Synthesis of *N,N*-Disubstituted 3-Oxo-2-phenyl-2,3-dihydro-1,2,4-thiadiazoles: Oxidative Debenzylation and Cyclization of 1,1,5-Trisubstituted *S*-Benzyl-2-thioisobiurets

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The chemistry of 1,2,4-thiadiazoles and their hydro derivatives has been extensively studied and reviewed[1]. 3-Oxo-2-phenyl-5-phenyliminotetrahydro-1,2,4-thiadiazole has been prepared by oxidation of a 1,5-diphenyl-2-thiobiuret[2], and other 2- or 4-substituted 3-oxo-5-aryliminotetrahydro-1,2,4-thiadiazoles have been obtained from the reaction of chloro-(phenylimino)-methanesulfenyl chloride with urea or substituted ureas[3], or from *S*-allyl-2-thioisobiurets[4]. However, there is no record of the synthesis of the related *N,N*-disubstituted 5-amino-3-oxo-2-phenyl-2,3-dihydro-1,2,4-thiadiazoles.

Our interest in the oxidative dealkylation and cyclization of N- and S-containing systems[5] led us to develop a method for

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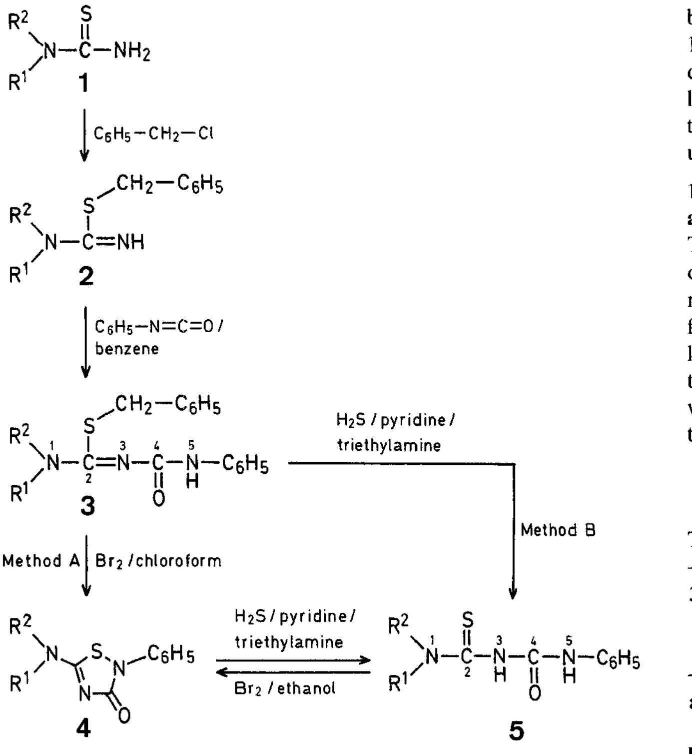
the synthesis of the hitherto unknown *N,N*-dialkyl-, *N*-alkyl-*N*-aryl-, and *N,N*-diaryl-5-amino-3-oxo-2-phenyl-2,3-dihydro-1,2,4-thiadiazoles (**4**) by the oxidative debenzylation and cyclization of *S*-benzyl-2-thioisobiurets (**3**) with bromine (Method A). We describe here the preparation of the starting materials **3** and their conversion into compounds **4**. The structure of compounds **4** was confirmed by microanalyses and I.R.-spectral data as well as by their alternative synthesis from compounds **3** via reductive debenzylation to the thiobiurets **5** and oxidative cyclization of compounds **5** (Method B) and by the reductive cleavage of compounds **4** to the thiobiurets **5** with hydrogen sulfide/pyridine/triethylamine.



	R¹	R²
a	C_6H_5	C_6H_5
b	C_2H_5	C_2H_5
c	n-C_4H_9	n-C_4H_9
d	CH_3	C_6H_5

Melting points are uncorrected. I.R. spectra were recorded on a Perkin-Elmer spectrophotometer, model 720.

Benzyl *N,N*-Diphenylcarbamimidothioate (2a); Typical Procedure[6]:

A solution of *N,N*-diphenylthiourea (**1a**; 10 g, 0.04 mol) and benzyl chloride (5.5 g, 0.04 mol) in ethanol (50 ml) is heated at 100 °C for 90 min and is then evaporated in vacuo to leave crude **2a** hydrochloride which on basification afforded the free base; yield: 8 g (80%); m.p. 80–81 °C (Ref.[10], m.p. 81–82 °C).

***S*-Benzyl-1,1,5-triphenyl-2-thioisobiuret (3a); Typical Procedure:**

A solution of benzyl *N,N*-diphenylcarbamimidothioate (**2a**; 8 g, 0.025 mol) and phenyl isocyanate (3 g, 0.025 mol) in benzene (40 ml) is refluxed for 4 h, and then evaporated in vacuo. The semisolid residual product is stirred with petroleum ether (10 ml) and triturated with ethanol (10 ml) affording **3a**; yield: 6 g (75%); m.p. 234–235 °C.

***N,N*-Disubstituted 5-Amino-3-oxo-2-phenyl-2,3-dihydro-1,2,4-thiadiazoles (4); Typical and General Procedures:**

Method A, Typical Procedure:

5-Diphenylamino-3-oxo-2-phenyl-2,3-dihydro-1,2,4-thiadiazole (**4a**): Bromine (1 ml) is gradually added to a well stirred suspension of *S*-benzyl-1,1,5-triphenyl-2-thioisobiuret (**3a**; 3 g, 0.006 mol) in chloroform (8 ml) until the color or bromine persists, benzyl bromide (lacrimatory fumes!) being developed in the reaction. Stirring is continued for 1 h at room temperature. The semisolid product is isolated by decantation of the solvent, washed with ether (10 ml), and triturated with ethanol. The resultant product **4a** is isolated by filtration and recrystallized from ethanol; yield: 2.2 g (75%); m.p. 284–285 °C.

Method B, General Procedure:

1,1-Disubstituted 5-Phenyl-2-thiobiurets (**5**): The respective *S*-benzyl-5-phenyl-2-thioisobiuret **3** (0.009 mol) is dissolved in pyridine/triethylamine (6/1; 30 ml). A stream of dry hydrogen sulfide is passed through the solution for 4 h[7] and the mixture then poured onto ice (20 g) and acidified with dilute hydrochloric acid. The precipitated product **5** is isolated by suction and recrystallized from ethanol.

5-Amino-3-oxo-2-phenyl-2,3-dihydro-1,2,4-thiadiazoles (**4**): The 2-thiobiuret **5** (0.01 mol) is dissolved in ethanol (15 ml) and bromine (2 ml, 10 mol) is added dropwise with stirring. Then, ether (0.025 ml) is added. The precipitated product **4** is isolated by suction and recrystallized from ethanol. [The products **4** thus obtained were identical (mixture m.p., superimposable I.R. spectra) with the corresponding products **4** obtained by Method A].

1,1-Disubstituted 5-Phenyl-2-thiobiurets (5) from the Reductive Cleavage of Compounds 4; General Procedure:

The *N,N*-disubstituted 5-amino-3-oxo-2-phenyl-2,3-dihydro-1,2,4-thiadiazole (**4**; 0.01 mol) is dissolved in pyridine/triethylamine (6/1; 30 ml). A stream of dry hydrogen sulfide is passed through the solution for 5 h whereafter the mixture is cooled to 5 °C and acidified with dilute hydrochloric acid. The precipitated product **5** is isolated by suction and recrystallized from ethanol. [The products **5** thus obtained were found to be identical with the corresponding products **5** obtained from compounds **3** with hydrogen sulfide].

Table 1. 1,1,5-Trisubstituted *S*-Benzyl-2-thioisobiurets (**3**)

3	Yield [%]	m.p. [°C]	Molecular formula[a]	I.R. (nujol), ν [cm⁻¹]		
				C=O	C=N	NH
a	75	234–235°	$C_{27}H_{23}N_3OS$ (437.5)	1660	1600	3310
b	70	210–212°	$C_{19}H_{23}N_3OS$ (341.4)	1620	1580	3300
c	70	208–209°	$C_{23}H_{31}N_3OS$ (397.5)	1615	1590	3320
d	78	239–240°	$C_{22}H_{21}N_3OS$ (375.4)	1650	1598	3305

[a] The microanalyses were in good agreement with the calculated values: C, ±0.04; H, ±0.00. Exception: **3b**, C −0.51.

Table 2. *N,N*-Disubstituted 5-Amino-3-oxo-2-phenyl-2,3-dihydro-1,2,4-thiadiazoles (**4**)

4	Yield [%]	m.p. [°C]	Molecular formula[a]	I.R. (nujol), ν [cm⁻¹]	
				C=O	C=N
a	75	283–285°	$C_{20}H_{15}N_3OS$ (345.4)	1660	1610
b	70	270–272°	$C_{12}H_{15}N_3OS$ (249.3)	1620	1580
c	71	270–271°	$C_{16}H_{23}N_3OS$ (305.4)	1615	1570
d	78	243–245°	$C_{15}H_{13}N_3OS$ (283.3)	1650	1600

[a] The microanalyses were in good agreement with the calculated values: C, ±0.03; H, ±0.03.

Table 3. 1,1,5-Trisubstituted 2-Thiobiurets (**5**)

5	Yield [%]	m.p. [°C]	Molecular formula[a]	I.R. (nujol), ν [cm^{-1}]	
				C=O	C=S
a	58	244-245°	$C_{20}H_{17}N_3OS$ (347.5)	1662	1290
b		[b]	$C_{12}H_{17}N_3OS$ (251.3)	1618	1300
c	55	217-218°	$C_{16}H_{25}N_3OS$ (307.4)	1615	1280
d	52	231-232°	$C_{15}H_{15}N_3OS$ (285.3)	1655	1250

[a] The microanalyses were in good agreement with the calculated values: C, ±0.01; H, ±0.01.

[b] Semisolid.

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