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A series of 5-substituted-2-(4-alkyl or phenyl-1,2,3-thia(or selena)diazol-5-yl)-1,3,4-oxadiazoles were prepared. 5-Substituted-2-(4-phenyl-1,2,3-selenadiazol-5-yl)-1,3,4-oxadiazoles upon pyrolysis afforded the corresponding alkynes. Also, a series of 5-substituted-4-amino-3-(1,2,3-thiadiazol-5-yl)-*s*-triazoles and 5-(1,2,3-thiadiazolyl)-*s*-triazolo[3,4-*b*]-1,3,4-thiadiazoles were prepared.

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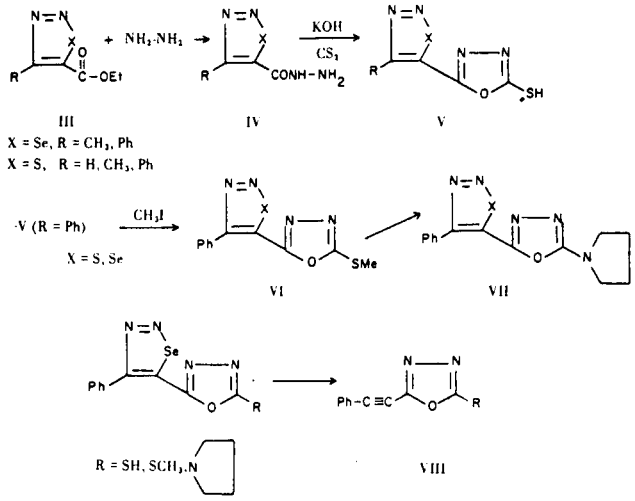
In previous papers (1-5) the synthesis of 1,2,3-selenadiazoles and the utility of this heterocyclic ring system for the preparation of alkynes was reported.

II

In continuation of our study on the chemistry of sulfur and selenium heterocyclic compounds (6-9) a series of 5-substituted-2-(4-alkyl or phenyl-1,2,3-selena(or thia)diazol-5-yl)-1,3,4-oxadiazoles were synthesized and their reaction toward heat was studied. The latter compounds were synthesized starting from the readily available ethyl 4-substituted-1,2,3-thia(or selena)diazole carboxylate (III) (3,9) (See Scheme I).

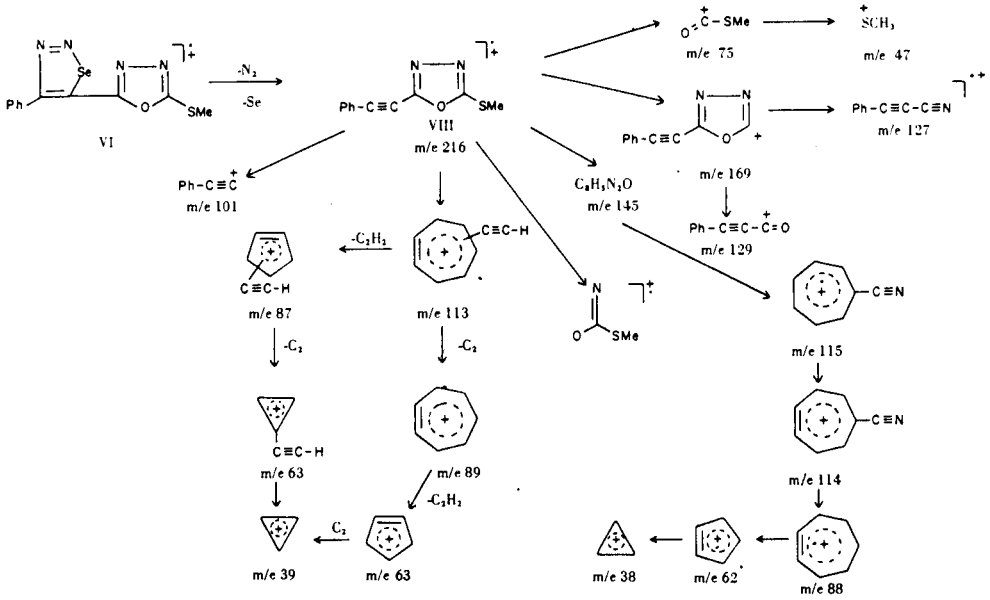
2-(1,2,3-Selenadiazol-5-yl)-1,3,4-oxadiazoles upon pyrolysis afforded alkynes while their corresponding thia-analog was stable under the similar conditions (See Scheme I).

Scheme I



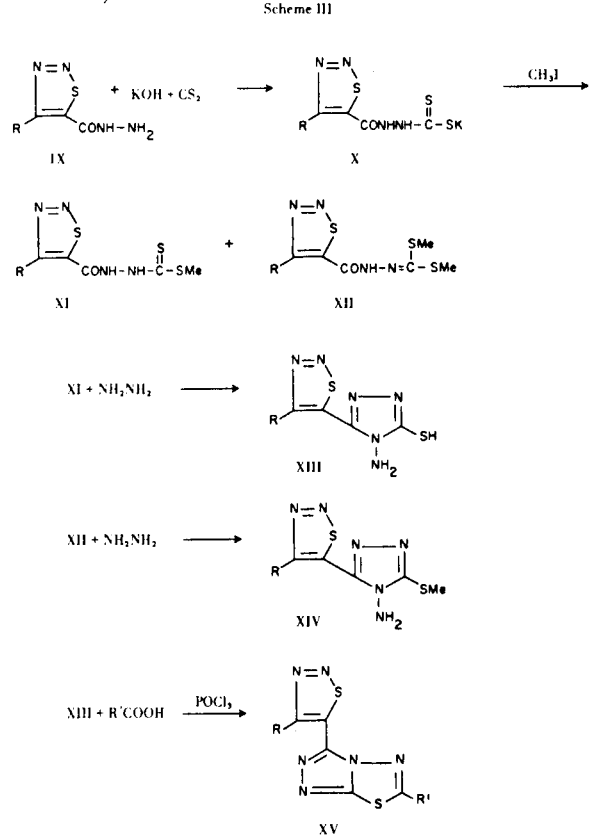
The mass spectra fragmentation pattern of compound VI (X = Se) is summarized in Scheme II, and is in good agreement with the structure VI. All the ions seen below 216 are identical with those of compound VIII (R = SCH_3) and are in accordance with the suggested pattern (See also 10,11).

Scheme II



Finally, in view of the potent pharmacological activity of 1,2,3-thiadiazole ring system (9) it was also of our interest to incorporate this moiety to triazole and triazolothiadiazole ring system. Therefore, 1,2,3-thiadiazole carboxyhydrazides (IX) was allowed to react with carbon disulfide in the presence of potassium hydroxide to give the compound X. Subsequent reaction of the latter with methyl iodide afforded two compounds XI and XII. Reaction of compound XI with hydrazine (12) gave 4-amino-5-mercapto-3-(1,2,3-thiadiazol-5-yl)-*s*-triazole (XIII). The reaction of XII with hydrazine gave 4-amino-5-methylmercapto-3-(1,2,3-thiadiazol-5-yl)-*s*-triazole (XIV) (See Scheme III).

Scheme III



Reaction of compound XIII with a number of carboxylic acids in the presence of phosphorous oxychloride similar to the method of preparation of 2-amino-1,3,4-thia and selenadiazoles (7,13) gave in high yield 2,5-disubstituted-*s*-triazolo[3,4-*b*]-1,3,4-thiadiazoles (XIV) (See Scheme III).

The physical data of all compounds prepared are summarized in Tables I and II. The structure of all compounds was confirmed by analytical and spectroscopic methods.

EXPERIMENTAL

Melting points were taken on a Kofler hot stage microscope and uncorrected. The ir spectra were obtained on a Perkin-Elmer Model 267 spectrograph. Nmr spectra were determined using a Varian T-60 spectrometer. Mass spectra were run on a Varian MAT CH-5 spectrometer at Aryamehr University of Technology.

2-(4-Methyl-1,2,3-selenadiazol-5-yl)-5-mercapto-1,3,4-oxadiazole (V, X = Se, R = CH_3).

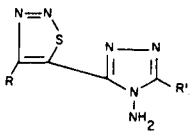
To a solution of 4-methyl-1,2,3-selenadiazole-5-carboxyhydrazide (IV) (9) (1.03 g., 5 mmoles) in 15 ml. of ethanol was added a solution of potassium hydroxide (0.28 g., 5 mmoles) in 0.5 ml. of water and 0.4 ml. of carbon disulphide. The mixture was refluxed for 6 hours, and filtered. The solvent was evaporated under reduced pressure. The residue was dissolved in water and acidified with acetic acid. The precipitate was filtered and crystallized from alcohol to give V (0.55 g., 44%), m.p. 206-208°; mass spectrum m/e (%): 248 (28), 246 (13), 220 (27), 218 (13), 177 (33), 160 (28), 140 (100), 131 (12), 119 (17), 118 (12), 117 (18), 107 (7), 93 (24), 91 (11), 80 (100), 65 (8), 67 (21), 64 (11), 59 (17), 52 (11), 51 (44), 50 (29), 42 (18), 39 (75), 38 (21), and 37 (16).

4-Phenyl-1,2,3-selenadiazole-5-carboxyhydrazide (IV, R = C_6H_5).

To a solution of hydrazine hydrate (15 g., 0.3 mole) in 60 ml. of ethanol was added a solution of 4-phenyl-1-2,3-selenadiazole-5-carboxylate (III)(3)(28.2 g., 0.1 mole) in 50 ml. of ethanol. After 2 hours at room temperature the precipitate was filtered and the residue was crystallized from ethanol to give V (R = Ph, 16 g., 60%), m.p. 115-117°.

Anal. Calcd. for $C_9H_8N_4OSe$: C, 40.45; H, 2.99; N, 20.97. Found: C, 40.68; H, 3.05; N, 20.78.

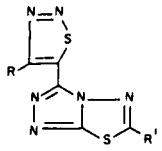
Table I



R	R'	M.p., °C	Yield (%)	Formula	C % Calcd.	C % Found	H % Calcd.	H % Found	N % Calcd.	N % Found
H	SH	196-198 (a)	42	$C_4H_4N_6S_2$	24.00	24.12	2.00	2.05	42.00	42.15
CH_3	SH	212-213 (a)	43	$C_5H_6N_6S_2$	28.04	28.19	2.80	2.65	39.25	39.10
H	SCH_3	234-235 (b)	43	$C_5H_6N_6S_2$	28.04	28.21	2.80	2.62	39.25	39.30
CH_3	SCH_3	255-257 (a)	45	$C_6H_8N_6S_2$	31.58	31.72	3.51	3.37	36.84	36.71

(a) The compound was crystallized from ethanol. (b) The compound was crystallized from DMSO.

Table II



R	R′	M.p., °C	Yield (%)	Formula	C % Calcd.	C % Found	H % Calcd.	H % Found	N % Calcd.	N % Found
H	H	224-225 (a)	85	$C_5H_2N_6S_2$	28.57	28.69	0.95	0.97	40.00	40.12
H	CH_3	249-250 (b)	96	$C_6H_4N_6S_2$	32.14	32.01	1.78	1.83	37.50	37.62
H	C_2H_5	209-210 (c)	96	$C_7H_6N_6S_2$	35.29	35.37	2.52	2.67	35.29	25.18
H	CF_3	234-235 (a)	95	$C_6H_1F_3N_6S_2$	25.90	25.81	0.36	0.35	30.22	30.37
H	C_6H_5	292-294 (b)	96	$C_{11}H_6N_6S_2$	46.15	46.02	2.10	2.25	29.37	29.22
H	$CH_2C_6H_5$	180-182 (c)	96	$C_{12}H_8N_6S_2$	48.00	48.15	2.67	2.75	28.00	28.17
CH_3	H	228-230 (d)	80	$C_6H_4N_6S_2$	32.14	32.21	1.78	1.63	37.50	37.65
CH_3	CH_3	230-232 (d)	96	$C_7H_6N_5S_2$	35.29	35.45	2.52	2.43	35.29	35.38
CH_3	C_2H_5	164-165 (c)	60	$C_8H_8N_6S_2$	38.10	38.01	3.17	3.03	33.33	33.17
CH_3	CF_3	184-185 (d)	74	$C_7H_3F_3N_6S_2$	28.77	28.64	1.03	1.15	28.77	28.89
CH_3	Ph	240-242 (c)	96	$C_{12}H_8N_6S_2$	48.00	47.86	2.67	2.78	28.00	28.16
CH_3	CH_2-Ph	146-147 (c)	50	$C_{13}H_{10}N_6S_2$	49.68	49.72	3.18	3.23	26.75	26.87

(a) The compound was crystallized from dimethyl sulfoxide-water. (b) The compound was crystallized from dimethyl sulfoxide. (c) The compound was crystallized from ethanol. (d) The compound was crystallized from ethanol-water.

2-(4-Phenyl-1,2,3-selenadiazol-5-yl)-5-mercapto-1,3,4-oxadiazole (V, X = Se, R = C_6H_5).

This compound was prepared similar to its methyl analog in 77% yield (See Table I).

Ethyl 1,2,3-Thiadiazole-5-carboxylate (III, X = S, R = H).

Thionyl chloride (100 ml.) was gradually added to ethyl formylacetate semicarbazone (69.2 g., 0.4 mole) at ice-bath temperature, and the mixture was kept 30 minutes at this temperature. Chloroform (200 ml.) was added and the mixture was decomposed with ice-cold saturated sodium bicarbonate solution. The organic layer was washed with water and dried. After evaporation of the solvent the residue was distilled to give III (X = S, R = H, 51 g., 80%), b.p. 114-115°/20 mm (14, b.p. 103-105°/14 mm).

Anal. Calcd. for $C_5H_6N_2O_2S$: C, 37.93; H, 3.79; N, 17.72. Found: C, 37.81; H, 3.85; N, 17.63.

Ethyl 4-Methyl-1,2,3-thiadiazole-5-carboxylate.

This compound was prepared similarly, b.p. 120-122°/20 mm.

Anal. Calcd. for $C_6H_8N_2O_2S$: C, 41.85; H, 4.65; N, 16.28. Found: C, 41.97; H, 4.72; N, 16.35.

Ethyl 4-Phenyl-1,2,3-thiadiazole-5-carboxylate.

This compound was prepared similarly, b.p. 185-190°/25 mm (9).

2-(1,2,3-Thiadiazol-5-yl)-5-mercapto-1,3,4-oxadiazole (V, X = S, R = H).

To a solution of 1,2,3-thiadiazole-5-carboxyhydrazide (IV, X = S, R = H) (14) (725 mg., 5 mmoles) in 10 ml. of ethanol was added a solution of potassium hydroxide (280 mg., 5 mmoles) in 1 ml. of water and 0.4 ml. of carbon disulphide. The solution was refluxed for 6 hours. The solvent was evaporated and the residue was dissolved in water. The solution was acidified (acetic acid). The precipitate was filtered and crystallized from water to give V (R = H, X = S, 418 mg., 45%), m.p. 223-225°, mass spectrum m/e (%): 186 (M^+, 100), 158 (21), 115 (83), 98 (55), 85 (16), 84 (11), 71 (18), 70 (16), 69 (67), 66 (13), 59 (29), 57 (51), and 45 (25).

Other 2-(4-substituted-1,2,3-thiadiazol-5-yl)-5-mercapto-1,3,4-oxadiazoles, were prepared similarly (See Table I).

2-(4-Phenyl-1,2,3-selenadiazol-5-yl)-5-methylmercapto-1,3,4-oxadiazole (VI, X = Se, R = CH_3).

To a solution of V (X = Se, R = Ph, 618 mg., 2 mmoles) and sodium hydroxide (160 mg., 4 mmoles) in 10 ml. of water at ice water temperature was added methyl iodide (284 mg., 2 mmoles). After 90 minutes the precipitate was filtered and crystallized from ethanol to give VI (X = Se, R = Ph, 580 mg., 90%), m.p. 114-115°; mass spectrum m/e (%): 296 (M^+-28, 29), 216 (95), 169 (100), 145 (63), 129 (44), 127 (61), 115 (19), 114 (6), 113 (22), 101 (10), 89 (19), 88 (3), 87 (9), 75 (61), 63 (19), 62 (5), 47 (19) and 39 (12).

2-(4-Phenyl-1,2,3-thiadiazol-5-yl)-5-methylmercapto-1,3,4-oxadiazole (VI, X = S).

This compound was prepared similarly, m.p. 107-108°, mass spectrum m/e (%): 276 (M^+, 10), 248 (69), 177 (24), 159 (11), 145 (100), 133 (23), 121 (30), 115 (15), 103 (14), 101 (23), 93 (10), 89 (49), 77 (22), 75 (69), 69 (20), 63 (18), 51 (20), 47 (30) and 39 (13).

2-(4-Phenyl-1,2,3-selenadiazol-5-yl)-5-pyrrolidinyl-1,3,4-oxadiazole (VII).

A solution of VI (X = Se, 323 mg., 1 mmole) and pyrrolidine (142 mg., 2 mmoles) in 10 ml. of benzene was refluxed for 14 hours, and filtered. The solvent was evaporated and the residue was crystallized from alcohol to give VII (208 mg., 60%), m.p. 123-124°; mass spectrum m/e (%): 319 (M^+-28, 25), 239 (100), 182 (33), 129 (50), 127 (54), 115 (14), 114 (26), 113 (24), 101 (10), 98 (78), 89 (16), 88 (4), 87 (9), 75 (23), 70 (26), 63 (11), 62 (4), 56 (38), 55 (66) and 39 (13).

1-Phenyl-2-(2-mercapto-1,3,4-oxadiazol-5-yl)acetylene (VIII, R = SH).

Compound V (X = Se, R = Ph, 61.8 mg., 0.2 mmole) was heated at 185° for 12 minutes. To the residue 2 ml. of 5% sodium hydroxide solution was added, filtered and acidified with acetic acid. The precipitate was crystallized from ethanol to give VIII (R = SH, 25 mg., 61%), m.p. 79-80°; ir (potassium bromide): 2230 (C≡C) cm^{-1}.

Anal. Calcd. for $C_{10}H_6N_2OS$: C, 59.41; H, 2.97; N, 13.86. Found: C, 59.53; H, 2.79; N, 13.68.

1-Phenyl-2-(2-methylmercapto-1,3,4-oxadiazol-5-yl)acetylene (VIII, R = SCH_3).

This compound was prepared similarly, m.p. 75-76° (ethanol); ir (potassium bromide): 2230 (C≡C) cm^{-1}, nmr (deuteriochloroform): δ 7.83-7.33 (m, 5H, C_6H_5) and 2.76 (s, 3H, SCH_3) ppm; mass spectrum m/e (%): 216 (M^+, 100), 169 (96), 145 (65), 129 (45), 127 (63), 115 (21), 114 (8), 113 (24), 101 (14), 89 (23), 88 (5), 87 (11), 75 (63), 63 (22), 62 (8), 47 (22) and 39 (16).

Anal. Calcd. for $C_{11}H_8N_2OS$: C, 61.11; H, 3.70; N, 12.96. Found: C, 61.30; H, 3.83; N, 12.98.

1-Phenyl-2-(2-pyrrolidinyl-1,3,4-oxadiazol-5-yl)acetylene [VIII, R = $N(CH_2)_4$].

This compound was prepared similarly in 60% yield, m.p. 92-93° (ethanol); ir (potassium bromide): 2230 (C≡C) cm^{-1}.

Anal. Calcd. for $C_{14}H_{13}N_3O$: C, 70.29; H, 5.44; N, 17.57. Found: C, 70.48; H, 5.26; N, 17.69.

Methyl 2-(1,2,3-thiadiazole-5-carboxylyl)dithiocarbazinate (XI) and Dimethyl 2-(1,2,3-thiadiazole-5-carboxylyl)dithiocarbazinate (XI).

A solution of IV (7.5 g., 0.05 mole), potassium hydroxide (2.8 g., 0.05 mole) and carbon disulphide (5.7 g., 0.075 mole) in 100 ml. of absolute ethanol was stirred at room temperature for two hours. The precipitate was filtered to give potassium 2-(1,2,3-thiadiazole-5-carboxylyl)dithiocarbazinate (X) (7 g.). To a solution of X (5.16 g., 0.02 mole) in 20 ml. of water was added methyl iodide (2.84 g., 0.02 mole). The mixture was stirred at room temperature for 2 hours. The precipitate was filtered and crystallized from ethanol to give XII (R = H) (0.83 g., 15%); m.p. 154-155°.

Anal. Calcd. for $C_6H_8N_4OS_3$: C, 29.03; H, 3.23; N, 22.58. Found: C, 29.15; H, 3.35; N, 22.39.

The mother liquid was evaporated and the residue was crystallized from ethanol to give XI (R = H, 3.74 g., 80%), m.p. 228-230°.

Anal. Calcd. for $C_5H_6N_4OS_3$: C, 25.64; H, 2.56; N, 23.93. Found: C, 25.55; H, 2.42; N, 23.81.

Methyl 2-(4-methyl-1,2,3-thiadiazole-5-carboxylyl)dithiocarbazinate (XI, R = CH_3) and Dimethyl 2-(4-methyl-1,2,3-thiadiazole-5-carboxylyl)dithiocarbazinate (XIII, R = CH_3).

These compounds were prepared similarly. For compound XI (R = CH_3) m.p. 116-120°.

Anal. Calcd. for $C_6H_8N_4OS_3$: C, 29.03; H, 3.23; N, 22.58. Found: C, 29.17; H, 3.14; N, 22.43.

For compound XII (R = CH_3) m.p. 166-168°.

Anal. Calcd. for $C_7H_{10}N_4OS_3$: C, 32.06; H, 3.82; N, 21.37. Found: C, 32.22; H, 3.65; N, 21.49.

4-Amino-5-mercapto-3-(1,2,3-thiadiazol-5-yl)-*s*-triazole (XIII, R = H).

A solution of XI (R = H, 2.34 g., 0.01 mole) and hydrazine hydrate (2 g., 0.04 mole) in 30 ml. of ethanol was refluxed for 6 hours. The solvent was evaporated and the residue was dissolved in 20 ml. of water and acidified with acetic acid. The precipitate was crystallized from ethanol to give XIII (R = H, 0.84 g., 42%), m.p. 196-198°; mass spectrum m/e (%): 200 (M^+, 100), 126 (88), 84 (15), 83 (12), 69 (13), 60 (22), 57 (17) and 45 (14).

4-Amino-5-mercapto-3-(4-methyl-1,2,3-thiadiazol-5-yl)-*s*-triazole (XIII, R = CH_3).

This compound was prepared similarly (See Table II).

4-Amino-5-methylmercapto-3-(1,2,3-thiadiazol-5-yl)-*s*-triazole (XIV, R = H).

A solution of XII (R = H, 496 mg., 2 mmoles) and hydrazine hydrate (500 mg., 10 mmoles) in 50 ml. of ethanol was refluxed for 6 hours. After cooling the precipitate was filtered and crystallized from dimethyl sulfoxide to give XIV (R = H, 193 mg., 45%), m.p. 234-235°.

4-Amino-5-methylmercapto-3-(4-methyl-1,2,3-thiadiazol-5-yl)-*s*-triazole (XIV, R = CH_3).

This compound was prepared similarly, m.p. 255-257° (See Table II).

5-(1,2,3-Thiadiazol-5-yl)-*s*-triazolo[3,4-*b*]-1,3,4-thiadiazole (XV, R = R′ = H).

To a mixture of XIII (R = H, 200 mg., 1 mmole) and 0.3 ml. of formic acid was added phosphorus oxychloride (1 to 2 ml.). The mixture was let to stand at room temperature for 3 hours. After cooling, water (10 ml.) was added and the mixture was heated for 10 minutes. The precipitate was filtered and crystallized from dimethyl sulfoxide-water to give XV (R = R′ = H, 178 mg., 85%), m.p. 225°.

2-Methyl-5-(1,2,3-thiadiazol-5-yl)-*s*-triazolo[3,4-*b*]-1,3,4-thiadiazole (XV, R = H, R′ = CH_3).

To a mixture of XIII (R = H, 200 mg., 1 mmole) and 0.5 ml. of acetic acid was added phosphorus oxychloride (2 ml.). The mixture was refluxed on water bath for two hours. After cooling, water (10 ml.) was added and the mixture was heated for 10 minutes. The precipitate was filtered and crystallized from dimethyl sulfoxide to give XV (R = H, R′ = CH_3, 215 mg., 96%), m.p. 249-250°, mass spectrum m/e (%): 224 (M^+, 6), 196 (22), 127 (39), 83 (93), 82 (14), 70 (25), 69 (100), 68 (11), 59 (95), 58 (17), 57 (36), 56 (15), 51 (12), 46 (15), 45 (70), 44 (31), 41 (15) and 38 (13).

Other 2,5-disubstituted-*s*-triazolo[3,4-*b*]-1,3,4-thiadiazoles were prepared similarly (See Table II).

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