3,4-Disubstituted-5-mercapto-1,2,4-triazoles and Related Compounds

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3,4-Diaryl-5-mercapto-1,2,4-triazoles have been prepared by the cyclization of the corresponding 1-aryl-4-substituted thiosemicarbazide with alkali. The resulting mercapto triazoles were converted into 3,4-disubstituted-5-alkylthio-1,2,4-triazoles with the action of different alkyl halides and some of the sulphides were converted into sulphones by oxidation with aqueous potassium permanganate.

Compounds containing N-C-S linkage which are of versatile biological interest as anti-tubercular,¹⁾ antiradiation agents²⁾ and their application as anthelmintics,³⁾ nematocides,⁴⁾ fungicides,⁵⁾ pesticides,⁶⁾ and insecticides⁷⁾ encouraged further investigation in this field.

It was, therefore, thought worthwhile to synthesize compounds having N-C-S linkage such as 3,4-disubstituted 5-mercapto-1,2,4-triazoles (I), related sulphides (II) and sulphones (III), 2-arylamino-1,3,4,5-thiatriazoles (IV) and 1-aryl-2-mercapto-1,3,4,5-tetrazoles (V).

Lieber *et al.*¹⁰⁾ and this method was found more convenient in respect of purity and yield of the compounds. The thiatriazoles (IV) on refluxing with sodium hydroxide (10%) and neutralising the solution with hydrochloric acid gave 2-mercapto-1,3,4,5-tetrazoles (V).

Few 5-mercapto-1,2,4-triazoles (I) and 5-alkyl arylthio-1,2,4-triazoles (II) were assayed for antifungal as well as seed germination activity.

The mercapto triazoles (I) were prepared by refluxing 1-aryl 4-substituted thiosemicarbazide with sodium hydroxide⁸⁾ (4%) and they were also prepared directly by aroyl hydrazide with alkyl aryl isothiocyanates in presence of sodium hydroxide (8%) and then acidifying with hydrochloric acid. The mercaptotriazoles were converted into 5-alkylthio-1,2,4-triazoles (II) by action of different alkyl halides in presence of ethanolic sodium hydroxide (10%) and the resulting sulphides were oxidised with aqueous potassium permanganate (3%) into corresponding sulphones⁹⁾ (III).

2-Arylamino-1,3,4,5-thiatriazoles (IV) were prepared by modifying the method of Eugene

EXPERIMENTAL

All the melting points are uncorrected.

3,4-Disubstituted-5-mercapto-1,2,4-triazoles (I). These were prepared following one of the two general methods: (A) 1-aryl-4-aryl thiosemicarbazide (0.01 mole) was dissolved in sodium hydroxide solution (30 ml, 4%) and refluxed gently for 2 hr. The resulting solution was cooled and filtered. The filtrate was adjusted to pH 5~6 with cold dilute hydrochloric acid and the precipitated solid filtered off after cooling, washed with water and crystallised from dilute alcohol.

(B) A mixture of hydrazide (0.01 mole) and appropriate isothiocyanate (0.01 mole) was dissolved in sodium hydroxide (17.5 ml, 8%) and refluxed gently for 5 hr, cooled and filtered. The filtrate was neutralised with dilute hydrochloric acid and the precipitated

TABLE I. 3,4-DISUBSTITUTED-5-MERCAPTO-1,2,4-TRIAZOLES (I)

S. No.	R	R'	mp °C	Yield %	Molecular formula	Found	N (%) Calcd.
1.	<i>p</i> -Chlorophenyl	<i>p</i> -Tolyl	220	70	C ₁₅ H ₁₂ ClN ₃ S	14.1	13.93
2.	<i>p</i> -Chlorophenyl	<i>p</i> -Iodophenyl	240	60	C ₁₄ H ₉ ClIN ₃ S	10.5	10.15
3.	2,4-Dichloro-phenoxymethyl	<i>o</i> -Tolyl	120	75	C ₁₆ H ₁₃ Cl ₂ N ₃ OS	11.8	11.47
4.	2,4-Dichloro-phenoxymethyl	<i>m</i> -Tolyl	165	82	C ₁₆ H ₁₃ Cl ₂ N ₃ OS	11.6	11.47
5.	2,4-Dichloro-phenoxymethyl	<i>p</i> -Tolyl	190	60	C ₁₆ H ₁₃ Cl ₂ N ₃ OS	11.3	11.47

TABLE II. 3,4-DISUBSTITUTED-5-ALKYL (OR BENZYL)THIO-1,2,4-TRIAZOLES

S. No.	R'	R''	mp °C	Yield %	Molecular formula	Found	N (%) Calcd.
1.	<i>p</i> -Tolyl	Benzyl	138	60	C ₂₂ H ₁₈ ClN ₃ S	10.5	10.7
2.	<i>p</i> -Tolyl	Chloroethyl	115	65	C ₁₇ H ₁₅ Cl ₂ N ₃ S	11.2	11.5
3.	<i>p</i> -Tolyl	Ethyl	145	68	C ₁₇ H ₁₆ ClN ₃ S	13.1	12.74
4.	<i>p</i> -Tolyl	<i>n</i> -Propyl	140	65	C ₁₈ H ₁₈ ClN ₃ S	12.5	12.23
5.	<i>p</i> -Tolyl	Carboxyl-methyl	182	70	C ₁₇ H ₁₄ ClN ₃ O ₂ S	12.1	11.68
6.	<i>p</i> -Iodophenyl	Benzyl	192	68	C ₂₁ H ₁₅ ClIN ₃ S	8.7	8.3
7.	<i>p</i> -Iodophenyl	Carboxyl-methyl	122	75	C ₁₆ H ₁₁ N ₃ ClIO ₂ S	9.1	8.9
8.	<i>p</i> -Iodophenyl	Ethyl	210	70	C ₁₆ H ₁₃ ClIN ₃ S	9.3	9.5
9.	<i>p</i> -Iodophenyl	<i>n</i> -Propyl	175	72	C ₁₇ H ₁₅ ClIN ₃ S	9.5	9.2
10.	<i>p</i> -Iodophenyl	<i>p</i> -Phenetyl-acetamido	182	30	C ₂₄ H ₂₀ ClIN ₄ O ₂ S	9.6	9.48

TABLE III. 3,4-DISUBSTITUTED-5-ALKYL(OR BENZYL)SULPHO-1,2,4-TRIAZOLES

S. No.	R	R'	R''	mp °C	Molecular formula	N (%) Found	Calcd.
1.	<i>p</i> -Chlorophenyl	<i>p</i> -Tolyl	Benzyl	198	C ₁₅ H ₁₂ ClN ₃ O ₂ S	13.1	12.59
2.	<i>p</i> -Chlorophenyl	<i>p</i> -Iodophenyl	Ethyl	210	C ₁₆ H ₁₃ ClIN ₃ O ₂ S	8.9	8.87
3.	2,4-Dichlorophenoxymethyl	<i>p</i> -Iodophenyl	Benzyl	162	C ₂₂ H ₁₆ Cl ₂ IN ₃ O ₃ S	7.2	7.0
4.	2,4-Dichlorophenoxymethyl	<i>o</i> -Tolyl	Benzyl	141	C ₂₃ H ₁₉ Cl ₂ N ₃ O ₃ S	8.3	8.6
5.	2,4-Dichlorophenoxymethyl	<i>m</i> -Tolyl	Benzyl	160	C ₂₃ H ₁₉ Cl ₂ N ₃ O ₃ S	8.5	8.6

solid crystallised with ethanol.

The mixed melting points of the compounds prepared by above two methods remained undepressed in each case. Their relevant data are recorded in Table I.

3,4-Disubstituted-5-alkyl/benzyl thio-1,2,4-triazoles (II). Mercapto triazole I (0.01 mole) was dissolved in ethanolic sodium hydroxide (8ml, 10%) and alkyl/benzyl halide (0.01 mole) in slight excess was added to it. The whole mixture was refluxed on water-bath for 2~3 hr. The reaction mixture was poured on ice and left for 3 hr. Thus solid obtained was filtered and washed with water and crystallised with suitable solvent.

In some cases where compounds do not solidify after pouring on ice, they were converted into crystalline solid by dissolving them in little ethanol and scratching the walls of the container.

The compounds thus prepared are listed along with relevant data in Table II.

3,4-Disubstituted-5-alkyl (or benzyl) sulpho-1,2,4-

triazoles. 3,4-Disubstituted-5-alkyl (or benzyl) thio triazole (0.001 mole) was dissolved in minimum amount of glacial acetic acid and to this an aqueous solution of potassium permanganate (3%) was added dropwise with vigorous shaking till the colour persists. The resulting mixture was cooled, filtered and washed with water. Crystallisation with dilute acetic acid afforded analytical sample.

All the sulphones thus prepared are listed in Table III.

2-(m) Tolylamino-1,3,4,5-thiatriazole. 4-(m) Tolythio-semicarbazide (3.5 gm) was dissolved in dimethylformamide (10 ml) and resulting solution was cooled up to 0°C and then hydrochloric acid (20 ml, 4 N) was added. To this mixture a solution of sodium nitrite (2.4 gm) was added dropwise during 10 min. The yellow-green creamy solid obtained was filtered and washed with distilled water a grayish mass obtained, yield 3.0 gm, mp 128°C. *Anal.* Found: N, 28.8 Calcd. for C₈H₈N₄S: N, 29.16%.

TABLE IV. ANTIFUNGAL ACTIVITY

S. No.	Compound	No. of replications	Average percentage inhibition after 96 hr.			Seed germination activity after 10 days at 100 ppm concentration	
			Concentrations used			Seeds soaked in solution of chemicals for 24 hr	Seeds soaked in solvent for 24 hr (control)
			1: 1,000	1: 10,000	1: 100,000		
1.	3-(2,4-dichlorophenoxy)-methyl-4-(<i>o</i> -) tolyl-5-mercapto-1,2,4-triazole	3	65.1	65.1	46.5	0	94
2.	3-(2,4-dichlorophenoxy)-methyl-4-(<i>m</i>)tolyl-5-mercapto-1,2,4-triazole	3	77.7	66.6	51	0	94
3.	3-(<i>p</i> -) chlorophenyl-4-(<i>p</i> -) iodophenyl-5-(<i>n</i> -) propyl thio-1,2,4-triazole	3	77.7	66.6	55.5	40	94
4.	3-(<i>p</i> -) Chlorophenyl-4-(<i>p</i> -) tolyl-5 carboxyl-methylthio-1,2,4-triazole	3	81.1	77	66	15	94
5.	3-(<i>p</i> -) Chlorophenyl-4-(<i>p</i> -) tolyl-5-benzylthio-1,2,4-triazole	3	62.2	60	40	20	94
6.	3-(<i>p</i> -) Chlorophenyl-4 (<i>p</i> -) iodophenyl-5-benzylthio-1,2,4-triazole	3	62.5	60	40	20	94
7.	3-(<i>p</i> -)Chlorophenyl-4-(<i>p</i> -) iodophenyl 5-ethylthio-1,2,4-triazole	3	65	60.3	53	18	94
8.	3-(<i>p</i> -)Chlorophenyl-4-(<i>p</i> -) iodophenyl-5-carboxyl-methylthio-1,2,4-triazole	3	79.3	68.5	60	22	94

2-(*p*-) Iodophenylamino-1,3,4,5-thiatriazole. It was prepared from 4-(*p*-) iodophenylthiosemicarbazide by the method described above, mp 122°C, yield 70%. *Anal.* Found: N, 18.7. Calcd. for $C_7H_5IN_4S$: N, 18.4%.

1-(*m*) Toly-2-mercapto-1,3,4,5-tetrazole. 2-(*m*) Toly amino 1,3,4,5-thiatriazole (2.5 gm) was refluxed with 10% sodium hydroxide for 2 hours and filtered. Filtrate on treatment with dilute hydrochloric acid (4 N) up to pH 5~6 gave grayish solid which was filtered and washed with little distilled water. Crystallisation with water-ethanol mixture afforded analytical sample, mp 1420, yield 60%. *Anal.* Found: N, 29.3. Calcd. for $C_8H_8N_4S$: N, 29.16%.

Biological activity

Fungicidal test. The anti-fungal activity of some compounds were evaluated against the fungus *Aspergillus-niger* by agar-plate technique⁽¹¹⁾ at three different concentrations namely 1:1000, 1:10,000 and 1:100,000. The average percentage inhibition by various compounds are recorded in Table IV. As it is evident from the Table IV that compounds No. 2,3, 4,7,8 are active even at low concentration, and is enhanced by the presence of carboxyl group and 3,4-dihalophenyl group.

Seed germination activity. The compounds screened as fungicides were also tested for seed germination activity on *Pisum-sativum* at 22.3°C and 100 ppm concentration in diffused day light and their effects

were observed. As it is clear from the observations recorded in Table IV that compounds 1 and 2 inhibited the germination completely whereas compounds 4,6,7 and 8 showed 15, 20, 18 and 22 percent germination.

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