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THE SYNTHESIS OF NEW
1,2,3-THIADIAZOLE DERIVATIVES

by

Ronald B. Patterson

A THESIS

Presented to the Faculty of
The Graduate College in the University of Nebraska
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For the Degree of Doctor of Philosophy
Department of Chemistry

Under the Supervision of Professor James H. Looker

Lincoln, Nebraska

January, 1970

TITLE

THE SYNTHESIS OF NEW 1,2,3-THIADIAZOLE DERIVATIVES

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THE SYNTHESIS OF NEW
1,2,3-THIADIAZOLE DERIVATIVES

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The reactions of 1,2,3-thiadiazole-4-carbonyl chloride with the appropriate amines led to formation of the following amides in good yield: N-ethyl-1,2,3-thiadiazole-4-carboxamide; N-methyl-1,2,3-thiadiazole-4-carboxamide; N-cyclohexyl-1,2,3-thiadiazole-4-carboxamide; N-hexyl-1,2,3-thiadiazole-4-carboxamide; 4-(1,2,3-thiadiazol-4-ylcarbonyl)morpholine; N,N-diphenyl-1,2,3-thiadiazole-4-carboxamide; N-(β -naphthyl)-1,2,3-thiadiazole-4-carboxamide; N-(4'-methyl-2',6'-dibromophenyl)-1,2,3-thiadiazole-4-carboxamide; and N-(3'-methyl-2'-pyridyl)-1,2,3-thiadiazole-4-carboxamide. These compounds were characterized by their infrared and NMR spectra, as well as elemental analyses.

4-Diazoacetyl-1,2,3-thiadiazole was prepared from the acid chloride and diazomethane in good yield and subjected to the Arndt-Eistert synthesis. The thiadiazole ring decomposed to unidentified products under these reaction conditions.

The Lund reaction was employed to synthesize 4-acetyl-1,2,3-thiadiazole in fair yield. The reaction of the methyl ketone and thiosemicarbazide gave a high yield of 4-acetyl-1,2,3-thiadiazole thiosemicarbazone. The method of Hurd and Mori was employed to prepare 4,4'-bi-1,2,3-thiadiazolyl using 4-acetyl-1,2,3-thiadiazole as the starting material. Their method was also employed to prepare the bi-ring compound starting from 2,3-butanedione. The attempted Willgerodt-Kindler synthesis with 4-acetyl-1,2,3-thiadiazole led to decomposition products, one of which was postulated as thiosuccinic bis-morpholide. Prolonged heating at reflux of 4-acetyl-1,2,3-thiadiazole in morpholine gave two decomposition products, of which one was identified as thioacetomorpholide.

N-[2-Diazo-3-oxo-3-(1,2,3-thiadiazol-4-yl)propionyl]-glycine ethyl ester was prepared from the acid chloride and N-(diazoacetyl)glycine ethyl ester.

The method of Hurd and Mori was employed to prepare 4-methyl-1,2,3-thiadiazole-5-carboglycine ethyl ester using N-(acetoacetyl)glycine ethyl ester as the starting material.

A previously described method employing the Wolff diazo synthesis was used to prepare 4,5'-bi-1,2,3-thiadiazolyl. The attempted formation of a Diels-Alder adduct with maleic anhydride led to almost quantitative recovery of the thiadiazole starting material.

ACKNOWLEDGEMENT

The author wishes to dedicate this thesis to his parents, Bonnie and Charles Patterson, whose help and love over the years made this work possible.

The author wants to take this opportunity to thank Dr. James H. Looker for his suggestions and guidance during the course of this work, and in the preparation of the thesis. Additional thanks goes to Norton Peet and Robert Cregge who supplied some of the starting materials, in addition to helpful advice. And thanks to Richard Comnick for his liaison during the final preparation of the thesis.

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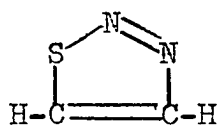
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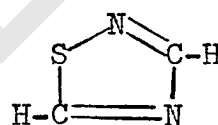
I. INTRODUCTION

History

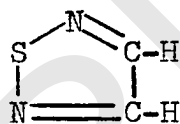
The thiadiazole (diazosulfide, thio [ab] diazole, or 3-thio-1,2-diazole) molecule is a five-membered heterocycle containing two carbon atoms, two nitrogen atoms, and one sulfur atom. Of the four possible isomers, the 1,2,3-thiadiazole isomer is one of the least studied.



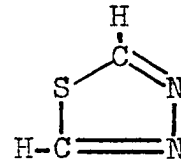
1,2,3-Thiadiazole



1,2,4-Thiadiazole

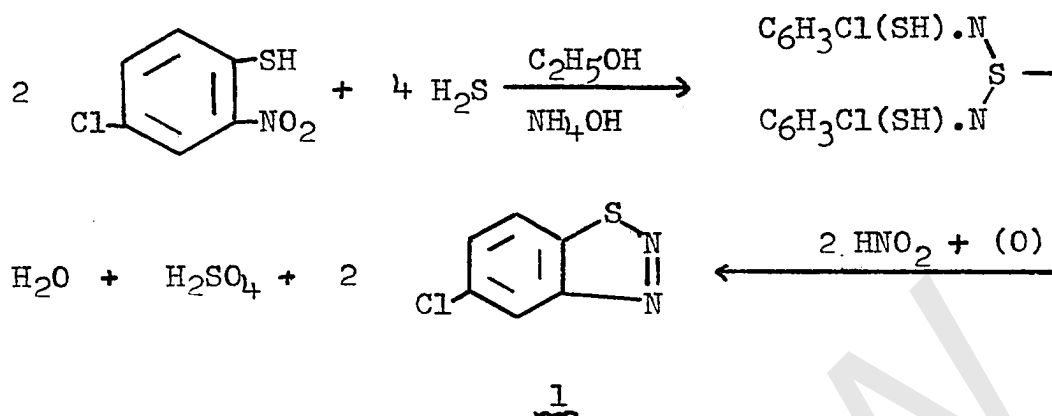


1,2,5-Thiadiazole

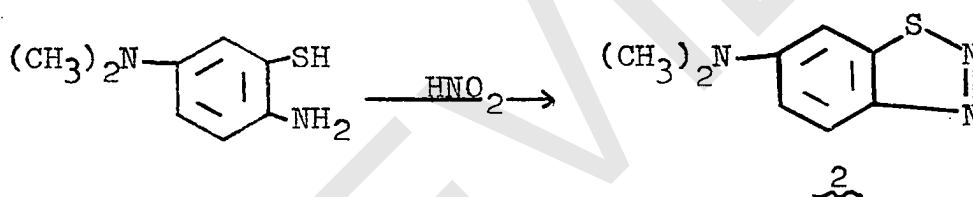


1,3,4-Thiadiazole

In 1879 Beilstein and Kurabatow¹ reported the first synthesis of a 1,2,3-thiadiazole nucleus in the form of a ring-fused compound. They observed that the reduction of 2-nitro-4-chlorothiophenol with hydrogen sulfide and ammonium hydroxide gave a dimeric product which could be converted to 5-chloro-1,2,3-benzothiadiazole (1) by nitrous acid.

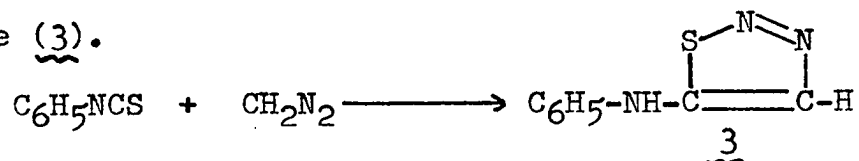


Ten years later Bernthsen² synthesized 5-dimethylamino-1,2,3-benzothiadiazole (2) by reacting 2-amino-5-dimethylamino-thiophenol with nitrous acid.



This diazotization of o-aminothiophenols, forming so-called "internal diazosulfides", has been the most widely investigated and simplest method of preparing 1,2,3-benzothiadiazoles³. This reaction has been extended to naphtho derivatives and other aromatic nuclei by other workers⁴.

The synthesis of non-fused 1,2,3-thiadiazoles originated with Pechmann and Nold⁵ who reacted diazomethane with phenylisocyanate to afford 5-anilino-1,2,3-thiadiazole (3).



Sheehan and Izzo⁶ re-examined this reaction, confirming Pechmann's results. They thought the reaction proceeded via an ionic mechanism where the methylene portion of diazomethane preferentially attacks the carbon atom of the thiocarbonyl function. The nucleophilicity of the sulfur atom then makes possible closure to the stable thiadiazole ring at a faster rate than nitrogen is eliminated.

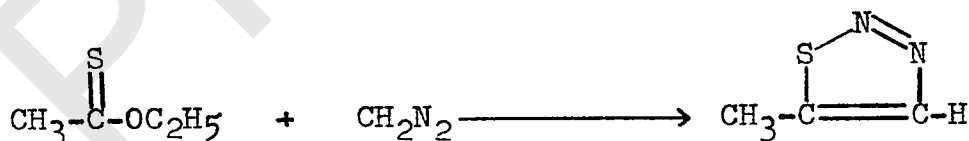
Tisler⁷ and co-workers also observed that in the Pechmann synthesis using either diazomethane or diazoethane, the reaction proceeded well with aromatic isothiocyanates, but different alkyl or arylalkyl isothiocyanates failed to react in an ethereal solution at room temperature. It was observed that diazomethane reacted less readily than diazoethane, probably owing to the electron donating nature of the methyl group.

In opposition to the ionic mechanism, Martin and Mucke^{8,9} proposed a 1,3-dipolar addition mechanism based on their studies of this reaction in which they observed that the addition velocity of the isothiocyanate increased with increasing electrophilicity of its carbon, whereas that of the diazo compounds was lowered by electrophilic groups. And the reaction velocity of the thiadiazole formation depended very strongly upon the concentration of the reagents, but was not affected by the polarity of the solvent.

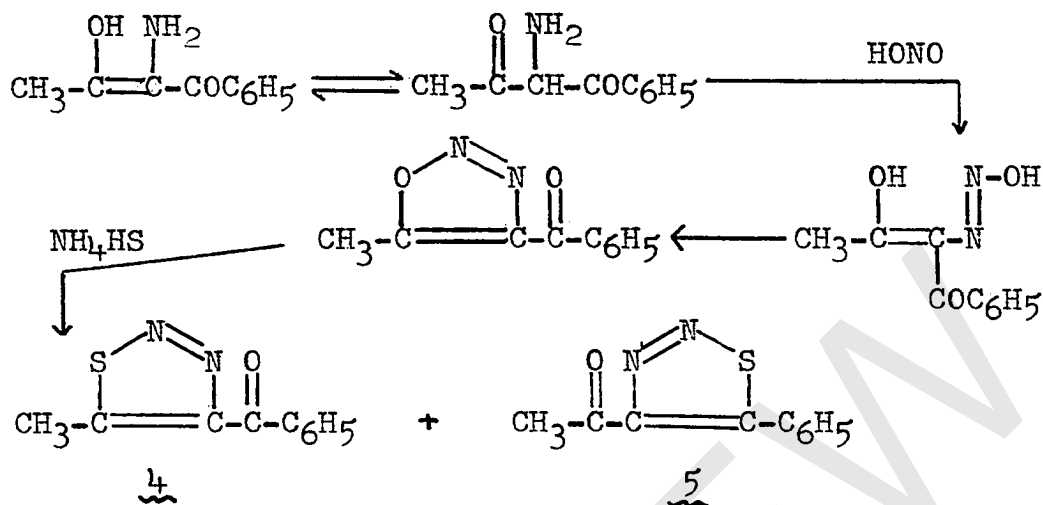
Rao¹⁰ and co-workers, as well as Martin and Mucke⁸, demonstrated the aromaticity of the 1,2,3-thiadiazole ring with the use of ultraviolet spectroscopy which exhibited the absorption maxima at 275-354 mμ. They also assigned the following infrared absorption bands for the 1,2,3-thiadiazole ring.

- (a) 1560-1475 cm⁻¹, variable intensity, one or more bands (ring stretching);
- (b) 1150-950 cm⁻¹, variable intensity, one or more bands (ring breathing);
- (c) 910-890 cm⁻¹, weak intensity (ring breathing).

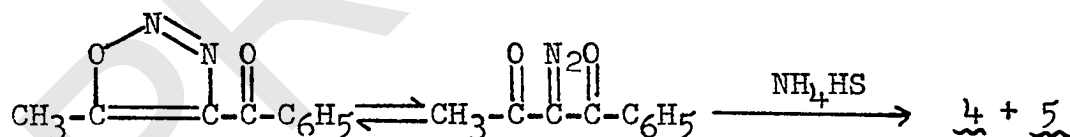
As the Pechmann synthesis always gives 1,2,3-thiadiazoles which are N-substituted in the five position, it was of interest when Schmidt¹¹ and co-workers were able to change the substrate and prepare 1,2,3-thiadiazoles (by reacting diazomethane with thioesters) which are no longer N-substituted in the five position.



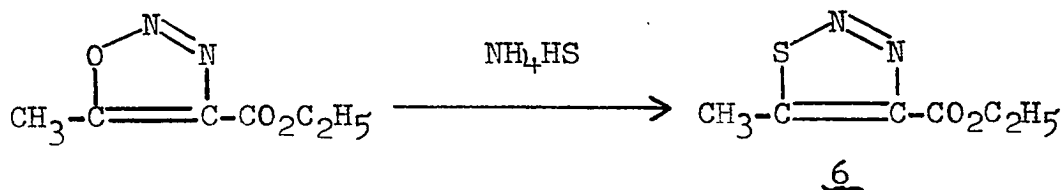
Another major method of synthesis was reported by Wolfr¹² who reacted α-diazocarbonyl compounds (isomeric with 1,2,3-oxadiazoles) with ammonium hydrogen sulfide to afford two isomeric products (4) and (5) as indicated below:



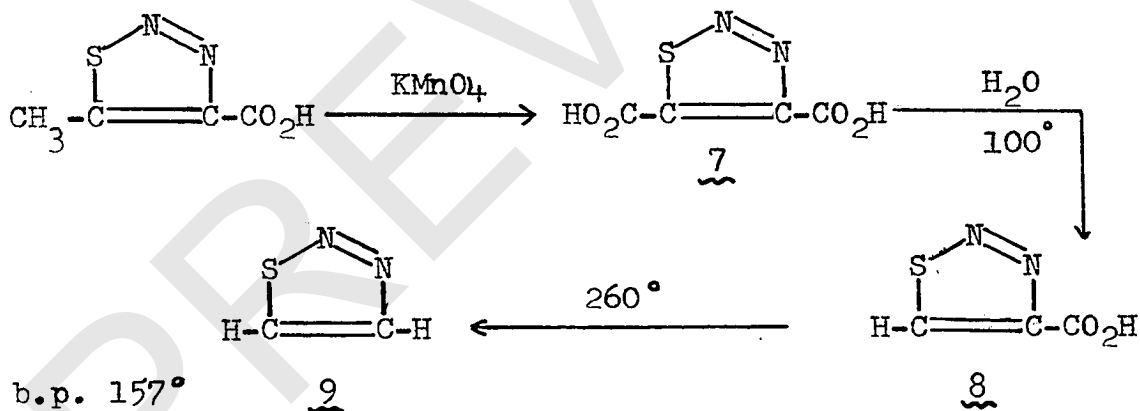
Because this reaction gave rise to the two isomeric products, Staudinger^{13,14} postulated that Wolff did not have the 1,2,3-oxadiazole, but its isomeric diazo compound which would also lead to the observed products (4) and (5). These isomeric products would form since the nitrogen atom can condense with either of the two keto carbonyl functions during ring closure.



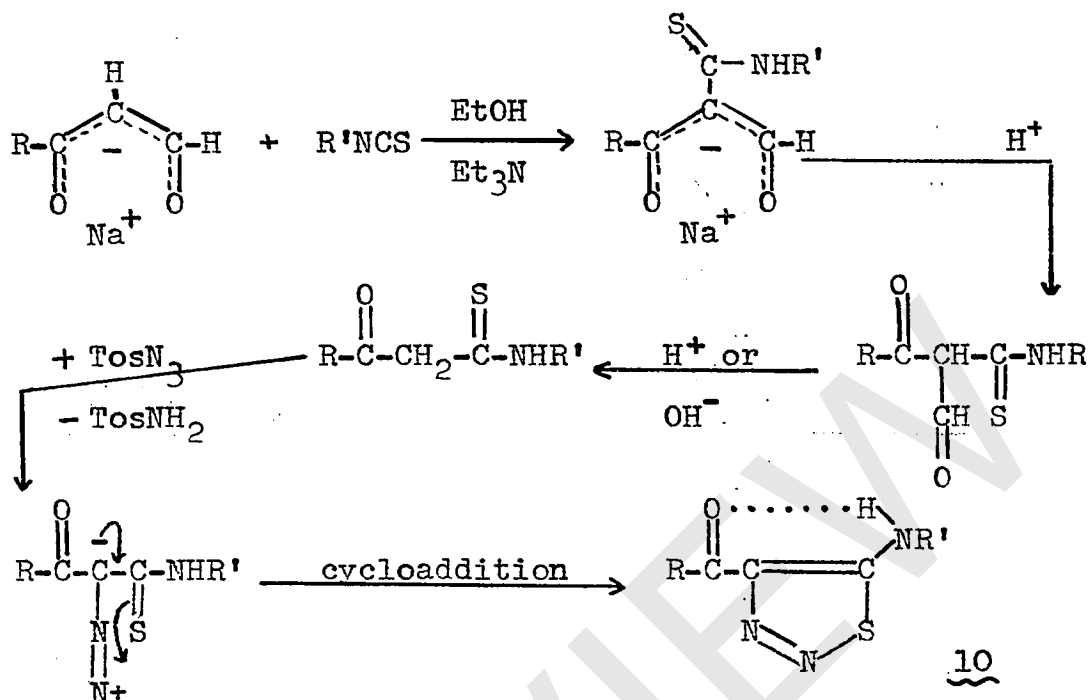
In order to eliminate the possibility of isomeric products, Wolff¹⁵ used the reaction of α -ketodiazoo esters and ammonium hydrogen sulfide as it was observed that the nitrogen atom would not close at the ester carbonyl.



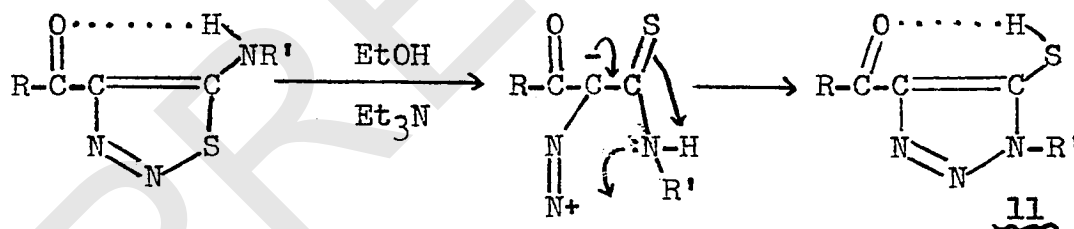
Wolff¹⁶ was able to saponify compound (6) to its 4-carboxylic acid and then oxidize it to the 4,5-dicarboxylic acid (7). Stepwise decarboxylation gave the 4-carboxylic acid (8) and finally the unsubstituted 1,2,3-thiadiazole (9). Staudinger¹³ also used α -ketodiazoo esters, although he prepared his starting materials by the reaction of the appropriate acid chloride with ethyl diazoacetate.



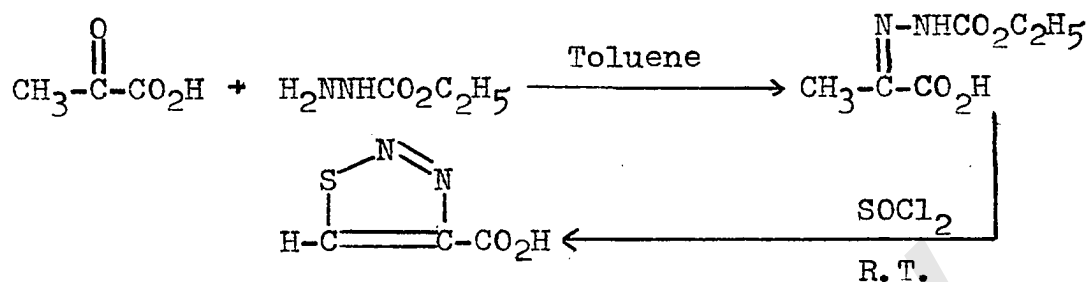
A similar method for preparing 5-N-substituted 1,2,3-thiadiazoles was reported by Regitz and Liedhegener¹⁷ who observed that diazo group transfer to $\text{RCOCH}_2\text{CSNHR}'$ or $\text{RCOCH}(\text{CHO})\text{CSNHR}'$ afforded high yields of 4-(RCO-substituted) 5-[(R'-substituted)amino]-1,2,3-thiadiazoles (10).



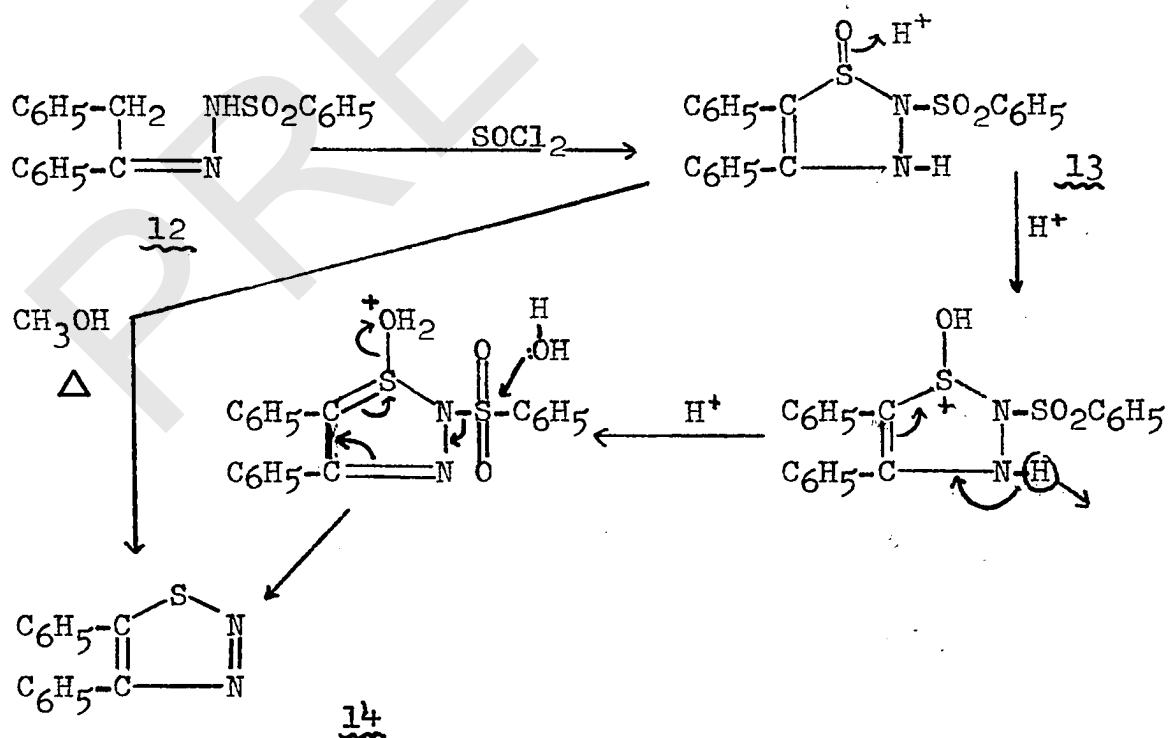
The Dimroth rearrangement was found to accompany 1,2,3-thiadiazole formation affording very small yields of the triazole (11).



In 1955 Hurd and Mori¹⁸ found a new pathway to the 1,2,3-thiadiazole system which utilizes the reaction of thionyl chloride with acylhydrazones. As an example, they prepared 1,2,3-thiadiazole-4-carboxylic acid from α -N-(carboethoxyhydrazono)propionic acid in good yield.



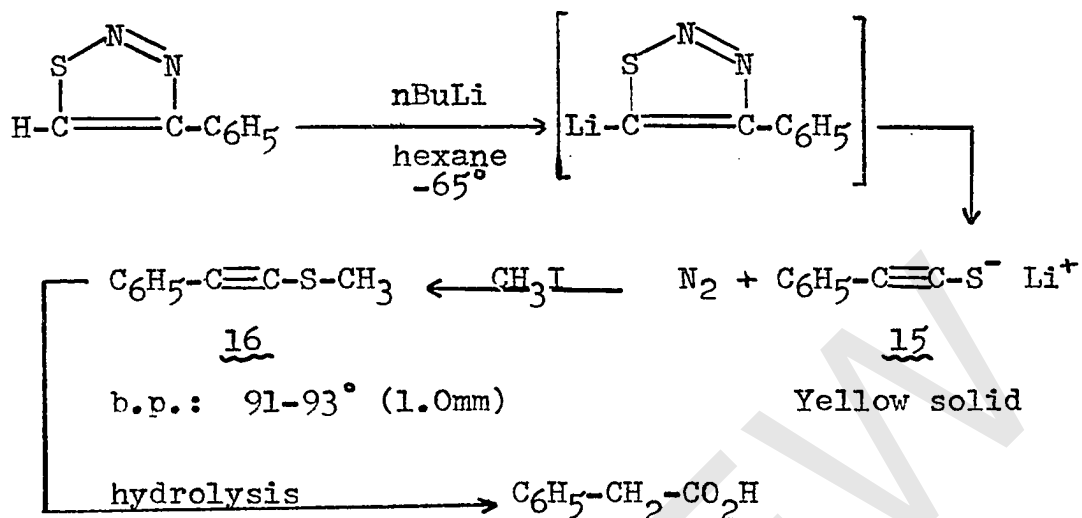
The mechanism proposed for this reaction was based on the isolation of an intermediate product (13) (12%) when deoxybenzoin benzenesulfonylhydrazone (12) was converted to 4,5-diphenyl-1,2,3-thiadiazole (14) (63%). Heating the intermediate (13) in boiling methanol afforded a 55% yield of the thiadiazole, with acid or base catalysis raising the conversion to about 90%. The acid-catalyzed reaction is shown below. The base-catalyzed conversion has a similar mechanism.



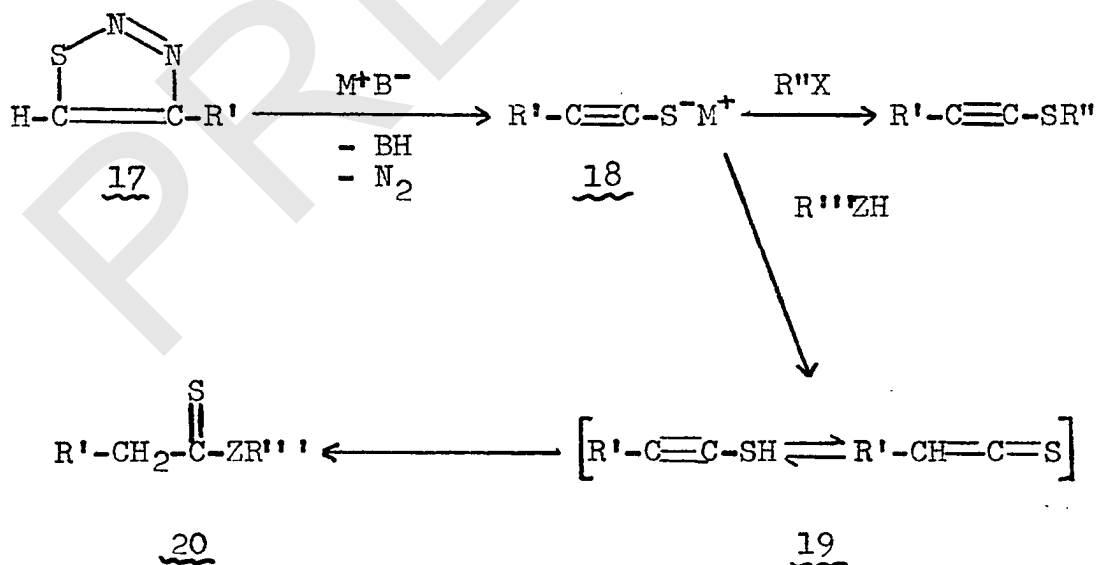
It appears that the reaction is an ionic one catalyzed by acid as well as base. Also, the oxidation-reduction is an intramolecular reaction and does not appear to proceed by prior formation of benzenesulfinic acid ion. This fact indicates that solvent participation makes the decomposition of (13) an intermolecular reaction.

Wolff¹⁵ initially stated that the 1,2,3-thiadiazoles are stable toward oxidation and acids, but unstable towards bases, giving off hydrogen sulfide. The ring was found to be weakly basic, forming salts with hydrochloric acid, gold chloride, and methyl halides. Additional evidence supporting the stability towards oxidation can be seen in a recent patent which states that 5-propyl-1,2,3-thiadiazole can be oxidized by V_2O_5 , MoO_3 , or $SnVO_4$ at 300-400° to 5-formyl-1,2,3-thiadiazole¹⁹.

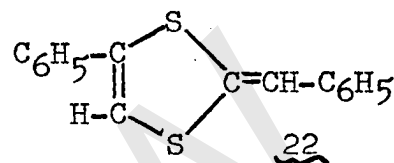
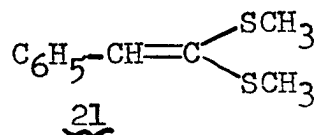
Raap and Micetich²⁰ found that the reaction between 1,2,3-thiadiazoles, unsubstituted in the five position, and a strong base (an organolithium compound, sodamide, sodium methyl sulfinyl carbanion, or potassium tert.-butoxide) resulted in the cleavage of the thiadiazole ring, with elimination of nitrogen. Subsequent addition of an alkyl or acyl halide to the reaction mixture produced an 1-alkynyl thioether (16).



In a second paper, Raap²¹ extended this work to the formation of thioneesters. He observed that the alkynethiolate (18) could abstract a proton from a protic substance to afford a thioketene (19), which would react further to give the thioneester (20).



	<u>R'</u>	<u>Z</u>	<u>R'''</u>
a	CO ₂ CH ₃	O	CH ₃
b	CONH ₂	O	CH ₃
c	C ₆ H ₅	O	CH ₃
d	C ₆ H ₅	S	C ₂ H ₅



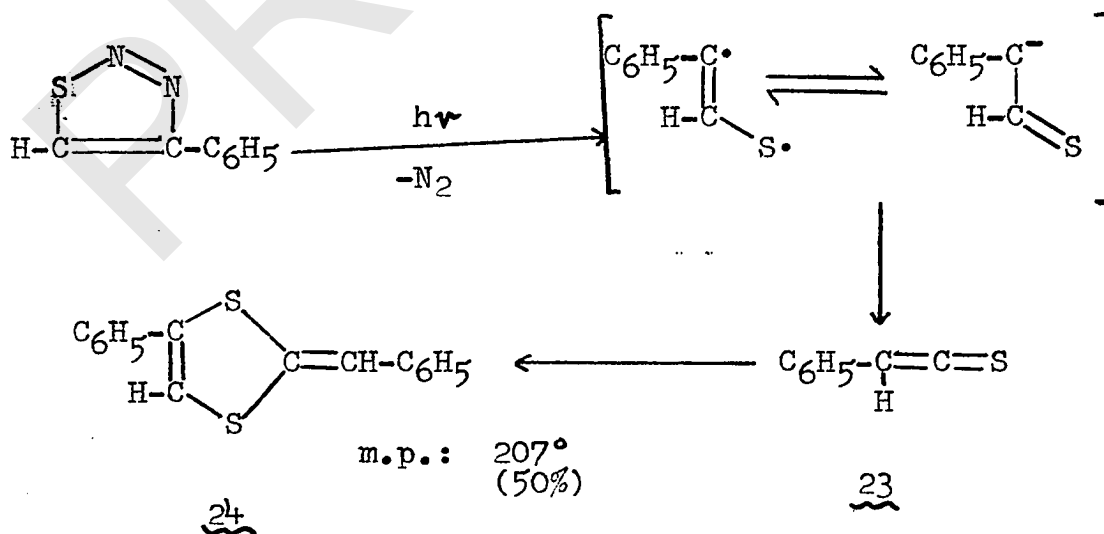
When 17a was added to threefold excess methanolic sodium methoxide at 0°, a rapid gas evolution took place, and 20a (dimethyl monothioemalonate) was isolated (71%). Compound 17b reacted to yield 20b (59%), and 17c under reflux gave 20c (69%). Prior to workup of this latter reaction mixture, treatment with dimethyl sulfate afforded β -methoxy- β -methylthiostyrene (21) (62%), for the medium is basic enough that the product can be present as an anion, which preferentially alkylate on the sulfur. Addition of water at -60° to lithium 2-phenylethynethiolate in tetrahydrofuran gave the dithiafulvene (22) resulting from the rapid reaction of the thioketene with unreacted thiolate.

Michelman²² and co-workers conducted a deuteration study of 1,2,3-thiadiazole using NaOD/D₂O and observed that only the proton in the five-position was exchanged. As with other five-membered heterocycles, it was evident that there is an extraordinary rate enhancement when a proton is on the carbon atom adjacent to the sulfur atom.

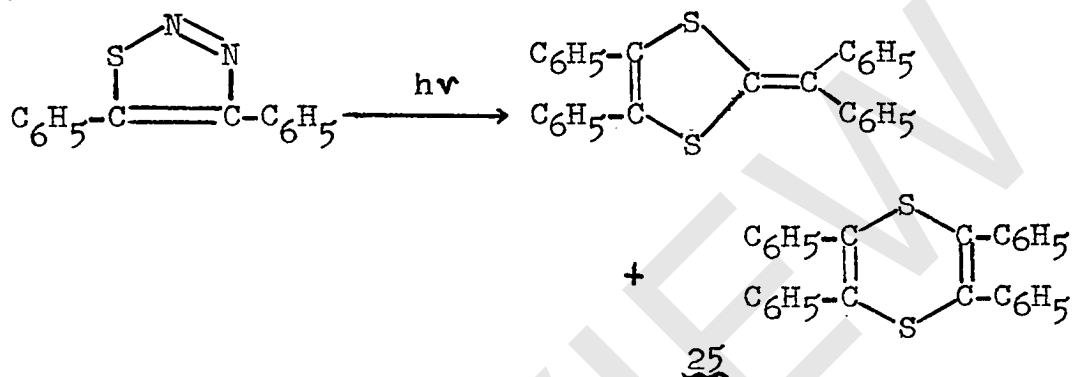
This suggests that d- σ overlap is a major factor in stabilizing these anions.

Zahradnik and Koutecky²³ studied the 1,2,3-thiadiazole nucleus using the simple M. O. method in the L. C. A. O. approximation. They attributed to sulfur two hybridized $3pd^2$ orbitals, which resemble the p_z orbitals of two carbon atoms in their bond properties. And they calculated that the four-position has a higher electron density than the five-position.

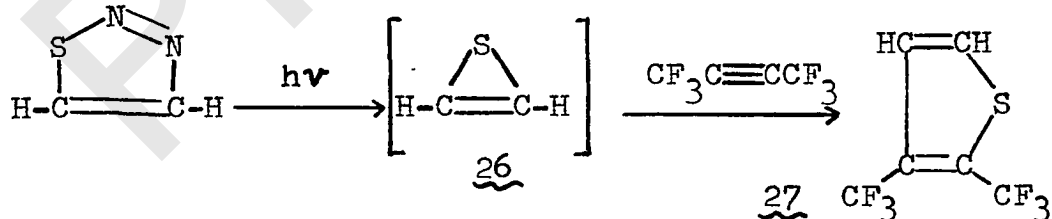
Many 1,2,3-thiadiazoles become colored on exposure to light. The nature of this change has not been ascertained. On the irradiation of aromatic substituted 1,2,3-thiadiazoles with ultraviolet light, nitrogen and 1,4-dithiafulvene (24) are obtained²⁴. This same product subsequently was obtained by Raap²¹ in his work with bases.



The disubstituted 1,2,3-thiadiazoles give rise to a small amount of the 1,4-dithiacyclohexadiene (25) as well as the expected 1,4-dithiafulvene.



Utilizing a novel technique of flash photolysis with kinetic mass spectrometry, Strausz²⁵ and co-workers produced a thiirene (26) upon photolysis of 1,2,3-thiadiazole. The thiirene was trapped with perfluorobutyne-2 to afford a good yield of 2,3-bis(trifluoromethyl)thiophene (27).



5-Methyl-1,2,3-thiadiazole was photolysed in the presence of perfluorobutyne-2 to give 2,3-bis-(trifluoromethyl)-5-methylthiophene (28) as the sole thiophene