

Oxidation of Binary Mixtures of 1,3-Dialkylthiourea and Thiourea: Formation of 3-Amino-4-Alkyl-5-Alkylimino- Δ^2 -1,2,4-Thiadiazolines

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Oxidation of a binary mixture of unsymmetrical dialkyl thiourea and thiourea yield the intermediate bis(formamidino)sulphide which rearranges into two amidinothioureas. From the final oxidation product it can be inferred that the migration terminal of the unsubstituted amidino group is regulated by the steric factor and the electronic effect of the substituents on the amidino group.

Key Words: Formation, 3-Amino-4-alkyl-5-alkylimino- Δ^2 -1,2,4-thiadiazolines, Oxidation, Binary mixtures, 1,3-Dialkylthiourea, Thiourea

INTRODUCTION

Oxidation of N-substituted thioureas in polar media leads to 1,2,4-thiadiazole derivatives¹⁻³ and in non-polar media to 2-amino benzothiazole derivatives when one substituent at least is an aryl group⁴⁻⁹. Two molecules of thiourea are involved in the formation of 1,2,4-thiadiazole derivatives whereas in the case of benzothiazoles, an intramolecular oxidative cyclization occurs. The oxidation of binary mixtures of 1,3-substituted thioureas and thiourea has been found to give 3-amino-4-substituted-5-substituted amino- Δ^2 -1,2,4-thiadiazolines¹⁰. In the formation of the thiadiazolines one molecule each of the two different thioureas used was found to be involved.

Oxidation of binary mixtures of s-diarylthioureas and thiourea¹⁰, s-diarylthioureas and alkylthioureas and 1-alkyl-3-arylthioureas and thiourea¹² is found to give 1,2,4-thiadiazole derivatives in good yields.

The substitution pattern in the thiadiazole formed is determined by that of the intermediate amidinothiourea which is formed by the isomerisation of the intermediate bis(formamidino) sulphide in which the two amidino groups are derived from each of the two thioureas used. During this rearrangement, the migration terminus of one of the amidino parts was always found to be a nitrogen bearing an aryl group and the group an unsubstituted¹⁰⁻¹⁵ or a monosubstituted amidino group of the bis(formamidino) sulphide. The electron releasing nature of the substituents on the aryl group in the bis(formamidino)sulphide is also found to influence the mode of isomerisation.

The study had been extended to systems containing only alkyl functions for

which unsymmetrical dialkylthiourea and thiourea systems have been chosen. In this case the expected mixed bis(formamidine) sulphide formed during the oxidation would contain two amidino groups, one carrying two functions and the other an unsubstituted one. The rearrangement of this sulphide into the amidinothiourea salt and its oxidation should lead to the thiadiazole derivative.

The substitution pattern in the final oxidation product would depend on the position of the substituents in the amidinothiourea formed.

EXPERIMENTAL

Oxidation of a mixture of 1-benzyl-3-cyclohexylthiourea and thiourea: Formation of 3-amino-4-benzyl-5-cyclohexylimino- Δ^2 -1,2,4-thiadiazoline

A mixture of 1-benzyl-3-cyclohexylthiourea (12.4 g, 0.05 M), thiourea (3.8 g, 0.05 M) and potassium iodide (1 g) was suspended in 1 : 1 ethanol-water mixture (100 mL) containing hydrochloric acid (11.5 mL, 32% 0.1 M). Hydrogen peroxide was added gradually with efficient stirring. When brown colour due to liberation of free iodine developed, the reaction mixture was kept on a boiling water bath.

Further addition of hydrogen peroxide was done only on disappearance of this brown colour. The addition of the oxidant was continued till a slight brown colour persisted in the reaction mixture. This occurred only after heating the reaction mixture for over 4 h. At this stage the oxidation was deemed complete and the reaction mixture stirred with decolourising charcoal and filtered. The filtrate after chilling in ice and salt was basified with aqueous ammonia. The white precipitate obtained was collected and crystallised from aqueous ethanol when white shining needles of 3-amino-4-benzyl-5-cyclohexylimino- Δ^2 -1,2,4-thiadiazoline, m.p. 125°C were obtained. Analysis: found: C, 62.5; H, 6.9; N, 19.4; S, 10.9%; $C_{15}H_{20}N_4S$ requires C, 62.5; H, 6.9; N, 19.4; S, 11.1%.

When a solution of the base in dilute hydrochloric acid was treated with aqueous picric acid, a picrate was obtained. It was crystallized from ethanol as needles, m.p. 186°C. No condensation product was formed when a solution of the base in benzene was refluxed with phenyl isothiocyanate or when the base was heated with carbon disulphide.

Reduction of 3-amino-4-benzyl-5-cyclohexylimino-4-benzyl- Δ^2 -1,2,4-thiadiazoline

Hydrogen sulphide was bubbled through a solution of 3-amino-4-benzyl-5-cyclohexylimino- Δ^2 -1,2,4-thiadiazoline (4 g) in dilute hydrochloric acid (0.2 N, 75 mL) for about 1 h. The precipitated sulphur was removed by filtration. Concentration of the solution did not afford any crystalline material.

The aqueous acidic solution was then diluted with water and divided into two portions and one portion was warmed with sodium bicarbonate and steam distilled. The oily droplets obtained in the distillate were extracted with ether and then refluxed with ammonia when needles of cyclohexyl thiourea m.p. 162°C were obtained. When picric acid was added to the residual solution, no picrate was formed. Possibly the benzyl guanidine underwent decomposition during steam distillation.

The other portion was oxidised with hydrogen peroxide at room temperature, basified with aqueous ammonia and cooled well. The product formed was collected, crystallized from acetonitrile-water when needles of the original base, 3-amino-4-benzyl-5-cyclohexylimino- Δ^2 -1,2,4-thiadiazoline were obtained, m.p. 125°C.

Similar reduction of 3-amino-4-propyl-5-cyclohexylimino- Δ^2 -1,2,4-thiadiazoline yielded the related amidinothiourea. Decomposition with sodium bicarbonate evolved cyclohexyl isothiocyanate indicating that the cyclohexyl group is on the 5-imino nitrogen of the thiadiazole.

Synthesis of 3-amino-4-benzyl-5-cyclohexylimino- Δ^2 -1,2,4-thiadiazolines

Interaction of 1-benzyl-3-cyclohexylthiourea with cyanamide in the presence of hydrochloric acid: Formation of 1-cyclohexyl-3-benzyl-3-amidinothiourea hydrochloride

To a solution of 1-benzyl-3-cyclohexylthiourea (12.4 g, 0.05 M) and cyanamide (2.1 g, 0.05 M) in acetone (100 mL) dry hydrogen chloride gas was passed for some time. The initially formed pale yellow solution became colourless on continued passage of hydrogen chloride gas. The solution obtained on concentration and chilling in ice did not yield any precipitate. Hence it was diluted with water and divided into two halves.

One portion on oxidation and subsequent work-up yielded a base identified as 3-amino-4-benzyl-5-cyclohexylimino- Δ^2 -1,2,4-thiadiazoline, m.p. and m.m.p. 125°C.

The other half when heated with sodium bicarbonate solution was found to form cyclohexyl isothiocyanate identified by conversion to cyclohexylthiourea by reaction with ammonia.

Interaction of 1-benzyl-3-cyclohexyl carbodiimide with thiourea in the presence of hydrochloric acid: Formation of 1-benzyl-3-cyclohexyl-3-amidinothiourea hydrochloride

To a solution of 1-benzyl-3-cyclohexylthiourea (12.4 g, 0.05 M) in dry acetone yellow lead oxide was added and the mixture heated on a boiling water bath for about 30 min. A further quantity of yellow lead oxide was added to ensure that the dehydrosulphurisation was complete. Then the precipitated lead sulphide and excess yellow lead sulphide were filtered off and the filtrate cooled in ice and salt. A solution of thiourea (3.8 g, 0.05 M) was mixed with this filtrate and dry hydrogen chloride gas passed through it for nearly 5 min. The initially formed pale yellow solution became colourless as passage of hydrogen chloride gas was continued. Partial evaporation of the acetone and chilling the residual solution did not yield any solid product. Hence it was diluted with water and was divided into two halves.

Oxidation with hydrogen peroxide

One half on treatment with hydrogen peroxide in the presence of a little potassium iodide followed by neutralization yielded a fluffy precipitate. This was collected and crystallized when needles of 3-amino-4-benzyl-5-cyclohexylimino- Δ^2 -1,2,4-thiadiazoline, m.p. and m.m.p. 125°C was obtained.

Decomposition in the presence of sodium bicarbonate

The other half of the solution obtained was warmed with saturated sodium bicarbonate solution. It was subsequently acidified and steam-distilled. The only droplets found in the distillate were extracted into ether and then treated with ammonia. The product formed was identified as cyclohexylthiourea, m.p. and m.m.p. 162°C.

The procedures adopted above were used for the synthesis of 3-amino-4-propyl-5-cyclohexylimino- Δ^2 -thiadiazoline also. The intermediate amidinothiourea hydrochloride obtained from both methods was found to afford cyclohexyl isothiocyanate on decomposition with sodium bicarbonate solution confirming the structure of the intermediate to be 1-cyclohexyl-3-*n*-propyl-3-amidinothiourea.

RESULTS AND DISCUSSION

In a typical oxidation reaction a suspension of 1-benzyl-3 cyclohexylthiourea, thiourea and potassium iodide in acidified aqueous ethanol solution hydrogen peroxide (30 per cent) diluted with water was added in a slow stream. After addition of about one-half of the oxidant the reaction mixture turned slightly brown due to liberation of free iodine. At this juncture the reaction mixture was heated on a boiling water bath. After a few minutes the light brown colour due to iodine disappeared and a turbidity developed due to liberation of sulphur. Slow addition of hydrogen peroxide was continued till a permanent pale brown colour persisted in the reaction mixture. This took nearly 3 h. The oxidation was now deemed complete. A little decolourising charcoal was added to the solution, stirred, heated and filtered. The clear filtrate was chilled in ice and neutralized with ice-cold aqueous ammonia when a fluffy precipitate was obtained. The product obtained after dissolution of this precipitate in dilute acid and reprecipitation with a base showed the presence of only one component on a thin layer chromatogram. It crystallised from benzene-petroleum ether (3 : 1) mixture. It did not undergo dehydrosulphurisation on heating with sodium plumbite solution indicating that sulphur is incorporated in a stable ring. The base did not give any addition product on heating with phenyl isothiocyanate and carbon disulphide.

Reduction of a solution of the base in dilute hydrochloric acid with hydrogen sulphide yielded a solution which showed the presence of a product whose subsequent reaction showed it to be 1-cyclohexyl-3-benzyl-3-amidinothiourea salt. The reduction product on reoxidation afforded the original base and on decomposition with sodium bicarbonate yielded cyclohexyl isothiocyanate and benzyl guanidine. This observation indicated that the base obtained by the oxidation is having a 3-amino-4-benzyl-5-cyclohexylimino- Δ^2 -1,2,4-thiadiazoline structure.

The non-reactivity of the thiadiazole towards isothiocyanates and carbon disulphide is in conformity with the suggested structure. The ready interconvertibility of 3-amino-4-benzyl-5-cyclohexylimino- Δ^2 -1,2,4-thiadiazoline to 1-cyclohexyl-3-benzyl-3-amidinothiourea and *vice versa* indicates that reduction with hydrogen sulphide does not bring about any isomerisation in the reduction product.

cyclohexylthiourea and thiourea and 1-propyl-3-cyclohexylthiourea and thiourea indicate that the unsubstituted amidino group migrated to the less crowded benzyl or the propyl substituted nitrogen. The cyclohexyl group offers nearly the same steric inhibition as the isopropyl group. In earlier experiments using binary mixtures of 1-(2',6'-dimethyl)-phenyl-3-alkylthiourea and thiourea it was observed¹⁶ that the migration terminus was an alkyl substituted nitrogen as long as the alkyl group was a primary one. When the alkyl group was an isopropyl or a tertiary butyl group the migration never occurred on to the nitrogen bearing these groups. The major product formed in these oxidations was 1-isopropyl-3-(2',6'-dimethyl phenyl) urea or 1-*tert*-butyl-3-(2',6'-dimethyl phenyl) urea.

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