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SYNTHESIS OF UNSYMMETRICAL SULFIDES DERIVED FROM TETRAZOLE-5-THIOLS

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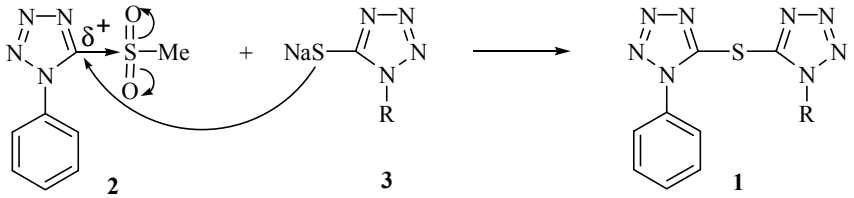
A series of unsymmetrical sulfides derived from 1-substituted tetrazole-5-thiols was prepared by fusion of the corresponding 1-R-tetrazole-5-thiol sodium salt with 1-R'-5-halotetrazole. The structure was confirmed by ^{1}H NMR and ^{13}C NMR spectra. The target compounds were prepared in 50-80% yields.

Keywords: 1-substituted 5-halotetrazoles, 1-substituted tetrazole-5-thiols, unsymmetrical bis-5,5'-tetrazolyl sulfides.

Both alkyl tetrazolyl sulfides and symmetrical ditetrazolyl sulfides are known, but unsymmetrical sulfides of substituted tetrazoles (**1**) have not been described yet. Two synthetic approaches chosen by us for their synthesis are presented below.

The first one was based on the reaction of 5-methylsulfonyl-1-phenyl tetrazole (**2**) with sodium salts of 1-substituted tetrazole-5-thiol (**3**) [1] under various conditions. The reaction started by the nucleophilic attack of thiolate as a base towards the C(5) of the tetrazole skeleton where a negative partial charge is formed due to the electronegativity of the sulfonyl group.



1-R-Tetrazole-5-thiols were prepared from the corresponding aromatic or aliphatic amines (see Experimental). First, tetrazolyl isothiocyanates were synthesized according to Hodgkins and Reewes [2]; these intermediates gave 1-R-tetrazole-5-thiols according to Altland [3]. Methylation of 1-phenyltetrazole-5-thiol was carried out under conditions of phase-transfer catalysis [4].

Condensation reactions of compounds **2** and **3** (R = Me, Ph, 2-$MeOC_6H_4$, 3-$MeOC_6H_4$, 4-FC_6H_4, 4-BrC_6H_4) were performed as follows: 1) in acetonitrile at room temperature [1]; 2) in boiling acetonitrile; 3) in DMF at 100°C; 4) in acetonitrile under ultrasound (20 kHz, 50 W, 25°C, 60°C); 5) in DMF under ultrasound (20 kHz, 50 W, 25°C, 100°C); 6) on fusion of the reaction mixture at the temperatures up to 110°C.

* Dedicated to Professor E. Lukevics on the occasion of his 65th birthday.

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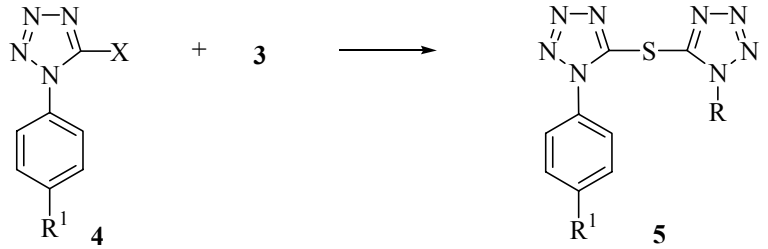
In a number of experiments the condensation reaction was performed under different conditions but the yields of the desired compounds were very low (0-20%). These unsatisfactory results were obtained in all variants of the reaction performed in acetonitrile. Only reactions of the sodium salt of 1-methyltetrazole-5-thiol exceptionally yielded about 20% of the desired sulfides. Stable yields ~15% were obtained by fusion of the reaction mixture for 2-3 h, but only for several products.

So, the preparation of unsymmetrical sulfides of tetrazoles this way proved impossible. The reason may be steric hindrance at the reaction center on the electron-deficient carbon of the tetrazole skeleton together with the low basicity of the sulfide anion.

The second and much more successful variant of the synthesis was based on the reaction of 1-aryl-5-halotetrazole **4** with the sodium salt of 1-R-tetrazole-5-thiol:



1-Phenyltetrazole was prepared according to Gaponik et al. [5]. The classical approach according to Stolle [6] was used first, but we were unable to reproduce these results in the preparation of 5-iodo-1-phenyltetrazole. Yields of intermediates and the final compound were considerably lower. The substitution with iodine was selected because of the presumed high reactivity of the iodine derivative, but the latter decomposed during the reaction with sodium tetrazole-5-thiolate and the reaction mixture became brown. Yields of unsymmetrical sulfides **1** in reactions performed by this method were very low (2-5%) and did not depend on the temperature of the reaction mixture. Even the reaction according to Musliner [7] performed analogously with chloro and iodo derivatives did not give products at all or gave only a minimal yield although the authors described yields over 90%.

TABLE 1. Unsymmetrical Sulfides **5** Prepared from 1-Aryl-5-halotetrazoles **4** and Sodium Tetrazole-5-thiolates **3**

Com-pound	R^1	R	Method of purification	mp, °C	Yield, %
5a	Cl	4-Bromophenyl	P-TLC*	178-182	79
5b	Cl	Phenyl	P-TLC	128-131	68
5c	Cl	4-Fluorophenyl	P-TLC	130-133	80
5d	Cl	4-Ethylphenyl	P-LC*[2]	168-170	66
5e	Cl	2,4,6-Trimethylphenyl	P-LC	137-140	72
5f	Cl	4-Methylphenyl	P-LC	156-159	59
5g	Cl	2-Methoxyphenyl	P-TLC	128-130	65
5h	H	Phenyl	P-LC	112-114	69
5i	H	Methyl	P-LC	127-129	75
5j	H	Cyclohexyl	P-LC	118-120	43
5k	F	Phenyl	Cryst. EtOH/H_2O	98-100	78
5l	F	4-Fluorophenyl	Cryst. EtOH/H_2O	117-120	77
5m	F	3-Methoxyphenyl	Cryst. EtOH/H_2O	109-112	50
5n	F	4-Bromophenyl	Cryst. EtOH/H_2O	138-141	63

* Preparative TLC (mobile phase – chloroform).

*[2] Preparative LC (mobile phase – chloroform).

TABLE 2. Elemental Analysis, ^{1}H and ^{13}C NMR Spectra of the Prepared Sulfides **5**

Compound	Empirical formula	Found, % / Calculated, %				NMR spectra, δ, ppm (*J*, Hz)	
		C	H	N	S	^{1}H	^{13}C
1	2	3	4	5	6	7	8
5a	$C_{14}H_8BrClN_8S$	38.39 / 38.59	1.97 / 1.85	25.42 / 25.72	7.15 / 7.36	7.86-7.79 (m, AA', BB', 2H, H2', H6'); 7.71-7.67 (m, 4H, H2, H3, H5, H6); 7.65-7.58 (m AA', BB', 2H, H3', H5')	124.7, 127.3, 127.4, 130.1, 131.7, 132.1, 133.0, 136.1, 148.8, 148.9
5b	$C_{14}H_9ClN_8S$	46.95 / 47.13	2.31 / 2.54	31.35 / 31.41	8.71 / 8.99	7.73-7.67 (m, 4H, H2, H6, H2', H6'); 7.67-7.60 (m, 5H, H3, H5, H3', H4', H5')	125.3, 127.3, 130.1, 130.2, 131.3, 131.7, 132.9, 136.1, 148.8, 148.9
5c	$C_{14}H_8ClFN_8S$	44.98 / 44.87	1.93 / 2.15	30.11 / 29.90	8.29 / 8.56	7.77-7.67 (m, 6H, H2, H3, H5, H6, H2', H6'); 7.53-7.42 (m, 2H, H3', H5')	116.9 and 117.2 (J = 23.5), 127.3, 128.1 and 128.2 (J = 9.4), 129.2 and 129.2 (J = 2.9), 130.1, 131.7, 136.1, 148.9, 149.0, 161.6 and 164.9 (J = 249.4)
5d	$C_{16}H_{13}ClN_8S$	49.68 / 49.93	3.18 / 3.40	28.89 / 29.12	8.45 / 8.33	7.72-7.65 (m, 4H, H2, H3, H5,H6); 7.56-7.49 (m AA', BB', 2H, H2', H6'); 7.47-7.41 (m AA', BB', 2H, H3', H5'); 2.71 (q, J = 7.42, 2H, CH_2); 1.22 (t, J = 7.42, 3H, CH_3)	15.5, 28.1, 125.2, 127.2, 129.3, 130.1, 130.5, 131.7, 136.0, 147.4, 148.9, 148.9
5e	$C_{17}H_{15}ClN_8S$	51.31 / 51.19	3.55 / 3.79	28.16 / 28.09	8.11 / 8.04	7.76-7.69 (m AA', BB', 2H, H2, H6); 7.68-7.62 (m AA', BB', 2H, H3, H5); 7.11 (s, 2H, H3', H5'), 2.32 (s, 3H, CH_3); 1.69 (s, 6H, CH_3)	16.6, 20.9, 127.2, 127.5, 129.9, 130.1, 131.5, 135.1, 136.2, 142.1, 147.3, 150.8
5f	$C_{15}H_{11}ClN_8S$	48.32 / 48.58	2.78 / 2.99	30.36 / 30.22	8.41 / 8.65	2.41 (s, 3H, CH_3); 7.44-7.35 (m, AA', BB', 2H, H3', H5'); 7.55-7.45 (m AA', BB', 2H, H2', H6'); 7.74-7.62 (m, 4H, H2, H3, H5, H6)	21.0, 125.1, 127.2, 130.1, 130.4, 130.4, 131.7, 136.0, 141.4, 148.8, 148.9
5g	$C_{15}H_{11}ClN_8OS$	46.41 / 46.57	2.82 / 2.87	28.88 / 28.97	8.21 / 8.29	3.74 (s, 3H, OCH_3); 7.17 (dt, 1H, J = 7.83, J = 1.1, H5); 7.35-7.30 (m, 1H, H3); 7.44 (dd, 1H, J = 7.83, J = 1.37, H6); 7.69-7.59 (m, 6H, H4, H2', H3', H4', H5', H6')	56.4, 113.3, 120.6, 121.4, 125.3, 127.7, 130.0, 131.3, 132.9, 133.6, 147.9, 150.7, 153.0

TABLE 2 (continued)

1	2	3	4	5	6	7	8
5h	$C_{14}H_{10}N_8S$	51.93 52.16	3.01 3.13	34.92 34.76	10.12 9.95	7.70-7.53 (m, 10H, H2, H3, H4, H5, H6, H2', H3', H4', H5', H6')	125.3, 130.1, 131.4, 132.8, 148.9
5i	$C_9H_8N_8S$	41.49 41.53	3.15 3.10	43.35 43.05	12.15 12.32	4.04 (s, 3H, CH_3); 7.72-7.67 (m, 3H, H3, H4, H5); 7.80-7.73 (m, 2H, H2, H6)	34.9, 125.5, 130.2, 131.4, 133.0, 147.8, 149.5
5j	$C_{14}H_{16}N_8S$	51.03 51.20	4.76 4.91	34.28 34.12	9.89 9.76	1.46-1.14 (m, 3H, CH_2); 1.89-1.58 (m, 5H, CH_2); 2.07-1.92 (m, 2H, CH_2); 4.66-4.50 (m, 1H, CH); 7.75-7.67 (m, 3H, H3, H4, H5); 7.84-7.76 (m, 2H, H2, H6)	24.6, 24.7, 32.3, 58.4, 125.4, 130.3, 131.4, 133.0, 146.6, 149.8
5k	$C_{14}H_9FN_8S$	49.30 49.41	2.49 2.67	32.86 32.92	9.22 9.42	7.53-7.44 (m, 2H, H3', H5'); 7.67-7.62 (m, 5H, H2, H3, H4, H5, H6); 7.77-7.68 (m, 2H, H2', H6')	117.0 and 117.3 (J = 23.5), 125.3, 128.1 and 128.2 (J = 9.4), 129.2 and 129.2 (J = 3.2), 130.1, 131.3, 131.4, 132.9, 148.9, 149.0, 161.6 and 164.9 (J = 249.1)
5l	$C_{14}H_8F_2N_8S$	46.68 46.93	2.11 2.25	31.35 31.27	8.87 8.95	7.53-7.43 (m, 4H, H3, H5, H3', H5'); 7.78-7.67 (m, 4H, H2, H6, H2', H6')	117.0 and 117.3 (J = 23.5), 128.1 and 128.2 (J = 9.4), 129.2 and 129.2 (J = 2.9), 149.0, 161.3 and 164.9 (J = 249.1)
5m	$C_{15}H_{11}FN_8OS$	48.41 48.64	3.12 2.99	30.08 30.25	8.52 8.66	3.79 (s, 3H, CH_3); 7.27-7.11 (m, 3H, H2', H4', H5'); 7.57-7.42 (m, 3H, H3, H5, H6'); 7.76-7.66 (m, 2H, H2, H6)	55.9, 111.0, 111.1, 117.0 and 117.3 (J = 23.8), 117.0, 117.3, 128.0 and 128.1 (J = 9.5), 129.2 and 129.2 (J = 2.9), 131.0, 133.7, 148.9, 149.0, 160.0, 161.6 and 164.9 (J = 249.1)
5n	$C_{14}H_8BrFN_8S$	39.89 40.11	1.61 1.92	26.49 26.73	7.46 7.65	7.51-7.42 (m, 2H, H3', H5'); 7.66-7.58 (m AA', BB', 2H, H3, H5); 7.76-7.67 (m, 2H, H2', H6'); 7.87-7.79 (m AA', BB', 2H, H2, H6)	116.9 and 117.2 (J = 23.8), 124.7, 127.5, 128.1 and 128.2 (J = 9.4), 129.2 and 129.2 (J = 2.9), 132.1, 133.1, 148.8, 149.0, 161.6 and 164.9 (J = 249.4)

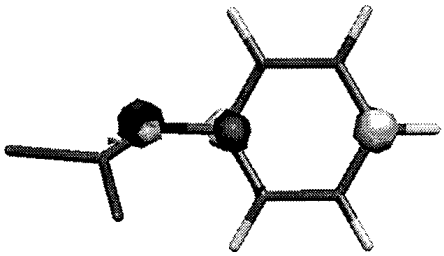
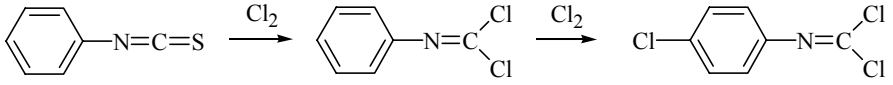


Fig. 1. HOMO orbital of phenyldichloroazomethine (cutoff = 0.11).

Only the last modification, *viz*. fusion of the reaction mixture, brought result. The low melting points of 1-R'-5-halotetrazoles **4**, which are significantly below the temperature of decomposition, were favorable for the reaction. The sodium salt of tetrazole-5-thiol in 10% excess was added to the melted starting compound and the product was isolated after 2 to 3 h of heating. The yields were in the range between 50-80%.

5-Chloro-1-(4-fluorophenyl)tetrazole was prepared according to Kauer and Sheppard [8] by the reaction of the corresponding dichloroazomethine with sodium azide. 5-Chloro-1-(4-chlorophenyl)tetrazole was prepared by the reaction of phenylisothiocyanate (**6**) with chlorine. The expected addition of chlorine molecule at the isothiocyanate group to form dichloroazomethine (**7**) proceeded, but the unexpected substitution in position 4 of the aromatic ring to give compound **8** also took place during the reaction.



6 **7** **8**

TABLE 3. Melting Points of 1-R-Tetrazole-5-thiols

R	mp (found), °C	mp, °C [lit.]
Phenyl	147-148	148-148.5 [9]
4-Bromophenyl	178-180	178-181 [10]
4-Fluorophenyl	155-156	155-156 [8]
4-Ethylphenyl	144-146	New compound*
4-Methylphenyl	153-155	154-156 [9]
2,4,6-Trimethylphenyl	155-156	156-157 [11]
2-Methoxyphenyl	139-140	139-140 [9]]
3-Methoxyphenyl	138-140 (decomp.)	Not described sufficiently in the literature*[2]
Methyl	124-125	124-125 [6]]
Cyclohexyl	100-102	101-102 [12]

* Found, %: C 52.35; H 4.57; N 27.01; S 15.48. $C_9H_{10}N_4S$. Calculated, %: C 52.41; H 4.89; N 27.16; S 15.55. ^{1}H NMR (300 MHz, $CDCl_3$), δ, ppm: 1.30 (t, 3H, J = 7.42 Hz, CH_3); 2.75 (q, 2H, J = 7.42 Hz, CH_2); 7.43-7.37 (m AA', BB', 2H, H3, H5); 7.84-7.77 (m AA', BB', 2H, H2, H6). ^{13}C NMR (75 MHz, $CDCl_3$), δ, ppm: 15.3, 28.6, 123.9, 128.8, 131.4, 146.5, 163.3.

*[2] Found, %: C 45.96; H 3.96; N 26.63; S 15.19. $C_8H_8N_4OS$. Calculated, %: C 46.14; H 3.87; N 26.90; S 15.40. ^{1}H NMR (300 MHz, $CDCl_3$), δ, ppm: 3.89 (s, 3H, OCH_3), 7.12-7.02 (m, 1H, H4); 7.57-7.42 (m, 3H, H2, H5, H6). ^{13}C NMR (75 MHz, $CDCl_3$), δ, ppm: 55.7, 109.2, 115.8, 116.0, 130.2, 134.7, 160.1.

The dichloroazomethine residue, as shown by quantum-chemical calculation, plays the role of an activating substituent and strongly activates position 4 of the aromatic ring. The activation is so high that electrophilic substitution of the ring can take place. For the explanation, an *ab initio* model of phenyldichloroazomethine was calculated and its HOMO orbital was displayed. This orbital is responsible for this type of reaction according to frontier orbital theory. The distribution of this orbital on the molecule (Fig. 1) shows that S_E of the aromatic ring must take place in position 4 of the ring. 4-Chlorophenyldichloroazomethine then reacts with sodium azide and gives the corresponding 5-chlorotetrazole.

Sulfides **5a**-**n** (Table 1) were prepared by the reaction of 1-aryl-5-chlorotetrazole with sodium tetrazole-5-thiolates.

EXPERIMENTAL

TLC was carried out on Silufol UV 254 (Czech Republic) plates. Chloroform was used as the mobile phase. Preparative TLC was carried out on Kieselgel 60 HF (MERCK) plates; chloroform was used as the mobile phase. Preparative column chromatography was carried out on Kieselgel 60 (0.040-0.063 mm; MERCK). Chloroform was used as the mobile phase.

Melting points were measured without correction using a Kofler apparatus.

Samples for elemental analysis were dried for 12 h in vacuum over phosphorus pentoxide at the temperature 78°C. Elemental analysis were carried out on CHNS-OCE analyzer, type FISONS EA 1110.

NMR spectra were measured in deuterated dimethylsulfoxide on the spectrometer Varian Mercury-Vx BB 300 working at 300 MHz for ^{1}H and at 75 MHz for ^{13}C. Chemical shifts were measured at δ values in ppm and relative to tetramethylsilane using the residual signals of the solvent (2.49 for ^{1}H and 39.7 for ^{13}C).

Quantum-chemical calculations were carried out by the following procedure. First the model of the compound was calculated using the AM1 semiempirical method; the lowest energy conformer was searched using the molecular dynamics (software HyperChem, version 6.03). This conformer was geometry optimized on B3LYP/6-311+G(d,p) level (program Gaussian 94) and then the HOMO orbital was calculated.

Tetrazole-5-thiols (General Procedure).

Triethylammonium Salts of Dithiocarbamic Acids. Primary amine (0.01 mol) was dissolved in dry diethyl ether (50 ml) and dry triethylamine (0.01 mol) was added. The solution was cooled to -10°C and dry carbon disulfide (0.01 mol) was added through silicon septum during 5 min. The reaction mixture was stored overnight at 2-5°C. Crystals of triethylammonium salt were filtered off and used for the next reaction without further characterization. Yields were 75-95%.

Isothiocyanates. The triethylammonium salt of dithiocarbamic acid and an equimolar amount of triethylamine was dissolved in 200 ml of dry chloroform and cooled to -50°C. An equimolar amount of ethyl chloroformate was added rapidly such that the temperature did not rise above -10°C. Then the reaction mixture was stirred, left to reach room temperature, extracted with 10% hydrochloric acid, and the water and organic layer evaporated. The crude isothiocyanate was distilled *in vacuo.* Yields were 70-85%.

1-Substituted tetrazole-5-thiols. The isothiocyanate, water (250 ml), and an equimolar amount of sodium azide were stirred under reflux for 3 h, cooled to room temperature, extracted by diethyl ether, and the water phase acidified by conc. hydrochloric acid. The white crystals were filtered off, washed with water, and recrystallized from aqueous ethanol.

1-Methyltetrazole-5-thiol was prepared according to Stolle [6]. All 1-substituted tetrazole-5-thiols prepared are presented in Table 3.

N-Dichloromethylene-4-chloroaniline (8). Dry chlorine was loaded into the solution of phenyl isothiocyanate (0.1 mol) in dry dichloromethane (250 ml) for 12 h. The excess of chlorine was then eliminated by a flow of dry nitrogen; the reaction mixture was then evaporated *in vacuo* at a bath temperature of ≤25°C and the oily residue was immediately used in the following reaction.

5-Chloro-1-(4-chlorophenyl)tetrazole. Activated sodium azide [13] (0.1 mol) was added to crude azomethine **8** dissolved in 250 ml of dry dimethoxyethane and this reaction mixture was stirred overnight. The solution was then poured into ice water. The resulting solid was filtered off, washed with water, and dried. The crude 5-chloro-4-chlorophenyltetrazole was recrystallized from benzene–petroleum ether mixture; mp 73-74°C (74-75°C [14]).

Preparation of Sulfides 5 (General Procedure). 5-Halotetrazole (1 mmol) was melted on an oil bath at 95°C. Sodium tetrazole-5-thiolate **3** (1.1 mmol) was then added in portions. The reaction mixture was stirred and the reaction process was monitored by TLC. The starting 5-halotetrazole **4** was used as a standard. The reaction was finished after 3 h. The reaction mixture was suspended in dry chloroform and the unreacted thiolate or sodium halogenide formed were filtered off. Filtrate was evaporated to dryness and recrystallized from aqueous ethanol.

If the purity of the obtained product was not sufficient, column chromatography or preparative TLC was performed.

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