Chemistry of Heterocyclic Compounds, Vol. 40, No. 9, 2004

SYNTHESIS OF SUBSTITUTED 1,2,4-TRIAZOLES AND 1,3,4-THIADIAZOLES

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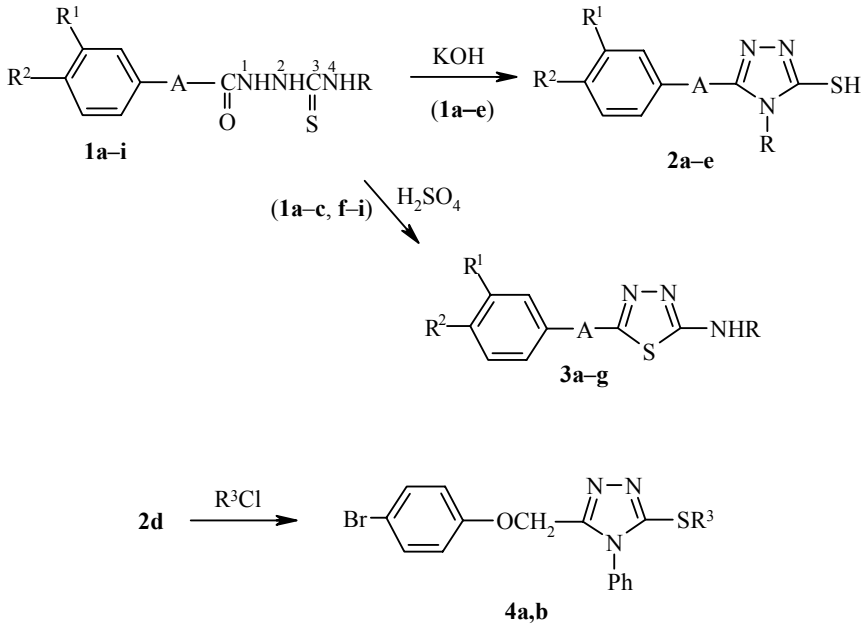
The cyclization of 4-substituted 1-arylacetyl- and 1-aryloxyacetylthiosemicarbazides and also the potassium salt of (4-bromophenoxy)acetodithiocarbazinic acid in the presence of base gives the novel 3-arylmethyl- and 3-aryloxymethyl-5-mercapto-1,2,4-triazoles and, in the presence of concentrated H_2SO_4, the novel 5-substituted 2-arylmethyl- and 2-aryloxymethyl-1,3,4-thiadiazoles.

Keywords: thiadiazole, thiosemicarbazide, triazole, cyclization.

Certain substituted 1,2,4-triazoles show anti-inflammatory [1], vasodilatory [2], and psychotropic [3] properties and derivatives of 5-amino-2-mercapto-1,3,4-thiadiazoles are active antimicrobial [4], hypoglycemic [5, 6], or antitumor [7] agents. In a search for novel, active compounds within this group we have synthesized, in this study, previously unrecorded 1,2,4-triazole and 1,3,4-thiadiazole derivatives having an arylmethyl or aryloxymethyl substituent.



1a–i **2a–e** **3a–g** **4a,b**

1a,**b**-**3a**,**b** R^1 = Br, R^2 = MeO, A = CH_2, **a** R = Me, **b** R = Ph; **1c**-**f**, **2c**-**e**, **3c**,**d** R^1 = H, R^2 = Br, A = OCH_2, **1c**-**3c** R = $PhCH_2$; **1d**, **2d** R = Ph, **1e**, **2e** R = All, **1f**, **3d** R = PhCO, **1g**, **3e** R^1 = H, R^2 = MeO, A = CH_2, R = Me; **1h**,**i**, **3f**,**g** R^1 = Br, A = CH_2, R = Ph, **1h**, **3f** R^2 = *i*-Pr, **1i**, **3g** R^2 = Bu; **4a** R^3 = $PhCH_2$, **4b** R^3 = NH_2COCH_2

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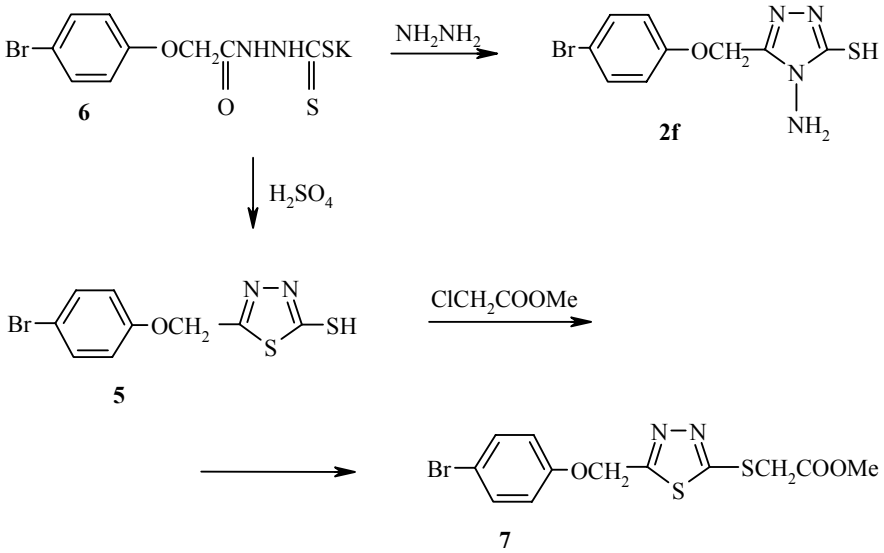
The starting 1,4-disubstituted thiosemicarbazides **1a-i** were prepared by us by treatment of arylacetic and aryloxyacetic acid hydrazides with different isothiocyanates [8, 9]. Compounds **1a-e** were cyclized in basic medium (4.5% aqueous KOH solution) with subsequent acidification of the reaction mixture using acetic acid to give the 3,4-disubstituted 5-mercapto-1,2,4-triazoles **2a-e**. Dehydrative cyclization of the thiosemicarbazides **1a-c,f-i** in the presence of conc. H_2SO_4 led to the corresponding 2,5-disubstituted 1,3,4-thiadiazoles **3a-g** which occurred as white, crystalline materials, difficultly soluble in conventional organic solvents.

The reaction of 5-mercaptotriazole **2d** with benzyl chloride or chloroacetamide in basic medium gave the corresponding S-substituted triazoles **4a,b** in close to quantitative yields.

The potassium salt of 4-amino-3-(4-bromophenoxy)acetodithiocarbazinic acid (**6**) was used for the synthesis of 4-amino-3-(4-bromophenoxymethyl)-5-mercapto-1,2,4-triazole (**2f**) and 2-(4-bromophenoxy-methyl)-5-mercapto-1,3,4-thiadiazole (**5**). The cyclization of **6** in hydrazine gave triazole **2f** and in conc. H_2SO_4 the 1,3,4-thiadiazole **5**.



Thiadiazole **5** was treated with methyl chloroacetate to give the corresponding S-substituted derivative **7**.

The composition and structure of the synthesized compounds **1-5, 7** were confirmed by the results of elemental analysis (Table 1), ^{1}H NMR spectroscopic data (Table 2), and mass spectrometry.

TABLE 1. Parameters for the Compounds Synthesized

Compound	Empirical formula	Found, % / Calculated, %				mp, °C	R_f*	Yield, %
		C	H	N	S			
1	2	3	4	5	6	7	8	9
2a	$C_{11}H_{12}BrN_3OS$	42.28 / 42.05	3.67 / 3.85	13.56 / 13.37	9.88 / 10.20	224-226	0.59	85.3
2b	$C_{16}H_{14}BrN_3OS$	51.24 / 51.07	3.76 / 3.75	11.08 / 11.17	8.67 / 8.52	203-205	0.71	90.4
2c	$C_{16}H_{14}BrN_3OS$	51.23 / 51.07	3.61 / 3.75	11.02 / 11.17	8.63 / 8.52	193-195	0.61	79.8
2d	$C_{15}H_{12}BrN_3OS$	49.61 / 49.79	3.28 / 3.34	11.73 / 11.60	8.57 / 8.85	211-213	0.57	75.6
2e	$C_{12}H_{12}BrN_3OS$	44.48 / 44.18	3.62 / 3.71	12.70 / 12.88	9.64 / 9.83	132-133	0.47	76.9

TABLE 1 (continued)

1	2	3	4	5	6	7	8	9
2f	$C_9H_9BrN_4OS$	34.25 34.08	2.70 2.86	17.32 17.67	10.01 10.11	186-187	0.52	83.3
3a	$C_{11}H_{12}BrN_3OS$	42.30 42.05	3.68 3.85	13.11 13.37	10.46 10.20	220-222	0.49	20.0
3b	$C_{16}H_{14}BrN_3OS$	50.93 51.07	3.57 3.75	11.24 11.17	8.29 8.52	180-182	0.85	85.1
3c	$C_{16}H_{14}BrN_3OS$	51.36 51.07	3.59 3.75	11.32 11.17	8.40 8.52	157-159	0.62	74.5
3d	$C_{16}H_{12}BrN_3O_2S$	49.51 49.24	3.31 3.10	10.61 10.77	8.53 8.27	210-212	0.70	84.6
3e	$C_{11}H_{13}N_3OS$	56.05 56.15	5.71 5.57	18.06 17.86	13.38 13.63	195-197	0.80	47.7
3f	$C_{18}H_{18}BrN_3OS$	53.64 53.47	4.36 4.49	10.11 10.39	8.23 7.93	161-163	0.78	85.0
3g	$C_{19}H_{20}BrN_3OS$	54.77 54.55	5.04 4.82	10.31 10.04	7.85 7.66	165-167	0.80	95.7
4a	$C_{22}H_{18}BrN_3OS$	58.64 58.40	4.32 4.01	9.11 9.29	7.25 7.09	109-110	0.57	97.3
4b	$C_{17}H_{15}BrN_4O_2S$	48.49 48.70	3.72 3.61	13.61 13.36	7.32 7.65	146-147	0.60	96.2
5	$C_9H_7BrN_2OS_2$	35.41 35.65	2.47 2.33	9.51 9.24	21.32 21.15	139-140	0.63	86.1
7	$C_{12}H_{11}BrN_2O_3S_2$	38.22 38.41	2.71 2.95	7.19 7.47	17.43 17.09	111-113	0.47	76.3

* Solvent systems; methanol–ether, 1:1 (compounds **2a,b**); dioxane–benzene, 1:2 (compounds **2c-f, 3c,d 4a,b, 5,** and **7**); acetone–benzene, 1:1 (compounds **3a,b,e-g**).

TABLE 2. ^{1}H NMR Spectra of the Synthesized Compounds

Compound	Chemical shifts, δ, ppm (SSCC, *J*, Hz)*
2a	3.37 (3H, s, NCH_3); 3.88 (3H, s, OCH_3); 4.03 (2H, s, CH_2); 6.92-7.50 (3H, m, C_6H_3); 13.4 (1H, br. s, SH)
2b	3.77 (2H, s, CH_2); 3.85 (3H, s, OCH_3); 6.80-7.55 (8H, m, C_6H_3, C_6H_5); 13.6 (1H, br. s, SH)
2c	4.85 (2H, s, CH_2); 5.25 (2H, s, OCH_2); 6.62-7.42 (9H, m, C_6H_4, C_6H_5); 13.82 (1H, br. s, SH)
2d	4.82 (2H, s, OCH_2); 6.65-7.59 (9H, m, C_6H_4, C_6H_5); 13.82 (1H, br. s, SH)
2e	4.70 (2H, d, J = 6.5, N–CH_2); 5.08 (2H, s, OCH_2); 5.09-5.20 (2H, m, CH=$\underline{CH_2}$); 5.90 (1H, m, $\underline{CH}$=CH_2); 6.90-7.42 (4H, m, C_6H_4); 13.72 (1H, br. s, SH)
3a	3.35 (3H, s, N–CH_3); 3.82 (3H, s, OCH_3); 4.15 (2H, s, CH_2); 6.82-7.35 (3H, m, C_6H_3); 10.10 (1H, br. s, NH)
3b	3.86 (3H, s, OCH_3); 4.17 (2H, s, CH_2); 6.88-7.58 (8H, m, C_6H_3, C_6H_5); 10.00 (1H, br. s, NH)
3d	5.43 (2H, s, OCH_2); 6.90-8.20 (9H, m, C_6H_4, C_6H_5); 12.90 (1H, br. s, NH)
4a	4.40 (2H, s, SCH_2); 5.04 (2H, s, OCH_2); 6.81-7.57 (14H, m, C_6H_4, $2C_6H_5$)
4b	3.87 (2H, s, SCH_2); 5.03 (2H, s, OCH_2); 6.78-7.60 (9H, m, C_6H_4, C_6H_5); 6.96 and 7.50 (2H, two br. s, NH_2)
5	5.50 (2H, s, OCH_2); 6.85-7.42 (4H, m, C_6H_4); 14.40 (1H, br. s, SH)
7	3.69 (3H, s, OCH_3); 4.13 (2H, s, SCH_2); 5.40 (2H, s, OCH_2); 6.90-7.40 (4H, m, C_6H_4)

* Spectra recorded in DMSO-d_6 (**2-5**) and CD_3OD (**7**).

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Mercury-300 (300 MHz) instrument and mass spectra on an MX-1320 spectrometer with direct introduction of the sample into the ion source. TLC was performed using Silufol UV-254 plates and revealed using iodine vapor.

3-(3-Bromo-4-methoxybenzyl)-4-R-5-mercapto-1,2,4-triazoles (2a,b) and 3-(4-Bromophenoxymethyl)-4-R-5-mercapto-1,2,4-triazoles (2c-e) (General Method). A solution of KOH (40 mmol) in water (30 ml) was added to a solution of the thiosemicarbazide **1a-e** (25 mmol) and the mixture was refluxed for 2 h. The cooled solution was acidified with glacial acetic acid and the precipitated product **2a-e** was filtered off and recrystallized from methanol. Mass spectrum of compound **2b**, *m/z* (I_{rel}, %): 375/377 $[M]^+$ (96/100), 360/362 (29/29), 199/201 (14/15), 77 (50).

2-(3-R^1-4-R^2-Phenylmethyl)-5-NHR-1,3,4-thiadiazoles (3a,b,e-g) and 2-(3-R^1-4-R^2-Phenoxymethyl)-5-NHR-1,3,4-thiadiazoles (3c,d) (General Method). The thiosemicarbazide **1a-c, f-i** (25 mmol) was dissolved portionwise in conc. H_2SO_4 (d = 1.836, 35 ml). The solution was poured into iced water (250 ml). The precipitated, white crystalline products **3a-g** were filtered off, washed on the filter to neutral reaction of the water washes, and recrystallized from ethanol. Mass spectrum of compound **3b**, *m/z* (I_{rel}, %): 375/377 $[M]^+$ (72/68), 257/259 (24/27), 199/201 (40/32), 77 (86).

5-Benzylthio- and 5-Acetamidothio-3-(4-bromophenoxymethyl)-4-phenyl-1,2,4-triazole (4a and 4b) (General Method). The triazole **2d** (5 mmol) was dissolved in 15 ml of a solution of KOH (5 mmol) in methanol at 40°C. Benzyl chloride or chloroacetamide (5 mmol) was added to the solution obtained and the mixture was refluxed for 1 h. After cooling, the precipitated product **4a,b** was filtered off and recrystallized from methanol.

4-Amino-3-(4-bromophenoxymethyl)-5-mercapto-1,2,4-triazole (2f). A mixture of the salt **6** (10 mmol), hydrazine (95%, 20 mmol), and water (1 ml) was refluxed with stirring to the evolution of hydrogen sulfide. Iced water (50 ml) was added to the reaction mass and the mixture was acidified using conc. HCl. The precipitated product **2f** was filtered off, washed on the filter with water, dried, and recrystallized from ethanol. Mass spectrum, *m/z* (I_{rel}, %): 300/302 $[M]^+$ (40/32), 172/174 (100/94), 129 (87), 75 (23).

2-(4-Bromophenoxymethyl)-5-mercapto-1,3,4-thiadiazole (5). The salt **6** (5 mmol) was added in small portions with stirring to H_2SO_4 (d = 1.836, 7 ml) at 0°C. After complete addition of the salt the stirring was continued for a further 15 min and the solution was poured into ice (100 g). The precipitated crystalline product **5** was filtered off, washed with water, dried, and recrystallized from ethanol.

2-(4-Bromophenoxymethyl)-5-carboxymethylmethylthio-1,3,4-thiadiazole (7). Prepared from the thiadiazole **5** (5 mmol) and methyl chloroacetate (5 mmol) as in the method for the synthesis of the products **4a,b** (see above).

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