

SUBSTITUTED TRIAZOLYLTHIOUREAS

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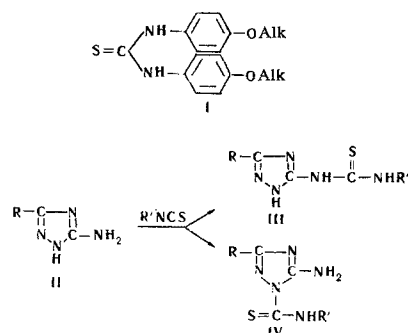
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Some substituted triazolylthioureas have been prepared by the reaction of esters of thiocyanic acid with aminotriazoles.

Symmetrical diarylureas of general formula I have high tuberculostatic activity. Replacement of one of the aryl radicals by a heterocycle leads to a change in activity [1-3], so that it was of interest to prepare compounds of this type containing a triazole ring.

Aminotriazoles, in common with other compounds containing the guanidine grouping, can react with electrophiles to form several series of derivatives. We have shown this to be so in the case of the acylation of aminotriazoles [4]. The reaction of isothiocyanate esters with unsubstituted aminotriazoles can also lead to the formation of two types of derivatives, III and IV:



Only a few derivatives of arylthioureas containing the triazole radical have been described in the literature [5]. Reaction of 3-methyl-5-amino-1,2,4-triazole (II, R = CH₃) with phenyl isothiocyanate under mild conditions gives 1-anilinoformyl-3-methyl-5-amino-1,2,4-triazole (IV, R = CH₃; R' = C₆H₅). In boiling amyl alcohol, on the other hand, these reagents give N-phenyl-N'-(3-methyl-1,2,4-triazol-5-yl)thiourea (III, R = CH₃, R' = C₆H₅). Reaction of the appropriate components in ethanol [6] gives 1-(methylaminothioformyl)-5-amino-1,2,4-triazole and 1-(anilinothioformyl)-5-amino-1,2,4-triazole, with a decomposition temperature of about 300° C.

Our work has shown that, according to the reaction conditions (temperature and solvent) and to the nature of the substituents in the triazole ring and in the isothiocyanate ester, compounds of either type III or type IV may be formed. Under mild conditions, reaction of aminotriazoles with isothiocyanate esters leads to the formation of derivatives of 1-(aminothioformyl)-5-amino-1,2,4-triazole (IV). We have assumed that the aminothioformyl group is located on the 1-nitrogen atom of the triazole ring by analogy with the acylation and alkylation of aminotriazoles [7], and the reaction of isocyanate esters [8]. By

heating, in the presence or absence of a solvent, the aminothioformyl derivatives IV are readily converted into the corresponding triazolylthioureas III. Compound IV is reminiscent in this respect of the N-acylated aminotriazoles [4]. If, however, in the case of the acylaminotriazoles intramolecular rearrangement is the most probable, then with IV the isothiocyanate ester is liberated, followed by combination with the amino group.

Dissociation to the base and the isothiocyanate ester is a general property of derivatives of thiourea. Derivatives of secondary amines dissociate at comparatively low temperatures, for example, N-methyl-N,N'-diphenylthiourea dissociates to N-methylaniline and phenyl isothiocyanate at temperatures as low as 100° C. 1-(n-Butylaminothioformyl)imidazole, as a result of the electron-acceptor properties of the imidazole ring, is stable only at low temperatures (-70° C), and is completely dissociated into its components at room temperature [10].

1-(Anilinothioformyl)-5-amino-1,2,4-triazole (IV, R = H, R' = C₆H₅) decomposes at 133-135° C. Phenyl isothiocyanate reacts with the primary amino group at this temperature to form compound III (R = H, R' = C₆H₅). 1-(Methylaminothioformyl)-5-amino-1,2,4-triazole (IV, R = H, R' = CH₃) breaks down at 160° C. In this case, the decomposition temperature exceeds the boiling point of methyl isothiocyanate.

Nucleophilic reagents such as alcohol, ammonia, and amines react readily with IV with displacement of the aminothioformyl group and formation of the corresponding thiocarbonic acid derivatives and the triazoles. Compounds III do not react under these conditions.

The best preparation method of the N-aryl-N'-triazolylthioureas III (R' = aryl) is by boiling the components in pyridine solution, but for the alkyl-substituted triazolylthioureas III (R' = alkyl), amyl alcohol is used.

The physical properties and analytical results of the compounds prepared are given in the table.

EXPERIMENTAL

1-(Anilinothioformyl)-5-amino-1,2,4-triazole: A) To a solution of 8.4 g of 3-amino-1,2,4-triazole in 50 ml of alcohol was added 13.5 g of phenyl isothiocyanate. The mixture was kept at room temperature for 24 hr, the crystalline solid filtered off, washed with alcohol and ether, and dried.

N-(4-Ethoxyphenyl)-N'-(3-amyl-1,2,4-triazol-5-yl)thiourea. B) A solution of 1.64 g of 3-amyl-5-amino-1,2,4-triazole and 0.9 g of 4-ethoxyphenyl isothiocyanate in 10 ml of alcohol was boiled for 2 hr. On cooling, compound III (R = CH₃, R' = 4-C₂H₅OC₆H₄) separated. The alcoholic filtrate was poured into water, and the precipitate of ethyl 4-ethoxyphenylthiocarbamate (0.48 g, 40% calc. on 4-

Triazolylthioureas

Prep. no.	Compound	Method of prep.	Solvent for re-crystallization	mp, °C	Molecular formula	N, %		Yield, %
						Found	Calc.	
1	1-(Methylaminothioformyl)-5-amino-1,2,4-triazole	B	Alcohol	160	C ₄ H ₇ N ₅ S	44.71	44.51	28
2	1-(Methylaminothioformyl)-3-methyl-5-amino-1,2,4-triazole	B	Alcohol	174—175	C ₅ H ₉ N ₅ S	41.63	40.91	47
3	1-(Anilinothioformyl)-5-amino-1,2,4-triazole	A	—	133—135	C ₉ H ₉ N ₅ S	31.88	31.94	38
4	1-(anilinothioformyl)-3-methyl-5-amino-1,2,4-triazole	A	—	136—137	C ₁₀ H ₁₁ N ₅ S	29.95	30.02	55
5	N-Methyl-N'-(1,2,4-triazol-5-yl)thiourea	C	Water	213	C ₄ H ₇ N ₅ S	45.71*	44.51	35
6	N-Methyl-N'-(3-methyl-1,2,4-triazol-5-yl) thiourea	C	Alcohol	219	C ₅ H ₉ N ₅ S	41.63 ² *	40.91	30
7	N-Phenyl-N'-(1,2,4-triazol-5-yl)thiourea	C	Acetic acid	205	C ₉ H ₉ N ₅ S	31.94	32.06	90
8	N-Phenyl-N'-(3-methyl-1,2,4-triazol-5-yl)thiourea	C	Acetic acid	198—200	C ₁₀ H ₁₁ N ₅ S	30.89	30.02	88
9	N-(4-Ethoxyphenyl)-N'-(1,2,4-triazol-5-yl)-thiourea	D,E	Alcohol	209—210	C ₁₁ H ₁₃ N ₅ OS	26.77	26.58	69
10	N-(4-Ethoxyphenyl)-N'-(3-methyl-1,2,4-triazol-5-yl)thiourea	B	Alcohol	212	C ₁₂ H ₁₅ N ₅ OS	25.04	25.24	30
11	N-(4-Propoxyphenyl)-N'-(3-methyl-1,2,4-triazol-5-yl)-thiourea	D	Alcohol	182—183	C ₁₃ H ₁₇ N ₅ OS	24.48 ³ *	24.00	77
12	N-(4-Butoxyphenyl)-N'-(3-methyl-1,2,4-triazol-5-yl)-thiourea	D	Alcohol	185—186	C ₁₄ H ₁₉ N ₅ OS	22.57	22.93	83
13	N-(4-Ethoxyphenyl)-N'-(3-propyl-1,2,4-triazol-5-yl)-thiourea	D	Aqueous alcohol	169—170	C ₁₄ H ₁₉ N ₅ OS	23.36	22.93	90
14	N-(4-Ethoxyphenyl)-N'-(3-amyl-1,2,4-triazol-5-yl)-thiourea	D	Alcohol-ethyl acetate	184—186	C ₁₆ H ₂₃ N ₅ OS	20.20	20.90	75

¹* Found, %: C 30.33; H 4.59; S 19.95. Calculated, %: C 30.58; H 4.49; S 20.35.

²* Found, %: C 34.90; H 4.78; S 18.12. Calculated, %: C 35.09; H 5.30; S 18.06.

³* Found, %: C 53.51; H 5.94; S 10.68. Calculated, %: C 53.59; H 5.81; S 11.00.

ethoxyphenyl isothiocyanate) was recrystallized from alcohol, mp 95–96° C. Found, %: N 6.63. Calculated for $C_{11}H_{15}NO_2S$, %: N 6.21.

N-Methyl-N'-(1,2,4-triazol-5-yl)thiourea. C) A mixture of 1.68 g of 3-amino-1,2,4-triazole and 1.46 g of methyl isothiocyanate in 6 ml of amyl alcohol was boiled for 2 hr, III (R = H, R' = CH₃) separated on cooling.

N-(4-Ethoxyphenyl)-N'-(3-amyl-1,2,4-triazol-5-yl)thiourea. D) A mixture of 1.64 g of 3-amino-5-amino-1,2,4-triazole and 1.8 g of 4-ethoxyphenyl isothiocyanate in 20 ml of pyridine was boiled for 2 hr, cooled and poured with stirring into 100 ml of water. The oil which separated (with other aminotriazoles, in some cases, a solid precipitate was obtained) was separated, from the aqueous layer by decantation, dissolved in ether, and treated with dil HCl. The precipitated III (R = C₅H₁₁, R' = 4-C₂H₅OC₆H₄) was filtered off and air-dried. It was purified by treatment with hot benzene, and the insoluble portion recrystallized.

N-(4-Ethoxyphenyl)-N'-(1,2,4-triazol-5-yl)thiourea. E) A mixture of 0.84 g of 3-amino-1,2,4-triazole and 1.8 g of 4-ethoxyphenyl isothiocyanate was kept at 190–200° C for 5 min. The mass, after cooling, was extracted twice with 10 ml of hot benzene. The residue was filtered off and recrystallized to give pure III (R = H, R' = 4-C₂H₅OC₆H₄), which gave no depression of mp on mixing with the analytical sample obtained by method D.

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