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The condensation reaction of thiobenzamide, (as well as thionicotinamide and isothionicotinamide) in the presence of dimethyl sulfoxide and of an acid, affords 3,5-diphenyl-1,2,4-thiadiazole. Under the same experimental conditions, *N*-substituted thioureas are also condensed to 1,2,4-thiadiazole derivatives; their structure is ascertained by spectroscopic properties and by X-ray diffraction. Some information on the mechanism of thiadiazoles formation from both starting classes of compounds, thiobenzamides and *N*-substituted thiourea, is collected and discussed.

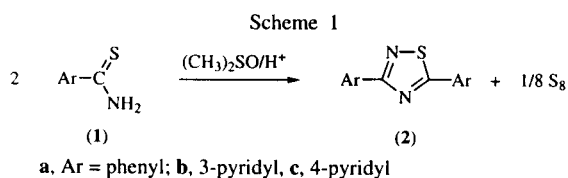
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The self-condensation reaction of thiobenzamides is a simple method for preparing 3,5-diaryl-1,2,4-thiadiazoles [1], in addition to the other methods for preparing 1,2,4-thiadiazole derivatives [2]. The reaction requires the presence of an oxidizing agent (iodine, *N*-bromosuccinimide, dimethyl sulfoxide) and has been tested in the presence of a number of electrophilic reagents such as aqueous hydrogen chloride.

Some biological properties of thiadiazoles are worthy of consideration [3], because of their activities as biocides. Furthermore, the mechanism of cyclization (and, in particular, the oxidizing power of dimethyl sulfoxide) offers some interesting points for investigation. We therefore present some results on the reactions of some aromatic thioamides (and of some *N*-substituted thioureas) in the presence of dimethyl sulfoxide and of an acid.

Results and discussion.

When thiobenzamide (**1a**) is dissolved in dimethyl sulfoxide in the presence of 0.5 equivalents of hydrogen chloride, a pale yellow solid precipitates (sulfur) and 3,5-diphenyl-1,2,4-thiadiazole (**2a**) is obtained in high yields (85-98 %), according to Scheme 1



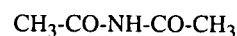
In the same way, from thionicotinamide (**1b**), and isothionicotinamide (**1c**) 3,5-di-(3-pyridyl)-1,2,4-thiadiazole (**2b**) and 3,5-di-(4-pyridyl)-1,2,4-thiadiazole (**2c**) are obtained, respectively. Physical properties and spectral data of thiadiazoles obtained are collected in Table 1.

Dimethyl sulfoxide is reported to be reduced to dimethyl sulfide [1]. The data in table 2 reports some conditions of cyclization of **1a** that are worthy of note:

i) The presence of an oxygen donor reagent (dimethyl sulfoxide) is also essential in solvents of high polarity such as dimethylformamide. ii) The reaction takes place in the presence of an acid catalyst. iii) The counter ion of the acid used is very important: hydrogen chloride and bromide are catalysts, but sulfuric acid, methanesulfonic acid and trifluoroacetic acid do not enable the formation of products. iv) Trifluoroacetic and methanesulfonic acids catalyze the cyclization reaction in the presence of chloride or bromide salts. v) When the cyclization of **1a** is carried out in the presence of 1 equivalent of benzonitrile (or of benzamide), the yields are the same: benzonitrile and benzamide are possible products arising from thiobenzamide. The data in table 2 indicates that benzonitrile and benzamide are not directly involved in the mechanism of the cyclization reaction as previously reported in the literature [1,4].

Condensation reactions of pyridine derivatives **1b** and **1c** are slower than the reaction of **1a**. The electron-withdrawing "aza" nitrogen (or its protonated form) depresses the reactivity indicating that an electrophilic step may be the rate-determining step.

Under the same experimental conditions, aliphatic thioamides afford tars and some hydrolysis product [5]. All attempts to obtain 1,2,4-thiadiazoles from thioacetamide failed. The major product recovered in moderate yields (about 50%) from the reaction mixtures carried out both in the presence of hydrochloric acid (36%) in dimethyl sulfoxide and in the presence of methanesulfonic acid was the diacetamide (**3**).



(3)

Table 1
Physical properties and spectroscopic data of 1,2,4-thiadiazoles **2**, **6** and **7**.

Compound (Yield %)	mp°C /solvent	¹ H NMR [a]	¹³ C NMR [a]		mass spectrum m/z (relative intensity)
			d _{C-3}	d _{C-5}	
2a (98)	89-90/ethanol	8.3(1 H, m), 8.1(1 H, m), 7.5(3 H, m)	188.5	173.3	C ₁₄ H ₁₀ N ₂ S requires 238.0565, found 238.056; M ⁺ 238(34), 135(100), 103(18), 77(17)
2b (90)	136-137/methanol	9.42(1 H, m), 9.28(1 H, m), 8.7-8.8 (2 H, m), 8.4-8.6(2 H, m), 7.5-7.7(2 H, m)	186.3	171.1	C ₁₂ H ₈ N ₄ S requires 240.0470, found 240.047; M ⁺ 240(43), 136(100), 104(19), 78(14)
2c (96)	195-196/methanol	8.03-8.06(1 H, m), 8.17-8.20(1 H, m) 8.7-8.9(2 H, m)	187.4	171.7	C ₁₂ H ₈ N ₄ S requires 240.0470, found 240.047; M ⁺ 240(47), 136(100), 104(26), 78(12)
6a (89)	oil (157-158)[b]	CDCl ₃ : 3.06(1 H, s), 3.09(1 H, s) 2.97(1 H, s), 2.99(1 H, s)	183.3	168.0	C ₆ H ₁₂ N ₄ S requires 172.0783, found 172.078; M ⁺ 172(100), 129(41), 102(76), 87(29), 69(12), 44(31)
6b (78)	oil (139-140)[b]	7.85(1 H, d)[c], 6.32(1 H, d)[c], 3.3-3.6 (2 H, m), 0.8-1.6(16 H, m)	180.5	166.6	C ₁₀ H ₂₀ N ₄ S requires 228.1409, found 228.141 M ⁺ 228(29), 199(100), 143(36), 124(11), 85(11), 68(15)
7c (88)	196-197/methanol	7.0-7.6(10 H, m), 8.01(1 H, b)[c], 8.10 (1 H, b)[c], CDCl ₃ : 7.0-7.7 (10 H, m)[d], 5.90(1 H, b)[c], 6.75(1 H, b)[c]	165.5	148.6	C ₁₄ H ₁₂ N ₄ S requires 268.0782, found 268.078; M ⁺ 268(100), 195(27), 150(49), 119(48), 92(18), 77(26)
7d (95)	143-144/methanol	4.36(2 H, d)[d], 4.99(2 H, s), 7.1-7.4 (11 H, m)[e], 7.95(1 H, sb), CDCl ₃ : 4.3(1 H, db)[c], 4.38-4.40(2 H, d)[d], 4.95(2 H, s), 6.75(1 H, b)[c], 7.2-7.4(10 H, m)	166.2	152.4	C ₁₆ H ₁₆ N ₄ S requires 296.1096, found 296.110; M ⁺ 296(51), 205(19), 191(13), 106(54), 91(100)
7e (80)	121-122/methanol	2.45(3 H, s), 2.80(3 H, s), 4.32(2 H, d)[d], 4.95(2 H, s), 7.05(4 H, s), 7.16(4 H, q) 7.28(1 H, t)[c], 7.9(1 H, s)[c] CDCl ₃ : 2.31(3 H, s), 2.32(3 H, s), 4.33(2 H, d)[d], 4.4(1 H, t)[c], 4.85(2 H, s), 5.6(1 H, s)[c], 7.06(4 H, q), 7.08(4 H, s)	166.4	152.4	C ₁₈ H ₂₀ N ₄ S requires 324.1408, found 324.143; M ⁺ 324(28), 219(11), 205(15), 120(41), 105(100)
7f (75)	96-97/methanol	CDCl ₃ : 3.78(6 H, s), 4.32(2 H, d)[d], 4.4(1 H, s)[c] 4.86(2 H, s) 6.7-7.2(8 H, m)	169.9	152.7	C ₁₈ H ₂₀ N ₄ O ₂ S requires 356.1307, found 356.131 M ⁺ 356(41), 235(15), 221(20), 136(21), 121(100)

[a] In dimethyl-d₆ sulfoxide, unless otherwise indicated. Internal reference: tetramethylsilane. [b] Picrate. [c] Broad signal which disappears after addition of deuterium oxide. [d] Singlet after addition of deuterium oxide. [e] 10 H after addition of deuterium oxide.

Thiadiazole **2a** is obtained in almost quantitative yields in the presence of electrophilic reagents from thiobenzamide S-oxide [6] (**4**), without the presence of oxidizing agents. In the presence of hydrochloric acid or of methanesulfonic acid, **4** reacts with a rate similar to that of the thiobenzamide. **2a** is also obtained by simply heating methanolic solutions of **4**. In addition when samples of **4** in which **2a** is absent are analyzed by gcms, the signals of molecular ion (M⁺ = 153) of **4** together with the signal of molecular ion (M⁺ = 238) of **2a** and the peak related to S₈ (256) are observed.

Scheme 2 shows results obtained to evaluate the importance of the thiobenzamide S-oxide on the cyclization pathway. In all cases, **2a** was obtained in almost quantitative yields. Dimethyl sulfoxide (which needs to be present in the reaction of thiobenzamide) may be absent when the **1a** is previously oxidized to **4**.

In disagreement with the conclusions reported in the literature [1], the results in Scheme 2 show that thiobenzamide S-oxide is unlikely to react with thiobenzamide to yield condensation product **2a**. The most probable reaction pathway involves the self-condensation (catalyzed by electrophilic reagents) of the thiobenzamide S-oxide [6]. This conclusion agrees with the observation that reaction of **4** carried out in the presence of thioamides gave the only

product of self-condensation **2a**. Probably, the rate-limiting step of this cyclization reaction is the oxidation of the thiobenzamide. Attempts to crystallize **4** in boiling methanol, without adding acids, afforded **2a**.

Hitherto, it has been difficult to state the step in which the chloride (or bromide) ion intervenes to promote the

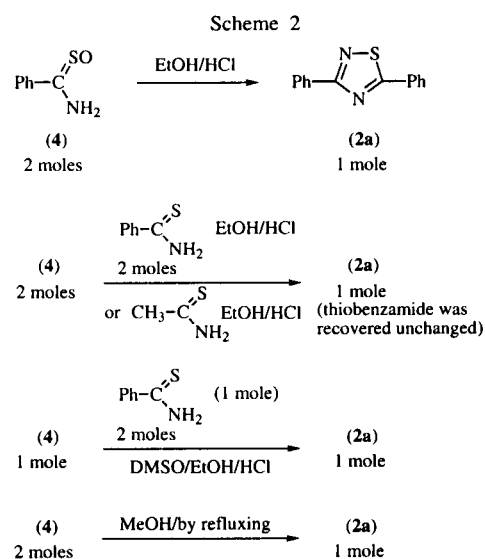


Table 2

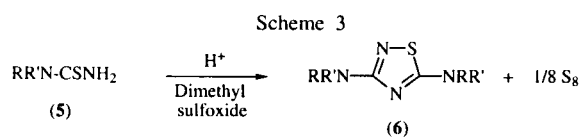
Solvent	Reagent	electrophile	yield%
Dimethyl sulfoxide	Dimethyl sulfoxide	Hydrochloric acid[a]	100
Ethanol	Dimethyl sulfoxide [b]	Hydrochloric acid	90
Dimethyl formamide	----	Hydrochloric acid	no reaction
Dimethyl formamide	Dimethyl sulfoxide [b]	Hydrochloric acid	93
Dimethyl sulfoxide	Dimethyl sulfoxide	Trifluoroacetic acid/X [c]	90
Dimethyl sulfoxide	Dimethyl sulfoxide	Sulfuric acid	no reaction
Dimethyl sulfoxide	Dimethyl sulfoxide	Sulfuric acid/X [c]	90
Dimethyl sulfoxide	Dimethyl sulfoxide	Methanesulfonic acid	no reaction
Dimethyl sulfoxide	Dimethyl sulfoxide	Methanesulfonic acid/X [c]	95
Dimethyl sulfoxide	Dimethyl sulfoxide	Trifluoroacetic acid	no reaction
Dimethyl sulfoxide	Dimethyl sulfoxide	Boron trifluoride [d]	no reaction [e]
Dimethyl sulfoxide	Dimethyl sulfoxide	2-Chloropyridine	
	Methyliodide		93 [f]
Ethanol	Dibenzyl sulfoxide [b]	Hydrochloric acid	85
Dimethyl sulfoxide	Dimethyl sulfoxide (PhCN)	Hydrochloric acid	95 [g]
Dimethyl sulfoxide	Dimethyl sulfoxide (PhCONH ₂)	Hydrochloric acid	100 [g]

[a] Hydrochloric acid 36% in water. [b] 1 Equivalent with respect to thiobenzamide. [c] X = calcium chloride or tetrabutyl ammonium bromide or tetraethyl ammonium chloride. [d] Boron trifluoride diethyl etherate. [e] At room temperature; 40 % of yields by refluxing. [f] Reference 1. [g] With respect to the starting thiobenzamide.

cyclization reaction. The specific effect of the counter ion of the acid used may be explained by considering the possibility that the halide ion is involved in the oxygen transfer from dimethyl sulfoxide to the thioamide sulphur. However, this problem deserves further in-depth investigation.

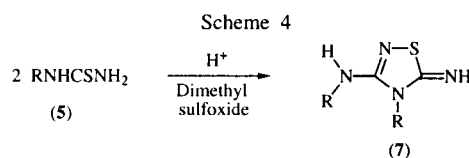
Derivatives of the thiadiazoles are also obtained from reactions of some asymmetric *N*-substituted thioureas under experimental conditions similar to that used for thiobenzamides. The oxidation reaction of mixtures of *N*-di-substituted thiourea to yield 3-amino-(1,2,4)-thiadiazole derivatives has been reported in the literature [7]. When hydrochloric acid (36%) is added to solutions of *N*-substituted thiourea in dimethyl sulphoxide, thiadiazole derivatives are formed in high yields. 3,5-Diamino-thiadiazoles derivatives are expected on the basis of the reported reactions of the thioamides. Physical properties and spectroscopic data of the obtained products are reported in Table 1. The spectral properties of the compounds obtained from phenylthiourea and benzylthiourea do not agree with the structure of the expected 3,5-diamino-(1,2,4)-thiadiazoles, while the condensation product of *N,N*-dimethyl-aminothiourea and the major product obtained from 2-butylthiourea show spectral data in agreement with proposed structure **6a** and **6b** (see Scheme 3).

In particular, ¹³C spectral data for heterocyclic carbon atoms of the product of *N*-benzylthiourea and *N*-phenylthiourea do not agree with the data of the aryl substituted



a, R = R' = Me
b, R = H, R' = 2-butyl

thiadiazole derivatives obtained from thiobenzamides compounds **2a**, **2b**, **2c**, see Table 1. In addition, the protons of only one of the benzyl groups show coupling constant with the N-H proton, whereas in compound **6b** the N-H protons couple with the hydrogen bonded to C2 of the butyl group. These data agree with structure **7d** in Scheme 4. In this case one benzyl group is far from the N-H proton. Therefore structures like **6** are not formed. Furthermore **7d** structure is confirmed by X ray diffraction analysis.



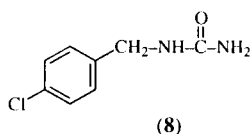
c; R = phenyl , d; benzyl , e; *p*-methyl-benzyl , f; *p*-methoxy-benzyl

In the case of the reaction of the *N,N*-dimethylamino thiourea (**5a**), as well as of *N*-2-butylthiourea (**5b**) the structure **6a** and **6b** respectively, may be attributed on the basis of the spectral properties reported in Table 1. In the case of the reaction of **5b**, very small amounts of an isomer of **6b** (to which the structure **7**-like may be tentatively attributed) were detected by gcm spectroscopy inspection of the crude reaction mixtures ($M^+ = 228$).

The cyclization reaction prefers ring closure with the substituted nitrogen; probably, in spite of the steric hindrance, the nucleophilic power of the substituted nitrogen is greater than that of the unsubstituted nitrogen. Steric hindrance is low in the case of the phenyl and of the benzyl groups. Obviously, the di-substituted nitrogen of the *N,N*-dimethylaminothiourea, as well as the nitrogen with a group as bulky as 2-butyl, cannot participate in the ring

closure. These observations agree with a nucleophilic attack of the nitrogen in the rate determining step of the cyclization reaction.

When the reaction is carried out with *p*-chlorobenzylthiourea (both with hydrochloric acid 36% and methanesulfonic acid and tetrabutylammonium bromide) the major product isolated from the reaction mixtures is the urea derivative **8** in 60 % of yields. A very small amount (less than 3%) of a cyclized compound was detected by gcms analysis of the crude reaction product: M^+ (m/z) 364. $C_{16}H_{14}N_4Cl_2S$ requires 364.0316, found 364.0310. For this compound, we cannot discriminate between forms **6** and **7**.



In the presence of acid, thiocarbonyl groups are hydrolyzed by usual reactions [5,8]. When a mixture of methanesulfonic acid and tetraalkylammonium bromide is used in dimethyl sulfoxide, it is possible to imagine that dimethyl sulfoxide may be the oxygen donor species either directly to the carbon of the thiocarbonyl group or to the sulfur atom. The $C=S^+-O^-$ species may be the intermediate in the formation of the oxygenated carbonyl compound [9]. In the case of the formation of compound **8**, the hydrolysis reaction probably takes place because the rate of the cyclization reaction to the thiadiazole derivative is lowered by the presence of the electron-withdrawing group. Indeed, when an electron releasing group (methyl and methoxy group) is present the major product is the 1,2,4-thiadiazole derivative.

Molecular geometry of 3-Benzylamino-4-*N*-benzyl-5-imino-4,5-dihydro-1,2,4-thiadiazole (**7d**).

X-Ray crystallographic analysis was carried out for the compound **7d**. Figure 1 is a perspective view of the compound with the numbering scheme, while in Table 3 bond distances and angles in the molecule are reported.

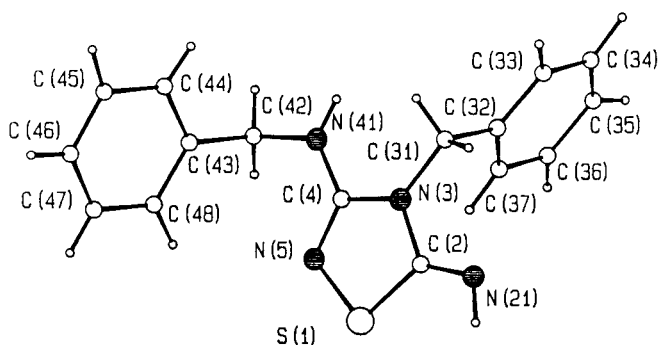


Figure 1. Perspective view of **7d**.

Table 3

Selected bond distances (Å) and angles (deg.) with e.s.d.'s in parentheses for compound (**7d**)

S(1)-C(2)	1.757(3)	C(4)-N(5)	1.308(2)
S(1)-N(5)	1.699(2)	C(4)-N(41)	1.346(3)
C(2)-N(21)	1.283(3)	C(31)-C(32)	1.513(3)
C(2)-N(3)	1.387(3)	N(41)-C(42)	1.464(3)
N(3)-C(4)	1.389(3)	C(42)-C(43)	1.511(3)
N(3)-C(31)	1.454(2)		
C(2)-S(1)-N(5)	95.2(2)	N(3)-C(4)-N(41)	119.4(4)
S(1)-C(2)-N(3)	105.4(2)	N(3)-C(4)-N(5)	117.2(2)
S(1)-C(2)-N(21)	130.8(3)	N(5)-C(4)-N(41)	123.0(3)
N(21)-C(2)-N(3)	123.8(4)	S(1)-N(5)-C(4)	108.2(2)
C(2)-N(3)-C(31)	120.6(2)	N(3)-C(31)-C(32)	113.0(4)
C(2)-N(3)-C(4)	113.7(3)	C(4)-N(41)-C(43)	120.9(3)
C(4)-N(3)-C(31)	125.0(2)	N(41)-C(42)-C(43)	114.0(2)

Table 4

Comparison of bond distances(Å) and angles(deg.) in 1,2,4-thiadiazole rings



	(a)	(b)	(c)	(d)	(e)
[a]	1.699(2)	1.308(2)	1.389(3)	1.387(3)	1.757(3)
[b]	1.683(3)	1.308(3)	1.393(3)	1.340(3)	1.715(3)
[c]	1.672(7)	1.286(9)	1.372(7)	1.355(7)	1.721(5)
[d]	1.697(10)	1.303(17)	1.403(16)	1.40714	1.754(13)
[e]	1.691(3)	1.294(4)	1.386(4)	1.402(4)	1.761(4)
	(ab)	(bc)	(cd)	(de)	(ae)
[a]	108.2(2)	117.5(5)	113.7(2)	105.4(2)	95.2(1)
[b]	109.2(2)	116.2(2)	111.9(2)	109.2(2)	93.4(1)
[c]	108.9(5)	116.7(6)	113.5(5)	106.3(4)	94.6(3)
[d]	110.6(9)	115.8(10)	113.3(10)	105.9(8)	94.3(5)
[e]	108.9(2)	117.6(3)	113.7(3)	104.2(2)	95.3(2)

[a] Present work. [b] H. Senda and J. Maruha, *Acta Cryst.*, **C41**, 1626 (1986). [c] F. Iwasaki and K. Akiba, *Acta Cryst.*, **B37**, 180 (1981). [d] A.F. Cuthbertson and C. Glidewell, *Acta Cryst.*, **B37**, 1419 (1981). [e] A. Butler, R. Glidewell and D.C. Liles, *Acta Cryst.*, **B34**, 3241 (1978).

Comparison of geometrical parameters in 2,4-thiadiazole rings [10] are listed in Table 4. The structure deserves some comments. Firstly, the exocyclic nitrogen (N(21) in Figure 1) is bonded to C(2) by a double bond. Its length, 1.283(3) Å, is in the usual range of the other exocyclic C-N double bonds of similar heterocyclic derivatives: in 3-*N*-(2,4-dinitrophenyl)-2-iminothiazole [11] 1.265 Å, in 2-(2,6)-dimethylphenylthiazolidine [12] 1.264 Å, in 2-(phenylimino) thiazolidine [13] 1.280 Å.

With regards to bond distances and angles in the thiazolidine ring, the endocyclic C(4)-N(5), 1.308(1) Å bond is close to the double bond distance. The hybridization of the C(4) atom is sp^2 , as indicated by the bond angles ranging from 117.5 to 125.0°. The N(3)-C(31), 1.454(2) Å is in agreement with a C-N single bond; the remaining C-N bonds are intermediate between single and double bonds. The C(21)-S distance, 1.757(1) Å, agrees well with that of the other thiazolidine rings, as reported in Table 4 and with the $C(sp^2)$ -S distance of 1.759 Å [14]. Moreover the S-N

bond, 1.699(1) Å, is comparable with those found in 1,2,4-thiadiazole rings.

The heterocyclic ring is almost planar, the N(21) being coplanar and N(41) displaced only 0.02 Å from the mean heterocyclic plane. The dihedral angles between this plane and the phenyl rings are 86.24(6)° [C(32)-C(37)] and 107.18(6)° [C(43)-C(45)], and the dihedral angle between the two phenyl rings is 28.26(8)°

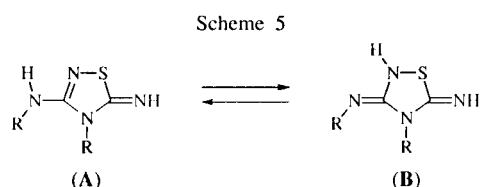
The packing is determined by a network of hydrogen bonds involving nitrogen atoms. The data is listed in Table 5.

Table 5
Hydrogen bond data.

D	H	A	D...A (Å)	D-H (Å)	H...A (Å)	D-H...A (Å)	Translation of A
N(21)	H(21)	N(5)	3.418(2)	0.94(2)	2.52(2)	161(2)	-x, 1/2+y, 1/2-z
N(41)	H(41)	N(21)	3.045(3)	0.87(2)	2.19(2)	166(2)	1-x, -1/2+y, 1/2-z

Conclusions.

In principle, compounds **7** may exist in two tautomeric forms as indicated in Scheme 5. [14] Generally in amino heteroaromatic "aza" containing compounds the amino form is more populated, because of the loss of energy associated with the migration of the double bond from the endocyclic nitrogen (in an aromatic form) to the exocyclic nitrogen (in a non-aromatic form). When the heterocyclic moiety is partially saturated, there are some instances [15,16] of the predominance of the isomer with the hydrogen bond to the endocyclic nitrogen. In the present case, in both solvents (dimethyl sulfoxide and deuteriochloroform), as well as in the solid state, form **A** of compound **7b** is the more populated form. It is likely that the hydrogen atom prefers the exocyclic nitrogen because the geometry of the enamine form is less strained than when the double bond is in the exocyclic position. In the case of compound **6b**, four potential tautomeric species are possible. On the basis of the N-H signals (two broad doublets which disappear after addition of deuterium oxide) it is possible to state that both hydrogen atoms are bonded at the exocyclic nitrogen atoms, near to the C-H protons, as represented by structure **6b** of Scheme 3.



Scheme 6 represents a possible reaction pathway which may be operative under both experimental conditions: in acid medium and in methanol without external catalysis of

acids. Tautomeric forms of S-oxide of thioamide (or of substituted thioureas) may also be active. As shown in Scheme 6 the oxidation of sulfur facilitates not only the formation of the N-S bond but also the elimination of sulfur. Acid catalysis may intervene in the step of oxygen transfer (from the dimethyl sulfoxide) and in the step of the elimination of water. Ring closure of intermediate **9** may take place simultaneously with the first attack. Formation of **9** (or of the now ring closed intermediate) is facilitated by delocalization of a positive charge by phenyl or amino groups. Obviously, this delocalization may be barely operative when X is an aliphatic group.

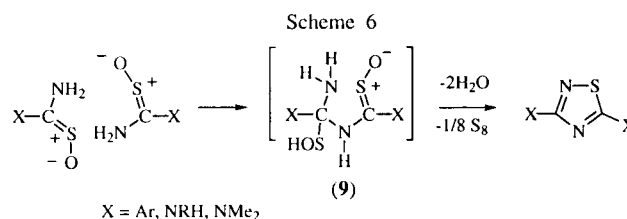


Table 6
Compound (**7d**). Fractional atomic coordinates ($\times 10^4$) and equivalent isotropic thermal parameters ($\times 10^4$ Å²) for non-H atoms with e.s.d.'s in parentheses

$$U_{eq} = 1/3 \sum_i \sum_j U_{ij} a_i^* a_j^* (a_i a_j)$$

	x	y	z	U _{eq}
S (1)	-23 (1)	3781 (1)	2381 ()	544 (2)
N (3)	3295 (2)	2924 (2)	2436 (1)	382 (4)
N (5)	444 (2)	2379 (2)	1937 (1)	484 (5)
N (21)	2997 (2)	4861 (2)	3091 (1)	497 (5)
N (41)	3053 (3)	1348 (2)	1730 (1)	453 (7)
C (2)	2282 (3)	3974 (2)	2700 (1)	411 (5)
C (4)	2229 (2)	2098 (2)	2021 (1)	396 (5)
C (31)	5211 (2)	2619 (2)	2660 (1)	412 (6)
C (32)	5355 (3)	1534 (2)	3162 (1)	475 (6)
C (33)	7121 (4)	1166 (3)	3420 (1)	679 (10)
C (34)	7312 (6)	165 (3)	3873 (1)	931 (14)
C (35)	5792 (8)	-469 (3)	4074 (1)	1056 (17)
C (36)	4011 (7)	-135 (3)	3819 (1)	947 (14)
C (37)	3800 (4)	877 (2)	3359 (1)	640 (9)
C (42)	2007 (1)	234 (2)	1255 (1)	494 (6)
C (43)	1707 (3)	1019 (2)	665 (1)	509 (7)
C (44)	3111 (4)	1100 (3)	284 (1)	666 (9)
C (45)	2826 (5)	1801 (4)	-266 (1)	817 (11)
C (46)	1129 (5)	2420 (3)	-428 (1)	855 (12)
C (47)	-272 (5)	2351 (3)	-61 (1)	835 (11)
C (48)	2 (4)	1615 (3)	491 (1)	651 (7)

EXPERIMENTAL

The thioamides used were commercial samples (Aldrich). The N-substituted thioureas [17] and benzothioamide S-oxide [6] were prepared according to literature. The nmr spectral data were recorded with a Varian Gemini 200 MHz spectrometer. Dimethyl-d₆ sulfoxide, deuteriochloroform (Carlo Erba) were used without purification. All ¹³C nmr signals, other than those

reported in Table 1, agree with the proposed structures. Low and high resolution mass spectra (hrms) were recorded on a VG 7070E spectrometer and gems with an HP-5890 gas chromatograph equipped with a methyl silicone capillary column and an HP-5970 mass detector. Melting points are uncorrected and were determined with a Buchi apparatus.

Preparation of 1,2,4-thiadiazole derivatives.

A typical procedure is described for the preparation of 3,5-diphenyl-1,2,4-thiadiazole (**2a**).

Aqueous hydrochloric acid (36%) (2.2 mmoles) were added under vigorous stirring to a solution of thiobenzamide (0.5 g, 3.6 mmoles) in 5 ml of dimethyl sulfoxide in a thermostatic bath at 35°. After 3 hours, tlc analysis (eluant: cyclohexane/ethyl acetate 10:4) indicated the absence of the starting thiobenzamide, at which time sulfur precipitated out of solution, and was collected by filtration. The reaction mixture was poured into water (20 ml) and the resultant 3,5-diphenyl-1,2,4-thiadiazole was collected by filtration (0.45 g; 1.6 mmoles) and re-crystallized from methanol (mp 89-90°) [1,18]. When no reaction was observed (as indicated in Table 2), the reaction mixture was checked (at 40-50°) for long reaction times (2-4 days). When the reaction of thiobenzamide was carried out in basic medium (Et₃N) in dimethyl sulfoxide, the thiobenzamide was recovered unchanged after long reaction times (3 days). The reactions performed with thioacetamide for 2-3 days afforded diacetamide **3** [13] as major product; **3** mp 71-72° (from methanol); ms: (m/z) 101 (M⁺, 6), 73 (15), 59 (25), 43 (100). ¹H nmr, in deuteriochloroform, internal reference tetramethylsilane: δ -NH 9.4 (1H sb), δ-CH₃ 2.25 (6H s). In some cases, a very low amount of **10** was obtained [16,19] mp 60-61°; ms: (m/z) 117 (M⁺, 83), 75 (58), 60 (18), 43 (100). Found (hrms) 117.026 of C₇H₇NOS requires 117.0248

It is likely that the formation of compound **10** precedes the formation of **3**. Attempts to obtain larger amounts of **10**, by quenching the reactions at short reaction times (12,24 hours), failed.

When *N*-(4-chlorobenzyl)thiourea was used the urea **8** [20] was obtained from the reaction mixtures by chromatographic separation on silica gel column, eluant dichloromethane/ethyl acetate 6/4; mp 193-194° (from ethanol); ms: (m/z) 184 (M⁺, 100%), 140 (74), 125 (42), 106 (78); ¹H nmr agrees with structure **8**.



(10)

Crystal structure 3-Benzylamino-4-*N*-benzyl-5-imino-4,5-dihydro-1,2,4-thia diazole (**7d**).

Crystals were pale yellow prisms. Lattice parameters and the orientation matrix were determined using a least-squares procedure which involves centered angle settings for the θ , χ , ϕ angles of thirty reflections. Crystal data: C₁₆H₁₆N₄S, *M* = 296.4. Monoclinic *a* = 7.190(2), *b* = 9.382(3), *c* = 22.377(4) Å, β = 94.9(1)°; *V* = 1504.0(7) Å³, *Z* = 4, *D*_c = 1.31 g cm⁻³; Cu-K α ; radiation λ = 1.54178 Å; μ = 18.9 cm⁻¹. Space group *P* 2₁/c (C_{2h}⁵ No.14) from systematic absences. X-ray measurements were performed at *T* = 295K on a Siemens AED single-crystal diffractometer in the range 3 ≤ θ ≤ 70° using Ni-filtered Cu-K α radiation. Intensity data were collected using a θ -2 θ scanning mode with a scan width range from (θ -0.60)° to (θ +0.60+ $\Delta\lambda/\lambda$ tg θ)°. The 3133 independent reflections (-8 ≤ *h* ≤ 8), 0 ≤ *k* ≤ 11, 0 ≤ *l* ≤ 27)

were measured of which 2172 (internal R merging factor 0.011) having $I_{hkl} > 3\sigma(I_{hkl})$ were used in the refinement. One standard reflection measured every 50 collected reflections to monitor crystal decomposition and instrumental stability, showed no significant variations. Intensities, I_{hkl} , were corrected for Lorentz and polarization effects. The dimensions of the crystal were 0.19, 0.14, 0.40 mm. No absorption corrections were applied.

The structure was solved by direct methods using the SHELX86 [21] program and refined using SHELX76 [22] program. Non hydrogen atoms were refined anisotropically (hydrogen atoms isotropically) to a *R* = 0.035, *R*_w = 0.041; the weighting function was of the form $1/w = \sigma^2(F_o) + 0.0033F_o^2$. Positional parameters together with their standard deviation are given in Table 6. All hydrogen atoms were located in the difference-Fourier map. Atomic scattering factors were obtained from International Tables for X-ray Crystallography. The study of molecular geometry was carried out by PARST93 [23]. All the calculations were performed on the Encore E91 computer of the Centro di Studio per la Strutturistica Diffraattometrica del CNR of Parma. The Cambridge Data File were used for bibliographic searches through the Servizio Italiano Diffusione Dati Cristallografici di Parma.

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