Synthesis of 1,3,5-Trisubstituted 6-Substituted-Imino-hexahydro-1,3,5-triazine-2,4-dithiones - A New Approach from Thioureas

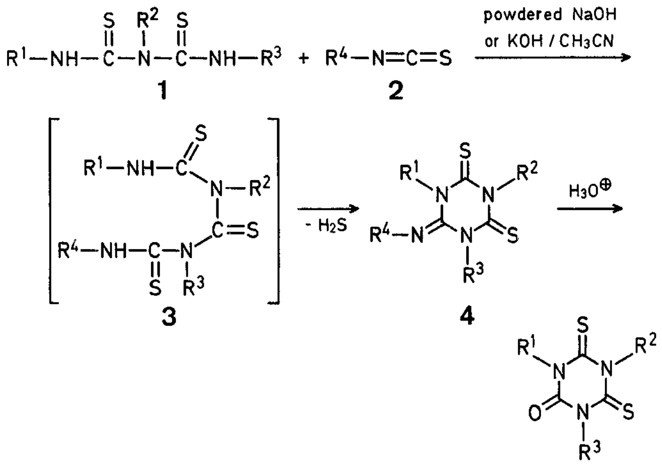
C. P. Joshua*, Saramma K. Thomas

Department of Chemistry, University of Kerala, Trivandrum-695001, India

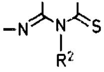
Compounds having extended urea-like chains of more than six alternate carbon and nitrogen atoms generally undergo spontaneous eliminative cyclization to yield 1,3,5-triazine derivatives. Such intermediates and their cyclization to 1,3,5-triazine-2-thiones are reported in the reactions of dicyandiamide with thioamides[1], thioureas[2], thiosemicarbazides[3], and thiocarbohydrazides[3] and in the interaction of isothiocyanates with amidinothioureas[4], biguanides[5,6], and dicyandiamides[7].

It has been observed that, in presence of strong alkali, equimolar quantities of thiourea[8] or substituted thioureas[8,9,10] and isothiocyanates react yielding 2,4-dithiobiurets. In this context, we felt that 1,3,5-trisubstituted 2,4-dithiobiurets with thioureido groupings could act as a nucleophile in the presence of alkali and attack the isothiocyanate and form a labile trithiotriuret having an extended urea-like chain. Eliminative cyclization of this could result in the formation of 1,3,5-triazine derivatives. These triazines could also be expected from the interaction of two equivalents of isothiocyanates with 1,3-disubstituted thioureas.

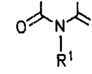
The reaction was carried out by stirring an equimolar mixture of 1,3,5-trisubstituted 2,4-dithiobiuret (**1**), an isothiocyanate **2**, and powdered sodium or potassium hydroxide in a polar organic medium for 1 h at room temperature. The reaction mixture on dilution afforded a product with the 1,3,5-trisubstituted 6-substituted-iminohexahydro-1,3,5-triazine-2,4-dithione structure **4**.



The product is believed to be formed by the cyclization of the not isolated, labile trithiotriuret intermediate **3**. In these reactions, the condensation of the isothiocyanate has never been found to occur on a nitrogen atom carrying an aryl substituent. In 1,3,5-trialkyl-2,4-dithiobiurets (**1**) when $R^1 \neq R^3$, condensation occurred invariably on a nitrogen atom carrying the less bulky substituent. The labile trithiotriuret could cyclize by eliminating either amine or hydrogen sulphide. Under the strongly alkaline conditions employed, the latter mode of cyclization was expected and found to occur. In the trithiotriuret **3** when $R^1 \neq R^4$, depending on which nitrogen is involved in the ring formation, two products (**4** and **6**) could result by cyclization. In all the cases examined, only one product was formed. The more nucleophilic nitrogen, that is the one carrying the more electron releasing substituent, was involved in ring formation. The product was assigned the structure **4** on the basis of its microanalytical, spectral, and hydrolytic studies.



6



7

The triazine **4** was found to be very sensitive to acid and underwent rapid hydrolysis to the related 6-oxo-1,3,5-triazine-2,4-dithione **5**. The structure **5** was confirmed by its microanalytical and mass spectral data.

To illustrate the structural assignment for products **4**, the condensation of 1,3-dimethyl-5-phenyl-2,4-dithiobiuret with *p*-tolyl isothiocyanate could lead to the formation of the triazine **4a** ($R^1 = R^2 = CH_3$, $R^3 = 4\text{-}H_3C—C_6H_4$, $R^4 = C_6H_5$) or **6a** ($R^3 = R^4 = CH_3$, $R^2 = C_6H_5$, $R^1 = 4\text{-}H_3C—C_6H_4$). Hydrolysis of the product afforded 1,3-dimethyl-5-*p*-tolyl-6-oxo-hexahydro-1,3,5-triazine-2,4-dithione (**5a**; $R^1 = R^2 = CH_3$, $R^3 = 4\text{-}H_3C—C_6H_4$) which was also obtained by the hydrolysis of 1,3-dimethyl-5-*p*-tolyl-6-*p*-tolylimino-hexahydro-1,3,5-triazine-2,4-dithione (**4**; $R^1 = R^2 = CH_3$, $R^3 = R^4 = 4\text{-}H_3C—C_6H_4$), the condensation product of 1,3-dimethyl-5-*p*-tolyl-2,4-dithiobiuret and *p*-tolyl isothiocyanate. Of the alternate triazines **4** and **6** only **4** could lead to the formation of the oxotriazine (**5a**; $R^1 = R^2 = CH_3$, $R^3 = 4\text{-}H_3C—C_6H_4$). A number of 1,3,5-triazine-2,4-dithiones could also be obtained by the direct interaction of 1,3-dialkylthioureas with two equivalents of alkyl

0039-7881/82/1232-1070 $ 03.00

Table 1. Triazene Derivatives **4** ($R^1 = R^2 = CH_3$) prepared

Product No.	R^3	R^4	Yield [%]	m.p. [°C]	Molecular formula[a]	I.R. (KBr) ν [cm^{-1}]	^{1}H-N.M.R. (CDCl$_3$) δ [ppm]	M.S. m/e (M^+)
4a	C_5H_5	C_6H_5	84	154°	$C_{17}H_{16}N_4S_2$ (340.5)	1660, 1590	—	340 (100%)
4b	p-H_3C—C_6H_4	p-H_3C—C_6H_4	78	145°	$C_{19}H_{20}N_4S_2$ (368.5)	1660, 1590	—	368 (100%)
4c	CH_3	CH_3	60	60°	$C_7H_{12}N_4S_2$ (216.3)	1670, 1600	—	216 (100%)
4d	CH_3	o-H_3C—C_6H_4	80	118°	$C_{13}H_{16}N_4S_2$ (292.4)	1665, 1590	2.23 (s, 3H, —OCH$_3$); 3.6 (s, 6H, N^{1}CH$_3$, N^{5}CH$_3$); 4.1 (s, 3H, N^{3}CH$_3$); 6.6-7.2 (m, 4H$_{arom}$)	292 (100%)
4e	CH_3	p-H_3CO—C_6H_4	77	109°	$C_{13}H_{16}N_4OS_2$ (308.4)	1650, 1590	3.44 (s, 6H, N^{1}CH$_3$, N^{5}CH$_3$); 3.66 (s, 3H, —OCH$_3$); 4.02 (s, 3H, N^{3}CH$_3$); 6-6.7 (m, 4H$_{arom}$)	307 (100%)
4f	p-Cl—C_6H_4	p-Cl—C_6H_4	58	152°	$C_{17}H_{14}Cl_2N_4S_2$ (409.4)	1670, 1590	—	409 (100%)

[a] Satisfactory microanalyses obtained: C ±0.2, H ±0.1, N ±0.2.

Table 2. Oxotriazenes **5a-f** obtained

Product No.[a]	Yield [%]	m.p. [°C]	Molecular formula[b]	I.R. (KBr) ν [cm^{-1}]	M.S. m/e (M^+)
5a	94	153°	$C_{11}H_{11}N_3OS_2$ (265.4)	1710, 1590	265 (70%)
5b	88	152°	$C_{12}H_{13}N_3OS_2$ (279.4)	1710, 1590	279
5c, d, e	85	123°	$C_6H_9N_3OS_2$ (203.3)	1710, 1580	203 (78%)
5f	92	165°	$C_{11}H_{10}ClN_3OS_2$ (299.8)	1710, 1590	299 (70%)

[a] See Table 1 for R^1, R^2, R^3, and R^4.

[b] Satisfactory microanalysis obtained: C ±0.2, H ±0.1, N ±0.2.

and arylisothiocyanates or by the interaction of 1-alkyl-3-arylthioureas with two equivalents of alkyl isothiocyanates. The initially formed dithiobiuret is believed to undergo further condensation with another equivalent of the isothiocyanate.

1,3,5-Trisubstituted-2,4-dithiobiurets **1** were prepared by the interaction of 1,3-disubstituted thioureas and isothiocyanates in presence of alkali[10].

1,3-Dimethyl-5-phenyl-6-phenyliminohexahydro-1,3,5-triazine-2,4-dithione (4a); Typical Procedure:

Phenyl isothiocyanate (**2**; $R^4 = C_6H_5$; 3.4 g, 0.025 mol) is added dropwise to a stirred suspension of 1,3-dimethyl-5-phenyl-2,4-dithiobiuret (**1**; $R^1 = R^2 = CH_3$, $R^3 = C_6H_5$; 6.0 g, 0.025 mol) and sodium hydroxide (1 g, 0.025 mol) in acetonitrile (25 ml) over a period of 5 min. The reaction mixture is stirred till the pungent smell of isothiocyanate vanishes. The mixture is then diluted with water (150 ml). The precipitated product is collected and extracted with diethyl ether. The ether extract on evaporation yields a pale yellow solid which is recrystallized from ethanol to give lemon yellow needles of the product; yield: 7.1 g (84%); m.p. 154 °C.

$C_{17}H_{16}N_4S_2$	calc.	C 59.99	H 4.74	N 16.46	S 18.81
(340.5)	found	60.0	4.7	16.4	18.7

1,3-Dimethyl-5-phenyl-6-oxohexahydro-1,3,5-triazine-2,4-dithione (5a); Typical Procedure:

A solution of 1,3-dimethyl-5-phenyl-6-phenyliminohexahydro-1,3,5-triazine-2,4-dithione (**4a**; 3.4 g, 0.01 mmol) in ethanol (20 ml) is heated under reflux in the presence of 12 normal hydrochloric acid (0.5 ml) for 10 min. Subsequent cooling yields the product which is recrystallised from ethanol to give yellow needles; yield: 2.5 g (94%); m.p. 153 °C.

$C_{11}H_{11}N_3OS_2$	calc.	C 49.81	H 4.16	N 15.85	S 24.13
(265.2)	found	49.7	4.1	15.8	24.0

We thank the University Grants Commission, New Delhi for the award of a fellowship to one of us (SKT) and the University of Kerala for the facilities provided.

Received: April 5, 1982

---

[1] C. P. Joshua, V. P. Rajan, *Aust. J. Chem.* **28**, 427 (1975).

[2] C. P. Joshua, V. P. Rajan, *Aust. J. Chem.* **27**, 2627 (1974).

[3] C. P. Joshua, V. P. Rajan, *Aust. J. Chem.* **29**, 1051 (1976).

[4] C. P. Joshua, V. P. Rajan, *Aust. J. Chem.* **29**, 415 (1976).

[5] F. Kurzer, E. D. Pitchfork, *J. Chem. Soc.* [C] **1965**, 6296; **1967**, 1878.

[6] L. Somogyi, Z. Gyorgydeak, R. Bognar, *Tetrahedron Lett.* **1966**, 871; *Chem. Ber.* **100**, 1975 (1967).

[7] Y. R. Rao, M. V. Konher, *Indian J. Chem.* **7**, 20 (1969).

[8] C. P. Joshua, E. Presannan, K. T. Saramma, *Aust. J. Chem.* **34**, 917 (1981).

[9] C. P. Joshua, E. Presannan, K. T. Saramma, *Indian J. Chem.*, in press.

[10] C. P. Joshua, K. T. Saramma, *Aust. J. Chem.* **35**, in press (1982).

0039-7881/82/1232-1071 $ 03.00