1,2,4-Triazoles. Improved Synthesis of 5-Substituted 4-Amino-3-mercato-(4*H*)-1,2,4-triazoles and a Facile Route to 3,6-Disubstituted 1,2,4-Triazolo[3,4-*b*][1,3,4]thiadiazoles

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The reaction of thiocarbohydrazide with carboxylic acids at the melting temperature allows an improved preparation of the 5-substituted 4-amino-3-mercapto-1,2,4-triazole heterocycles. The crude 4-amino-5-mercapto-1,2,4-triazoles react easily with carboxylic acids or carboxylic acid chlorides to afford the 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole ring system.

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3,6-Disubstituted 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazoles constitute a class of compounds hitherto scarcely studied. From a biological point of view it has been reported that some 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole derivatives have antibacterial [1-3] and antiinflamatory activity [4] as well as interesting CNS depressant action [5]. Previously, we reported on the preparation and pharmacological evaluation of some 6-substituted 3-(pyridine-4-yl)-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazoles, some of them exhibiting moderate antimalarial and antitumor activity [6].

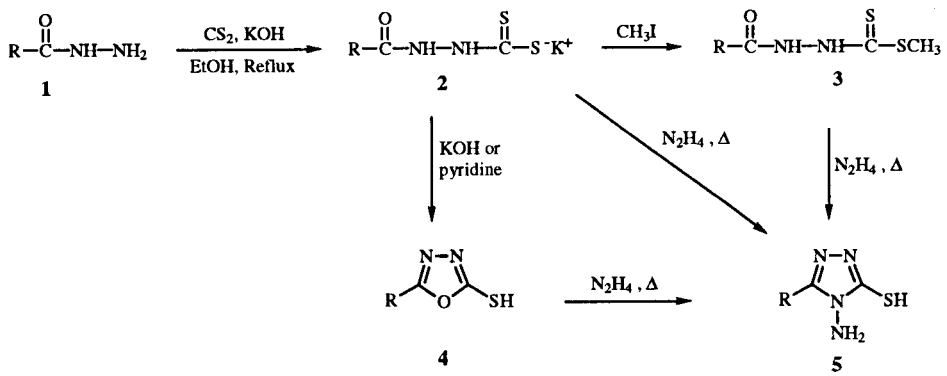
As a part of our research program to explore the potential biological properties of the 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole ring system, we now present a novel procedure for the preparation of the 4-amino-3-mercato-(4*H*)-1,2,4-triazole which in turn allows an easier entry to the above cited 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole system.

Alkyl- and aryl-substituted derivatives of this heterocyclic system were obtained first by Kanaoka [7] both through dehydrative ring closure of 4-acylamino-*s*-triazole-5-thiols or by the reaction of 1,3,4-thiadiazol-2-ylhydrazines with *ortho*-esters. More recently, similar compounds were prepared by Potts and Huseby [8] by ring closure of 5-substituted 4-amino-3-mercapto-(4*H*)-1,2,4-triazoles using suitable acyl chlorides in the presence of phosphoryl chloride.

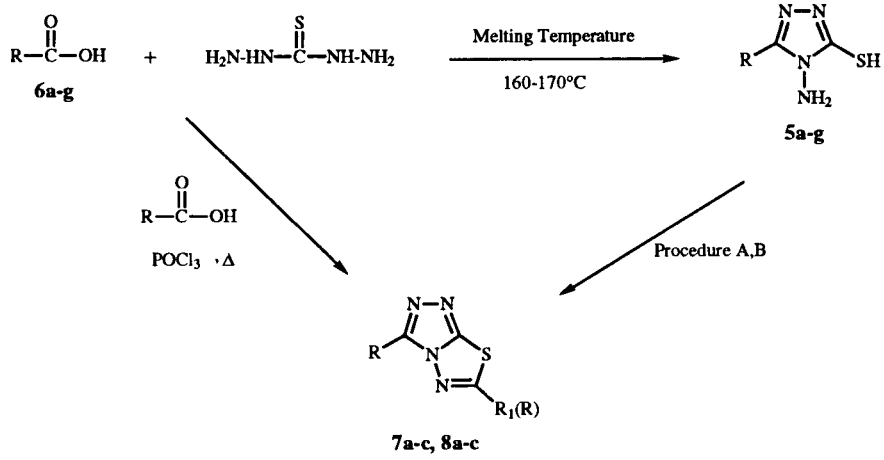
Furthermore, Hoggarth's synthesis of the 4-amino-3-mercato-(4*H*)-1,2,4-triazole has been widely utilized as the method of choice for preparation of this useful class of heterocyclic compounds [9]. This methodology involves the condensation of carboxylic acid hydrazides with carbon disulfide and potassium hydroxide to yield the potassium dithiocarbazates **2** which, after *S*-alkylation with methyl iodide, underwent ring closure with an excess of hydrazine to produce the aminothioles **5** in good yields (Scheme 1). More recently, Heindel and Reid have reported the direct conversion of the carbazate salts by reaction with an excess of hydrazine; this modification avoids *S*-methylation, resulting in a higher yield and a shorter reaction time [10]. Alternatively, the oxadiazoles **4** can be converted to the triazoles **5** by reaction with hydrazine. Finally, it has been also reported that the same aliphatic carboxylic acids react with thiocarbohydrazide to afford directly the 5-substituted 4-amino-3-mercapto-1,2,4-triazoles [11,12].

We found that the reaction of thiocarbohydrazide with carboxylic acids (Scheme 2) can be conveniently applied

Scheme 1



Scheme 2



to both aliphatic and aromatic acid derivatives thus providing a pratical means for the procurement of the 5-substituted 4-amino-3-mercapto-1,2,4-triazoles [13]. Thus, when equimolecular amounts of carboxylic acids **6a-g** and thiocarbohydrazide were mixed together and warmed at the melting temperature (160-170°) for 15-60 minutes, the corresponding 5-substituted 4-amino-3-mercapto-1,2,4-triazoles **5a-g** were obtained in good to excellent yields (71-96%). In summary, this new procedure avoids the preparation not only of the starting acid chlorides but of the derived carboxylic acid hydrazides and potassium dithiocarbazate salts, resulting in higher overall yields and shorter working time, thus comparing very favorably with the alternative methodology, *i.e.*, the Hoggarth synthesis.

Interestingly, we found that 1,2,4-triazolo[3,4-*b*]-[1,3,4]thiadiazole derivatives **7a-c** can easily be

Table 1

Yields, Melting Points and Elemental Analyses of Compounds **5a-g**, **7a-c** and **8a-c**

Compound	R	R'	% Yield	Mp °C [a]	Molecular formula	Analysis % Calcd./Found C	H	N
5a	C_6H_5-CH_2-		88	179-180	$C_9H_{10}N_4S$	52.41	4.89	27.16
					(206.26)	52.12	5.11	26.99
5b	CH_3-		91	205	$C_3H_6N_4S$	27.68	4.65	43.04
					(130.16)	27.69	4.44	43.15
5c	*p*-CH_3-C_6H_4-		95	207-208	$C_9H_{10}N_4S$	52.41	4.89	27.16
					(206.26)	52.78	4.65	27.11
5d	C_6H_5-		71	210-212	$C_8H_8N_4S$	49.98	4.19	29.14
					(192.23)	49.79	3.85	28.87
5e	C_6H_5-$(CH_2)_2$-		86	203	$C_{10}H_{12}N_4S$	54.52	5.49	25.43
					(220.29)	54.36	5.51	25.23
5f	C_6H_5-$(CH_2)_3$-		89	120-123	$C_{11}H_{14}N_4S$	56.39	6.02	23.91
					(234.32)	56.55	6.11	24.15
5g	$(CH_3)_2$CH-CH_2-		95	80-81	$C_6H_{12}N_4S$	41.84	7.02	32.53
					(172.25)	42.03	7.33	32.79
7a	C_6H_5-CH_2-	CH_3CH_2-	58 [b]	85	$C_{12}H_{12}N_4S$	58.99	4.95	22.93
			44 [c]		(244.31)	58.99	4.95	22.93
7b	CH_3-	CH_3CH_2-	89 [b]	98	$C_6H_8N_4S$	42.84	4.79	33.31
			51 [c]		(168.21)	42.88	4.79	33.31
7c	*p*-CH_3-C_6H_4-	CH_3CH_2-	81 [b]	130	$C_{12}H_{12}N_4S$	58.99	4.95	22.93
			38 [c]		(244.31)	59.00	4.95	22.93
8a	$(CH_3)_2$CH-CH_2-	$(CH_3)_2$CH-CH_2-	35	oil	$C_{11}H_{18}N_4S$	55.43	7.61	23.51
					(238.35)	55.69	7.41	23.39
8b	C_6H_5-	C_6H_5-	32	204-205	$C_{15}H_{10}N_4S$	64.73	3.62	20.13
					(278.33)	64.52	3.61	19.98
8c	CH_3-	CH_3-	22	102-103	$C_5H_6N_4S$	38.95	3.92	36.36
					(154.19)	38.90	3.92	36.22

[a] Compounds **5a-e** and **8c** were crystallized from ethanol whereas derivative **5f** was from toluene and **5g**, **8b** and **7a-c** were from ligroin. [b] Procedure A. [c] Procedure B.

Table 2

Spectroscopic Data of Compounds **5a-g**, **7a-c** and **8a-c**

Compound	IR (potassium bromide) ν_{max} cm^{-1}	^{1}H-NMR, δ (ppm) (deuteriochloroform)	^{13}H-NMR, δ (ppm) (deuteriochloroform)
5a	3240, 1630, 1570	4.11 (s, 2H, CH_2), 5.57 (s, 2H, NH_2), 7.35 (s, 5H, phenyl-H), 13.7 (s br, 1H, SH)	30.3, 126.7, 128.4, 128.8, 135.4, 151.3, 165.9
5b	3230, 1635, 1570	2.27 (s, 3H, CH_3), 5.43 (s, 2H, NH_2), 13.38 (s br, 1H, SH)	10.3, 149.1, 165.3
5c	3230, 1630, 1570	2.34 (s, 3H, CH_3), 5.78 (s, 2H, NH_2), 7.29 and 7.94 (dd, 4 H, A_2B_2 system, J = 8.2 Hz, phenyl-H), 13.85 (s br, 1H, SH)	20.9, 122.9, 127.8, 128.9, 129.8, 140.4, 149.4, 166.6
5d	3230, 1640, 1550	5.81 (s, 2H, NH_2), 7.55 (m, 3H, phenyl-H), 9.06 (m, 2H, phenyl-H), 13.95 (s br, 1H, SH)	125.9, 127.9, 128.4, 130.3, 149.4, 166.4
5e	3240, 1640, 1570	2.94 (s, 4H, CH_2-CH_2), 5.57 (s, 2H, NH_2), 7.35 (m, 5H, phenyl-H), 13.46 (s br, 1H, SH)	29.1, 31.1, 126.1, 128.0, 128.2, 140.3, 151.4, 165.7
5f	3230, 1630, 1570	1.44 (m, 2H, CH_2), 2.71 (t, 2H, J = 7.3 Hz, Ar-CH_2), 2.81 (t, 2H, J = 7.3 Hz, Ar-CH_2), 5.62 (s, 2H, NH_2), 7.29 (m, 5H, phenyl-H), 13.06 (s br, 1H, SH)	13.5, 28.5, 31.2, 126.3, 128.1, 140.3, 151.3, 165.4
5g	3240, 1620, 1550	1.12 (d, 6H, $(CH_3)_2$), 2.05 (m, 1H, CH), 2.51 (d, 2H, CH_2), 5.49 (s, 2H, NH_2), 13.71 (s br, 1H, SH)	21.3, 25.3, 31.1, 151.2, 165.9
7a	1600, 1520, 1500	1.40 (t, 3H, J = 7.3 Hz, CH_3), 2.96 (q, 2H, J = 7.3 Hz, CH_2), 4.40 (s, 2H, phenyl-CH_2), 7.24-7.43 (m, 5H, phenyl-H)	12.5, 25.9, 31.2,127.1, 128.6, 128.9, 135.0, 146.6, 153.8, 170.9
7b	1600, 1510	1.40 (t, 3H, J = 7.5 Hz, CH_2CH_3), 2.66 (s, 3H, CH_3), 2.96 (q, 2H, J = 7.5 Hz, CH_2)	10.4, 12.6, 26.0, 144.4, 153.3, 170.7
7c	1600, 1500	1.48 (t, 3H, J = 7.3 Hz, CH_2CH_3), 2.42 (s, 3H, CH_3), 3.11 (q, 2H, J = 7.3 Hz, CH_2), 7.31 and 8.19 (dd, 4 H, A_2B_2 system, J = 8.2 Hz, phenyl-H)	12.8, 21.6, 26.1, 122.9, 126.2, 129.6, 140.5, 146.5, 154.5, 170.9
8a	1600, 1525, 1500	1.04 (m, 12H, CH_3), 2.15 (m, 1H, CH), 2.25 (m, 1H, CH), 2.51 (d, 2H, CH_2), 2.97 (d, 2H, CH_2)	22.1, 22.3, 27.2, 28.8, 32.5, 41.0, 147.4, 168.5
8b	1600, 1520	7.64 (m, 6H, phenyl-H), 8.04 (m, 2H, phenyl-H), 8.34 (m, 2H, phenyl-H)	125.5, 125.9, 127.3, 129.0, 129.2, 129.7, 133.0, 166.9
8c	1600, 1525, 1500	2.70 (s, 3H, CH_3), 2.75 (s, 3H, CH_3)	18.2, 22.8, 148.0, 167.4

obtained directly from the crude 1,2,4-triazole intermediates **5a-g** by adding phosphoryl chloride and the corresponding acid chloride and refluxing for 5 hours. The resulting crude 1,2,4-triazole intermediates **5a-g** underwent ring closure with carboxylic acid derivatives in the presence of phosphoryl chloride. Finally, it is worth noting that, the interaction of **6a-g** with thiocarbohydrazide gave **5a-g** as the major products along with traces of the 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole heterocycles bearing two substituents in positions 3 and 6. However, **8a-c** could be directly obtained by heating an excess of the appropriate carboxylic acid and thiocarbohydrazide in the presence of phosphoryl chloride. Although this procedure has been previously claimed, to our knowledge, no data and experimental details have been reported [11].

In conclusion, the reaction of thiocarbohydrazide with carboxylic acids has proven to be of general utility for the preparation of the 5-substituted 4-amino-3-mercapto-(4*H*)-1,2,4-triazole heterocycles allowing an easier preparation of the 1,2,4-triazolo[3,4-*b*]-[1,3,4]thiadiazole ring system; moreover, the simplicity of the reaction could suggest a possible application of this methodology for generating combinatorial 5-substituted 4-amino-3-mercapto-(4*H*)-1,2,4-triazole libraries.

EXPERIMENTAL

Melting points were taken on a Buchi-Tottoli capillary apparatus and are uncorrected. Reaction courses and product mixtures were routinely monitored by thin-layer chromatography (tlc) on silica gel precoated F254 Merck plates. Infrared spectra (ir) were measured on a Perkin Elmer 257 instrument. The ^{1}H and ^{13}C nmr spectra were determined for solution in deuteriochloroform with a Bruker AC-200 spectrometer (tetramethylsilane as an internal standard). All drying operations were performed over anhydrous magnesium sulfate. Elemental analyses were in agreement with calculated values within ± 0.4%.

General Procedure for the Preparation of 5-Substituted 4-Amino-3-mercapto-(4*H*)-1,2,4-triazoles **5a-g**.

A mixture of thiocarbohydrazide (0.1 mmole) and the appropriate carboxylic acid (0.1 mmole) was warmed carefully at 160-170° until melting occured [12], then it was warmed again for 15 minutes. The reaction mixture was cooled, mixed with water (80 ml) and acidified with concentrated hydrochloric acid. The precipitate was filtered, washed with water and oven dried.

3,6-Disubstituted 1,2,4-Triazolo[3,4-*b*][1,3,4]thiadiazoles **7a-c**. Procedure A.

A mixture of the crude aminothiole (0.01 mole) and the appropriate acyl chloride (0.01 mole) in phosphoryl chloride (20 ml) was refluxed for 5 hours. The excess of phosphoryl chloride was removed under reduced pressure, the residue added to crushed ice and the mixture was stirred at room temperature for

one hour, during this time the solution was gradually neutralized with solid sodium bicarbonate. The precipitated solid product was filtered, washed with diluted aqueous solution of sodium bicarbonate (20%) and water. The collected solid was dried and crystallized.

3,6-Disubstituted 1,2,4-Triazolo[3,4-*b*][1,3,4]thiadiazoles **7a-c.** Procedure B.

A mixture of the crude aminothiole (0.01 mole) and the appropriate carboxylic acid (0.01 mole) solubilized in phosphoryl chloride (20 ml) was refluxed for 5 hours. The excess of phosphoryl chloride was removed under reduced pressure, the residue added to crushed ice and the mixture stirred at room temperature for one hour. During this time the solution was gradually neutralized with solid sodium bicarbonate. The mixture was extracted with chloroform and the combined extracts were dried over magnesium sulfate, then concentrated *in vacuo* and purified by flash chromatography using 1% ethyl acetate in methylene dichloride. The residual oil was triturated with ligroin and the solid obtained then crystallized.

General Procedure for the Preparation of 3,6-Disubstituted 1,2,4-Triazolo[3,4-*b*][1,3,4]thiadiazoles **8a-c.**

A mixture of thiocarbohydrazide (0.1 mmole), the appropriate carboxylic acid (0.3 mmole) and phosphoryl chloride (70 ml) was heated carefully at reflux for 5 hours. The excess of phosphoryl chloride was removed under reduced pressure, the residue added to crushed ice, and the mixture was stirred at room temperature for one hour, during which time the solution was gradually neutralized with solid sodium bicarbonate. The mixture was extracted with chloroform and the combined extracts were dried over magnesium sulfate, then concentrated *in vacuo* and purified by flash chromatography using 1% ethyl acetate in methylene dichloride.

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REFERENCES AND NOTES

[1] J. Mohan and G. S. R. Anjaneyulug, *Curr. Sci.*, **58**, 1028 (1989).

[2] A. M. M. E. Omar and O. M. Aboulwafa, *J. Heterocyclic Chem.*, **23**, 1339 (1986).

[3] M. A. Ghannoum, N. F. Eweiss, A. A. Bahajaj and M. A. Quereshi, *Microbios*, **37**, 151 (1983).

[4] A. R. Rasad, T. Ramalingamat, A. B. Rao, P. W. Diwan and P. B. Sattur, *Indian J. Chem.*, **25B**, 556 (1986).

[5] A. A. Deshmukh, M. K. Mody, T. Ramalingamt and P. B. Sattur, *Indian J. Chem.*, **25B**, 793 (1985).

[6] F. P. Invidiata, S. Grimaudo, P. Giammanco and L. Giammanco, *Farmaco*, **46**, 1489 (1991).

[7] M. Kanaoka, *Chem. Pharm. Bull.*, **5**, 385 (1957).

[8] K. J. Potts and R. M. Huseby, *J. Org. Chem.*, **31**, 3528 (1966).

[9] E. Hoggarth, *J. Chem. Soc., Perkin Trans. 1*, 4811 (1952).

[10] J. R. Reid and N. D. Heindel, *J. Heterocyclic Chem.*, **13**, 925 (1976).

[11] H. Golgolab, I. Latezari and L. Hosseini-Gohari, *J. Heterocyclic Chem.*, **10**, 387 (1973).

[12] H. Beyer and C. F. Kroger, *Liebigs Ann. Chem.*, **637**, 144 (1960).

[13] Although thiocarbohydrazide has been reported to explode when heated, we never observed this to occur using our reaction conditions, but CAUTION should be observed during the reaction.