The Reaction of 4-Amino-3,5-bis[methylthio]-1,2,4-triazole with Alkylating Reagents

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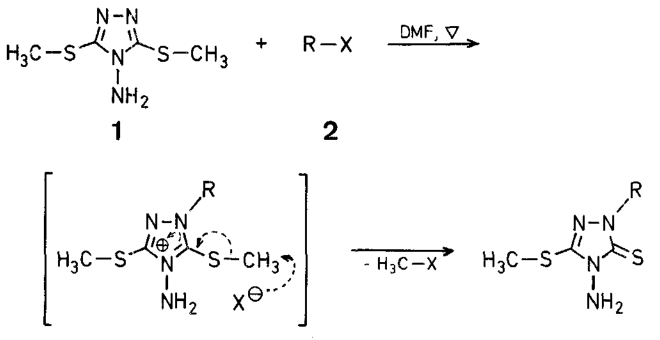
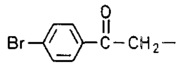
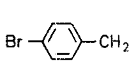
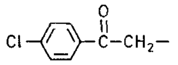
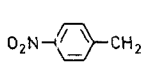
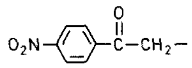
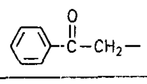
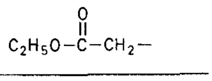
In the course of our investigation on the synthesis of fused meso-ionic compounds[1,2], a simple and convenient method for the preparation of 1-substituted 4-amino-5-thioxo-4,5-dihydro-1,2,4-triazoles was required. Two methods for their preparation have been reported; the first involves sequential treatment of alkylhydrazines with carbon disulfide, methyl iodide, hydrazine, and carboxylic acids[3]; however, limited availability of substituted hydrazine reagents severely restricts the scope of this process. The second method involves alkylation of 4-amino-1,2,4-triazole followed by treatment with elemental sulfur in the presence of triethylamine[4,5].

We report here an apparently widely applicable synthesis of 1-substituted 4-amino-3-methylthio-5-thioxo-4,5-dihydro-1,2,4-triazoles **4** from 4-amino-3,5-bis[methylthio]-1,2,4-triazole (**1**; readily available from thiocarbohydrazide, carbon disulfide[6] or ethyl xanthate[7]) and methyl iodide or other alkyl bromides **2**.



1 **2** **3** **4**

2,4	R	2,4	R
a	H_3C-	e	
b		f	
c		g	
d		h	 $C_2H_5O-\overset{O}{\overset{\parallel}{C}}-CH_2-$

When treated with a slight excess of alkylating reagent in dry dimethylformamide under reflux, the *N*-aminoheterocycle **1** is directly converted to the corresponding 4-amino-5-thioxo-4,5-dihydro-1,2,4-triazole **4** in excellent yield. Furthermore, product isolation is easily accomplished by pouring the reaction mixture into ice/water and filtration of the crude **4**. Structural elucidation of **4** was accomplished on the basis of spectral data and microanalyses.

Compound **1** reacts with methyl iodide (**2**) in dry methanol under reflux to give the quaternized salt **3** ($R = CH_3$; $X = J$), which, on being heated at reflux in benzene solution, is converted into **4a** in nearly quantitative yield. We believe that this type of compounds **3** could be the intermediates in the **1**→**4** conversion.

The reaction appears to be quite general: it proceeds satisfactorily for methyl iodide and for arylmethyl, alkyl, phenacyl, and functionally substituted aliphatic bromides **2** (Table).

A conceptually similar reaction has only been briefly mentioned[8]: 1*H*-4-amino-5-thioxo-4,5-dihydro-1,2,4-triazole (**4**; R = H) may be obtained in 72% yield by reaction of 4-amino-3,5-bis[methylthio]-1,2,4-triazole (**1**) with hydrazine, but this has remained the sole example of this type of reaction.

1-Substituted 4-Amino-3-methylthio-5-thioxo-4,5-dihydro-1,2,4-triazoles 4; General Procedure:

A mixture of 4-amino-3,5-bis[methylthio]-1,2,4-triazole (**1**; 1.76 g, 10 mmol), the appropriate alkylating reagent **2** (12 mmol), and dry dimethylformamide (20 ml) is refluxed for 1 h. After cooling, the reaction mixture is poured into ice/water (30 ml), the precipitate is collected by

Table. Compounds **4** prepared

Compound No.	Yield[a] [%]	m.p.[b] [°C] (solvent)	Molecular formula[c]	I.R. (Nujol)[d] ν [cm^{-1}]	^{1}H-N.M.R.[e] (DMSO-d_6) δ [ppm]	M.S.[f] m/e (M$^+$) (rel. int., %)
4a	81	150–152° (methanol)	$C_4H_8N_4S_2$ (176.3)	3300, 3170, 1635, 1600, 1490, 1360, 1100, 960, 840, 720, 660	5.65 (s, 2 H)[g]; 3.66 (s, 3 H); 2.52 (s, 3 H)	176 (32)
4b	85	142–144° (methanol)	$C_{10}H_{11}BrN_4S_2$ (331.3)	3290, 3180, 1610, 1490, 1400, 1300, 1260, 1070, 1010, 840, 795, 730	7.2–7.5 (m, 4 H); 5.68 (s, 2 H)[g]; 5.30 (s, 2 H); 2.51 (s, 3 H)	332 (13); 330 (13)
4c	81	201–203° (benzene)	$C_{10}H_{11}N_5O_2S_2$ (297.4)	3320, 3190, 1610, 1520, 1350, 1100, 1040, 860, 845, 745	7.3–8.1 (m, 4 H); 5.70 (s, 2 H)[g]; 5.35 (s, 2 H); 2.51 (s, 3 H)	297 (24)
4d	82	186–188° (benzene)	$C_{11}H_{12}N_4OS_2$ (280.4)	3320, 3260, 1695, 1600, 1500, 1330, 1230, 1050, 995, 865, 765, 690	7.5–8.0 (m, 5 H); 5.75 (s, 2 H); 5.70 (s, 2 H)[g]; 2.51 (s, 3 H)	280 (13)
4e	94	205–207° (benzene)	$C_{11}H_{11}BrN_4OS_2$ (359.3)	3320, 3250, 1695, 1590, 1490, 1330, 1230, 1050, 990, 860, 820	7.7–8.0 (m, 4 H); 5.81 (s, 2 H); 5.70 (s, 2 H)[g]; 2.50 (s, 3 H)	360 (19); 358 (19)
4f	93	197–199° (benzene)	$C_{11}H_{11}ClN_4OS_2$ (314.8)	3320, 3250, 1695, 1590, 1490, 1330, 1220, 1100, 990, 860, 820	7.6–8.0 (m, 4 H); 5.75 (s, 2 H); 5.68 (s, 2 H)[g]; 2.51 (s, 3 H)	314 (12)
4g	95	196–198° (benzene)	$C_{11}H_{11}N_5O_3S_2$ (325.4)	3300, 3190, 1700, 1600, 1525, 1350, 1220, 1000, 845, 745, 690	7.3–8.3 (m, 4 H); 5.85 (s, 2 H); 5.72 (s, 2 H)[g]; 2.50 (s, 3 H)	325 (21)
4h	45	105–107° (ethanol)	$C_7H_{12}N_4O_2S_2$ (248.3)	3330, 3200, 1745, 1620, 1500, 1350, 1220, 1060, 1020, 890, 840, 740	5.70 (s, 2 H)[g]; 4.90 (s, 2 H); 4.11 (q, 2 H); 2.51 (s, 3 H); 1.20 (t, 3 H)	248 (15)

[a] Yield of pure isolated product.

[b] Uncorrected.

[c] Satisfactory microanalyses obtained (C ±0.18, H ±0.12, N ±0.16, S ±0.18).

[d] Recorded on a Perkin-Elmer 457 spectrometer.

[e] Recorded at 80 MHz on a Varian FT-80 spectrometer, with TMS as internal standard.

[f] Recorded at 70 eV in a Hewlett-Packard 5980 A.

[g] Exchangeable with deuterium.

filtration, washed with additional water, dried, and crystallized from the appropriate solvent to give products **4** as crystalline solids (Table).

4-Amino-1-methyl-3,5-bis[methylthio]-1,2,4-triazolium Iodide (3; R = CH$_3$, X = J):

Methyl iodide (1.71 g, 12 mmol) is added to a solution of 4-amino-3,5-bis[methylthio]-1,2,4-triazole (**1**; 1.76 g, 10 mmol) in dry methanol (35 ml), and the reaction mixture is refluxed for 7 h. After cooling, the solvent is evaporated under reduced pressure and the remaining solid crystallized from methanol/diethyl ether to give **3** (R = CH$_3$, X = J); yield: 2.76 g (87%); colourless prisms; m.p. 132–133 °C.

$C_5H_{11}N_4JS_2$	calc.	C 18.87	H 3.48	N 17.60	S 20.15
(318.2)	found	18.72	3.49	17.53	20.03

I.R. (Nujol): ν = 3205, 3110, 3090, 1620, 1520, 1480, 1410, 1340, 1310, 1270, 1100, 990, 970, 930, 800, 680 cm^{-1}.

^{1}H-N.M.R. (DMSO-d_6): δ = 2.67 (s, 3 H); 2.76 (s, 3 H); 4.05 (s, 3 H); 6.65 ppm (s, 2 H).

When a benzene solution of **3** (R = CH$_3$, X = J) is heated under reflux for 24 h, compound **4a** is obtained in nearly quantitative yield.

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