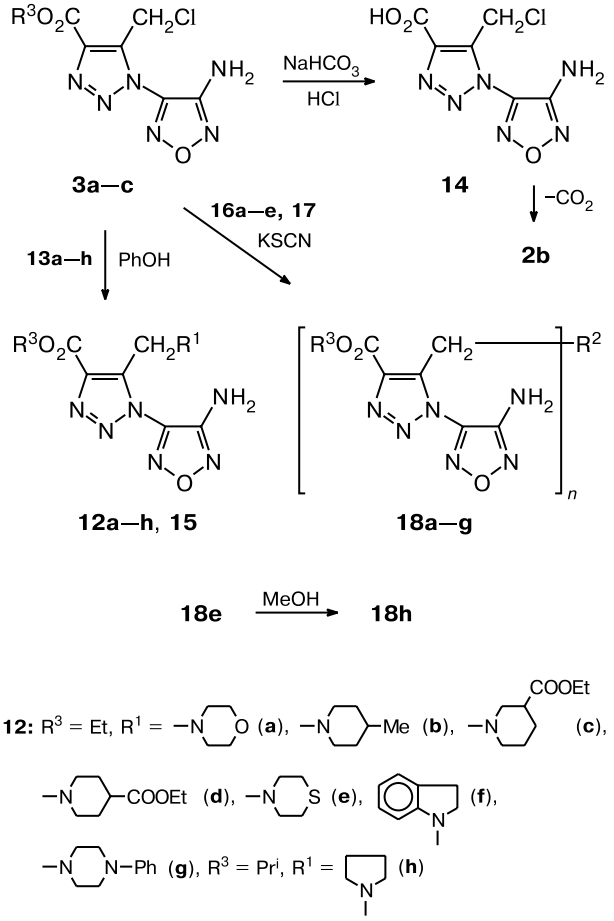
Scheme 3



Compound	R^1	R^2
10a	CH_2N_3	H
10b	H	CH_2N_3
11a	CO_2Et	CH_2N_3
11b	CO_2Me	CH_2N_3
11c	CO_2Pr^i	CH_2N_3

in good yields (Scheme 4). The reaction of chloromethyl derivative **3c** with pyrrolidine (**13h**) afforded product **12h** (see Scheme 4). The structures of compounds **12a—h** were proved by elemental analysis and spectroscopic studies (see Tables 1—3).

Scheme 4



12: R^3 = Et, R^1 = N(O) (**a**), N–Me (**b**), N–COOEt (**c**), N–COOEt (**d**), N(S) (**e**), indolyl (**f**), N–Ph (**g**), R^3 = Pr^i, R^1 = pyrrolyl (**h**)

15: R^1 = OPh, R^3 = Et

18: n = 2, R^3 = Et, R^2 = SCH_2CH_2S (**a**); n = 1, R^3 = Et, R^2 = benzimidazolyl-2-thio (**b**), benzoxazolyl-2-thio (**c**), benzothiazolyl-2-thio (**d**), pyridyl-2-thio (**e**), SCN (**f**); n = 2, R^3 = Et, R^2 = S (**g**); n = 1, R^3 = Me, R^2 = pyridyl-2-thio (**h**)

An investigation of reactions of 4- and 5-chloromethyl derivatives **2a,b** and **3a,b** with O-nucleophiles (in particular, with water and phenol) revealed that the reactivity of the Cl atom depends on the position of the CH_2Cl group in the triazole ring, the nature of the reagent, and the presence of the COOEt group (**3a**).

Hydrolysis of isomeric chlorides **2a** and **2b**, as well as their mixtures, was carried out in boiling water or aqueous 0.1 *N* NaOH and 1 *N* $NaHCO_3$. Both the isomers were hydrolyzed completely in alkaline and bicarbonate solutions; in water, they behaved differently: the 4-isomer was hydrolyzed completely, while the 5-isomer, only slightly. The results obtained were used to find appropriate conditions for the preparation of hydroxymethyl derivatives **6a** and **6b** in high yields (see Scheme 3). In the case of chloride **2a**, compound **6a** was obtained as a mixture of two crystalline α- and β-forms[8] or as either individual form,[8] depending on the hydrolysis conditions. For instance, hydrolysis of chloride **2a** in $NaHCO_3$ gave compound **6a** as the α- (72%) and β-forms (22%), while hydrolysis in NaOH afforded only the β-form (78%).

Attempted displacement of the Cl atom from compound **3b** by the OH group in boiling water failed. In a boiling aqueous solution of $NaHCO_3$ used in an equimolar amount, the ester group was hydrolyzed to give acid **14** in high yield (see Scheme 4, Tables 1—3); its decarboxylation in boiling AcOH yielded product **2b**, which was spectroscopically identical with an authentic sample.[8]

A reaction of compound **3a** with phenol in boiling EtOH gave substitution product **15** (see Scheme 4, Tables 1—3).

We studied reactions of chloromethyl derivative **3a** with thiols **16a—e** (ethane-1,2-dithiol (**16a**), benzimidazole-2-thiol (**16b**), benzoxazole-2-thiol (**16c**), benzothiazole-2-thiol (**16d**), and pyridine-2-thiol (**16e**)), KSCN, and thioacetamide **17**. The reactions with the thiols and amide **17** were carried out in boiling EtOH (3—6 h) in the presence of K_2CO_3 or $NaHCO_3$. The reagents were used in the following molar ratios:

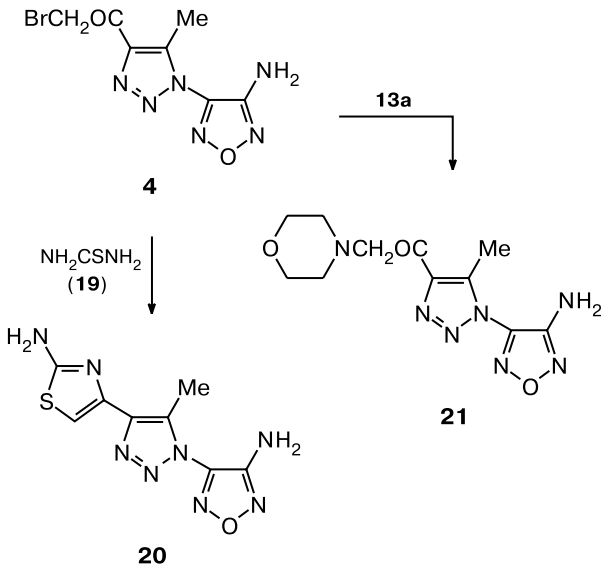
Reagents	Ratio
3a : **16a** : K_2CO_3	2.1 : 1.0 : 1.0
3a : **16b—d** : K_2CO_3	1.0 : 1.1 : 0.5
3a : **16e** : $NaHCO_3$	1.0 : 1.1 : 1.0
3a : **17** : K_2CO_3	1.0 : 1.2 : 0.5

In the reaction with KSCN, its double excess was used. The resulting substitution products **18a—g** were obtained in high yields (82—97%) (see Scheme 4). The formation of compound **18g** involves two molecules of chloride **3a**: one interacts with the thiol form of thioacetamide, while the other, with their adduct; apparently, MeCN is detached. In boiling MeOH, compound **18e** underwent transesterification to give compound **18h**. Like known diamines of the furazan series,[17—19] diamines **18a** and **18g** (see Scheme 4) are of interest as starting material for the synthesis of the corresponding macrocyclic compounds containing the N=N fragment.

The reactivity of bromoacetyl derivative **4** toward nucleophilic reagents were studied in reactions with

morpholine (**13a**) and thiourea (**19**). It is known[20,21] that reactions of haloacetyltriazoles and -furazans with thiourea give rise to an aminothiazole fragment. The reaction of compound **4** with thiourea in acetone in the presence of K_2CO_3 yielded diamine **20** containing a thiazole ring (Scheme 5). The reaction of compound **4** with a double excess of morpholine in boiling EtOH gave substitution product **21** (see Scheme 5). The physicochemical characteristics of compounds **18a—h**, **20**, and **21** are given in Tables 1—3.

Scheme 5



The ^{1}H NMR spectra of the compounds obtained (see Table 2) show signals at δ 5.7—6.8 for the NH_2 group bound to the furazan ring and at δ 4.0—5.6 for the CH_2 group in the CH_2R substituents to the triazole ring; for triazolylfurazans with the COOEt group, signals for the CH_2O fragment and the Me group appear at δ 4.4—4.5 and 1.4—1.5, respectively. The ^{13}C NMR spectra of the compounds bearing the ester and oxo groups show signals for the carbonyl group at δ 159.3—160.6 and 191.5—194.1, respectively. In the IR spectra of these compounds, the absorption bands of the carbonyl group appear at 1700—1755 cm^{-1}.

Thus, in the present study, we obtained novel triazolylfurazans with the $COCH_2Br$ and CH_2Cl groups in the triazole ring by 1,3-dipolar cycloaddition of aminoazidofurazan to acetylacetone followed by bromination of the reaction product or to alkyl chloroacetoacetates. The reactions of these compounds and earlier synthesized hydroxymethyl and nitro derivatives with N-, S-, and O-nucleophiles afforded a large number of substituted triazolylfurazans, which are promising for use in further transformations.

Experimental

The course of the reactions was monitored and the purity of the compounds obtained was checked by TLC on Silufol UV-254 plates (Czechoslovakia). IR spectra (pellets with KBr) were recorded on UR-20 and Specord M-80 spectrometers. ^{13}C and ^{1}H NMR spectra (DMSO-d_6) were recorded on Bruker WM-250 (62.80 and 250 MHz, respectively), Bruker AM-300 (75.5 and 300 MHz, respectively), and Bruker DRX-500 spectrometers (500 MHz (^{1}H)). ^{13}C and ^{1}H chemical shifts were measured with reference to DMSO-d_6 (δ(^{13}C) 39.50; δ(^{1}H) 2.50). Mass spectra were recorded on a Varian MAT CH-6 instrument. Melting points were determined on a Boetius hot stage.

Synthesis of chloromethyl derivatives 2a,b and 3a—c. Chlorination of hydroxymethyl derivatives 6a and 6b

3-Amino-4-(4-chloromethyl-1*H*-1,2,3-triazol-1-yl)-1,2,5-oxadiazole (2a). Pyridine (0.6 mL, 75 mmol) and freshly distilled $SOCl_2$ (5 mL, 75 mmol) were added dropwise at 2—5 °C to a suspension of compound **6a** (0.85 g, 4.67 mmol) in $CHCl_3$ (75 mL). The reaction mixture was stirred at room temperature (~20 °C) for 1 h. The solvent was removed *in vacuo* and ice water (100 mL) was added to the residue (oil with crystals). The precipitate was filtered off, washed with water, and dried in air to give chloride **2a** (0.87 g, 92.9%) (see Ref. 8).

3-Amino-4-(5-chloromethyl-1*H*-1,2,3-triazol-1-yl)-1,2,5-oxadiazole (2b). Pyridine (1.2 mL, 150 mmol) and freshly distilled $SOCl_2$ (10 mL, 150 mmol) were added dropwise at 2—5 °C to a suspension of compound **6b** (1.71 g, 9.4 mmol) in $CHCl_3$ (110 mL). Cooling was stopped and the reaction mixture was stirred at ~20 °C for 5 h. The mixture still containing the starting reagent was allowed to stand for 16 h; after one day, the solvent was removed *in vacuo*. The residue was treated as described for compound **2a** to give chloride **2b** (1.74 g, 92.5%) (see Ref. 8).

Ethyl 1-(4-amino-1,2,5-oxadiazol-3-yl)-5-chloromethyl-1*H*-1,2,3-triazole-4-carboxylate (3a). ***A.*** A solution of azide **5** (3.5 g, 27.8 mmol) (see Ref. 15) and ethyl chloroacetoacetate (4.57 g, 27.8 mmol) in acetone (20 mL) was stirred at ~20 °C for 1 h in the presence of K_2CO_3 (0.5 g, 3.62 mmol). Then water (50 mL) was added with stirring. The precipitate that formed was filtered off and washed with water and ether. The yield of compound **3a** was 6.3 g.

B. A mixture of azide **5** (1 g, 7.93 mmol) (see Ref. 15), ethyl chloroacetoacetate (1.39 g, 9.53 mmol), and $MgCO_3$ (0.3 g, 3.57 mmol) in EtOH (50 mL) was refluxed for 3 h. The hot solution was filtered to remove inorganic salts and then evaporated to dryness. The residue was washed with water and ether. The yield of compound **3a** was 1.96 g.

Methyl 1-(4-amino-1,2,5-oxadiazol-3-yl)-5-chloromethyl-1*H*-1,2,3-triazole-4-carboxylate (3b). The reaction of azide **5** (2.47 g, 19.6 mmol) (see Ref. 15) with methyl chloroacetoacetate (2.95 g, 19.6 mmol) was carried out in acetone (20 mL) in the presence of K_2CO_3 (0.2 g, 1.45 mmol) by analogy with the synthesis of compound **3a** (*A*). The yield of chloride **3b** was 3.85 g.

Isopropyl 1-(4-amino-1,2,5-oxadiazol-3-yl)-5-chloromethyl-1*H*-1,2,3-triazole-4-carboxylate (3c). The reaction of azide **5** (1 g, 7.93 mmol) (see Ref. 15) with isopropyl chloroacetoacetate (1.7 g, 9.52 mmol) was carried out in acetone (10 mL) in the

presence of K_2CO_3 (0.3 g, 2.17 mmol) by analogy with the synthesis of compound **3a** (*A*). The yield of compound **3c** was 1.85 g.

1-[1-(4-Amino-1,2,5-oxadiazol-3-yl)-5-methyl-1*H*-1,2,3-triazol-4-yl]-2-bromoethanone (4). A solution of Br_2 (0.77 g, 4.81 mmol) in AcOH (10 mL) was added at 5—10 °C to a stirred solution of ketone **7** (1 g, 4.81 mmol) (see Ref. 10) in glacial AcOH (25 mL). After 30 min, water (10 mL) was added dropwise. The precipitate that formed was filtered off, washed with water, and dried in air to give compound **4** (1.19 g).

Reactions of nitro derivatives 1a and 1b with NaN_3

1-(4-Azido-1,2,5-oxadiazol-3-yl)-1*H*-1,2,3-triazol-5-ylmethanol (8a). Sodium azide (0.48 g, 7.36 mmol) was added at ~20 °C to a stirred solution of nitro compound **1a** (0.78 g, 3.68 mmol) in MeCN (30 mL). After the starting reagent was consumed completely (TLC data), the inorganic precipitate was filtered off and the filtrate was evaporated to dryness *in vacuo*. The yield of azide **8a** (α-form[8]) was 0.6 g.

4-Azido-3-(4-nitro-1*H*-1,2,3-triazol-1-yl)-1,2,5-oxadiazole (8b) was obtained from dinitro derivative **1b** and NaN_3 as described for compound **8a** (see Ref. 12).

Reaction of compound 1b with morpholine. 5-Morpholino-4-(4-nitro-1*H*-1,2,3-triazol-1-yl)-1,2,5-oxadiazole (9). A solution of morpholine (1.53 g, 17.6 mmol) in benzene (30 mL) was added dropwise for 2 h to a stirred solution of compound **1b** (1 g, 4.4 mmol) in benzene (50 mL). After 2 h, the precipitate was filtered off, the mother liquor was evaporated to dryness, and the solid residue was washed with water and dried in air to give compound **9** (0.8 g).

Reactions of compounds 2a and 2b with NaN_3

3-Amino-4-(4-azidomethyl-1*H*-1,2,3-triazol-1-yl)-1,2,5-oxadiazole (10a). A mixture of compound **2a** (0.1 g, 0.5 mmol) and NaN_3 (0.1 g, 1.53 mmol) in MeCN (10 mL) was refluxed for 1 h. The precipitate was filtered off and the mother liquor was concentrated *in vacuo*. The oily residue that crystallized in air was washed with water and dried in air to give azide **10a** (0.09 g).

3-Amino-4-(5-azidomethyl-1*H*-1,2,3-triazol-1-yl)-1,2,5-oxadiazole (10b). A mixture of compound **2b** (0.3 g, 1.5 mmol) and NaN_3 (0.20 g, 3 mmol) in MeCN (20 mL) was refluxed for 4 h. The precipitate was filtered off, the mother liquor was evaporated to dryness *in vacuo*, and the residue was washed with water and dried in air to give azide **10b** (0.29 g).

Reactions of compounds 3a—c with NaN_3

Ethyl 1-(4-amino-1,2,5-oxadiazol-3-yl)-5-azidomethyl-1*H*-1,2,3-triazole-4-carboxylate (11a). A solution of compound **3a** (0.5 g, 1.83 mmol) and NaN_3 (0.14 g, 2.2 mmol) in EtOH—H_2O (1 : 1, 30 mL) was refluxed for 2 h. The precipitate that formed at room temperature was filtered off and washed with water to give azide **11a** (0.41 g).

Methyl 1-(4-amino-1,2,5-oxadiazol-3-yl)-5-azidomethyl-1*H*-1,2,3-triazole-4-carboxylate (11b). A solution of compound **3b** (0.5 g, 1.93 mmol) and NaN_3 (0.15 g, 2.3 mmol) in acetone—water (1 : 1) was refluxed for 2 h. Water (30 mL) was added without cooling the mixture. The precipitate that formed was filtered off and washed with water to give azide **11b** (0.44 g).

Isopropyl 1-(4-amino-1,2,5-oxadiazol-3-yl)-5-azidomethyl-1*H*-1,2,3-triazole-4-carboxylate (11c) was obtained from chloride **3c** (0.19 g, 0.66 mmol) and NaN_3 as described for compound **11b**. The yield of azide **11c** was 0.16 g.

Reactions of compound 3a with amines 13a—g

Synthesis of amino derivatives 12a—f. A mixture of compound **3a** (1 g, 3.67 mmol) with a double excess of the corresponding amine (**13a—f**) was refluxed in EtOH (30 mL) for 3 to 8 h. Water (30 mL) was added at ~20 °C and the precipitate that formed was filtered off and washed with water and cold ether to give **ethyl 1-(4-amino-1,2,5-oxadiazol-3-yl)-5-morpholinomethyl-1*H*-1,2,3-triazole-4-carboxylate (12a)** (1.13 g), **ethyl 1-(4-amino-1,2,5-oxadiazol-3-yl)-5-(4-methylpiperidinomethyl)-1*H*-1,2,3-triazole-4-carboxylate (12b)** (1.07 g), **ethyl 1-(4-amino-1,2,5-oxadiazol-3-yl)-5-(3-ethoxycarbonylpiperidinomethyl)-1*H*-1,2,3-triazole-4-carboxylate (12c)** (1.35 g), **ethyl 1-(4-amino-1,2,5-oxadiazol-3-yl)-5-(4-ethoxycarbonylpiperidinomethyl)-1*H*-1,2,3-triazole-4-carboxylate (12d)** (1.27 g), **ethyl 1-(4-amino-1,2,5-oxadiazol-3-yl)-5-thiomorpholinomethyl-1*H*-1,2,3-triazole-4-carboxylate (12e)** (1.21 g), and **ethyl 1-(4-amino-1,2,5-oxadiazol-3-yl)-5-indolinomethyl-1*H*-1,2,3-triazole-4-carboxylate (12f)** (1.26 g).

Ethyl 1-(4-amino-1,2,5-oxadiazol-3-yl)-5-(4-phenylpiperazin-1-yl)methyl-1*H*-1,2,3-triazole-4-carboxylate (12g). A mixture of chloromethyl derivative **3a** (1 g, 3.67 mmol), amine **13g** (6.5 g, 4 mmol), and $NaHCO_3$ (3.1 g, 3.69 mmol) was refluxed in EtOH (20 mL) for 5 h. Water (10 mL) was added to the hot solution and the mixture was kept for 16 h. The precipitate that formed was filtered off, washed with water, and dried in air to give compound **12g** (1.1 g).

Reaction of chloromethyl derivative 3c with pyrrolidine 13h

Isopropyl 1-(4-amino-1,2,5-oxadiazol-3-yl)-5-pyrrolidinomethyl-1*H*-1,2,3-triazole-4-carboxylate (12h). A mixture of compound **3c** (1 g, 3.49 mmol) and pyrrolidine (**13h**) (0.55 g, 7.68 mmol) was refluxed in Pr^iOH (20 mL) for 1 h and then treated as described for compound **12g**. The yield of ester **12h** was 1.01 g.

Reactions of compounds 2a,b and 3a,b with O-nucleophiles

Hydrolysis of 4-chloromethyl derivative 2a. 1-(4-Amino-1,2,5-oxadiazol-3-yl)-1*H*-1,2,3-triazol-4-ylmethanol (6a). ***A.*** A suspension of chloride **2a** (0.2 g, 1 mmol) in 1 *N* $NaHCO_3$ (30 mL) was refluxed for 30 min. After three days, hydroxymethyl derivative **6a** (0.13 g, 72%) was filtered off in the α-form.[8] Organic material was extracted from the filtrate with AcOEt. The extract was dried with $MgSO_4$ and evaporated to dryness *in vacuo* to give compound **6a** (0.04 g, 22%) in the β-form.[8] The total yield of compound **6a** was 0.17 g (94%).

B. A suspension of compound **2a** (0.1 g, 0.5 mmol) in 0.1 *N* NaOH (15 mL) was refluxed for 10 min. The reaction mixture was cooled to ~20 °C and acidified with conc. HCl to pH 1. The product was extracted with AcOEt to give compound **6a** (0.07 g, 78%) in the β-form.[8]

Hydrolysis of 5-chloromethyl derivative 2b. 1-(4-Amino-1,2,5-oxadiazol-3-yl)-1*H*-1,2,3-triazol-5-ylmethanol (6b). A suspension of chloride **2b** (0.1 g, 0.5 mmol) in 1 *N* $NaHCO_3$ (10 mL) was refluxed for 30 min. The precipitate that formed was filtered off at ~20 °C to give compound **6b** (0.08 g, 88%).

Hydrolysis of chloromethyl derivative 3b. 1-(4-Amino-1,2,5-oxadiazol-3-yl)-5-chloromethyl-1*H*-1,2,3-triazole-4-carboxylic

acid (14). A suspension of compound **3b** (0.5 g, 1.93 mmol) and $NaHCO_3$ (0.16 g, 1.93 mmol) in water (30 mL) was refluxed for 1 h to complete dissolution. The reaction mixture was acidified at ~20 °C with 18% HCl to pH 2. The precipitate was filtered off, washed with water, and dried in air to give acid **14** (0.40 g).

Decarboxylation of compound 14. A solution of compound **14** (0.2 g, 0.82 mmol) in AcOH (10 mL) was refluxed for 2 h. The solvent was removed and the residue was washed with water to give chloride **2b** (0.14 g, 86%) (see Ref. 8).

Reaction of chloromethyl derivative 3a with phenol. Ethyl 1-(4-amino-1,2,5-oxadiazol-3-yl)-5-phenoxymethyl-1*H*-1,2,3-triazole-4-carboxylate (15). A solution of chloride **3a** (1 g, 3.67 mmol) and phenol (0.41 g, 4.4 mmol) was refluxed in EtOH (25 mL) in the presence of K_2CO_3 (0.25 g, 1.84 mmol) for 5 h. The solvent was removed *in vacuo* and the residue was recrystallized from EtOH to give compound **15** (0.82 g).

Reactions of compound 3a with S-nucleophiles (16)

Synthesis of 1,2-bis[1-(4-amino-1,2,5-oxadiazol-3-yl)-4-ethoxycarbonyl-1*H*-1,2,3-triazol-4-ylmethylthio]ethane (18a). A mixture of compound **3a** (0.41 g, 1.5 mmol), ethane-1,2-dithiol (**16a**) (0.07 g, 7.1 mmol), and K_2CO_3 (0.21 g, 1.52 mmol) was refluxed in EtOH (10 mL) for 5 h. The precipitate that formed was filtered off at room temperature and washed with water to give diamine **18a** (0.40 g).

Compounds 18b—d. A mixture of compound **3a** (1 g, 3.67 mmol), the corresponding thiol (**16b—d**), and K_2CO_3 in the molar ratio 1 : 1.1 : 0.5 was refluxed in EtOH (30 mL) for 5 (**16b,c**) or 6 h (**16d**). Water (15 mL) was added to the warm solution (**16b**) or to the reaction mixtures at room temperature (**16c,d**). The precipitate that formed was filtered off, washed with cold water, and dried in air to give **ethyl [1-(4-amino-1,2,5-oxadiazol-3-yl)-5-benzimidazol-2-ylthiomethyl]-1*H*-1,2,3-triazole-4-carboxylate** (**18b**) (1.18 g), **ethyl [1-(4-amino-1,2,5-oxadiazol-3-yl)-5-benzoxazol-2-ylthiomethyl]-1*H*-1,2,3-triazole-4-carboxylate** (**18c**) (1.16 g), and **ethyl [1-(4-amino-1,2,5-oxadiazol-3-yl)-5-benzothiazol-2-ylthiomethyl]-1*H*-1,2,3-triazole-4-carboxylate** (**18d**) (1.22 g).

Ethyl (18e) and methyl [1-(4-amino-1,2,5-oxadiazol-3-yl)-5-pyridin-2-ylthiomethyl]-1*H*-1,2,3-triazole-4-carboxylate (18h). A mixture of compound **3a** (1.1 g, 4.04 mmol), thiol **16e** (0.50 g, 4.5 mmol), and $NaHCO_3$ (0.35 g, 4.17 mmol) was refluxed in EtOH (20 mL) for 3 h. Water (10 mL) was added to the stirred hot solution and the precipitate that formed was filtered off at ~20 °C, washed with water, and dried in air. The yield of compound **18e** was 1.45 g. The whole amount of this compound was refluxed in MeOH (40 mL) for 30 min and then cooled to room temperature. The precipitate that formed was filtered off to give compound **18h** (1.19 g).

Ethyl [1-(4-amino-1,2,5-oxadiazol-3-yl)-5-thiocyanatomethyl]-1*H*-1,2,3-triazole-4-carboxylate (18f). A solution of chloride **3a** (1.32 g, 4.84 mmol) and KSCN (0.7 g, 7.22 mmol) in EtOH (20 mL) was refluxed for 8 h and then concentrated to a quarter of its original volume. The precipitate that formed was washed with water and dried in air to give thiocyanate **18f** (1.36 g).

Di[1-(4-amino-1,2,5-oxadiazol-3-yl)-4-ethoxycarbonyl-1*H*-1,2,3-triazol-4-ylmethyl] sulfide (18g). A mixture of compound **3a** (1 g, 3.67 mmol), amide **17** (0.33 g, 4.4 mmol), and K_2CO_3 (0.26 g, 1.88 mmol) was refluxed in EtOH (30 mL) for 8 h. Water (20 mL) was added at ~20 °C and the precipitate was filtered off and dried in air to give compound **18g** (0.71 g).

Reactions of bromoacetyl derivative 4 with nucleophiles

4-Amino-3-[4-(2-aminothiazol-4-yl)-5-methyl-1*H*-1,2,3-triazol-1-yl]-1,2,5-oxadiazole (20). A mixture of compound **4** (0.6 g, 2.09 mmol), thiourea (**19**) (0.17 g, 2.2 mmol), and K_2CO_3 (0.14 g, 1.05 mmol) was refluxed in acetone (20 mL) for 30 min. The precipitate was filtered off, washed with cold water, and dried in air to give compound **20** (0.48 g).

1-[1-(4-Amino-1,2,5-oxadiazol-3-yl)-5-methyl-1*H*-1,2,3-triazol-4-yl]-2-morpholinoethanone (21). A mixture of compound **4** (0.5 g, 1.74 mmol) and morpholine (0.33 g, 3.80 mmol) was refluxed in EtOH (10 mL) for 5 min. After 2 to 3 h, the precipitate that formed was filtered off, washed with EtOH and ether, and dried in air to give compound **21** (0.5 g).

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Received May 24, 2005