SYNTHESIS OF NOVEL HETEROCYCLES FROM THIAZOLECARBOHYDRAZIDES

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Cyclization of 2-methyl (or -phenyl)-5-phenylthiazole-4-carbohydrazides (1) and (2) under various conditions gives differing oxadiazoles: 2-(2'-substituted-5'-phenyl-4'-thiazolyl)-1,3,4-oxadiazole-5-thiones (7) and (8), and 2-(2'-substituted-5'-phenyl-4'-thiazolyl)-1,3,4-oxadiazoles (9) and (10). Cyclodehydration of thiazolecarbonylthiosemicarbazides (3)-(6) with NaOH gives the 3-(2'-substituted-5'-phenyl-4'-thiazolyl)-4-substituted-4H-5-mercapto-1,2,4-triazoles (11)-(14), while H_3PO_4 gives the 2-(2'-substituted-5'-phenyl-4'-thiazolyl)-5-phenylamino-1,3,4-thiadiazoles (15) and (16).

Keywords: *hydrazide, thiosemicarbazide, thiazole, oxadiazole, triazole, thiadiazole.*

With the aim of obtaining novel functionally substituted thiazoles having biological activity, we previously synthesized 2-[2'-(2'-methyl-5'-phenyl-4'-thiazolylcarbonyl)]-5-phenylthiazole-4-carboxylic acid and 2-methyl-5-phenyl-4(3-phenyl-1,3-thiazolidin-4-on-2-ylidene)carboxyhydrazinothiazole from 1-(4-thiazolcarbonyl)thiosemicarbazides [1]. Continuing this work, we here report the synthesis of novel diheterocyclic compounds from 2-methyl (or -phenyl)-5-phenylthiazolecarbohydrazides. There have been reports of oxadiazoles, triazoles, and thiadiazoles with phenyl [2-6], indolyl [7, 8], benzofuryl [9], benzotriazolyl [10], quinolinyl [11], imidazolyl [12], and other substituents. There is, however, little information on such compounds containing thiazolyl groups [13].

The cyclization of 5-phenyl-2-substituted thiazolecarbohydrazides (**1**), (**2**) [1] to 2-(2'-substituted-5-phenylthiazolyl)-1,3,4-oxadiazole -5-thiones (**7**), (**8**) has been effected by reacting (**1**) and (**2**) with CS_2 in methanolic KOH [14]. The presence in the IR spectra of (**7**) and (**8**) of absorption for C=S, C=N, and N—H at 1380 and 1365, 3370 and 3340, 1610 and 1615 cm^{-1}, respectively, and the absence of absorption for S—H, show that the thiolactam form H—N=C=S is present.

Prolonged heating of hydrazides (**1**) and (**2**) in triethoxymethane gives the oxadiazoles (**9**) and (**10**). Conversion of the hydrazide moiety in (**1**) and (**2**) into the oxadiazole moiety is shown by the disappearance in their IR spectra of absorption for C=O and N—H, and the appearance in the PMR spectra of a singlet signal at 8.20 ppm.

TABLE 1. Spectral Features of Compounds (**7**)-(**16**)

Compound	ν, cm^{-1}	δ, ppm
7	1380 (C=S), 1610 (C=N), 3370 (N–H)	2.37 s (CH_3), 7.30–7.56 m (C_6H_5), $(CD_3)_2SO$
8	1365 (C=S), 1615 (C=N), 3340 (N–H)	7.06–8.06 m ($2C_6H_5$), $(CD_3)_2SO$
9	1585 (C=N), 3125 (C–H)	2.52 s (CH_3), 7.10–7.53 m (C_6H_5), 8.20 s (CH), $CDCl_3$
10	1580 (C=N), 3140 (C–H)	7.00–7.43 m ($2C_6H_5$), 8.20 s (CH), $CDCl_3$
11	1590 (C=N), 2580 (S–H), 3110 (NH)	2.70 s (CH_3), 3.30 br.s (NH), 7.33 s (C_6H_5), 13.3 br.s (SH), $(CD_3)_2SO$
12	1595 (C=N), 2560 (S–H)	2.63 s (CH_3), 6.60–7.26 m ($2C_6H_5$), 19.26 br.s (SH), $CDCl_3$
13	1585 (C=N), 2580 (S–H)	7.30–8.13 m ($2C_6H_5$), 13.3 br.s (SH), $(CD_3)_2SO$
14	1595 (C=N), 2590 (S–H)	7.16–8.13 m ($3C_6H_5$), 21.16 br.s (H), $(CD_3)_2SO$
15	1620 (C=N), 3190 (N–H)	2.66 s (CH_3), 7.00–7.66 m ($2C_6H_5$), $(CD_3)_2SO$
16	1620 (C=N), 3200 (N–H)	7.10–7.86 m ($3C_6H_5$), $(CD_3)_2SO$

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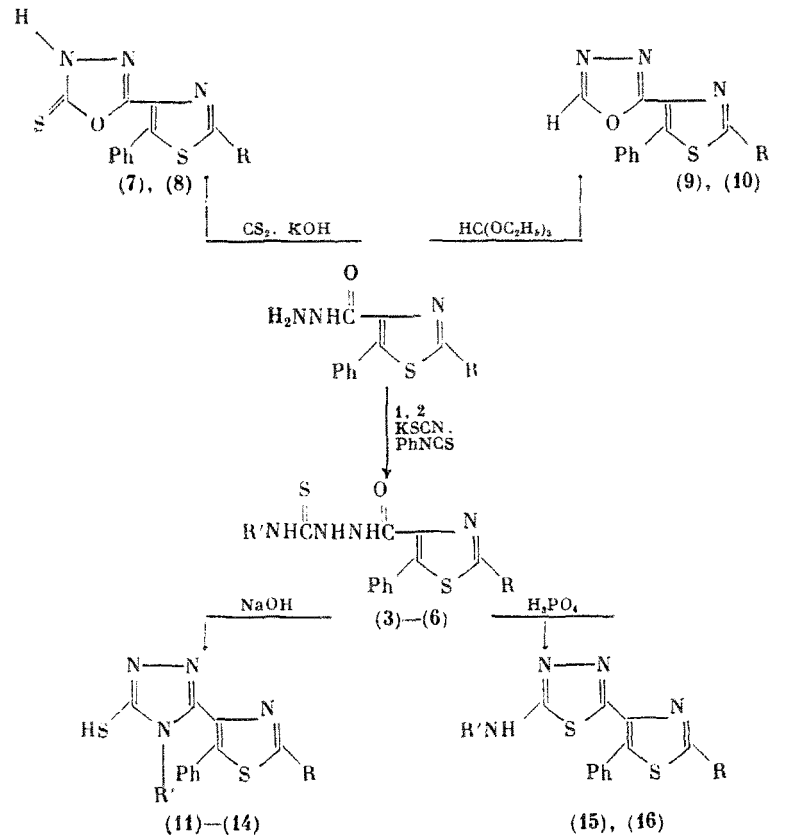
Cyclization of the thiosemicarbazides (3)-(6) has given the triazoles (11)-(14). The required thiosemicarbazides were obtained from the hydrazides (1) and (2), and potassium thiocyanate or phenyl isothiocyanate under the appropriate conditions [1]. On boiling thiosemicarbazides (3) and (6) with 4% aqueous NaOH for 3 h, there were obtained the 3-(2′-substituted-5′-phenylthiazolyl)-4-substituted-4H-5-mercapto-1,2,4-triazoles (11)-(14). The absence of C=S absorption in the IR spectra, and the appearance of S—H absorption at 2560-2590 cm^{-1}, show that the compounds are in the thiolactim forms —N=C—SH.

Cyclodehydration of 1′-[2-methyl (or phenyl)-5-phenyl-4-thiazolylcarbonyl]-4′-phenylthiosemicarbazides (5) and (6) by heating briefly with anhydrous H_3PO_4 afforded the 2-(2′-methyl (or phenyl)-5′-phenyl-4′-thiazolyl)-5-phenylamino-1,3,4-thiadiazoles (15) and (16). The absence from the IR spectra of C=O absorption and the appearance of absorption for C=N at 1620 cm^{-1} confirms the formation of the thiadiazoles (15) and (16).

The structures of all the products (7)-(16) were confirmed by their IR and PMR spectra (Table 1) and elemental analyses (Table 2).



No.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
R	Me	Ph	Me	Ph	Me	Ph	Me	Ph	Me	Ph	Me	Ph	Me	Ph	Me	Ph
R′	—	—	H	H	Ph	Ph	—	—	—	—	H	H	Ph	Ph	Ph	Ph

EXPERIMENTAL

PMR spectra were obtained on a Varian T-60, operating frequency 60 MHz, with TMS as internal standard. IR spectra were recorded on a UR-20 as pastes in vaseline grease.

2-(2′-Methyl-5′-phenyl-4′-thiazolyl)-1,3,4-oxadiazole-5-thione (7). To a solution of 4.15 g (0.017 mole) of (1) and 1.00 g (0.017 mole) of KOH in 100 ml of absolute ethanol was added portionwise 4.07 g (3.22 ml, 0.051 mole) of CS_2 with ice-water cooling. The mixture was shaken for a few minutes, then heated on the water bath to the boil. Boiling was continued for 4 h to remove the H_2S formed; then the solvent was removed under reduced pressure, and the residual crystalline solid dissolved in ~50 ml of cold water. Acidification with dilute HCl precipitated a crystalline solid which was filtered off, air-dried, and recrystallized.

Similarly, from (2) there was obtained 2-(2′,5′-diphenyl-4′-thiazolyl)-1,3,4-oxadiazole-5-thione (8).

2-(2′-Methyl-5′-phenyl-4′-thiazolyl)-1,3,4-oxadiazole (9). A solution of 2.30 g (0.010 mole) of (1) in 40 ml of triethoxymethane was boiled for 40 h; then the triethoxymethane was removed under reduced pressure, and the residue recrystallized from ethanol.

Similarly, from (2) there was obtained 2-(2′,5′-diphenyl-4′-thiazolyl)-1,3,4-oxadiazole (10).

TABLE 2. Yields, Solvents for Recrystallization, Melting Points, and Elemental Analyses for Compounds (7)-(16)

Compound	Yield, %	Solvent	Mp, °C	Empirical formula	Found / Calculated, %			
					C	H	N	S
7	78	EtOH	180–181	$C_{12}H_9N_3OS_2$	52.19 / 52.36	3.24 / 3.26	15.32 / 15.25	23.40 / 23.29
8	72	MeOH	212–213	$C_{17}H_{11}N_3OS_2$	60.70 / 60.53	3.28 / 3.26	12.53 / 12.45	20.11 / 19.01
9	58.8	EtOH	139–140	$C_{12}H_9N_3OS$	60.01 / 59.26	3.70 / 3.70	17.32 / 17.27	13.30 / 13.18
10	45.7	EtOH	141–142	$C_{17}H_{11}N_3OS$	69.11 / 68.89	3.75 / 3.60	13.44 / 13.76	10.87 / 10.50
11	67	*i*-PrOH	276–277	$C_{12}H_{10}N_4S$	52.77 / 52.55	3.69 / 3.64	20.40 / 20.42	22.97 / 23.38
12	88.8	–	255–256	$C_{17}H_{12}N_4S_2$	60.97 / 60.71	3.69 / 3.56	15.98 / 16.65	18.62 / 19.06
13	63.9	*i*-PrOH	188–189	$C_{18}H_{14}N_4S_2$	61.50 / 61.71	3.96 / 3.99	15.76 / 15.98	18.44 / 18.30
14	89.5	–	226–227	$C_{23}H_{16}N_4S_2$	67.08 / 66.98	3.90 / 3.88	13.65 / 13.58	15.66 / 15.54
15	68.4	Dioxane	258–260	$C_{18}H_{14}N_4S_2$	62.05 / 61.71	3.97 / 3.99	15.66 / 15.98	18.27 / 18.30
16	70	Dioxane	255	$C_{23}H_{16}N_4S_2$	66.80 / 66.98	3.65 / 3.88	13.63 / 13.58	15.41 / 15.54

The thiosemicarbazides (3)-(6) were obtained as described in [1].

3-(2′-Methyl-5′-phenyl-4′-thiazolyl)-4H-5-mercapto-1,2,4-triazole (11). A solution of 2.00 g (0.008 mole) of (3) in 4% NaOH solution was boiled for 3 h. The mixture was filtered, cooled to ~20°C, and the filtrate acidified with dilute HCl to pH 5-6. The crystalline solid which separated was filtered off, washed until neutral, and air-dried.

Triazoles (12)-(14) were obtained similarly.

2-(2′-Methyl-5′-phenyl-4′-thiazolyl)-5-phenylamino-1,3,4-thiadiazole (15). To anhydrous H_3PO_4, obtained by mixing 50 ml of 85% H_3PO_4 with 21.05 g of P_2O_5, was added portionwise with stirring 2.00 g (0.005 mole) of (5). The temperature of the mixture was raised gradually to 110°C, and stirring continued for 0.5 h. After cooling to 20°C, the mixture was poured into ice water, and the solid which separated was filtered off, washed with water, air-dried, and recrystallized.

Obtained similarly was 2-(2′,5′-diphenyl-4′-thiazolyl)-5-phenylamino-1,3,4-thiadiazole (16).

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