5-ALKYL(ARYL)THIO-sym-TRIAZOLO]1,5-*a*]-sym-TRIAZINES

SYNTHESIS AND TRANSFORMATIONS

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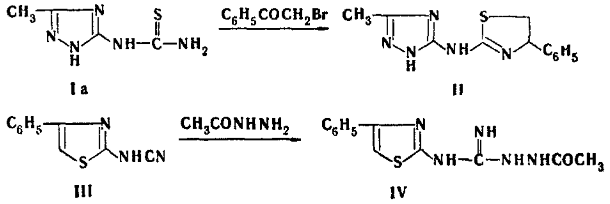
Alkylation of triazolylthioureas gave S-alkyl(aryl)triazolylisothiourea hydrochlorides, which form 5-alkyl(aryl)thio-symtriazolo[1,5-*a*]-sym-triazines with ethyl orthogormate.

We have previously established [1] that 5-amino-1,2,4-triazoles react with benzoyl isothiocyanate to give 1-benzoylthiocarbamoyl-5-amino-1,2,4-triazoles. However, further investigations of this reaction demonstrated that the reaction proceeds at the amino group rather than at the N_1 nitrogen atom, i.e., the reaction products are N-(1,2,4-triazol-5-yl)-N'-benzoylthioureas, the hydrolysis of which gives (1,2,4-triazol-5-yl)thioureas (I). The correctness of the structure of the latter was confirmed by alternative synthesis of 3-methyl-5-(4-phenyl-2-thiazolyl)amino-1,2,4-triazole (II) from Ia and also from 2-cyanoamino-4-phenylthiazole (III) and acetylhydrazine through acetamidoguanidine derivative IV.



Ia II III IV

In the present study, triazolylthioureas were used for the synthesis of thio derivatives of sym-triazolo-sym-triazines, individual representatives of which have already been described [2-4]. The synthesis of 3-phenyl-7-methylthio- and 3-phenyl-5,7-dimethylthio-sym-triazolo[4,3-*a*]-sym-triazines by oxidative cyclization of 2-benzylidenehydrazino derivatives of 1,3,5-triazine by means of lead tetraacetate, i.e., by building up a triazole ring from a triazine ring, was described in [3]. Kobe and co-workers supposed that the possibility of the formation of sym-triazolo[1,5-*a*]-sym-triazines is excluded under these reaction conditions. There are no data available on the chemical properties of the compounds obtained.

It was found that I does not form triazolotriazines on refluxing in the reagents usually employed for acylation and cyclization (formic acid or formamide); this can be explained by the action of the reagents on the sulfur atom.

In order to exclude the possibility of the reaction of I with the cyclizing agents at the sulfur atom, we synthesized S-alkyl(aryl) derivatives of triazolylisothioureas. The S-alkylation and S-arylation of I were carried out, respectively, with alkyl and aryl halides; hydrohalide salts V and free bases VI were obtained in this case. The bases were resistant to the action of dilute acids and bases and decomposed only on prolonged refluxing.

On refluxing with ethyl orthoformate, hydrohalide salts V smoothly form 5-alkyl(aryl)thio-sym-triazolo[1,5-*a*]-sym-triazines (VII). In contrast to V, VII could not be isolated from the reaction mixture on refluxing VI with ethyl orthoformate, and traces of VIIa were isolated only in the case of VIa.

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TABLE 1. S-Alkyl(aryl)-N-(1,2,4-triazol-5-yl)isothioureas (VIa-e) and 5-Alkyl(aryl)thio-sym-triazolo[1,5-*a*]-sym-triazines (VIIa-e)

Compound	mp, °C (solvent)	Empirical formula	Found, %				Calc., %				Yield, %
			C	H	N	S	C	H	N	S	
VIa	164[a]	$C_5H_9N_5S$	34,8	5,2	41,0		35,1	5,3	40,9		60
VIb	126—127[b]	$C_{11}H_{13}N_5S$	53,8	5,6	27,6		53,4	5,4	28,3		64
VIc	167[c]	$C_{10}H_{11}N_5S$	51,7	5,0	30,9	13,9	51,5	4,8	30,0	13.7	78
VId	157[d]	$C_{16}H_{15}N_5S$	62,1	4,9	23,3	10,5	62,1	4,9	22,6	10,4	80
VIe	199[e]	$C_{16}H_{14}N_6O_2S$	54,7	4,2	23,2	9,0	54,2	4,0	23,7	9,0	84
VIIa	122[f]	$C_8H_{14}N_5S$	39,2	4,0		17,6	39,2	3,9		17,7	53
VIIb	123[f]	$C_{12}H_{11}N_5S$	55,4	4,2	26,7	12,6	56,0	4,3	27,2	12,5	61
VIIc	232[g]	$C_{11}H_9N_5S$	54,3	3,8	28,5	13,2	54,3	3,7	28,8	13,2	82
VIId	195[h]	$C_{17}H_{13}N_5S$	64,0	3,9	21,9	10,1	63,9	4,1	21,9	10,0	81
VIIe	225—226[h]	$C_{17}H_{12}N_6O_2S$	56,1	3,3	23,0	9,0	56,0	3,3	23,0	8,8	62

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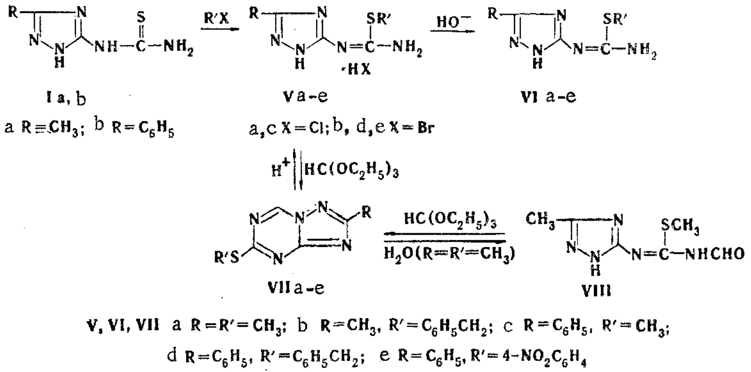
[a] With decomposition, from water. [b] From benzene. [c] From 50% ethanol. [d] From ethanol. [e] From propyl alcohol. [f] From petroleum ether. [g] From benzene–dimethylformamide. [h] From dimethylformamide.

The different behavior of V and VI in cyclization reactions with ethyl orthoformate confirms the opinion that acid catalysis is of great importance [5-7].



Triazolotriazines VII are readily hydrolyzed in aqueous solutions of inorganic acids and bases to give, respectively, V and VI. The rate of hydrolysis is greatest in the case of 2-alkyl and S-alkylthio derivatives. In contrast to the other compounds, VIIa is also hydrolyzed in water to give formyl derivative VIII, which on further hydrolysis in the presence of acid or alkali gives, respectively, Va and VIa. On refluxing in ethyl orthoformate or ethanol, VIII again cyclizes to VIIa. In this case, ethyl orthoformate is the solvent and promotes cyclization [8]. The VIIa ⇄ VIII transformations confirm triazolotriazine structure VII.

On reaction with ethyl orthoformate, triazolylthioureas may form sym-triazolo[1,5-*a*]-sym-triazines or sym-triazolo[4,3-*a*]-sym-triazines. Kobe and co-workers [3] supposed that 3-phenyl-7-methoxy-sym-triazolo[4,3-*a*]-sym-triazine is formed in the cyclization of O-methyl-N-(3-phenyl-1,2,4-triazol-5-yl)isourea with ethyl orthoformate. On the basis of the following consideration, the formation of [1,5-*a*] isomers in the cyclization of triazolylthioureas V seems more likely to us: first, it has been proved [2] that N-(1,2,4-triazol-5-yl)-N'-carbethoxythioureas are cyclized at the N_1 atom; second, the synthesis of VII from V and also from VIII indicates the same direction of cyclization in the case of reactions of triazole derivatives with the hydrocarbon component and in the case of derivatives that already contain elements of the triazine ring.

The PMR spectra of VIIa and VIIc, recorded in CD_3SOCD_3, contain proton signals at τ 0.40 and 0.20 ppm, respectively. According to the data in [3], the signal of the 5-H proton in the PMR spectrum of 3-phenyl-7-methylthio-sym-triazolo[4,3-*a*]-sym-triazine is observed at τ 0.25. Thus the PMR spectra do not make it possible to distinguish between the two proposed triazolotriazine structures.

In order to additionally elucidate the structures of the triazolotriazines obtained, we determined the dipole moment of VIIa and compared it with the calculated values. The calculation was performed in analogy with the methods in [9, 10] starting from the valence state of the nitrogen atoms and using the following values of the dipole moments of the fragments of the molecules: +1.80 D (in analogy with pyrrole) for the nitrogen atom common to both rings, −2.20 D for the remaining nitrogen atoms, and +1.34 D for the SCH_3 group ($\varphi = 77.5°$). Both rings are assumed to be planar regular polyhedra. This method of calculation does not take into account the interaction of the heteroatoms in the molecule and enables one to make only an extremely rough estimate of the dipole moment. However, this method may give information regarding the preferred structure. The calculated dipole moments for the two planar rotational conformations of VIIa (i.e., sym-triazolo[1,5-*a*]-sym-triazine) are 1.9 and 4.0 D, respectively. The values for the corresponding rotational conformations of sym-triazolo[4,3-*a*]-sym-triazine are 6.25 and 4.15 D.

A comparison with the experimental value of the dipole moment for VIIa (1.00 D) made it possible to choose between the two structures of sym-triazolo-sym-triazines, which have markedly different dipole moments, in favor of sym-triazolo]1,5-*a*]-sym-triazine.

EXPERIMENTAL

1-Acetamido-3-(4-phenyl-2-thiazolyl)guanidine (IV). A mixture of 0.2 g (1 mmole) of III, 0.12 g (1.5 mmole) of acetylhydrazine, and 4 ml of absolute ethanol was refluxed for 6 h. Cooling of the mixture precipitated 0.19 g (70%) of IV with mp 225° (dimethylformamide–water). Found: C 52.1; H 4.7; N 25.1%. $C_{12}H_{13}N_5OS$. Calculated: C 52.3; H 4.8; N 25.4%.

3-Methyl-5-(4-phenyl-2-thiazolyl)amino-1,2,4-triazole (II). A. A 0.35-g (1.2 mmole) sample of IV was refluxed in 5 ml of 10% sodium hydroxide solution for 20 min, after which the mixture was cooled and acidified with hydrochloric acid. The precipitate was removed by filtration to give 0.3 g (94%) of a product with mp 259° (from aqueous methanol). Found: C 56.0; H 4.2; N 27.4%. $C_{12}H_{11}N_5S$. Calculated: C 56.0; H 4.3; N 27.2%.

B. A mixture of 0.32 g (2 mmole) of Ia, 0.4 g (2 mmole) of phenacyl bromide, and 20 ml of ethanol was refluxed for 2 h. The mixture was then distilled to remove ~10 ml of ethanol, after which a solution of 0.15 g of sodium acetate in 10 ml of water was added to isolate 0.16 g (31%) of II with mp 259° (from ethanol).

S-Alkyl(aryl)-N-(1,2,4-triazol-5-yl)isothioureas (Va-e, VIa-e, Table 1). Equimolar amounts of Ia,b and the corresponding alkyl(aryl) halides were refluxed in absolute ethanol for 30 min, after which the ethanol was removed by distillation to give Va-e. Compounds Va-e were dissolved in the minimum amount of ethanol, and the solutions were treated with aqueous sodium carbonate to give VIa-e.

5-Alkyl(aryl)thio-sym-triazolo[1,5-*a*]-sym-triazines (VIIa-e, Table 1). A. A 10-mmole sample of Va-e (immediately after preparation via the method described above) was refluxed with ethyl orthoformate (20, 20, 35, 30, and 50 ml, respectively) for 1 h, after which the mixture was cooled to precipitate crystalline VIIc-e. The crystals were removed by filtration and washed with the minimum amount of ethyl orthoformate. Compounds VIIa,b were obtained by evaporation of the reaction mixture and extraction with petroleum ether.

B. A 0.3-g (1.5 mmole) sample of VIII was refluxed for 45 min in 4 ml of ethyl orthoformate. After the mixture was cooled, 0.1 g (31%) of VIIa with mp 122° (from petroleum ether) crystallized out.

C. A 0.2-g (1 mmole) sample of VIII was refluxed in 10 ml of absolute ethanol for 1 h, after which the ethanol was removed by distillation, and the dry residue was extracted with 10 ml of ether. The ether was evaporated to give 0.12 g (39%) of VIIa with mp 122° (from petroleum ether).

Hydrolysis of VIIa-e and IX. The hydrolysis was carried out with 15% hydrochloric acid or 15% ammonia at room temperature for 0.5-1 h or on a boiling-water bath in the course of a few minutes. The hydrolysis products were identified as the bases (VIa,b,d,e). Only VIc with mp 234° (dec., from ethanol) was isolated. Found: C 44.2; H 4.7; Cl 12.0%. $C_{10}H_{11}N_5S \cdot HCl$. Calculated: C 44.5; H 4.5; Cl 12.0%.

S-Methyl-N-(3-methyl-1,2,4-triazol-5-yl)-N'-formylisothiourea (VIII). The addition of 0.54 g (3 mmole) of VIIa to 10 ml of boiling water gave an immediate precipitate of VIII [0.53 g (93%)] with mp 164° (dec., from ethanol). IR spectrum: 1710 (CO), 1625 cm^{-1} (C=N). Found: C 36.1; H 4.7; N 35.5; S 17.1%. $C_6H_9N_5OS$. Calculated: C 36.2; H 4.6; N 35.1; S 16.1%.

The dipole moment of VIIa was determined in benzene solutions at 25° via the method in [11]. The data from the determination and calculation of the dipole moment by the method in [12] are as follows: $\alpha_{av} = 0.9376$, $\beta_{av} = 0.9303$, $P_\alpha = 68.140$, MR_D 47.270. The dipole moment of VIIa is 1.00 ± 0.03 D.

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