

CONVENIENT ONE-POT SYNTHESIS OF SODIUM SALT OF 5-MERCAPTO-1, 2, 3- THIADIAZOLE

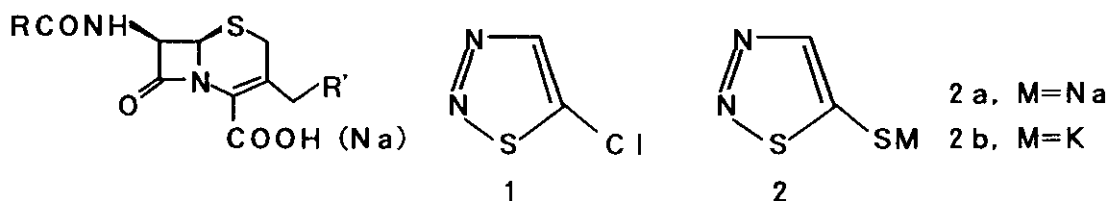
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Abstract- Trichloroacetaldehyde-*p*-toluenesulfonylhydrazone

(3) derived from chloral hydrate reacted *in situ* with polysulfide salt in the range of pH 10-11 to afford the corresponding 5-mercapto-1,2,3-thiadiazole salt(2) in high yield (69.5 %).

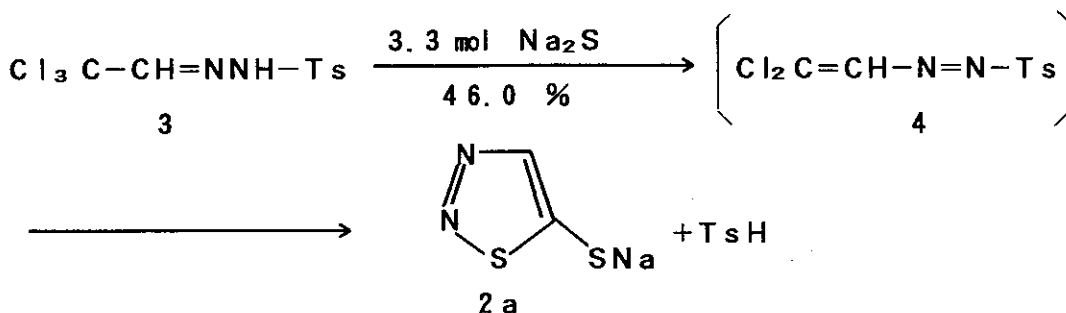
One of the more important reactions in the preparation of cephalosporin antibiotics is the displacement of the allylic acetoxy group at C₃ by nucleophiles. A wide range of heteroaromatic thiols have been used in the reaction, and some of the products have shown enhanced activity against Gram-negative bacteria, depending on the nature of the heterocycle and the substituent at C₇.^{1a} Among those compounds which have reached to advanced testing or clinical use are the compounds derived by displacement of the acetoxy group with 5-methyl-1,3,4-thiadiazole-2-thiol, 1-methyl-1,2,3,4-tetrazole-5-thiol, 1,2,3-triazole-5-thiol, and 1,2,3-thiadiazole-5-thiol.



Although these derivatives¹ are still under active investigation, the synthetic method of 2 has been less studied. One of the usable methods so far reported was that 5-chloro-1,2,3-

thiadiazole (1) reacted with Na_2S .² However, this method inevitably incurs problems because the starting material (1) is explosive.³ Therefore, a new and secure synthetic method of 2 has been sought.

In the course of our study on the diazo compounds, we found a new method for preparation of 2 by the reaction of chloral *N*-tosylhydrazone (3) with Na_2S in 46 % yield⁴ as shown below. However, the low yield made it difficult to safely isolate 2a in a pure form and, therefore, our method could be inapplicable to large-scale production. This paper presents a new unhazardous method for preparation of 2 for industrial purposes.



In this process the hydrazone (3) can be easily obtained by the reaction of chloral with *N*-tosylhydrazine in a mixed solvent of methanol and water.⁵ The insolubleness of 3 in the reaction system is important to the accomplishment of this reaction because 3 also easily reacts with *N*-tosylhydrazine under the same reaction conditions, and hence it is preferable that 3 is not soluble in the solvent. However, the resulting heterogeneous solution interferes with a smooth transfer of 3 to another reaction vessel. Moreover, it was doubtful that 3 was free of hazardous properties because 3 easily reacts with the base to give an azo compound⁵ (4) which has a typical explosive structure according to Bretherick's standard.⁶ Indeed, 3 has a low decomposition point (85–86°C).

Prior to practical utilization, our new procedure necessitated to solve two problems. One was how to overcome the explosive hazard of 3 (A one-pot reaction might be preferable in order to avoid the isolation or transfer of 3). The other problem was how to improve the low yield 46 % of 2. After many trials, we found that the yield of 2b starting from 3 could be improved by simply replacing sodium sulfide with commercially available potassium

sulfide (purity : about 40 %). The results of the reactions are shown in Table 1 .

Two reaction methods were employed. (A): the addition of M_2S (M : K or Na) in a 50 % aq. methanol solution into 3 in a methanol solution. (B): the reverse addition of the reagents employed in method (A). Method (A) is preferable because the isolation or transfer of 3 was unnecessary to avoid the explosive hazard. However, the reaction system requires the use of excess sulfide because it serves not only as a reagent to construct the thiadiazole ring and the mercapto group but also as a base to neutralize chloride anion and *p*-toluenesulfinic acid formed by the reaction. The total amount of M_2S (M : K or Na) is theoretically three mole equivalents to 3, but the optimum mole ratio(M_2S / 3) was 3.3 ; less than 3.3 resulted in a marked decrease in yield while more than 3.3 had no effect on the yield.

Table 1. The effect of K_2S (purity : 40 %) added¹⁾

Run No.	M_2S / 3 M_2S mole ratio		Reaction method	pH ²⁾			Yield(%) of 2 based on 3
				a	b	c	
1.	Na_2S	(3.3)	(A)	—	13.4	13.5	46.0
2.	Na_2S	(3.3)	(B)	14.0	13.5	13.5	12.0
3.	K_2S	(3.3)	(A)	—	11.0	10.5	66.2
4.	K_2S	(1.5)	(B)	13.2	11.0	10.5	66.4

1) All reactions were performed at room temperature for 1 h. 2) a: before reaction, b: 5 min. c: 30 min. later from adding M_2S .

In the case of Na_2S , the pH is maintained at around 13-14 from the beginning to the end of the reaction and the by-products are mainly sodium *p*-toluenesulfinate ($TsNa$) and some of derivatives from the hydrolysis of 3. The pH easily drops down to 10-11 by using commercially available K_2S and the main by-product is not the sulfinate but the thiosulfonate ($TsSK$) which is an oxidized compound of sulfinate, although there is no oxidant. We tried to use other different kinds of K_2S , i.e., made from H_2S and 2 KOH , but we could not improve the yield of 2b. Finally, we found that the commercially available K_2S includes substantial S_8 which may serve as a good sulfur-transfer agent. We examined not only the effect of S_8 by adding S_8 to the ordinary Na_2S but also the one-pot reaction from chloral to 2a without the isolation of 3. K_2S or Na_2S was added to the methanol solution of 3 which was previously

obtained from the reaction of chloral with *N*-tosylhydrazine in methanol. (Table 2)

The addition of S_8 to aq. Na_2S solution resulted in a higher yield of 2a, while the pH of the solution should be controlled with aq. $NaOH$ solution because the pH of the reaction mixture drops down to below 10. However, the addition of S_8 to commercially available K_2S had no effect on the yield of 2b. On the other hand, we tried to use many kinds of sulfide compounds without S_8 or with S_8 but potassium or sodium sulfide was better than the others in spite of the presence of S_8 . One of the reasons is that the nucleophilicity of sulfide depends on the cation species of sulfide or polysulfide.

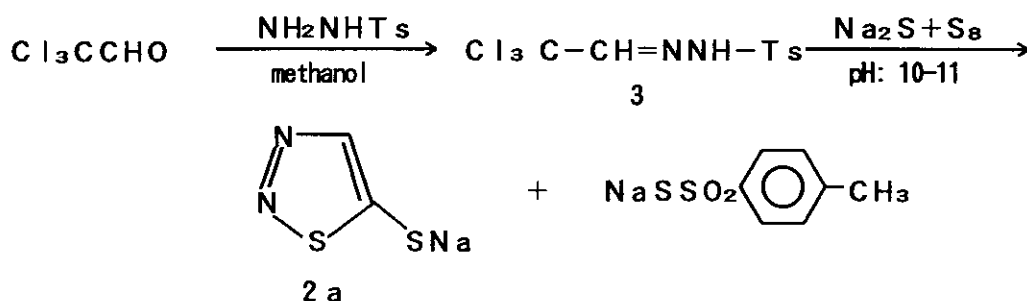


Table 2. One-pot Reaction

Run No.	Reaction conditions (mmol)					Yield (%) of 2 based on $TsNHNH_2$
	$TsNHNH_2$	chloral	S_8	M_2S		
1.	20.0	20.8	—	Na_2S	66.0	45.0
2.	20.0	20.8	10.0	$Na_2S^{1)}$	66.0	69.9
3.	20.0	20.8	16.0	$Na_2S^{1)}$	66.0	66.2
4.	20.0	20.8	30.0	$Na_2S^{1)}$	80.0	69.5
5.	20.0	20.8	—	K_2S	66.0	66.2
6.	20.0	20.8	16.0	K_2S	66.0	65.8

1) The pH of the reaction solution was kept at around 10-11 with aq. $NaOH$.

We conclude that the addition of S_8 plays an effective role in keeping the pH of the reaction solution around 10-11 to avoid the hydrolysis of 3 and also keeping the concentration of polysulfide ions⁹ to avoid the dimerization of the intermediate and/or 2 because the

oxidation of *p*-toluenesulfinate with S_8 results in an increase of polysulfide ions and keeping the excess amount of polysulfide anion hence the yield of 3 is greatly increased.

In summary, we have succeeded in a one-pot procedure for the synthesis of 2 from chloral without the isolation of the intermediate (3).

EXPERIMENTAL

Preparation of 2a from 3 and K_2S

A solution of K_2S (16.56 g, 66 mmol) produced by Katayama Kagaku in water (30 ml) was added to a solution of 3 (6.28 g, 20 mmol) in methanol (30 ml). The reaction mixture was stirred for 1 h at room temperature and then filtered. The filtrate was concentrated to 1/3 under reduced pressure and filtered in order to remove TsSK and KCl. Sodium chloride (6 g, 102 mmol) was added to the filtrate and then the mixture was concentrated under reduced pressure. The precipitate was collected and crystallized from a mixed solvent of methanol/water (1/20) saturated with sodium chloride to afford 2.11 g (60.0 %) of 2a dihydrate. mp 265–267°C(decomp.) (Lit.,² 266–268°C(decomp.)) 1H Nmr (D_2O): 8.2 (s, 1H, C_4-H). Ir (KBr), 3350, 1665, 1640, 1400, 1200, 1120, 1040, 870, 820. Anal. Calcd for $C_2H_5N_2O_2NaS_2$: C, 13.63; H, 2.86; N, 15.90. Found: C, 13.70; H, 2.45; N, 16.90.

One-pot synthesis of 2a dihydrate

In 20 ml of methanol were dissolved 0.99 g (6.0 mmol) of chloral hydrate and 0.93 g (5.0 mmol) of *p*-tosylhydrazine and the mixture was stirred at room temperature for 30 min. Meanwhile, 3.98 g (16.6 mmol) of sodium sulfide nonahydrate and 2.11 g (66.0 mmol) of sulfur were added to 20 ml of water at room temperature and stirring was continued until the mixture became a homogeneous solution. The resulting solution was added to the previously prepared solution of 3 for 1 min and stirring was continued for 2 h while maintaining the pH of the reaction mixture. After completion of the reaction, precipitated inorganic compounds were removed by filtration. The reaction yield of 2a was determined by hplc analysis of the filtrate with *N*-phenylurea as an internal standard on a Finepak SIL C18 column from Jasco Co., (eluent: H_3PO_4 aq./ CH_3CN) to be found 69.5 %. The filtrate was evaporated under reduced pressure. The resulting crude solid was recrystallized from a mixed solvent of methanol/water(1/20) saturated with sodium chloride to afford 0.55 g(62.6 %) of 2a. The compound (2a) dihydrate was

identified by elemental analysis, ^1H -nmr and ir spectrum. 44 mp 265-266 $^{\circ}\text{C}$ (decomp.) (*Lit.*, 22 266-268 $^{\circ}\text{C}$ (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. The heat of decomposition of 3 by differential scanning calorimeter(DSC) has been known as a useful method for examination of hazardous properties.⁸ DSC shows the decomposition temperature and calorific value per unit(mJ/mg). We compared these values of 3 with those of 1 and other explosive compounds. 1: 180.0 $^{\circ}\text{C}$ 1,674 mJ/mg.⁸ 2: 196.0 $^{\circ}\text{C}$ 778 mJ/mg. 3: 105.9 $^{\circ}\text{C}$ 1,577 mJ/mg. Perbenzoic Acid: 108.1 $^{\circ}\text{C}$ 1,428 mJ/mg. 2,4-Dinitrotoluene: 319.8 $^{\circ}\text{C}$ 4,246 mJ/mg. Decomposition temperature of 3 is lower than that of 1 though the

calorific value is almost the same. Therefore, 3 should be as explosive as 1, perbenzoic acid and 2,4-dinitrotoluene.

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