The Synthesis of 4-Substituted-4*H*-1,2,4-triazole-3-thiols and 3-Methylthio-4-substituted-4*H*-1,2,4-triazoles

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The synthesis of 4-substituted-4*H*-1,2,4-triazole-3-thiols and 3-methylthio-4-substituted-4*H*-1,2,4-triazoles by the condensation of 4-substituted-3-thiosemicarbazides with dimethylformamide dimethyl acetal or dimethylacetamide dimethyl acetal is described. A discussion of the mechanistic pathway is included.

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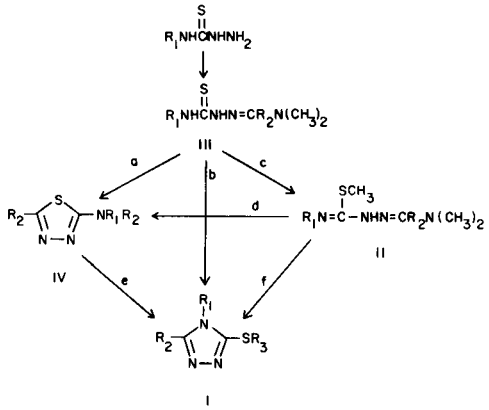
A number of syntheses of the 1,2,4-triazole-3-thiol ring systems are reported in the literature. The system can be prepared by the rearrangement of aminothiazoles (2), the condensation of thiosemicarbazides with esters (3-7), the condensation of thiosemicarbazides with acids (7-8), the cyclization of acylthiosemicarbazides (7,8,9-13), degradation of amino or hydrazino-3-thio-1,2,4-triazoles (14-15) and the displacement on halotriazoles by mercaptide ion (7,8,16). The 3-methylthio-1,2,4-triazoles can be prepared by direct alkylation of the thiols (17), by basic or oxidative cyclizations of substituted isothiosemicarbazides (10,18-19) and by deaminations (20) of amino-1,2,4-triazoles.

We report a simple one-step synthesis of 4-substituted-4*H*-1,2,4-triazole-3-thiols and 3-methylthio-4-substituted-4*H*-1,2,4-triazoles from the condensation of 4-substituted-3-thiosemicarbazides with dimethylformamide dimethyl acetal or dimethylacetamide dimethyl acetal.

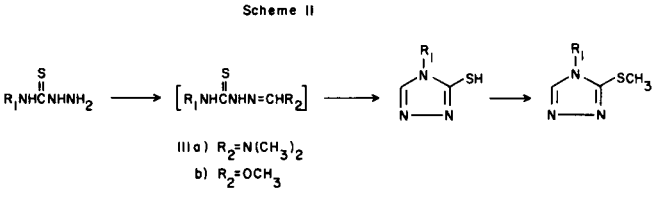
Scheme I



Ik, $R_1 = p\text{-}ClC_6H_4$, $R_2 = R_3 = H$
Ia, $R_1 = p\text{-}ClC_6H_4$, $R_2 = H$, $R_3 = CH_3$

The initial experiment was conducted using 4-(4-chlorophenyl)-3-thiosemicarbazide and excess dimethylformamide dimethyl acetal at 100°. The sole product possessed an empirical formula of $C_9H_8ClN_3S$ and the pmr showed two singlets at δ 2.74 and 8.46 consistent with structure Ia

Scheme II

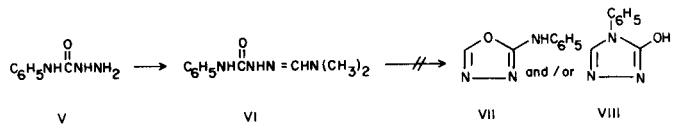


IIIa) $R_2 = N(CH_3)_2$
b) $R_2 = OCH_3$

or IV ($R_1 = CH_3$, $R_2 = p\text{-}ClC_6H_4$). The C-13 nmr showed a signal at δ 14.7. The C-13 resonance was more indicative of an *S*-methyl in the triazole (Ia) although the thiadiazole (IV) could not be unequivocally ruled out.

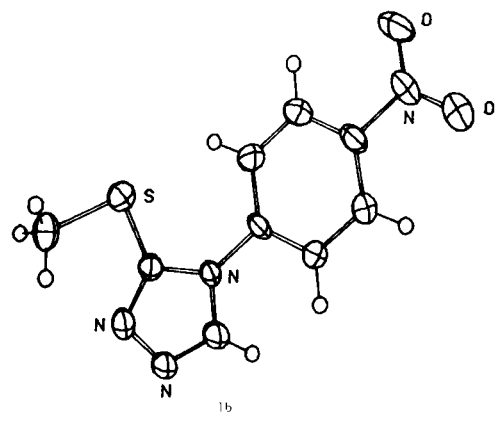
X-ray structure analysis of the compound obtained from the reaction of 4-(4-nitrophenyl)-3-thiosemicarbazide and dimethylformamide dimethyl acetal showed the structure to be 3-(methylthio)-4-(4-nitrophenyl)-4*H*-1,2,4-triazole (Ib). Crystals of Ib (from chloroform-methanol-ethyl acetate) are monoclinic, space group Pc with a = 3.890 (1), b = 12.685 (4), c = 10.454 (3) Å, β = 98.84° (3) and Z = 2; calculated density 1.538 cm^{-3}, observed 1.534 g. cm^{-3} (flotation in carbon tetrachloride/hexane).

Scheme III



V VI VII VIII

FIGURE 1

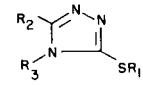


Ib

0022-152X/80/051077-04$02.25

Table I

Triazoles Prepared



Compound	R_1	R_2	R_3	M.p. °C	Yield %	Formula	MW	Anal. Calcd. Found. or Lit. M.p., °C
1a	CH_3	H	p-ClC_6H_4	150-152	83	$C_9H_8ClN_3S$	225.7	C, 47.9; H, 3.57; N, 18.6; S, 14.2; Cl, 15.7 C, 48.2; H, 3.61; N, 18.8; S, 14.4; Cl, 15.9 Lit. m.p. 174-175 (a)
1b	CH_3	H	p-$O_2NC_6H_4$	199-201	68	$C_9H_8N_4O_2S$	236.2	C, 45.7; H, 3.28; N, 23.7; S, 13.6 C, 45.7; H, 3.28; N, 23.8; S, 13.8
1c	H	H	C_6H_5	170-172	74	$C_8H_7N_3S$	177.2	Lit. m.p. 168-170 (d,e,f), 170 (b,c)
1d	CH_3	H	C_6H_5	75-77	58	$C_9H_9N_3S$	191.3	Lit. m.p. 76 (f)
1e	H	H	p-$O_2NC_6H_4$	194-196	61	$C_8H_6N_4O_2S$	222.2	C, 43.2; H, 2.71; N, 25.2; S, 14.4 C, 43.0; H, 2.71; N, 25.1; S, 14.1
1f	H	H	p-$CH_3OC_6H_4$	186-188	55	$C_9H_9N_3OS$	207.3	C, 52.2; H, 4.37; N, 20.3; S, 15.5 C, 52.2; H, 4.33; N, 20.4; S, 15.2
1g	H	CH_3	p-CH_3-OC_6H_4	202-204	62	$C_{10}H_{11}N_3OS$	221.3	C, 54.3; H, 5.01; N, 19.0; S, 14.5 C, 54.3; H, 5.11; N, 19.1; S, 14.7
1h	H	CH_3	C_6H_5	216-218	40	$C_9H_9N_3S$	191.3	Lit. m.p. 218-219 (g) 224 (h), 220 (i,j), 214-215 (f)
1i	CH_3	CH_3	C_6H_5	120-122	30	$C_{10}H_{11}N_3S$	205.3	Lit. m.p. 119-120 (g), 119 (h)
1j	H	H	t-Bu	188-190	60	$C_6H_{11}N_3S$	157.2	Lit. m.p. 199-200 (k)
1k	H	H	p-ClC_6H_4	183-186	78	$C_8H_8ClN_3S$	211.7	Lit. m.p. 214 (d,f) C, 45.2; H, 2.85; N, 19.9; S, 15.1; Cl, 16.8 C, 45.2; H, 3.05; N, 19.8; S, 15.1; Cl, 16.8
1l	H	CH_3	p-ClC_6H_4	237-239	58	$C_9H_8ClN_3S$	225.7	C, 47.9; H, 3.57; N, 18.6; S, 14.2; Cl, 15.7 C, 47.8; H, 3.66; N, 18.8; S, 14.3; Cl, 15.7
1m	CH_3	H	o-$CF_3C_6H_4$	196-198	73	$C_{10}H_8F_3N_3S$	259.3	C, 46.3; H, 3.10; N, 16.2; S, 12.4; F, 22.0 C, 46.2; H, 3.14; N, 16.4; S, 12.4; F, 21.8
1n	CH_3	CH_3	3,4-$Cl_2C_6H_4$	153-155	35	$C_{10}H_9Cl_2N_3S$	274.2	C, 43.8; H, 3.30; N, 15.3; S, 11.7; Cl, 25.9 C, 44.0; H, 3.30; N, 15.5; S, 11.6; Cl, 26.2
1o	H	H	p-IC_6H_4	202-204	48	$C_8H_6IN_3S$	303.2	C, 31.7; H, 2.00; N, 13.9; S, 10.6; I, 41.9 C, 31.6; H, 2.02; N, 13.6; S, 10.5; I, 42.2
1p	H	H	m-$CH_3SC_6H_4$	132-134	77	$C_9H_9N_3S_2$	223.3	C, 48.4; H, 4.06; N, 18.8; S, 28.7 C, 48.1; H, 3.93; N, 18.9; S, 28.9
1q	H	H	$CH_3OCH_2CH_2$	119-120	56	$C_5H_9N_3OS$	159.2	C, 37.7; H, 5.69; N, 26.4; S, 20.1 C, 37.5; H, 5.61; N, 26.2; S, 19.9
1r	H	CH_3	$CH_3OCH_2CH_2$	118-120	60	$C_6H_{11}N_3OS$	173.2	C, 41.6; H, 6.39; N, 24.3; S, 18.5 C, 41.3; H, 6.35; N, 24.3; S, 18.7
1s	H	H	Cyclohexyl	143-146	74	$C_8H_{13}N_3S$	183.3	Lit. m.p. 164-166 (k) C, 52.4; H, 7.14; N, 22.9; S, 17.5 C, 52.4; H, 7.14; N, 22.7; S, 18.0

(a) Reference 17. (b) Reference 7. (c) Reference 8. (d) Reference 5. (e) Reference 6. (f) Reference 3. (g) Reference 10. (h) Reference 9. (i) Reference 5. (j) Reference 11. (k) Reference 4.

Intensity measurements (crystal size 500 × 160 × 50 microns) were made on a Syntex P2(1) diffractometer using the $\theta/2\theta$ scan method with nickel filtered copper Kα radiation. In the range ($3 < \theta < 60$) 774 reflections were monitored of which 723 were classified as observed ($1 \geq 3.0\ \sigma\ (1)$); no absorption corrections were applied.

The structure was solved by the heavy atom method after determining the sulfur position by analysis of the Patterson Junction. Lease squares refinement, anisotropic for non-hydrogens and isotropic for hydrogen gave R = .066 for observed reflections.

An ORTEP drawing appears in Figure 1.

The triazole could mechanistically arise by initial formation of the dimethylaminomethylene adduct (III) with subsequent cyclization. The thiadiazole IV then would thermally rearrange to the triazole I (Scheme I).

The use of 1 equivalent dimethylformamide dimethyl acetal in dioxane at 100° gave exclusively the 4*H*-1,2,4-triazole-3-thiols in good yields. The use of two equivalents gave in some cases exclusively the 3-methylthio-4*H*-1,2,4-triazoles and in other cases a mixture of the 3-thiol and 3-methylthio-4*H*-1,2,4-triazoles. This limits the probable

pathway as shown in Scheme I to a or b.

The rearrangement of aminothiazoles to thiotriazoles (2) is reported to proceed at 150° in methanol/methylamine. To attempt to rule out the thermal rearrangement pathway e, the reaction was run at room temperature utilizing the thiosemicarbazide with either 1 or 2 equivalents of dimethylformide dimethyl acetal in dioxane or excess dimethylformamide dimethyl acetal as the solvent. Under these conditions, the sole product isolated was the 4*H*-1,2,4-triazole-3-thiol. No trace of the thiazole was detected.

The *S*-methyl derivatives were then obtained by heating with 1 equivalent or excess dimethylformamide dimethyl acetal neat or in dioxane at 100°. The probable mechanistic pathway is outlined in Scheme II. The transient intermediate III is not observed even at room temperature.

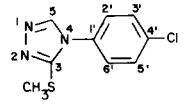
By contrast, the reaction of 4-phenylsemicarbazide (V) with dimethylformamide dimethyl acetal gave a 60% yield of the amidine (VI). Analogous attempts to prepare the oxadiazole (VII) or hydroxytriazole (VIII) by refluxing VI in xylene, acetic acid or potassium hydroxide/ethanol failed (Scheme III).

EXPERIMENTAL

All melting points were observed on a Mel-Temp apparatus, H-1 nmr were determined with a Varian HA-100 spectrometer, the C-13 nmr were determined with a Varian instrument, the X-ray data were collected on a Syntex P2(1) diffractometer; chemical shifts are reported in ppm relative to internal TMS. DMSO when in association with a spectra refers to DMSO-d_6. The 4-substituted-3-thiosemicarbazides were obtained from Trans World Chemicals with the exception of 4-phenyl-3-thiosemicarbazide which was obtained from Eastman.

4-(*p*-Chlorophenyl)-3-(methylthio)-4*H*-1,2,4-triazole (1a).

A suspension of 5.0 g. (0.025 mole) in 15 ml. of dimethylformamide dimethyl acetal was heated on a steam bath in an open flask for 1.5 hours. The excess reagent was removed *in vacuo* and the residue crystallized from chloroform-hexane to give 5.5 g. (83%) of 1a as a white powder, m.p. 150-152°, lit. m.p. 174-175° (17);



H-1 nmr (deuteriochloroform/DMSO): δ 2.74 (s, 3), 7.48 (pair of doublets, 4), 8.46 (s, 1). C-13 nmr (DMSO, 50 mg./0.5 ml.): δ 14.7 (SMe, s) 127.0 (C'$_2$, C'$_6$), 129.6 (C'$_3$, C'$_5$), 132.0 (C'$_4$), 133.8 (C'$_1$) 145.1 (C_5), 150.0 (C_3); ms: M^+ 225, M-CH_3 210.

3-Methyl-5-methylthio-4-phenyl-4*H*-1,2,4-Triazole (1i) and 5-methyl-4-phenyl-4*H*-1,2,4-triazole-3-thiol (1h).

A suspension of 10 g. of 4-phenyl-3-thiosemicarbazide in 30 ml. of dimethyl acetamide dimethyl acetal was heated in an open flask on a steam bath for 1.5 hours. Solvent removal gave a mixture which was chromatographed on silica gel eluting with 2% methanol/dichloromethane. The first eluting material (4.2 g.) was identified as 5-methyl-4-phenyl-3-4*H*-1,2,4-triazole-3-thiol, m.p. 195-196°. The second eluting material was identified as 3-methyl-5-methylthio-4-phenyl-4*H*-1,2,4-triazole (3.2 g.), m.p. 120-122°, lit. m.p. 119° (10), 119-120° (9); nmr (1h) (DMSO): δ 3.37 (s, 3), 7.28 (m, 2), 7.47 (m, 3), 8.50 (SH); nmr (1i) (deuteriochloroform): δ 2.87 (s, 3), 3.32 (s, 3), 7.46 (m, 5).

4-Phenyl-4*H*-1,2,4-triazole-3-thiol (1c).

A suspension of 4-phenyl-3-thiosemicarbazide (8.4 g., 0.05 mole) and dimethylformamide dimethyl acetal (5.9 g., 0.05 mole, 6.6 ml.) in 100 ml. of dioxane was heated in an open flask on a steam bath for 0.5 hour. Solvent removal and recrystallization (chloroform-hexane) gave 6.5 g. (74%) of (1c) as a white powder, m.p. 170-172°, lit. m.p. 170° (7,8).

The same material was obtained by either stirring the above suspension at room temperature for 5 hours or by stirring a suspension of 4-phenyl-3-thiosemicarbazide and > 4 equivalents of dimethylformamide dimethyl acetal also at room temperature for 5 hours. The respective yields were 75% and 65%; nmr (DMSO): 7.46 (m, 2), 7.76 (m, 3), 8.64 (s, 1), 13.9 (SH).

3-Methylthio-4-phenyl-4*H*-1,2,4-triazole (1d).

A suspension of 8.4 g. (0.05 mole) of 4-phenyl-3-thiosemicarbazide and dimethylformamide dimethyl acetal (11.8 g., 0.1 mole, 13.2 ml.) in 50 ml. of dioxane was heated on a steam bath for 1.5 hours. The residue obtained after solvent removal was chromatographed on silica gel to give 5.5 g. (58%) of a white powder, m.p. 75-77°, lit. m.p. 76° (3).

Alternately, the material could be prepared by heating 4-phenyl-4*H*-1,2,4-triazole-3-thiol (1c) with 1 equivalent of dimethylformamide dimethyl acetal in dioxane on a steam bath for 1 hour, yielding 76% of a material melting at 76-77°.

4-(4-Nitrophenyl)-4*H*-1,2,4-triazole-3-thiol (1e).

A suspension of 4-(4-nitrophenyl)-3-thiosemicarbazide (4.2 g., 0.02 mole) and dimethylformamide dimethyl acetal (2.4 g., 0.02 mole, 2.7 ml.) in 50 ml. dioxane was heated in an open flask on a steam bath for 0.5 hour. Solvent removal and recrystallization from chloroform gave 2.7 g. (61%) of yellow powder, m.p. 194-196°; nmr (deuteriochloroform/-DMSO): 8.10 (d, 2), 8.38 (d, 2), 8.54 (s, 1).

4-(4-Methoxyphenyl)-5-methyl-4*H*-1,2,4-triazole-3-thiols (1g).

A suspension of 4-(4-methoxyphenyl)-3-thiosemicarbazide (4 g., 0.02 mole) and dimethylacetamide dimethyl acetal (2.7 g., 0.02 mole, 3. ml.) in 50 ml. of dioxane was heated on a steam bath in an open flask for 0.5 hour. Solvent removal and recrystallization gave 2.4 g. (55%) of white cubes, m.p. 202-204°; nmr (deuteriochloroform/DMSO): δ 3.88 (s, 3), 7.02 (d, 2), 7.50 (d, 2), 8.18 (s, 1), 13.74 (SH).

4-Methylthio-4-(α,α,α-trifluoro-*o*-tolyl)-4*H*-1,2,4-triazole (1m).

A suspension of 4-(2-trifluoromethylphenyl)-3-thiosemicarbazide (2.4 g., 0.01 mole) and dimethylformamide dimethyl acetal (2.4 g., 0.02 mole, 2.7 ml.) in 50 ml. of dioxane was heated on a steam bath for 1 hour. Solvent removal and crystallization (chloroform-hexane) of the residue gave 1.9 g. (73%) of white powder, m.p. 196-198°; nmr (deuteriochloroform): δ 2.14 (s, 3), 7.50 (m, 2), 7.77 (s, 1), 7.80 (m, 2).

4-(3,4-Dichlorophenyl)-3-methyl-5-methylthio-4*H*-1,2,4-triazole (1n).

A suspension of 4-(3,4-dichlorophenyl)-3-thiosemicarbazide (4.7 g., 0.02 mole) and dimethylacetamide dimethyl acetal (5.4 g., 0.04 mole, 6 ml.) in 50 ml. of dioxane was heated on a steam bath for 1.5 hour. Solvent removal and chromatography on silica gel gave 1.6 g. (35%) of a white powder, m.p. 153-155°; nmr (DMSO): δ 2.20 (s, 3), 2.45 (s, 3), 7.75 (m, 1), 7.94 (m, 2).

1-[(Dimethylaminomethylene)amino]-3-phenylurea.

A suspension of 4-phenylsemicarbazide (7.6 g., 0.05 mole) and dimethylformamide dimethyl acetal (5.9 g., 0.05 mole, 6.6 ml.) in 50 ml. of dioxane was either stirred at room temperature for 3 hours or heated on a steam bath for 0.5 hour. Solvent removal and recrystallization from chloroform-hexane gave 7.4 g. (71%) of white needles, m.p. 132-134°; nmr (deuteriochloroform): δ 2.82 (s, 6), 7.26 (m, 2), 7.46 (m, 3), 7.48 (s, 1), 7.92 (NH), 9.48 (NH).

Anal. Calcd. for $C_{10}H_{14}N_4O$ (206.2): C, 58.2; H, 6.83; N, 27.4. Found: C, 58.2; H, 6.85; N, 27.4.

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REFERENCES AND NOTES

(1) 1979 R & D Summer Intern from Mt. Holyoke College.

(2) J. Goerdeler and J. Galinke, *Chem. Ber.*, **90**, 202 (1957).

(3) M. Pesson, G. Polmans and S. Dupin, *Compt. Rend.*, **248**, 1677 (1959).

(4) S. A. Greenfield, M. C. Seidel and W. C. Von Meyer, German Patent 1,943,915, March 12, 1970; *Chem. Abstr.*, **72**, 100713q (1970).

(5) R. Bellon, French Patent 1,273,881, February 2, 1962; *Chem. Abstr.*, **57**, 9860e (1962).

(6) V. Zotta and A. Gasmet, *Farmacie (Bucharest)*, **11**, 731 (1963); *Chem. Abstr.*, **61**, 4337h (1964).

(7) M. Pesson and S. Dupin, *Compt. Rend.*, **252**, 3830 (1961).

(8) M. Pesson and S. Dupin, *Bull. Soc. Chim. France*, 250 (1962); *ibid.*, 1581 (1961).

(9) J. D. Kendall, G. F. Duffin and H. R. J. Waddington, British Patent 766,380, January 23, 1957; *Chem. Abstr.*, **51**, 16162h (1957).

(10) R. M. Herbst and J. E. Klingbeil, *J. Org. Chem.*, **23**, 1912 (1958).

(11) G. F. Duffin, J. D. Kendall and H. R. J. Waddington, *J. Chem. Soc.*, 3799 (1959).

(12) E. Hoggarth, *ibid.*, 1979 (1950).

(13) M. Y. Mhasalkar, M. H. Shah, S. T. Nikani, K. G. Anantanarayanan and C. V. Delivala, *J. Med. Chem.*, **13**, 672 (1970); *ibid.*, **14**, 260 (1971).

(14) H. Schaefer, B. Bartho, K. Gewald, *J. Prakt. Chem.*, 149 (1977).

(15) K. Kurzer and K. Douraght-Zadeh, *J. Chem. Soc. C*, 1 (1966).

(16) T. G. S. Nath, S. Husain and V. R. Srinwasan, *Indian J. Chem., Sect. B*, **15B**, 341 (1977).

(17) I. YaPostovskii and I. L. Shegal, *Khim. Geterotsikl. Soedin.*, 443, 449 (1965); *Chem. Abstr.*, **63**, 13242b,f,g (1965).

(18) S. C. De and T. K. Chakravorty, *J. Indian Chem. Soc.*, **7**, 875 (1930); *Chem. Abstr.*, **25**, 2119 (1931).

(19) E. Hoggarth, *J. Chem. Soc.*, 1918 (1949).

(20) C. F. Kröger, E. Tenor and H. Beyer, *Ann.*, **643**, 131 (1961).