SYNTHESIS OF 3-METHYL-6-R-6H-THIAZOLO-[4,3-*b*]-1,2,4-TRIAZOLO[4,3-*d*]-1,3,4-THIADIAZOLES

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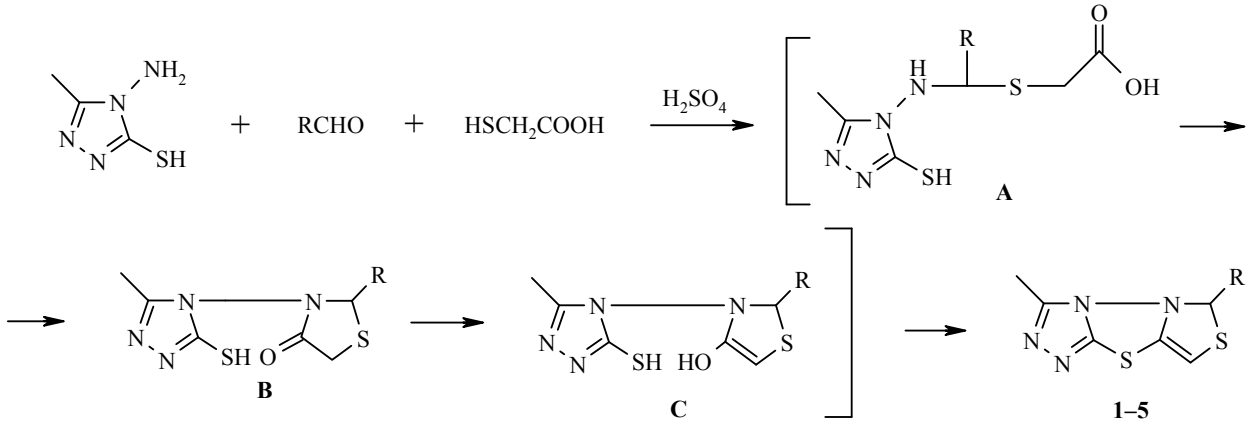
A one-reactor method has been developed for the synthesis of 3-methyl-6-R-6H-thiazolo[4,3-b]-1,2,4-triazolo[4,3-d]-1,3,4-thiadiazoles by the condensation of aromatic aldehydes, thioglycolic acid, and 4-amino-5-methyl-1,2,4-triazole-3(2H)-thione in a sulfuric acid medium.

Keywords: 4-amino-5-methyl-1,2,4-triazole-3(2H)-thione, 3-methyl-6-R-6H-thiazolo[4,3-*b*]-1,2,4-triazolo-[4,3-*d*]-1,3,4-thiadiazole, thioglycolic acid.

For some time past investigations have been carried out intensively on the synthesis of polycondensed derivatives of 1,3,4-thiadiazole, which are evidently linked with the discovery of the set of useful properties of polycondensed derivatives of 1,3,4-thiadiazole [1-8].

In this connection and also as a continuation of our investigations on the synthesis of derivatives of hydrothiazolo[4,3-*b*]-1,3,4-thiadiazole [9, 10] we have studied the cyclization reaction of hemithioacetals of thioglycolic acid with 4-amino-5-methyl-1,2,4-triazole-3(2H)-thione.



1 R = Ph; **2** R = 4-FC_6H_4 ; **3** R = 4-$Me_2NC_6H_4$; **4** R = 2-HO-5-BrC_6H_3; **5** R = 4-$MeOC_6H_4$

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In particular, it has been established that 4-amino-5-methyl-1,2,4-triazole-3(2H)-thione in a medium of conc. H_2SO_4 reacts with aromatic aldehydes and thioglycolic acid giving 6-R-6H-thiazolo[4,3-*b*]-1,2,4-triazolo[4,3-*d*]-1,3,4-thiadiazoles.

The optimum conditions for carrying out the reaction are the introduction of components into the reaction in equimolar ratios. With this aim thioglycolic acid was added to the aromatic aldehyde and 4-amino-5-methyl-1,2,4-triazole-3(2H)-thione was introduced after 15-20 min. After homogenization of the reaction mass cyclodehydration was conducted in a medium of conc. H_2SO_4 at room temperature.

The yield of final product under these conditions was high and reached 77-94%. As became clear, a substituent in the benzene ring had no effect on the course of the reaction, since the yield of final product did not depend in practice on the nature of this substituent.

A possible route for the formation of compounds **1-5** seemed to us to be the following. The hemithioacetal formed by thioglycolic acid interacts with the cyclic thionehydrazine with conversion into the thioglycolic acid derivative **A**, which is dehydrated and converted into 3-(3-mercapto-5-methyl-4H-1,2,4-triazol-4-yl)-2-R-4-thiazolidone **B**. The intermediate compound **B**, by enolizing, is transformed into 2,3-dihydro-3-(3-mercapto-5-methyl-4H-1,2,4-triazol-4-yl)-R-thiazol-4-ol **C** and after cyclodehydration is converted into 3-methyl-6-R-6H-thiazolo[4,3-*b*]-1,2,4-triazolo[4,3-*d*]-1,3,4-thiadiazole.

TABLE 1. Characteristics of 3-Methyl-6-R-6H-thiazolo[4,3-*b*]-1,2,4-triazolo[4,3-*d*]-1,3,4-thiadiazoles **1-5**

Compound	Empirical formula	Found, % / Calculated, %		mp, °C	Yield, %
		C	H		
1	$C_{12}H_{10}N_4S_2$	52.34 / 52.53	3.55 / 3.67	202-204	73
4	$C_{12}H_9FN_4S_2$	49.08 / 49.30	2.89 / 3.10	157-158	94
3	$C_{14}H_{15}N_5S_2$	52.70 / 52.97	4.57 / 4.76	214-216	69
4	$C_{12}H_9BrN_4OS_2$	38.79 / 39.03	2.37 / 2.46	222-224	77
5	$C_{13}H_{12}N_4OS_2$	51.10 / 51.30	3.69 / 3.97	226-228	89

TABLE 2. Spectral Characteristics of Compounds **1-5**

Compound	IR spectrum, ν, cm^{-1}	^1H NMR spectrum, δ, ppm (*J*, Hz)
1	2860, 1605, 1550, 1775, 1370, 1300, 1230, 950, 875, 760	9.98 (1H, s, CH); 7.98 (1H, s, CH); 7.92 (2H, m, C_6H_5); 7.64 (3H, m, C_6H_5); 2.33 (3H, s, CH_3)
2	2820, 1595, 1545, 1470, 1375, 1300, 1235, 950, 860, 643	10.00 (1H, s, CH); 8.10 (1H, s, CH); 7.90 (2H, m, C_6H_4); 7.28 (2H, m, C_6H_4); 2.22 (3H, s, CH_3)
3	3405, 3250, 3175, 2825, 1605, 1545, 1475, 1378, 1305, 1235, 945, 850, 640	11.43 (1H, s, CH); 9.43 (1H, s, CH); 7.64 (2H, d, J = 8.6, C_6H_4); 6.74 (2H, d, J = 8.6, C_6H_4); 2.92 (3H, s, CH_3); 2.90 (3H, s, CH_3); 2.22 (3H, s, CH_3)
4	3260, 3180, 2980, 2850, 1610, 1540, 1360, 1300, 1235, 940, 850, 740	11.22 (1H, s, CH); 8.30 (1H, s, CH); 8.06 (1H, d, $J_{4,6}$ = 3.0, C_6H_5); 7.28 (1H, m, C_6H_3); 6.76 (1H, d, $J_{3,4}$ = 8.6, C_6H_3); 2.22 (3H, s, CH_3)
5	1665, 1605, 1475, 1370, 1300, 1230, 950, 875, 760	13.03 (1H, s, CH); 9.76 (1H, s, CH); 7.69 (2H, d, J = 8.2, C_6H_4); 6.93 (2H, d, J= 8.2, C_6H_4); 4.70 (3H, s, OCH_3); 2.22 (3H, s, CH_3)

The structures of the obtained compounds **1-5** were confirmed by the presence in their ^{1}H NMR spectra of singlet signals in the 9.43 ppm region corresponding to the proton in position 2 of the ring. The protons of the phenyl groups were displayed at 7.69 ppm, and the methyl group protons as singlets in the 2.22 ppm region.

EXPERIMENTAL

The IR spectra were described on a UR-20 spectrometer in KBr disks, the ^{1}H NMR spectra on a Tesla 5873 C (100 MHz) instrument in DMSO-d_6, internal standard was HMDS. Melting points were determined on a Boetius microhotstage.

Synthesis of 3-Methyl-6-R-6H-thiazolo[4,3-*b*]-1,2,4-triazolo[4,3-*d*]-1,3,4-thiadiazoles (General Method). The aromatic aldehyde (10 mmol) and thioglycolic acid (10 mmol) were placed in a small beaker. The mixture was stirred with a small glass stirrer for 15-20 min, then 4-amino-5-methyl-1,2,4-triazole-3(2H)-thione (10.0 mmol) was added in portions. After the reaction mixture had become homogeneous (30-40 min) the glass beaker was submerged in an ice bath, and conc. H_2SO_4 (10 ml) was added in portions, and the mixture left for 18-20 h at room temperature. Ice (50 g) was added to the reaction mixture, which was then neutralized with 10% NaOH solution to pH 7-8. The precipitated solid was filtered off, the product air-dried, and recrystallized from aqueous dioxane.

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