Improved Syntheses of 5-Substituted-4-amino-3-mercapto-(4*H*)-1,2,4-triazoles

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Two improved methods have been developed for the synthesis of 5-substituted-4-amino-3-mercapto-(4*H*)-1,2,4-triazoles. One of these involves the direct hydrazinolysis of potassium 3-aroyldithiocarbazates and the other involves ring-opening and reclosure of 5-substituted-2-mercapto-1,3,4-oxadiazoles to the aminomercaptotriazoles. Both of these methods offer advantages over the classic Hoggarth synthesis.

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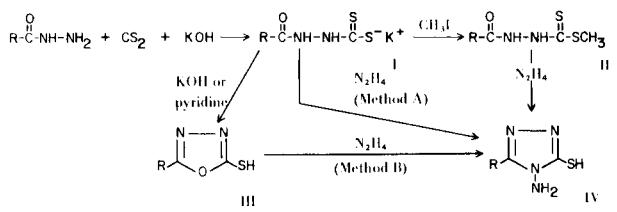
The Hoggarth synthesis (1) of 5-substituted-4-amino-3-mercapto-(4*H*)-1,2,4-triazoles has been widely utilized as the method of choice for preparation of this useful class of heterocyclic compounds (2-5). Procedurally, carboxylic acid hydrazides are condensed with carbon disulfide in ethanolic potassium hydroxide to yield the potassium 3-aroyldithiocarbazates (I) which are *S*-alkylated with methyl iodide. These methyl 3-aroyldithiocarbazates (II) are cyclized with hydrazine to the triazoles (IV). Although treatment of these unmethylated carbazate salts (I) with such bases as pyridine or aqueous caustic has long been known to effect closure to 5-aryl-2-mercapto-1,3,4-oxadiazoles (1,6), no previous researchers appear to have noted that the salts can be converted directly to IV with an excess of hydrazine. This modification (Method A) avoids the *S*-methylation, results in a higher overall yield, and permits a shorter working time (see Table I).

Scheme I



Alternatively, we have found that the oxadiazoles themselves can be condensed with hydrazine and converted to

Table I

5-R-4-Amino-3-mercapto-(4*H*)-1,2,4-triazoles

Compound	R	Formula	% Yield	Method	M.p.	Analyses Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
IVa	C_6H_5	$C_8H_8N_4S$	87	A	203-206 (a)						
			73	B							
IVb	*p*-FC_6H_4	$C_8H_7FN_4S$	77	A	223-225	45.70	3.36	26.65	45.50	3.53	26.73
IVc	*o*-BrC_6H_4	$C_8H_7BrN_4S$	61	A	172-175	35.43	2.60	20.66	35.38	2.80	20.37
IVd	*o*-$CH_3OC_6H_4$	$C_9H_{10}N_4SO$	68	A	216-219	48.63	4.54	25.21	48.95	4.62	25.00
IVe	4-pyridyl	$C_7H_7N_5S$	27	A	259-261 (b)	43.51	3.65	36.25	43.28	3.82	36.30
			64	B							
IVf	2-thienyl	$C_6H_6N_4S$	62	A	215-218	36.34	3.05	28.26	36.22	3.06	28.42
IVg	cyclohexyl	$C_8H_{14}N_4S$	80	A	163-165	48.46	7.12	28.26	48.70	7.36	28.42

(a) Lit. m.p. 204-206°, reference (5). (b) Lit. m.p. 248-252°, reference (8).

the triazoles. Thus, IIIa gave IVa in a 73% yield and IIe provided IVe in 64%. This technique (Method B) is similar to the well-known transformation of furans to pyrroles with nucleophilic amines (7). Although these results might imply that oxadiazoles are intermediates in the hydrazinolysis of I to IV, more detailed studies would be required to permit definitive conclusions. However, at least in the case of IVe, only a modest yield could be isolated from the direct condensation of hydrazine and Ie while an excellent conversion was obtained from the oxadiazole IIIe. This oxadiazole was prepared from Ie by cyclization in aqueous caustic according to a published procedure (6).

EXPERIMENTAL

Infrared spectra were obtained as 1 to 2% potassium bromide disks on a Perkin-Elmer 257 Spectrophotometer. Pmr spectra were obtained in DMSO-d_6 on a Hitachi Perkin Elmer R20A spectrometer. Melting points were determined on a Thomas-Hoover apparatus and are reported uncorrected. Dr. G. I. Robertson of Florham Park, N. J. supplied the combustion analyses.

General Procedure for Preparation of Potassium 3-Aroyldithiocarbazates (I).

A solution of 8.40 g. (0.15 mole) of potassium hydroxide, 200 ml. of absolute ethanol, and 0.10 mole of the aroylhydrazide was treated to the addition of 11.4 g. (0.15 mole) of carbon disulfide. This mixture was diluted with 150 ml. of absolute ethanol and agitated for 12-16 hours. It was then diluted with 200 ml. of dry ether, and the precipitated solids filtered, washed with 2 x 50 ml. of ether, and vacuum dried at 65°. The salts, prepared as described above, were obtained in nearly quantitative yield and were employed without further purification. Their characteristic spectral features were infrared bands at 3300, 1630, 1280, 1240 and 1070 cm^{-1}.

General Procedure for Preparation of 5-*R*-4-amino-3-mercapto-(4*H*)-1,2,4-triazoles (IV): Method A.

A suspension of 20 mmoles of the potassium salts (I), 40 mmoles of 95% hydrazine, and 2 ml. of water was refluxed with stirring for 0.5 to 1 hour. The color of the reaction mixture changed to green, hydrogen sulfide was evolved (lead acetate paper and odor!), and a homogeneous solution resulted. Dilution with 100 ml. of cold water and acidification with concentrated hydrochloric acid precipitated a white solid. This product was filtered, washed with 2 x 30 ml. portions of cold water, and recrystallized from ethanol or ethanol-water to analytical purity (see Table I). Spectrally, the triazoles displayed infrared bands at 3230, 2920, 1635, 1570, and 1470 cm^{-1} and pmr resonances at δ 5.6 (s, 2H, NH_2) and 13.5 (s, 1H) ppm.

General Procedure for Preparation of Triazoles from Oxadiazoles: Method B.

A solution of 30 mmoles of either IIIa (6) or IIIe (6), 20 ml. of water, and 16 g. of 95% hydrazine was refluxed for 4 hours, diluted with 200 ml. of cold water, acidified by the dropwise addition of concentrated hydrochloric acid, and filtered. The solid was washed with a minimum of cold water, and recrystallized from 1:1 ethanol:water to give respectively, IVa or IVe. The infrared and pmr spectra of the triazoles obtained by this route superimposed on those for the same substance obtained by Method A.

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