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Reactivity and Synthesis of 1,2,5-Thiadiazolidine 1,1-Dioxides: Synthesis of 4-Aryl-3-imino-1,2,5-thiadiazolidine 1,1-Dioxides

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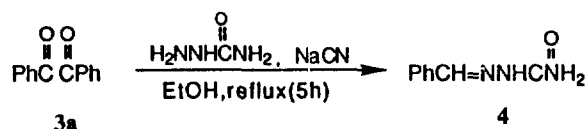
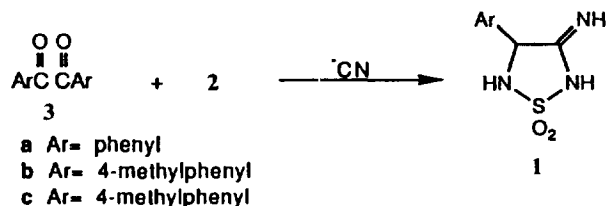
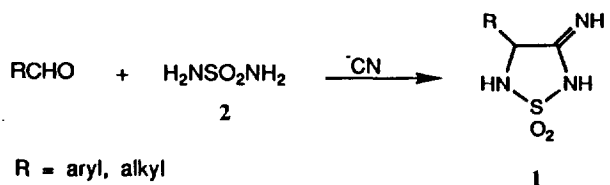
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Received October 15, 1991

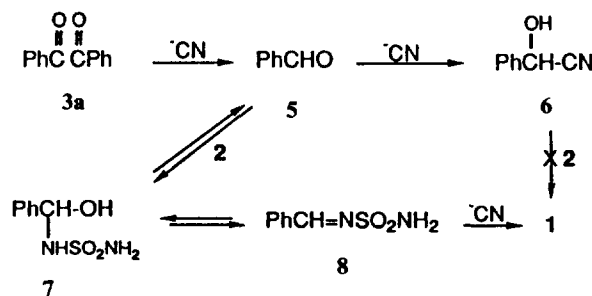
In recent years, an increasing number of articles describing the synthesis, properties, and biological activities of 1,2,5-thiadiazolidine 1,1-dioxides which contain the sulfamide moiety has appeared¹. Previously, Lee and Kohn have reported a general method for the synthesis of 3-imino-1,2,5-thiadiazolidine 1,1-dioxides **1** from aldehydes, sodium cyanide and sulfamide (**2**) by modifying the Strecker synthesis of hydantoins³. The compounds **1** have been known to possess anticonvulsant effect⁴.



In this paper, we wish to describe a new route for the preparation of **1** from benzil derivatives **3** instead of aldehydes, which were originally used in the Lee-Kohn procedure. Table 1 summarizes the experimental results. Shown re-

Table 1. Synthesis of **1** from Benzil Derivatives **3**

Products		mp. (°C) ²	Isolated yields (%)
No.	Ar		
1a	phenyl	272-273	51
1b	4-methylphenyl	252-254	50
1c	4-methoxyphenyl	247-248	62



ted in 1971 that the cyanide-mediated cleavage of benzil (**3a**) furnished benzaldehyde along with benzoic acid⁵. When we repeated this experiment in the presence of semicarbazide hydrochloride benzaldehyde semicarbazone was obtained in 75% yield. Treatment of benzil (**3a**) with sodium cyanide and sulfamide also produced 4-phenyl compound **1a** in 51% yield.

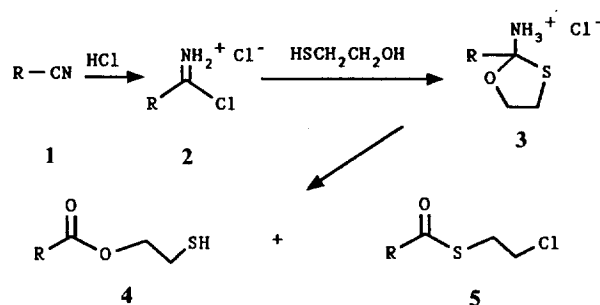
A typical experimental procedure for the synthesis of **1** from benzil derivatives is as follows: An ethanolic solution (20 ml) of 4-methylbenzil (240 mg, 10 mmol), sulfamide (290 mg, 300 mmol), and sodium cyanide (54 mg, 11 mmol) was heated at reflux for 5 h and then cooled to room temperature. The mixture was acidified to pH 2.0 and then allowed to stand at 0-5°C for 24 h. The resulting crystalline material was collected by filtration and dried *in vacuo* to give 115 mg (50%) of **1b**: mp. 252-254°C (dec); IR (KBr) 3450, 1645, 1355, 1120 cm⁻¹; ¹H-NMR (DMSO-d₆) δ 2.35 (s, 3H), 5.20 (d, 1H, J=6.0 Hz), 7.00-7.30 (m, 4H), 7.34 (s, 1H, exchangeable with D₂O), 7.50 (s, 1H, J=6.0 Hz, exchangeable with D₂O), 8.10 (s, 1H, exchangeable with D₂O).

The probable mechanism of this reaction is depicted in Scheme 1. When N-benzylidenesulfamide (**8**)⁶, which was prepared by the reaction of N,N'-dibenzilidene-sulfamide with aniline, was reacted with sodium cyanide, the compound **1a** was obtained in 15% yield. However reaction of mandelonitrile (**6**) with sulfamide under the same reaction conditions did not produce compound **1**. This fact suggests that the mechanism should be **3a**→**5**→**7**→**8**→**1**. Although this procedure permitted the preparation of aryl derivatives **3** from benzil derivatives **4**, reaction of aliphatic diones such as 1,2-cyclohexanedione proved to be unsuccessful. Further application of this procedure to various aromatic heterocyclic diones and reactivity studies of the resulting products **1** are in progress.

Acknowledgement. This paper supported by NON DIRECTED RESEARCH FUND, Korea Research Foundation, 1990.

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Schem 1.

Table 1. Yields of 2-Chloroethyl Thioesters and 2-Mercaptoethyl Esters Formed by Pinner Type Reaction of Diethyl Ether Soluble Nitriles in the Presence of 2-Mercaptoethanol in Anhydrous Diethyl Ether

Nitrile	RCOSCH ₂ CH ₂ Cl	RCOOCH ₂ CH ₂ SH
CH ₃ CH ₂ CH ₂ CN	42.2%	10.2%
Ph-CH ₂ CN	62.0%	5.6%
p-O ₂ N-Ph-CH ₂ CN	23.0%	9.4%
Ph-CN	10.4%	7.3%
Ph-CH(OH)-CN	14.0%	—

Another Evidence for the Formation of 2-Amino-1,3-oxathiolane Tetrahedral Intermediate in the Pinner Type Reaction of Nitriles with 2-Mercaptoethanol; Formation of 2-Chloroethioesters and 2-Mercaptoethyl Esters from Nitriles

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Received October 17, 1991

We recently proposed a bifunctional group-participated tetrahedral intermediate model for the active sites of the nitrile group hydrolyzing enzymes¹. We examined many bifunctional compounds for the activity of hydrolyzing a nitrile group to the corresponding amide², and found that 2-mercaptoethanol had the highest catalytic activity on the hydrolysis of α -aminophenylacetone nitrile to phenylglycinamide³. Stirring various nitrile compounds with 2-mercaptoethanol in a phosphate buffer (50 mM, pH 7.0) gave amides in good yields⁴. The nitrile group having an α -amino group, or those attached to the electron withdrawing aromatic ring was easily hydrolyzed to the amides⁵. 2-Mercaptoethanol seemed to react with nitrile compounds to produce bifunctional group-participated tetrahedral intermediates, decomposition of which should give the imidate analog, which should hydrolyzed to amides. During investigation of the reaction mechanism, we attempted to synthesize the tetrahedral intermediate, 2-amino-1,3-oxathiolane (3) by Pinner reaction⁶. The Pinner type reaction of nitriles with 2-mercaptoethanol produced amides in good yields. Conversion of nitriles to amides in the presence of 2-mercaptoethanol under anhydrous condition seemed to imply formation of 2-amino-1,3-oxathiolane (3) as an intermediate. Decomposition of this tetrahedral intermediate by at-

tack if the sulfur atom on C-5 carbon atom should yield amides.

α -Amino nitriles-HCl did not dissolved well in diethyl ether and we employed THF for the Pinner type reaction. Recently we tried the same reaction in diethyl ether with diethyl ether soluble nitriles, and we found that nitriles were not converted to amides. Instead, we isolated 2-chloroethyl thioesters and 2-mercaptoethyl esters from the reaction mixture, and these products should be formed also from the tetrahedral intermediate, 2-amino-1,3-oxathiolane (3) and we wish to report our finding in this report.

When the solution of butanenitrile (2.44 mL, 0.028 mol) in freshly distilled (over Na with benzophenone) anhydrous diethyl ether at 0°C was bubbled with dry HCl gas (dried with c-H₂SO₄) in the presence of 2-mercaptoethanol (1.96 mL, 0.028 mol) for 2 hrs, crystals were started to suspend in the reaction mixture. The reaction mixture was stirred for 3 hrs more at the same temperature and then for 10 hrs at 10°C. The crystals suspended in the reaction solution was found to be ammonium chloride. After the crystal was filtered off, the residue obtained after evaporation of the solution was chromatographed over silica gel to give S-(2-chloroethyl) butanethiolate (3.73 g, 44.4% yield)⁷ and 2-mercaptoethyl butanoate (422 mg, 10.2% yield)⁸. Further examination of the reaction with other diethyl ether soluble nitriles gave similar results (Table 1)⁹.

S-(2-Chloroethyl) thiolates should be formed from 2-amino-1,3-oxathiolane (3) in which C-5 carbon atom was attacked by chloride ion with liberation of ammonium chloride. The liberation of ammonium chloride without attack of chloride ion should give the 1,3-oxathiolane carbonium ion, which should be hydrolyzed by water during working up, followed by cleavage of the weak carbon-sulfur bond to produce 2-mercaptoethyl ester (Scheme 1). When THF was employed