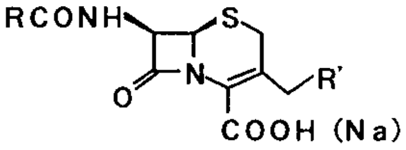
# CONVENIENT ONE-POT SYNTHESIS OF SODIUM SALT OF 5-MERCAPTO-1, 2, 3-THIADIAZOLE

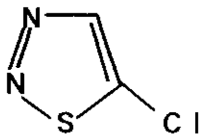
Katsumasa Harada,* Teruhiko Inoue, and Hiroshi Yoshida

*Ube Reseach Laboratory, UBE Industries, Ltd., 1978-5 Kogushi, Ube City, Yamaguchi 755, Japan*

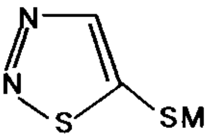
**Abstract-** Trichloroacetoaldehyde-*p*-toluenesulfonylhydrazone (3) derived from chloral hydrate reacted *in situ* with polysulfide salt in the range of pH 10~11 to afford the corresponding 5-mercapto-1, 2, 3-thiadiazole salt(2) in high yield (69.5 %).

One of the more important reactions in the preparation of cephalospolin antibiotics is the displacement of the allylic acetoxy group at $C_3$ 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 $C_7$.[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.





1



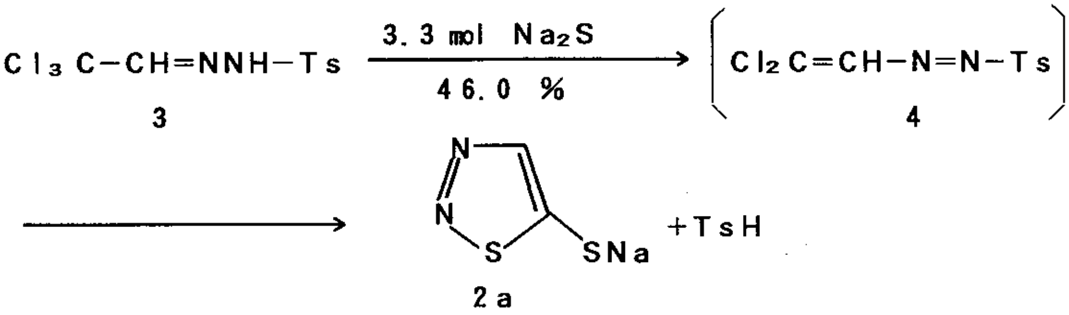
2

2a, M=Na
2b, M=K

Although these derivatives[1] 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 % yield[4] as shown below. However, the low yield made it difficult to safely isolate 2a in a pure form and, therefore, our method could be inappliable 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 compound[5] (4) which has a typical explosive structure according to Bretherick's standard.[6] Indeed, 3 has a low decomposition point (85-86℃).

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 constract 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 % ) added[1)]

| Run No. | $M_2S$ / 3<br>$M_2S$ | mole ratio | Reaction method | pH[2)]<br>a | b | c | Yield(%) of 2 based on 3 |
|---|---|---|---|---|---|---|---|
| 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.

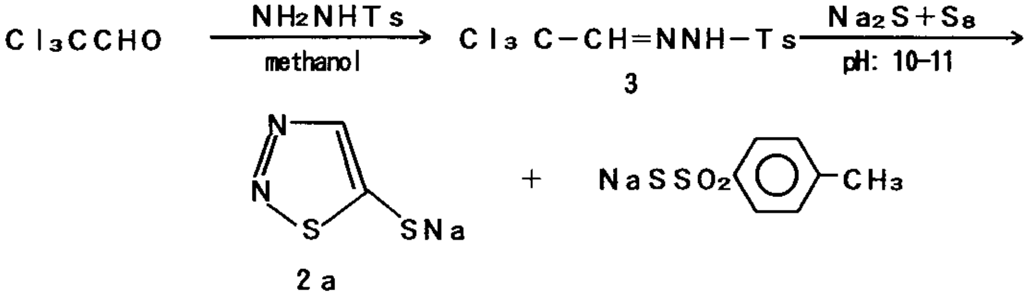


Table 2. One-pot Reaction

| 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 ions[9] 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℃(decomp.) ( *Lit.*,[2] 266-268℃(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, $^1$H-nmr and ir spectrum.[4a] mp 265-266 ℃(decomp.) ( *Lit.*,[2] 266-268℃(decomp.))

## ACKNOWLEDGMENTS

We are grateful to Mr. Asumaru Nakamura, Director of Ube Research Laboratory, UBE Industries, Ltd., for his help in this work and also Prof. Naomichi Furukawa at Tsukuba University for his advice.

## REFERENCES AND NOTE

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

1. *a)* G. C. Lewis and P. H. Nelson, *J. Med. Chem.*, 1979, **22**, 1214. *b)* C. B. J. Ziegler, W. V. Curran, N. A. Kuck, S. M. Harris, and Y. I. Lin, *J. Heterocycl. Chem.*, 1989, **26**, 1141. *c)* S. Shibahara, *29th Intersci, Antimicro. Agents Chemother. Abstr.*, 1989, 358. *d)* K. Iwamatsu, K. Sakagami, K. Atsumi, T. Yoshida, S. Shibahara, T. Tusuoka, and S. Kondo, *EP* 315997 A2 890517 (*Chem. Abstr.*, 1989, 111, 214321). *e)* C. B. Ziegler, W. V. Curran, N. A. Kuck, and S. M. Harris, *J. Heterocycl. Chem.*, 1989, **26**, 1141. *f)* K. Kawabata, T. Terasawa, A. Ohki, F. Shirai, and H. Yamamoto, *WO* 9507283 A1 950316 (*Chem. Abstr.*, 1995, **122**, 290587. *g)* K. Obi, A. Kojima, H. Fukuda, and K. Hirai, *Bioorg. Med. Chem. Lett.*, 1995, **5**, 2777.

2. P. Demaree, M. C. Doria, and J. M. Muchowski, *Can. J. Chem.*, 1977, 55, 243.

3. S. Morisaki, *Thermchimica Acta*, 1981, 47, 85.

4. At the same time H. Kondo also developed the same procedure for the synthesis of 2.
*a)* K. Sakai, D. Tsunemoto, T. Kobori, and H. Kondo, *EP* 103, 840(*Chem. Abstr.*, 1984, **101**, 72730q).
*b)* K. Harada, F. Iwata, and T. Nakamura, *JP* 59-95282(*Chem. Abstr.*, 1984, **101**, 171263w).

5. K. Bott, *Chem. Ber.*, 1975, **108**, 402.

6. L. Bretherick: *Handbook of Reactive Chemical Hazards*, Second Edition, Butterworth, 1979

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℃ 1,674 mJ/mg.[8] 2: 196.0 ℃ 778 mJ/mg. 3: 105.9℃ 1,577 mJ/mg. Perbenzoic Acid: 108.1℃ 1,428 mJ/mg. 2,4-Dinitrotoluene: 319.8 ℃ 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.

8. S. Morisaki, K. Muranaga, S. Tamura, and T. Yoshida, *Kogyo Kayaku*, 1984, **45**, 73.

9. *a)* G. T. P. Levenson, *J. Appl. Chem.*, (London) 1964, **4**, 13. *b)* R. E. Davis, *J. Am. Chem. Soc.*, 1958, **80**, 3565.

Received, 25th April, 1996