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Triflamidomethyl and Oxymethyl Derivatives of 1,2,3-Triazoles

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Abstract—The reactions of some 1,2,3-triazoles with formaldehyde and triflamide have been studied. *N*-(Hydroxymethyl)-2-phenyl-2*H*-1,2,3-triazole-4-carboxamide reacts with triflamide in sulfuric acid to afford 2-phenyl-2*H*-1,2,3-triazole-4-carboxamide, bis(triflamido)methane, and *N,N*-bis[(trifluoromethylsulfonyl)aminomethyl]-triflamide. In the presence of K_2CO_3 4-amino-5-nitro-2-ethyl-1,2,3-triazole is reduced with hydrazine hydrate to 2-ethyl-2*H*-1,2,3-triazole-4,5-diamine, and with formaldehyde in the presence of K_2CO_3 it gives *N,N*-bis(2-ethyl-5-nitro-2*H*-1,2,3-triaxol-4-yl)methanediamine, which reacts with paraformaldehyde under acidic conditions with the formation of 4-aminomethyl-5-nitro-2-ethyl-1,2,3-triazole.

Keywords: triazoles, oxymethylation, trifluoromethanesulfonamide

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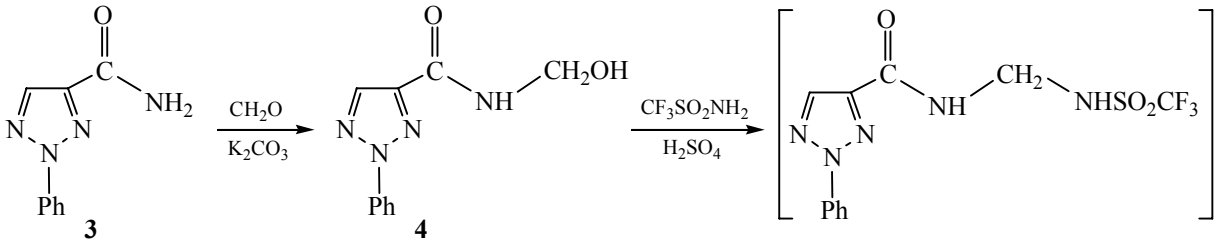
In continuation of our studies on the reactions of oxymethylation involving triflamide $CF_3SO_2NH_2$ **1** [1], here we report on the investigation of the possibility of heterocyclization of some 1,2,3-triazoles with amide **1** and formaldehyde in order to synthesize new triflamide derivatives of heterocycles. The mechanism of condensation with participation of amide **1** and CH_2O includes the initial step of formation of oxymethyltriflamide $CF_3SO_2NHCH_2OH$ **2**, its protonation and dehydration to cation $CF_3SO_2NHCH_2^+$, which further reacts with amide **1** or another amide available in the reaction mixture [1]. In order to prepare the triflamide derivatives of heterocycles by amidomethylation of triflamide we tried to synthesize the methylol derivatives of amino- and amidotriazoles. In the case of amide **3** the methylol derivative **4** was obtained but the subsequent attempt to perform its condensation with triflamide led unexpectedly to regeneration of the starting amide **3**. Besides, according to ^{1}H NMR spectroscopy data, in the reaction mixture the earlier described [1] linear products of condensation of triflamide and formaldehyde $(CF_3SO_2NH)_2CH_2$ **5** and $CF_3SO_2N(CH_2NHSO_2CF_3)_2$ **6** were formed. Apparently, this occurs due to transamination of compound **4** by triflamide [scheme (1)].

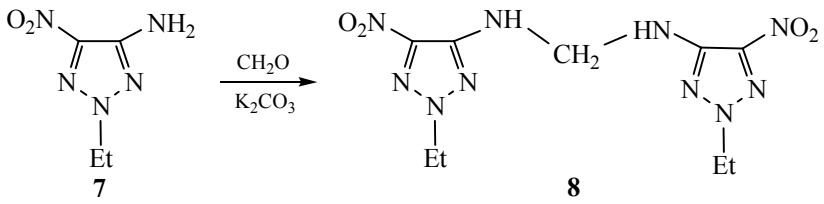
The reaction of more basic aminotriazole **7** with aqueous formaldehyde in the presence of K_2CO_3 does not stop at the stage of oxymethylation but leads to the product of condensation **8** as a result of the reaction of



3 **4**

$$\longrightarrow \mathbf{3} + (CF_3SO_2NH)_2CH_2 + CF_3SO_2N(CH_2NHSO_2CF_3)_2. \quad (1)$$

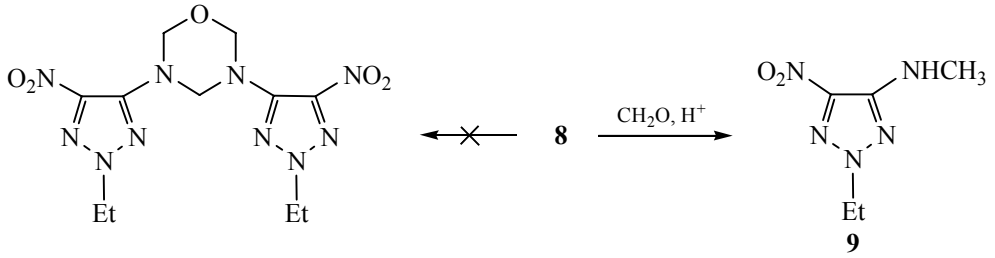
5 **6**



(2)

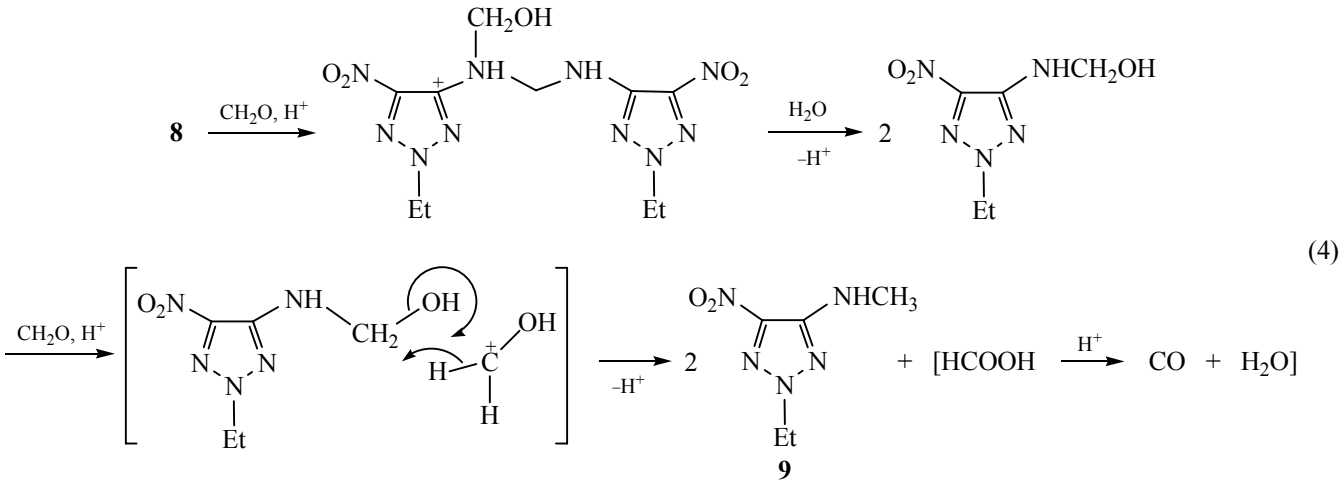
two molecules of aminotriazole with one molecule of formaldehyde [scheme (2)].

Since compound **8** contains a fragment $RNHCH_2$·NHR, which is a building block for the formation of oxadiazine ring; by the analogy with our previous [1] and the literature data [2] it can be expected that its reaction with paraformaldehyde in sulfuric acid would yield the corresponding disubstituted oxadiazine. However, unexpectedly the reaction led to the formation of the product of reduction, 4-aminomethyl-5-nitro-2-ethyl-1,2,3-triazole **9** [scheme (3)]:



(3)

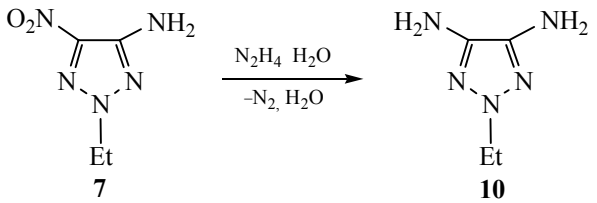
The formation of compound **9** was proved by the coincidence of its melting point and ^{1}H NMR spectrum with those in [3], in particular, by the presence of a doublet of NCH_3 group equal in intensity to the triplet of CCH_3 group. The formation of the reduction product can be tentatively ascribed to the oxymethylation of diamine **8** with subsequent splitting and the redox interaction of the intermediate oxymethyltriazole $RNHCH_2OH$ with formaldehyde, which is oxidized to formic acid that, in turn, is decomposed in conc. sulfuric acid to CO and water [scheme (4)].



(4)

Scheme (4) is proved by practically quantitative yield of compound **9**, since in the alternative route of its formation by disproportionation of compound **8** to compound **9** and any oxidation products of the second fragment of the molecule the yield of product **9** cannot exceed 50%.

Compound **7** is reduced by hydrazine hydrate to 2-ethyl-2*H*-1,2,3-triazole-4,5-diamine **10**, whose structure was proved by ^{1}H, ^{13}C NMR spectroscopy and elemental analysis [scheme (5)].



7 **10** (5)

Earlier, we have shown that *N*-[(trifluoromethylsulfonyl)aminomethyl]acetamide $CF_3SO_2NHCH_2NHCOCH_3$ in the reaction with paraformaldehyde in sulfuric acid undergoes transamination with elimination of acetamide and affords exclusively the symmetrically substituted 3,5-bis(trifluoromethylsulfonyl)tetrahydro-1,3-5-oxadiazine **11** [4] [scheme (6)].

Heterocycle **11** was also obtained when trying to perform the three-component condensation reaction of triflamide with 4-nitro-1,2,3-triazole and paraformaldehyde. As follows from Eq. (7), nitrotriazole does not enter the reaction.

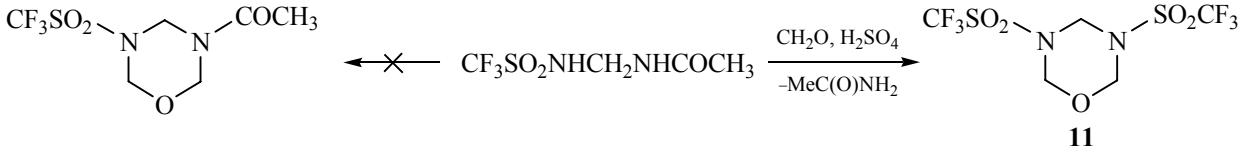
To summarize, 1,2,3-triazoles containing the NH group in the ring, as well as N-substituted 1,2,3-triazoles containing the amine or amide group in the side chain, do not enter the reactions of three-component condensation with triflamide and paraformaldehyde, but rather the intermediate methylol derivatives suffer transamination or reduction with the second molecule of formaldehyde. Taking into account the above reaction (6), as well as the absence of condensation products with participation of acetamide in the three-component reaction of triflamide with paraformaldehyde and acetamide in the acidic medium [4], a conclusion can be made that the reason of inertness of amines and amides in the present case is their ability to be protonated at the nitrogen atom (in amines) or oxygen atom (in amides). The resulted cations, as should be expected, are inert towards cation $CF_3SO_2NHCH_2^+$, which is a key intermediate in the condensation reaction.

EXPERIMENTAL

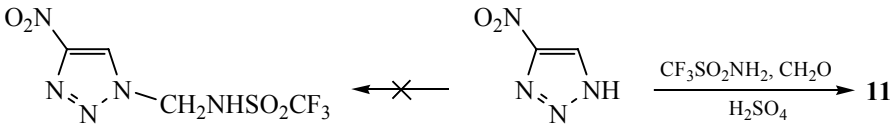
NMR spectra were registered on a Bruker DPX-400 spectrometer with working frequencies of 400 (^{1}H), 100 (^{13}C), 376 MHz (^{19}F), internal reference HMDS, chemical shifts are given relative to TMS (^{1}H, ^{13}C) and CCl_3F (^{19}F). The reactions were monitored by TLC on silica gel plates 60 F-254, eluent hexane – ether (1 : 2).

2-Phenyl-2*H*-1,2,3-triazole-4-carboxamide (3) was obtained by the procedure described in [5]. mp 142–143°C. ^{1}H NMR spectrum, DMSO-d_6, δ, ppm: 7.45 t (1H, H$_p$, *J* 7.0 Hz), 7.58 t (2H, H$_m$, *J* 7.5 Hz), 7.74 s (1H, NH), 8.06 d (2H, H$_o$, *J* 7.9 Hz), 8.09 s (1H, NH), 8.42 s (1H, =CH). ^{13}C NMR spectrum, DMSO-d_6, δ, ppm: 118.92 (C$_o$), 128.51 (C^5), 129.77 (C$_m$), 136.52 (C$_p$), 138.91 (C^1), 144.36 (C^4), 160.91 (C=O). Found, %: C 55.77; H 4.57; N 25.70. $C_{10}H_{10}N_4O_2$. Calculated, %: C 55.04; H 4.62; N 25.68.

***N*-(Hydroxymethyl)-2-phenyl-2*H*-1,2,3-triazole-4-carboxamide (4).** To the solution of 1.6 g (8.5 mmol) 2-phenyl-1,2,3-triazole-4-carboxamide **3** and 0.62 g (4.5 mmol) of K_2CO_3 in 50 mL of 50% aqueous isopropanol heated to 40°C 4 mL (0.043 mol) of 30% aqueous solution of CH_2O was added dropwise at



11 (6)



11 (7)

stirring. The reaction mixture was stirred for 2 h at room temperature, the formed precipitate was filtered off and washed with small amount of ice water. After acidification of the filtrate with 10% HCl an additional amount of precipitate was formed. The combined precipitates (1.5 g, 81%) were crystallized from ethyl acetate. mp 163–164°C. ^{1}H NMR spectrum, DMSO-d_6, δ, ppm: 4.75 s (2H, CH_2), 5.81 s (1H, OH), 7.48 s (1H, H_p), 7.60 s (2H, H_m), 8.07 s (2H, H_o), 8.48 s (1H, =CH), 9.26 s (1H, NH). ^{13}C NMR spectrum, DMSO-d_6, δ, ppm: 62.42 (CH_2), 118.93 (C_o), 128.61 (C^5), 129.82 (C_m), 136.51 (C_p), 138.87 (C^1), 144.18 (C^4), 159.24 (C=O). Found, %: C 55.77; H 4.57; N 25.70. $C_{10}H_{10}N_4O_2$. Calculated, %: C 55.04; H 4.62; N 25.68.

***N,N'*-Bis(2-ethyl-5-nitro-2*H*-1,2,3-triazol-4-yl)-methanediamine (8)**. To the solution of 1 g (6.4 mmol) of 4-amino-5-nitro-2-ethyl-1,2,3-triazole **7** and 0.04 g (0.3 mmol) of K_2CO_3 in 15 mL of isopropanol 1.86 mL (27.6 mmol) of 40% formaldehyde water solution was added dropwise at stirring. The reaction mixture was stirred for 2 h at room temperature, kept overnight, and acidified with 10% HCl to pH 4. The formed precipitate was filtered off and dried in air to give 0.95 g (91%) of the product, which was purified by crystallization from isopropanol. mp 152–153°C. ^{1}H NMR spectrum, $CDCl_3$, δ, ppm: 1.56 t (3H, CH_3, *J* 7.3 Hz), 4.36 q (2H, CCH_2, *J* 7.3 Hz), 4.97 t (1H, NCH_2, *J* 6.7 Hz), 6.63 t (1H, NH, *J* 6.7 Hz). ^{13}C NMR spectrum, $CDCl_3$, δ, ppm: 14.11 (CH_3), 51.88 ($C\underline{C}H_2$), 52.16 (NCN), 147.73 (C^4). Found, %: C 33.40; H 4.37; N 43.83. $C_9H_{14}N_{10}O_4$. Calculated, %: C 33.13; H 4.32; N 42.93.

***N*-(2-Ethyl-5-nitro-2*H*-1,2,3-triazol-4-yl)methyl-amine (9)**. To the solution of 0.5 g (1.5 mmol) of *N,N'*-bis(2-ethyl-5-nitro-2*H*-1,2,3-triazol-4-yl)methanediamine **8** in 20 mL of conc. H_2SO_4 at vigorous stirring 0.23 g (7.7 mmol) of paraformaldehyde was added in small portions. After complete dissolution, the mixture was heated at 50°C for 30 min. After cooling the reaction mixture was poured into ice water and extracted twice with ethyl acetate. The extract was dried over $MgSO_4$ and evaporated. Yield 0.5 g (98%), mp 78°C (78°C [3]). ^{1}H NMR spectrum, CD_3CN, δ, ppm: 1.51 t (3H, CCH_3, *J* 7.3 Hz), 2.96 d (3H, NCH_3, *J* 5.1 Hz), 4.34 q (2H, CCH_2, *J* 7.3 Hz), 5.95 br.s (1H, NH). ^{13}C NMR spectrum, $CDCl_3$, δ, ppm: 14.29 ($C\underline{C}H_3$), 30.39 (NCH_3), 52.57 (NCH_2), 138.72 (C^5), 151.42 (C^4).

2-Ethyl-2*H*-1,2,3-triazol-4,5-diamine (10). The solution of 2 g (12.7 mmol) of 4-amino-5-nitro-2-ethyl-2*H*-1,2,3-triazole **7** in 20 mL of hydrazine hydrate was heated with stirring at 100–110°C for 4 h. After cooling the reaction mixture was kept overnight. The crystalline precipitate was filtered off and crystallized from isopropanol. Yield 1.05 g (65%), mp 148–150°C. ^{1}H NMR spectrum, DMSO-d_6, δ, ppm: 1.21 t (3H, CH_3, *J* 7.2 Hz), 3.83 q (2H, CH_2, *J* 7.2 Hz), 4.50 s (4H, NH_2). ^{13}C NMR spectrum, DMSO-d_6, δ, ppm: 14.26 (CH_3), 47.61 (CH_2), 139.83 ($C^{4,5}$). Found, %: C 37.40; H 7.37; N 54.83. $C_4H_9N_5$. Calculated, %: C 37.79; H 7.13; N 55.08.

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