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Studies on 1,2,4-Thiadiazolidine Derivatives. IV.[1] The Isomers of 2,4-Disubstituted 3,5-(Disubstituted imino)-1,2,4-thiadiazolidines

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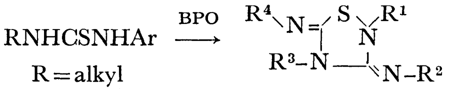
Synopsis. Several 2-alkyl-5-alkylimino-4-aryl-3-arylimino-1,2,4-thiadiazolidines and 4-alkyl-5-alkylimino-2-aryl-3-arylimino-1,2,4-thiadiazolidines were synthesized by the oxidation of 1-alkyl-3-arylthioureas with benzoyl peroxide along with 2,4-dialkyl-3,5-bis(arylimino)-1,2,4-thiadiazolidines.

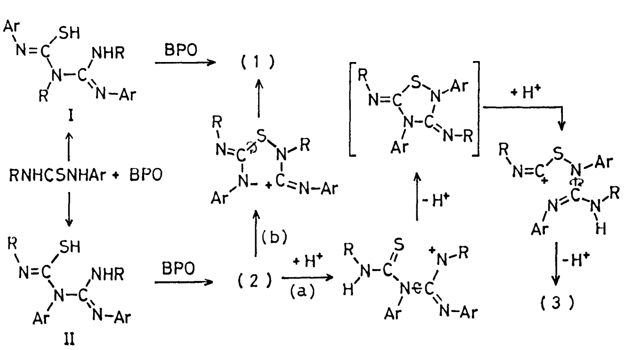
In a previous paper,[2] we reported that the oxidation of 1-alkyl-3-arylthioureas with benzoyl peroxide (BPO) was found to afford 2,4-dialkyl-3,5-bis(arylimino)-1,2,4-thiadiazolidines (**1**) and their isomers (**2** and **3**), and the three positional isomers of **1**,[2] **2**,[3] and **3**[4] were determined by X-ray analyses.



R=alkyl
Ar=aryl

1; $R^1=R^3=$alkyl, $R^2=R^4=$aryl
2; $R^1=R^4=$alkyl, $R^2=R^3=$aryl
3; $R^1=R^2=$aryl, $R^3=R^4=$alkyl

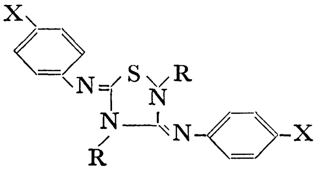
In the course of the studies on 1,2,4-thiadiazolidines, **2** was found to be rearranged into **1** and/or **3** depending on the reaction conditions, whereas **1** and **3** could not be further converted into any of the other type isomers, which are reported herein. When the following solutions of **2** were allowed to stand for a week at room temperature, each solution gave the mixture of 1,2,4-thiadiazolidines (%): **2a** (1.5 mg) in CH_2Cl_2–AcOH (500 μl–50 μl); **1a**: **2a**: **3a**=8: 0: 92, **2a** (1.5 mg) in CH_2Cl_2–AcOH–pyridine (500 μl–50 μl–50 μl); **1a**: **2a**: **3a**=68: 18: 14, **2a** (1.5 mg) in CH_2Cl_2–AcOH–pyridine (500 μl–50 μl–100 μl); **1a**: **2a**: **3a**=53: 44: 3.



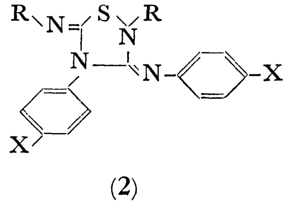
Scheme 1.

From the above results, it may be concluded that the rate of the isomerization of **2** to **3** is accelerated by acid but decelerated by the addition of base. Furthermore the more the base added, the less **3** and the more **1** are produced. However, the total rate of the rearrangement of **2** is reduced when a base is added. Consequently, for the purpose of obtaining **3** from the oxidation of thioureas with BPO, no addition of base is preferable, whereas for the purpose of obtaining the labile isomer **2**, the addition of base to the reaction system is preferable. Table 1 shows the ratio of these products for the oxidation of some thioureas with BPO in dichloromethane–pyridine (8: 1). As shown in Table 1, **2** was gradually converted mainly into **1** in the presence of pyridine, whereas in the acidic medium[†] converted mainly into **3**. In view of these results the formation of **1** and **2** is expected to proceed through the intermediates I and II,[5] and in the case of **3**, it may be formed through route (a) as shown in Scheme 1. There is no definitive information on a driving force for the isomerization of **2** to **1** (route (b)). The physical properties and analytical data for the 1,2,4-thiadiazolidines (**2** and **3**) are summarized in Table 2.

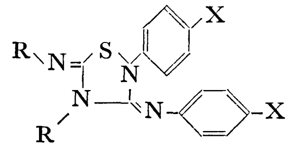
TABLE 1. PRODUCT RATIO OF THE ISOMERS **1**, **2**, AND **3**[a]



(1)



(2)



(3)

X	R	Ratio,[b] %			Ratio,[c] %		
		1	**2**	**3**	**1**	**2**	**3**
H	Me	53	40	7	69	17	14
(H	Me	55	32	13	59	0	41)[d]
H	Et	28	52	20	39	39	22
OMe	Me	65	26	9	80	6	14
(OMe	Me	65	23	12	67	0	33)[d]
OMe	Et	28	54	18	49	30	21

a) Determined by GLC. b) Reaction time: 1 h at 5—10 °C. c) Reaction time: 1 h at 5—10 °C and 14 days at 15—20 °C. d) Solvent: CH_2Cl_2 only.

Recently Joshua and Rajasekharan have reported 2,4-dialkyl-3,5-bis(arylimino)-1,2,4-thiadiazolidines,[6] which correspond to our **1**, arising from the oxidation of 1-alkyl-3-arylthioureas with hydrogen peroxide in acidic aqueous ethanol. However, it may not be possible to

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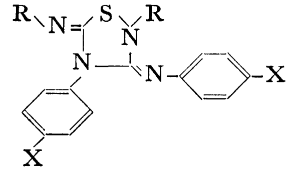
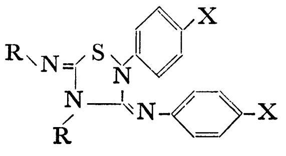
[†] Benzoic acid would be produced from BPO as a by-product in this reaction.

Table 2. Physical properties and analytical data of 1,2,4-thiadiazolidines (**2** and **3**)



2a—d



3a—d

Compd	R	X	Yield[a] %	Mp/°C	NMR (δ)[b] N-CH_3	(N-CH_2-)	IR[c] (cm^{-1}) C=N	Molecular[d] formula	Found (Calcd)% C	H	N	S
2a	Me	H	15	118.5	2.83,	2.86	1615	$C_{16}H_{16}N_4S$	64.63 (64.84	5.33 5.44	18.92 18.90	10.95 10.82)
2b	Me	OMe	7	123	2.85,	2.89	1630	$C_{18}H_{20}N_4O_2S$	60.58 (60.65	5.71 5.66	15.65 15.72	8.96 8.99)
2c	Et	H	28	68	(3.06,	3.19)	1630	$C_{18}H_{20}N_4S$	66.63 (66.64	6.09 6.21	17.43 17.27	10.07 9.88)
2d	Et	OMe	23	75	(3.06,	3.18)	1628	$C_{20}H_{24}N_4O_2S$	62.37 (62.48	6.25 6.29	14.54 14.57	8.35 8.34)
3a	Me	H	38	103.5	2.94,	3.37	1635	$C_{16}H_{16}N_4S$	65.03 (64.84	5.35 5.44	19.07 18.90	10.86 10.82)
3b	Me	OMe	29	oil	2.92,	3.33	1635	$C_{18}H_{20}N_4O_2S$	60.61 (60.65	5.70 5.66	15.68 15.72	9.07 8.99)
3c	Et	H	17	60	(3.07,	4.07)	1630 1640*	$C_{18}H_{20}N_4S$	66.62 (66.64	6.14 6.21	17.18 17.27	10.16 9.88)
3d	Et	OMe	16	91	(3.06,	4.02)	1615 1625*	$C_{20}H_{24}N_4O_2S$	62.40 (62.48	6.23 6.29	14.41 14.57	8.56 8.34)

a) Isolated yields under the following reaction conditions: reaction time; 1 h at 5—10 °C, solvent; CH_2Cl_2–pyridine (8: 1) for **2a**—**d**, and reaction time; 1 h at 5—10 °C and 14 days at 15—20 °C, solvent; CH_2Cl_2 for **3a**—**d**. b) Observed in CCl_4. c) Measured in Nujol mulls (*shoulder). d) Determined by high resolution mass spectrometry.

produce the other type isomers (**2** and **3**) under their experimental conditions.

Experimental

Materials. Commercially available benzoyl peroxide of a reagent grade was used. Thiourea derivatives were prepared according to methods in the literature.[7]

Preparation of 2-Alkyl-5-alkylimino-4-aryl-3-arylimino-1,2,4-thiadiazolidines (2). The following procedure illustrates the general method. From a dropping funnel, a solution of BPO (1.4 g, 5.8 mmol) in CH_2Cl_2–pyridine (80 ml: 10 ml) was added to a solution of 1-methyl-3-phenylthiourea (0.83 g, 5 mmol) in CH_2Cl_2–pyridine (80 ml: 10 ml) at 5—10 °C, and the reaction mixture was stirred for 1 h at 5—10 °C. The reaction mixture was washed with an aqueous solution of NaOH to remove benzoic acid, and the solvent was evaporated *in vacuo*, and the residue was subjected to preparative TLC on alumina eluting with ethyl acetate–petroleum ether (1: 3) to give 0.11 g of 2-methyl-5-methylimino-4-phenyl-3-phenylimino-1,2,4-thiadiazolidine (**2a**) along with 0.25 g of **1a** and 0.04 g of **3a**. An analytical sample was recrystallized from ether.

Preparation of 4-Alkyl-5-alkylimino-2-aryl-3-arylimino-1,2,4-thiadiazolidines (3). A typical run is as follows: a solution of BPO (14 g, 58 mmol) in CH_2Cl_2 (200 ml) was added dropwise to a solution of 1-methyl-3-phenylthiourea (8.3 g, 50 mmol) in CH_2Cl_2 (200 ml) at 5—10 °C, and the reaction mixture was stirred for 1 h at 5—10 °C and allowed to stand for 14 days at 15—20 °C. The reaction mixture was washed with an aqueous solution of NaOH, and the solvent was evaporated *in vacuo*, and the residue was dissolved in cold acetone and filtered to remove the insoluble sulfur. The filtrate was subjected to column chromatography on silica gel eluting with ethyl acetate–petroleum ether (1: 6) to give 2.8 g of 4-methyl-5-methylimino-2-phenyl-3-phenylimino-1,2,4-thiadiazolidine (**3a**) along with 4.1 g of **1a**. An analytical sample was recrystallized from ethanol.

References

1) Part III: T. Kinoshita, H. Nagaki, and C. Tamura, *Mass Spectroscopy, Japan*, **25**, 109 (1977).

2) T. Kinoshita, S. Sato, and C. Tamura, *Bull. Chem. Soc. Jpn.*, **49**, 2236 (1976).

3) S. Sato, T. Kinoshita, T. Hata, and C. Tamura, *Acta Crystallogr., Sect B*, **33**, 550 (1977).

4) S. Sato, T. Kinoshita, T. Hata, and C. Tamura, to be published.

5) Using a smaller amount of BPO on the oxidation of 1,3-diethylthiourea, such intermediate could be isolated; see Ref. 2.

6) C. P. Joshua and K. N. Rajasekharan, *Aust. J. Chem.*, **30**, 1819 (1977).

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