

Oxidation of 1-Alkylthioureas: Formation of 3-Alkylimino-4-Alkyl-5-Imino- Δ^2 -1,2,4-Thiadiazolines

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Oxidation of certain 1-alkylthioureas has been found to follow the overall pattern as observed in the case of 1-aryl and 1-aryl-3-alkyl substituted thioureas. The primary product in all cases is the corresponding bis(substituted formamidine) disulphide salt which eliminates an atom of sulphur affording the related monosulphide salt which rearranges into the isomeric amidinothiourea. These on further oxidation form the corresponding 1,2,4-thiadiazolines. Their structures have been established by chemical degradation and spectral, studies.

Key Words: Oxidation, 1-Alkylthioureas, Formation, 3-Alkylimino-4-alkyl-5-imino- Δ^2 -1,2,4-thiadiazolines.

INTRODUCTION

Oxidation of thioureas in polar medium is the most well established route for the synthesis of 3,5-diamino/imino-1,2,4-thiadiazole derivatives. Lack of knowledge regarding the reaction pathways has been hindering any significant advance in the utilization of this elegant method for the synthesis of desired suitably substituted 1,2,4-thiadiazole derivatives. The oxidation of 1-arylthioureas in non-polar medium yields bis(formamidino) disulphides only under controlled conditions. If the oxidant was in excess there was a tendency for these disulphide salts to undergo cyclization to 2-amino benzothiazole derivatives.

The disulphide salts were found to be highly unstable and undergo rapid decomposition in protic solvents extruding sulphur. From the decomposition products depending upon the substituents present on the nitrogen bis(formamidine) sulphide and amidinothioureas are believed to be formed by the isomerisation of the bis(formamidine) sulphide. Further oxidation of amidinothiourea salts are found to yield the related substituted thiadiazole derivatives.

Hector¹⁻³ in his first report on the oxidation of 1-arylthioureas observed that the final product formed in a polar acidic solution was always 1,2,4-thiadiazole derivative. He has not examined the reaction pathway in any detail. In the oxidation of 1-alkyl-1-arylthiourea in acidic polar medium, Hofmann and Gabriel also observed the formation of a 3,5-bis-(alkyl aryl amino)-1,2,4-thiadiazole derivative. Hegershoff⁴⁻⁹ who examined the oxidation of 1,3-diphenylthiourea in acidic polar medium observed that a product which he wrongly identified as a thiadiazole derivative is formed. In all the above oxidations in the building up of

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the final product two molecules of the thiourea were involved and an equivalent of sulphur was always liberated during the oxidation.

The above background led us to adopt different conditions for the oxidation of 1-alkylthioureas to produce 1,2,4-thiadiazoline derivatives.

EXPERIMENTAL

Melting points are uncorrected. IR spectra (KBr) were run on a Perkin-Elmer-397 infrared spectrophotometer. The PMR spectra were taken on an EM-390 90 MHz NMR spectrometer using tetramethylsilane as internal standard and dimethyl sulphoxide as the solvent. Purity of the compounds was checked by TLC. The spectral data of a representative compound is given.

Preparation of title compounds

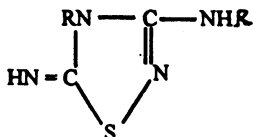
To a solution of 1-methylthiourea (18 g, 0.2 m) in ethanol-water mixture (11.5 mL) and potassium iodide (1 g) hydrogen peroxide was added gradually with stirring. After addition of about half the quantity of the required hydrogen peroxide development of brown colour due to liberation of iodine was observed. At this juncture the reaction mixture was kept on a boiling water-bath and heated. In a few minutes turbidity developed and the brown colour due to free iodine disappeared. On continuing the heating and adding of hydrogen peroxide in a slow stream elemental sulphur was found to separate. The addition of hydrogen peroxide was continued till a brown colour persisted in the reaction mixture even after several minutes. By this time the turbidity due to liberation of sulphur also ceased. The separated sulphur was then removed by filtration. The filtrate was then refrigerated for a few hours and then neutralized with ice-cold aqueous ammonia. The fluffy precipitate which separated was dissolved in minimum quantity of dilute hydrochloric acid and reprecipitated with ammonia. The product (5.8 g, 40%) was crystallized from boiling water as white shining needles. PMR: δ 2.8–2.9 (doublet, 3H, NH—CH₃), δ 3.18 (singlet, 3H of >N—CH₃), δ 4.0 (singlet, —C=NH), δ 6.5 (singlet, NH—CH₃). On deuterium exchange the doublet seen for the —NH—CH₃ between δ 2.8 and 2.9 changes into a singlet and both the peaks due to NH groups disappear. Oxidation of other 1-alkyl thioureas was also carried out under similar conditions. The details are given in Table-1.

RESULTS AND DISCUSSION

In a typical oxidation reaction of an acidified aqueous ethanolic solution of 1-alkylthiourea the following procedure was adopted. An aqueous ethanolic solution of 1-alkylthiourea containing concentrated hydrochloric acid and potassium iodide was kept heated on a boiling water-bath. Hydrogen peroxide (30%) diluted with water was added in a slow stream not allowing the reaction to become too vigorous. After addition of half the required quantity of hydrogen peroxide, the mixture developed a pale brown colour due to liberation of iodine. At this juncture a turbidity was found to develop and sulphur started separating and the colour of iodine disappeared. Heating and slow addition of hydrogen peroxide

was continued till a permanent brown colour persisted in the solution and no more separation of sulphur occurred. The oxidation was then deemed complete. The liberated sulphur removed by filtration and the filtrate stirred with decolourising charcoal, heated and filtered. The filtrate was then refrigerated for a couple of hours and then neutralized with ice-cold aqueous ammonia. The fluffy precipitate formed was collected and redissolved in dilute hydrochloric acid and again treated with aqueous ammonia. The precipitate formed was collected and crystallized from boiling water when 3-alkylimino-4-alkyl-5-imino- Δ^2 -1,2,4-thiadiazoline was obtained as needle-shaped crystals. Dissolution of the base in warm hydrochloric acid and cooling precipitated the hydrochloride. The base also formed a monopicrate when mixed with aqueous picric acid. The nitrate was also found to separate from an aqueous nitric acid solution as a crystalline material. These observations suggest that the base obtained is a monoacid base. The thiadiazolines resisted dehydrosulphurisation by sodium plumbite solution indicating the absence of —HN—(C=S)—NH— or =N—(C=S)—NH_2 grouping in its structure and the sulphur to be incorporated in a ring. The observation that the 1,2,4-thiadiazoline derivative separates a hydrochloride from aqueous acidic solution indicates that an alkyl group is possibly present on the nitrogen in the 4-position of the thiadiazoline.

TABLE-1
3-ALKYLIMINO-4-ALKYL-5-IMINO- Δ^2 -1,2,4-THIADIAZOLINE

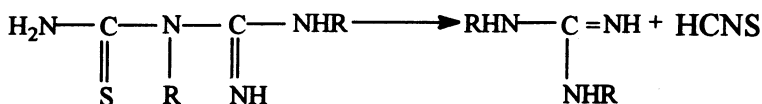
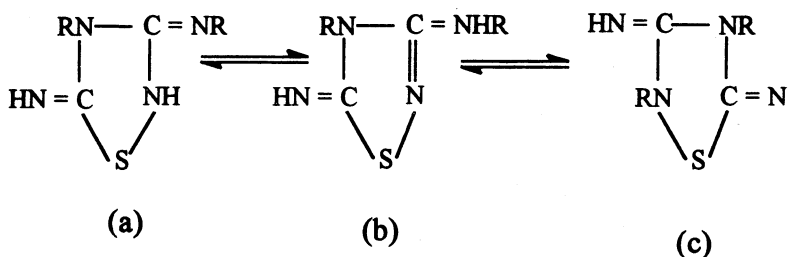


| Compound | R- | m.p. (°C) | m.f. | Elemental Analysis (%): Found (Calcd.) | | | |
|----------|---|--------------|--|--|--------------|----------------|----------------|
| | | | | C | H | N | S |
| 1. | CH ₃ | 165 | C ₄ H ₈ N ₄ S | 33.5 (33.3) | 5.7 (5.6) | 38.4 (38.9) | 22.4 (22.2) |
| 2. | C ₂ H ₅ | 185 | C ₆ H ₁₂ N ₄ S | 41.8 (41.9) | 6.9 (6.9) | 32.1 (32.6) | 18.2 (18.6) |
| 3. | C ₃ H ₇ | 80 | C ₈ H ₁₆ N ₄ S | 47.5 (48.0) | 7.9 (8.0) | 28.0 (27.3) | 15.5 (16.0) |
| 4. | <i>i</i> -C ₃ H ₇ | 77 | C ₈ H ₁₆ N ₄ S | 47.3 (48.0) | 7.8 (8.0) | 27.0 (28.0) | 15.5 (16.0) |
| 5. | C ₆ H ₅ CH ₂ | 142 | C ₁₆ H ₁₆ N ₄ S | 65.0 (64.9) | 5.4 (5.4) | 18.9 (18.9) | 11.5 (10.8) |

An ice-cold solution of the base in dilute hydrochloric acid on reaction with an aqueous solution of sodium nitrite yielded a mononitroso derivative as greenish yellow powder which turns yellow when dried. Like the Hector's base derivative as greenish yellow powder which turns yellow when dried. Like the Hector's base derived from 1-phenylthiourea it is believed that the nitrosation occurs on the 5-imino nitrogen. It formed 1 : 1 adduct with carbon disulphide and phenyl isothiocyanate.

Like the aromatic analogue the base on reduction with hydrogen sulphide in ammoniacal solution was observed to yield *N,N'*-dialkyl guanidine and thiocyanic acid. The solution obtained after reduction on evaporation and extraction with benzene and subsequent chromatography on a column of silica gel afforded *N,N'*-dialkyl guanidine. The benzene insoluble matter on dissolution in water and treatment with a few drops of dilute ferric chloride developed intense blood red colouration. The blood coloured complex could be extracted into ether. The above observation shows that thiocyanic acid is produced during the reductive ring opening of the thiadiazoline

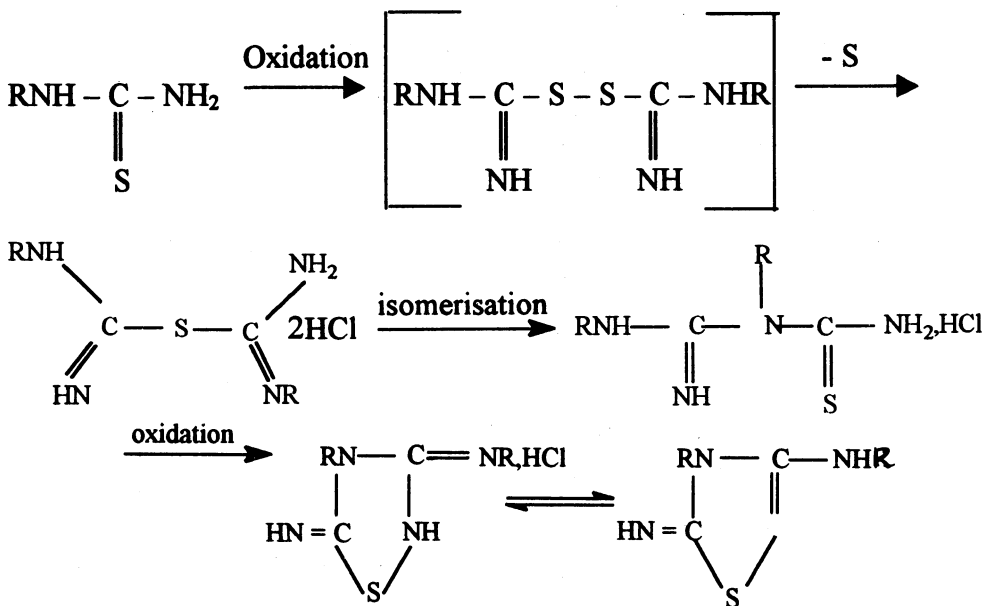
All these observations indicate that (i) the base has a ring structure which opens up readily, (ii) it has a 1,2,4-thiadiazole ring structure with an alkyl group at 4-position and an imino group at 5-position like in the aryl analogue described by Hector. The formation of dialkyl guanidine and thiocyanic acid can be explained if the reduction product formed from the base is having a 1-alkylamidino-1-alkylthiourea structure. 1-alkylamidino-1-alkylthiourea would be formed only from a thiadiazole derivative having structure (a), (b) or (c).



The oxidation of 1-alkylthiourea was conducted by varying the reaction conditions and it was observed that the maximum yield is obtained when one equivalent of the thiourea and half equivalent of the acid was used. When the acid was in excess the reaction was found to proceed very slowly, possibly because the bis(formamidine) salt is more stable in acidic solutions. The volume of the solvent affected the yield to a certain extent because of the solubility of the base. Hence in all oxidation reactions the volume of the final reaction mixture was reduced by evaporating the solvent by keeping it on a boiling water bath.

The IR spectral data of the base is in agreement with structure (b). The characteristic ring skeletal vibrations of 1,2,4-thiadiazolines¹¹ occur at 1030–1020 cm^{-1} and 860–825 cm^{-1} . The base shows weak and medium absorption in the above region. Strong absorptions resulting from C=N stretching modes of vibration are present in the region 1660–1500 cm^{-1} . The base exhibits strong absorption 3350–3225 cm^{-1} due to the N—H stretching vibrations¹⁰. The PMR spectra of these compounds support the thiadiazoline structure. The spectral properties are all in agreement with the assigned structure.

From the results of the oxidation reactions it can be surmised that the earlier failure in obtaining the related thiadiazoline derivatives by the oxidation of 1-alkylthioureas was due to sluggishness of the bis(formamidine) disulphides extruding sulphur and yielding the related bis(formamidine) sulphide and the slow rearrangement of the bis(formamidine) sulphide salts to the easily oxidizable amidinothiourea salt also occurred slowly under the reaction conditions. Hence the sequence of reactions occurring in these oxidations should be similar to the one proposed for the oxidations of 1-arylthioureas.



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