

## A NOVEL SYNTHESIS OF PYRIDO [1,2-a] 1,3,5-TRIAZINE-2,4-DITHIONES

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**Abstract** - A convenient one step synthesis of pyrido [1,2-a] 1,3,5-triazine-2,4-dithiones from the interaction of aryl isothiocyanates and 1-(2-pyridyl)-3-substituted thioureas is being reported.

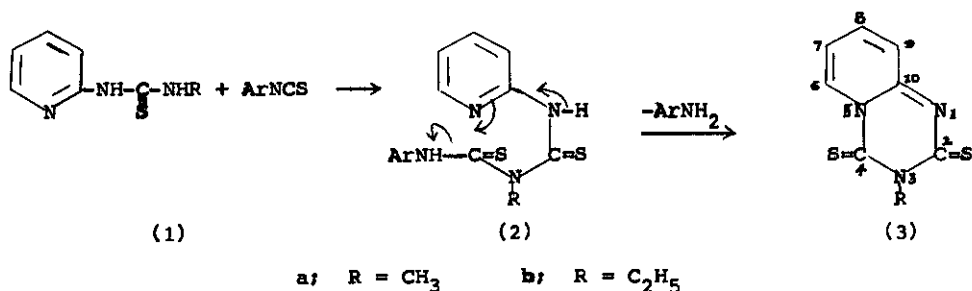
Reports on the formation of pyrido [1,2-a] 1,3,5-triazines include the dimerization reaction of 2-pyridyl isothiocyanate<sup>1,2,3</sup> and 2-pyridyl isocyanate.<sup>4,5</sup> A novel and elegant route to these derivatives has now been found.

Numerous 2,4-dithiobiuret derivatives have recently been prepared in these laboratories from the interaction of isothiocyanates with thiourea and substituted thioureas under alkaline conditions.<sup>6-8</sup> In continuation of these investigations, the interaction of aryl isothiocyanates with 1-(2-pyridyl)-3-substituted thioureas was attempted as a feasible route to 2,4-dithiobiuret derivatives incorporating a heterocyclic substituent which has an extended urea like chain of more than six atoms, inclusive of the pyridyl ring nitrogen, having alternate carbon and nitrogen atoms. Ring closure of such a dithiobiuret with the elimination of either a molecule of hydrogen sulphide or a molecule of amine was also anticipated. The former mode of cyclization would lead to a pyridotriazine with a thiono and a substituted imino group in 2 and 4 positions respectively and the latter to a triazine having thiono groups in both 2 and 4 positions.

The reaction was carried out by stirring an equimolar mixture of 1-alkyl-substituted 3-(2-pyridyl)-thiourea, isothiocyanate and powdered sodium or potassium hydroxide in a polar organic medium for an hour at room temperature. Acetonitrile was preferably used as the condensing medium. The reaction mixture on dilution and acidification afforded a product with molecular composition  $RC_7H_4N_3S_2$  (R=alkyl) in about 60% yield. The structure (3) consistent with the above molecular formula, has been assigned to the product based on elemental analysis and chemical evidences. The structure (3) has been confirmed further by nmr spectral data also. The nmr spectrum of (3a) shows a singlet at  $\delta$  4.3 (3H) due to N-CH<sub>3</sub>, a triplet at  $\delta$  6.8-6.96 (1H) due to the proton on C<sub>6</sub>, a doublet at  $\delta$  7.16-7.3 (1H)

due to the proton on C<sub>9</sub>, a triplet at  $\delta$  7.5-7.74 (1H) due to the proton on C<sub>7</sub> and a doublet at  $\delta$  9.16-9.34 (1H) due to the proton on C<sub>6</sub>. The nmr spectrum of (3b) shows a triplet at  $\delta$  1.36-1.48 (3H) due to -CH<sub>2</sub>-CH<sub>3</sub>, a quartet at  $\delta$  5-5.2 (2H) due to -CH<sub>2</sub>-CH<sub>3</sub>, a triplet at  $\delta$  6.8-6.96 (1H) due to the proton on C<sub>8</sub>, a doublet at  $\delta$  7.14-7.2 (1H) due to the proton on C<sub>9</sub>, a triplet at  $\delta$  7.56-7.74 (1H) due to the proton on C<sub>7</sub> and a doublet at  $\delta$  9.2-9.3 (1H) due to the proton on C<sub>6</sub>. The assignment of the doublet signal at lowest field centered around  $\delta$  9.2-9.3 to the proton on C<sub>6</sub> in both 3a and 3b is in accordance with the assignment of a doublet signal to the proton on C<sub>6</sub> in 3-(2-pyridyl)pyrido [1,2-a]1,3,5-triazine-2,4-dithione<sup>1</sup> (3; R=2-pyridyl).

The reaction is believed to proceed as follows.



In the 1-(2-pyridyl)-3-substituted thiourea (1), the initial attack of the isothiocyanate is believed to occur on the nitrogen atom carrying the substituent R which leads probably to the formation of the unisolated intermediate (2), cyclization of which with the elimination of a molecule of amine affords the pyridotriazine (3).

The interaction of isothiocyanates with 1-aryl-3-(2-pyridyl)-thiourea did not proceed to yield the expected pyridotriazine derivatives. Analogous results were observed in the reaction of isothiocyanates with substituted thioureas; i.e., the condensation of isothiocyanates never occurred on a nitrogen atom carrying an aryl substituent.<sup>8</sup> The filtrate after the removal of the 3-substituted pyrido [1,2-a] 1,3,5-triazine-2,4-dithione gave positive dye test which confirmed the elimination of a molecule of arylamine during cyclization. Moreover, the interaction of the same 1-alkyl-3-(2-pyridyl)-thiourea with different aryl isothiocyanates also led to one and the same product. For instance, the interaction of 1-methyl-3-(2-pyridyl)-thiourea with phenyl, p-tolyl, p-chlorophenyl and

p-anisyl isothiocyanates afforded one and the same pyridotriazine (3a) and that of 1-ethyl-3-(2-pyridyl)-thiourea with phenyl, p-tolyl and p-chlorophenyl isothiocyanates yielded the same pyridotriazine (3b).

Routes to bridgehead heterocycles of this type are very few. In fact not many compounds belonging to this family are presently known. The reaction which we have carried out now in these laboratories appears to be a very convenient and elegant method for the synthesis of pyrido [1,2-a] 1,3,5-triazine-2,4-dithiones. The scope of this novel reaction is under further investigation.

#### EXPERIMENTAL

Reported procedures were adopted for the preparation of the isothiocyanates.<sup>9</sup> 1-(2-Pyridyl)-3-substituted thioureas were prepared by the condensation of isothiocyanates with 2-aminopyridine at room temperature. Melting points were determined on a Thomas Hoover Unimelt apparatus and are uncorrected. Nmr spectra were recorded on a Varian instrument (XL-100).

#### Interaction of isothiocyanates with 1-alkyl-3-(2-pyridyl)-thioureas: Formation of 3-alkyl-pyrido [1,2-a] 1,3,5-triazine-2,4-dithiones

In a typical experiment, phenyl isothiocyanate (3.4g, 0.025 mol) was added dropwise into a stirred mixture of 1-methyl-3-(2-pyridyl)-thiourea (4.2g, 0.025 mol), powdered sodium hydroxide (1g, 0.025 mol) and acetonitrile (20 ml) over a period of 5 min. The stirring was continued for 1 h at room temperature. The reaction mixture was then diluted with water (150 ml) and filtered. The alkaline filtrate was acidified with concentrated hydrochloric acid till the pH was between 2-1. The precipitated product (3a) was collected and crystallised from ethanol as shining orange red needles (3.1g, 60%), mp 202°. The condensations of 1-methyl-3-(2-pyridyl)-thiourea with p-tolyl, p-chlorophenyl and p-anisyl isothiocyanates were also carried out in the same way and it was found that 3-methyl-pyrido [1,2-a] 1,3,5-triazine-2,4-dithione (3a) was the only product. The procedure adopted for the preparation of (3a) was used for the interaction of 1-ethyl-3-(2-pyridyl)-thiourea with phenyl, p-tolyl and p-chlorophenylisothiocyanates also.

Table I. 3-Substituted pyrido [1,2-a] 1,3,5-triazine-2,4-dithiones (3)

Sl. No.	R	Molecular formula	mp °C	Analysis	
				Required	Found
3a	CH <sub>3</sub>	C <sub>8</sub> H <sub>7</sub> N <sub>3</sub> S <sub>2</sub>	202	C 45.9	45.8
				H 3.4	3.3
				N 20.1	20.2
				S 30.6	30.4
3b	C <sub>2</sub> H <sub>5</sub>	C <sub>9</sub> H <sub>9</sub> N <sub>3</sub> S <sub>2</sub>	174	C 48.4	48.2
				H 4.0	4.1
				N 18.8	18.9
				S 28.7	28.4

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