

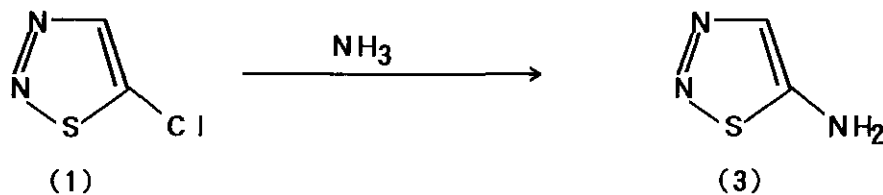
A SECURE AND CONVENIENT SYNTHESIS
OF 5-AMINO-1,2,3-THIADIAZOLE BY
DIAZOACETONITRILE

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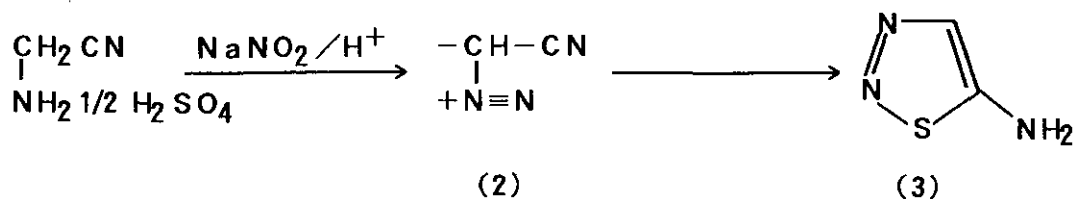
Abstract- A new synthesis of 5-amino-1,2,3-thiadiazole (3) by diazoacetone nitrile (2) and H_2S in the presence of a base is described. The compound (2) is undoubtedly explosive but with our method we found it could be used for industrial purposes.

5-Amino-1,2,3-thiadiazole (3) has been widely utilized as an intermediate for preparation of pharmaceuticals and agrochemicals,¹ particularly as an important compound for the synthesis of β -lactam antibiotics.² The compound (3) had been synthesized by the reaction of 5-chloro-1,2,3-thiadiazole (1) with ammonia.³ However, this method inevitably incurs problems because the starting material (1) is explosive.⁴ Therefore, a new and secure synthetic method has been sought.



The present report describes a new improved synthesis of 3 by the cycloaddition of hydrogen sulfide to diazoacetone nitrile (2) which is well known to be explosive⁵ but obtainable in high yield by diazotization of glycinonitrile with sodium nitrite under acidic conditions.⁶

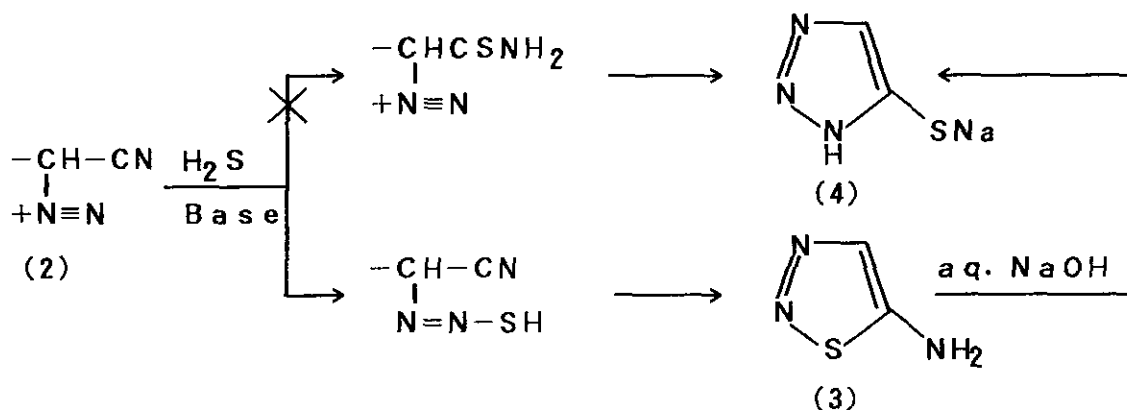
First of all, we carefully examined the explosive properties of 2⁷ to determine its use for industrial purposes.



As a result, it was found diazoacetonitrile was very explosive and sensitive to shock and/or pressure and this property had made it difficult for its use for industrial purposes. However, the explosive property was found to depend on the concentration of 2, for example, the 70 wt% solution of 2 in dichloromethane should be very explosive, but the 30 wt% solution of 2 in dichloromethane is not so dangerous. Therefore, it is important to note that 2 can be used only in dilute solution; additionally, it must be avoided concentration and isolation of 2, especially on a large scale. The suitable solvents are ether, dichloromethane,^{5, 6} chloroform. However, the compound (3) is explosive⁴ just like the compound (2) is. 3 can be isolated only at below room temperature; hence choice of the solvent of the cycloaddition was also important for not only obtaining high yield of 3 but also ensuring the safe operations of the isolation procedure. We selected a mixed solvent of dichloromethane and carbon tetrachloride in the ratio of 1:1 (volume) as a suitable solvent in both diazotization and cycloaddition reactions not only for the extraction of 2 but also because the solubility of 3 in the mixed solvent was low. Dichloromethane and chloroform are also suitable but concentration of the mother liquor would be necessary to isolate 3. In addition to the choice solvents, other reaction conditions such as the reaction time, temperature, and the kind and amount of the base seriously effect the isolated yield of 3. For example, the longer reaction time and higher temperature are apt to decrease the yield of 3. The base has been chosen from among amino compounds which were soluble but did not react with the solvent at below room temperature. By careful treatment we have developed the cyclization of 2 with hydrogen sulfide in the presence of such a base as triethylamine, the yield of 2 increased reproducibly at around 75 % or more. In our present reaction conditions, the compound (3)

can be completely separated as crystals from the reaction mixture and easily isolated by filtration at low temperature. The isolated compound (3) can be used for further reaction without purification. For example, 3 was treated with aq. sodium hydroxide to give sodium salt of 5-mercapto-1,2,3-triazole in quantitative yield⁸ and also treated with phenyl isocyanate to give thidiazulon(Dropp)⁹, which is well known in agrochemicals as a defoliant, in 86 % yield. In order to recover the solvent safely, the filtrate should be treated with aqueous acid solution at below room temperature because the residue of 2 perfectly decomposes to glyconitrile which is a stable compound under acidic conditions.¹⁰

Although the reaction mechanism is not clear, it is assumed that the sulfide anion attacks not to the carbon of the cyano group to form thioamide but to the nitrogen of the diazo group to form a σ -bond because the compound (4) has been made by Dimroth reaction¹¹ of 3 with aq. sodium hydroxide. It is clear that the cleavage of the S-N bond in the compound (3) leads to the compound (4) quantitatively.



We have safely used the present procedure for the synthesis of 3 on a large scale since 1984.

EXPERIMENTAL

Preparation of diazoacetonitrile (2)

Diazoacetonitrile (2) was prepared *via* diazotization of aminoacetonitrile sulfate according to the literature by Dewar and Pettit¹² but the low yield and the difficult procedure necessitated a change in the acid and solvent used. The acid has changed from sulfuric acid to

phosphoric acid because the rate of hydrolysis of 2 depends on the pH in the solution and hence it is difficult to control the pH in the solution with sulfuric acid. The solvent was changed from ether to a mixed solvent of dichloromethane and carbon tetrachloride in the ratio of 1:1 (volume). One reason for this change was that extraction had to be repeated several times until finally the reaction was completed and hence it was better that the organic layer was lower than the water layer. The other reason was that diazoacetonitrile thus prepared was pure enough for further use in the following reaction without purification. The yield determined by the volume of nitrogen liberated when an aliquot portion of the organic solution was shaken with dilute acid was usually between 80 and 88 %.

Preparation of 5-amino-1,2,3-thiadiazole (3)

To the above organic solution (200 g) of the compound (2) (5.57 g, 83.1 mmol), triethylamine (4.0 g, 39.6 mmol) was added dropwise over 7 min at around -10 °C, and then hydrogen sulfide gas was introduced over 30 min at a rate of 62 ml/min. Then, the reaction mixture was stirred for 15 min at around -10 °C. Crystals of the desired product began to precipitate in 5-7 min. The crude crystals of 3 were collected by filtration and recrystallized from water. The yield of pure 3 was 6.14 g (73 %).

The nmr spectrum in chloroform-d showed singlets at 7.934 ppm (1H, C₄-H) and 4.757 ppm (2H, NH₂), the infrared spectrum showed C-NH₂ absorption at 3335.2, 3277.4 cm⁻¹ and the uv spectrum agreed with the data of literature.¹¹ mp 144-146°C(decomp.) {lit.,⁸ 144-146 °C(decomp.) }

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REFERENCES AND NOTE

This paper is dedicated to Professor Shigeru Oae for the celebration of his 77th birthday.

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7. Drop hammer and lead tube tests have been carried out by Nippon Carlit Co. Ltd. at our request. The numerical values of the drop hammer test indicate how easily the sample explodes by the shock of the drop of the hammer: lower height, more sensitive to the shock. The value for the 70 wt% solution of 2 is less than height of 10 cm and for the isolated 3 it is more than 100 cm to explode by the shock of the drop of a 5-kg hammer. For other well-known explosive compounds, for example, for nitroglycerine it is 4 cm, it is 57-90 cm for TNT, and 100 cm for black gunpowder explode by the shock of the drop of a 2-kg hammer. The numerical values of lead tube test indicate the violence of explosion when the sample explodes by ignition: larger value indicates greater violence. The value for the 30% solution of 2 is 11.3 and for the pure and dry 3 it is 70 as a number of the violence. For other well-known explosive compounds, for examples, 250-400 for general gunpowder and 80 for black gunpowder.
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