

## A CONVENIENT SYNTHESIS OF 1,2,3-TRIAZOLES USING DICHLOROACETALDEHYDE

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**Abstract-** 1-Substituted 1,2,3-triazoles were prepared by the reaction of dichloroacetaldehyde tosyl- or mesylhydrazone with ammonia, amino derivatives, and hydrazine in good yield.

Although so many kinds of cephalosporin bearing 1,2,3-triazole or its heterocyclic analogs as a partial structure have been still under active investigation for the search of more active and more safe compounds,<sup>1</sup> the synthetic method of 1,2,3-triazole has been less studied since 1,2,3-triazole and also its precursors such as diazo and azido derivatives are not only thermally unstable but also explosive as reported before.<sup>2,3</sup> According to the literatures reported, the synthesis of 1,2,3-triazole has involved the preparation of substituted 1,2,3-triazole and following desulfurization or decarboxylation of 5- or 4,5-substituted 1,2,3-triazoles or hydrogenolysis of 1-benzyl-1,2,3-triazole.<sup>4-11</sup> However, the explosive property makes every handling troublesome, especially for a large scale production of 1,2,3-triazole. We have already reported the synthetic method of 5-mercapto-1,2,3-thiadiazole by one-pot reaction of trichloroacetaldehyde tosylhydrazone (**1a**) with polysulfide ion.<sup>3</sup> This reaction system is both convenient and secure for a large scale production because trichloroacetaldehyde tosylhydrazone acts as an excellent precursor of diazo derivatives by treatment with polysulfide ion and spontaneously cyclizes to 5-mercapto-1,2,3-thiadiazole under mild conditions as shown in Figure 1.

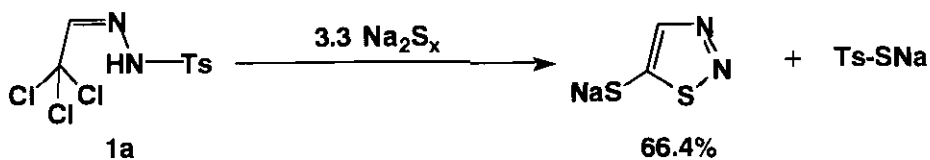


Figure 1.

As for the preparation of 1,2,3-triazoles reported in the literatures, the reactions of  $\alpha$ -polyhalo ketone tosylhydrazones with primary amines have been known as shown in Figure 2.<sup>12</sup>

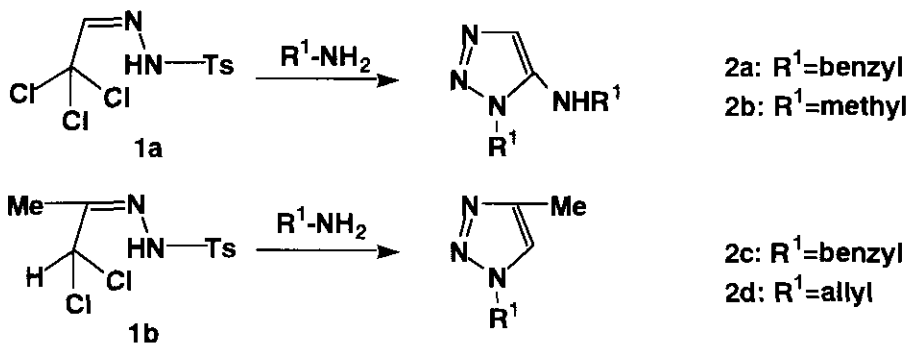
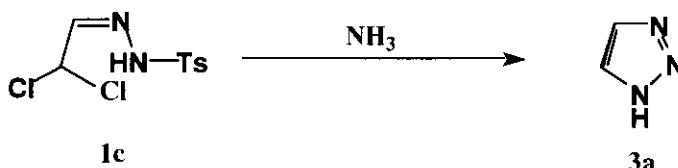


Figure 2.

1-Benzyl-5-benzylamino-1,2,3-triazole (**2a**) and 1-methyl-5-methylamino-1,2,3-triazole (**2b**) could be prepared by the reaction of trichloroacetaldehyde tosylhydrazone (**1a**) with excess benzylamine and methylamine in methanol in 30 % and 25 % yields, respectively, but treatment of the same substrate with aqueous ammonia could not provide 5-amino-1,2,3-triazole but no identified materials. 1-Benzyl-4-methyl-1,2,3-triazole (**2c**) and 1-allyl-4-methyl-1,2,3-triazole (**2d**) could be prepared by the reaction of  $\alpha, \alpha$ -dichloroacetone tosylhydrazone (**1b**) with benzylamine or allylamine. These results did not show that this reaction system was usable for the synthesis of 1-unsubstituted 1,2,3-triazole by the reaction with ammonia. However, this reaction system is thought to be one of the best method for the synthesis of 1,2,3-triazole and 1,2,3-thiadiazole derivatives for a large scale production because it is convenient and secure, compared with the other methods. On the other hand, 1,2,3-triazole and 1-substituted 1,2,3-triazoles among 1,2,3-triazole derivatives are of great value as various purposes such as modifiers of cephalosporin antibiotics or precursors of insecticides for industry. Therefore, we carefully tried again to study this reaction system for synthesis of 1,2,3-triazoles. Dichloroacetaldehyde tosylhydrazone (**1c**) is a known compound and was prepared as described in the literature.<sup>13</sup> First of all, we studied the preparation method of 1,2,3-triazole by treatment of **1c** with aqueous ammonia. The reaction conditions were as follows; into an excess aqueous ammonia solution was added **1c** and the solution was stirring for 4 h at room temperature and excess ammonia was removed under reduced pressure and the residue was extracted with a large amount of ethyl acetate. After drying, evaporation of the solvent gave a residual oil. Although the isolation and identification of 1,2,3-triazole **3a** were very difficult, we succeeded in isolation of **3a** (23.3 % yield) from the residual oil by chromatography on silica gel. This result really encouraged us to study the reaction even though the yield of **3a** is low and also isolation of **3a** from

reaction mixture is difficult. We changed the solvent in order to make isolation of **3a** easy. The cyclization reaction was carried out as follows; into a solution of excess amount of ammonia in methanol the hydrazone was added. The solution was filtrated to remove ammonium chloride and the filtrate was concentrated to be chromatographed on silica gel to isolate 1,2,3-triazole. The reaction conditions and results are summarized in Table 1.

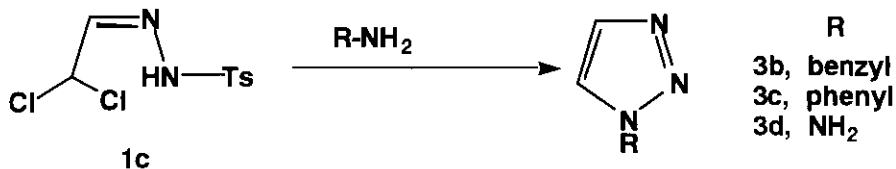
**Table 1. Preparation of 1,2,3-triazole.**



Run No.	<b>1c</b> (mM)	NH <sub>3</sub> (mM)	molar ratio of NH <sub>3</sub> / <b>1c</b>	MeOH (mL)	Temp. (°C)	Time (h)	Yield of <b>3a</b> (%)
1	27.1	224	9	110	18-27	2	45.6
2	17.6	300	17	100	-4	2	52.8
3	15.7	522	33	100	22-25	9	74.7
4	16	573	35	100	15-18	2	42.7

We got the good results by this reaction conditions but direct introduction of ammonia gas to a methanol solution of the hydrazone did not give successful result and also diisopropyl ether instead of methanol also did not give **3a** in high yield. Additional triethylamine to alcoholic ammonia solution was also not effective to increase the yield of **3a**. As an application of this reaction, we tried to prepare 1-substituted 1,2,3-triazole by the same manner. The reaction conditions and results are summarized in Table 2.

**Table 2. Preparation of 1-substituted 1,2,3-triazole.**



Run No.	<b>1c</b> (mM)	RNH <sub>2</sub> R	MeOH (mM)	MeOH (mL)	Temp. (°C)	Time (h)	Product	Yield of <b>3</b> (%)
1	3.6	benzyl	9	12	0	1	<b>3b</b>	70
2	3.6	phenyl	17	12	0	1	<b>3c</b>	83
3	3.6	NH <sub>2</sub>	33	12	10	4	<b>3d</b>	75

As a result, there was no big difference in the yield of **3b-3d** from the yield of **3a**, so that this reaction must be useful for the synthesis of not only 1,2,3-triazole but also 1-substituted 1,2,3-triazole including 1-amino derivatives which are now under investigation for a new inflator using air bag instead of explosive and strongly poisonous sodium azide.

We have already reported a synthetic method of 5-amino-1,2,3-thiadiazole by the reaction of diazoacetonitrile and hydrogen sulfide under basic conditions.<sup>2</sup>

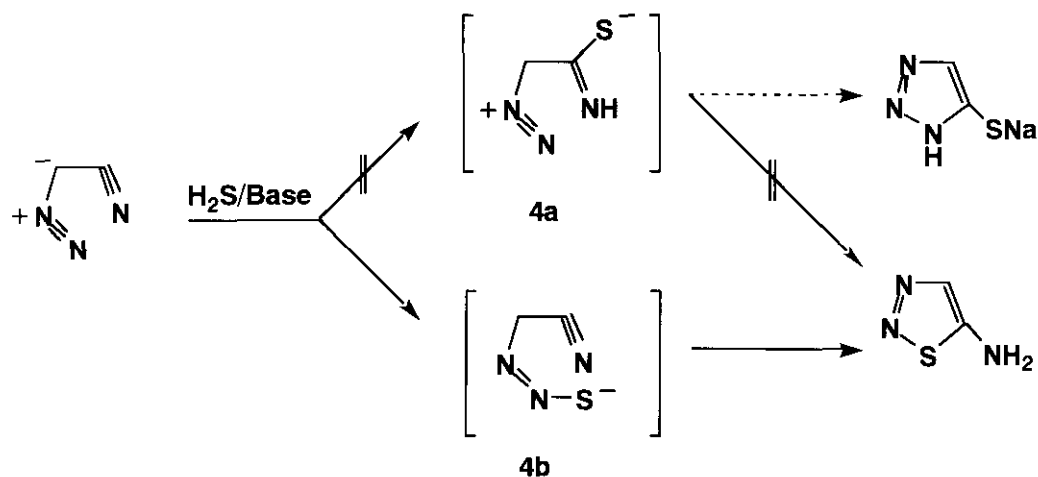


Figure 3.

From the mechanistic view point, we speculated that the formation of 5-amino-1,2,3-thiadiazole might proceed involving not thioamide(**4a**) but mercapto-azo-acetonitrile(**4b**). On the other hand, we have already reported a synthetic method of sodium salt of 5-mercapto-1,2,3-thiadiazole by the reaction of trichloroacetaldehyde *p*-tosylhydrazone with sodium polysulfide instead of using sodium sulfide.<sup>3</sup> We speculated this reaction as follow ; the addition of sodium polysulfide initiates a removal of hydrogen chloride from the substrate to give tosyl-azo-vinylidene chloride(**1a-1**) and then the second sulfide anion should work for substitution of not the chlorine atom but the toluenesulfate ion generated and from **1a-2** to the final product, cyclization may occurs initially to give stable 5-chloro-1,2,3-thiadiazole(**1a-3**). The pH in the reaction system strongly affects the yield. We found the pH range 10-11 is suitable for this reaction.

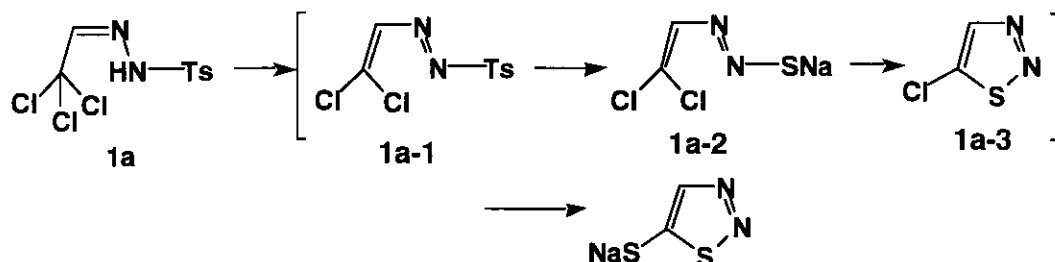


Figure 4

Based on these considerations, we postulated the reaction of dichloroacetaldehyde tosylhydrazone (**1c**) with ammonia would proceed as follows; ammonia is a base strong enough to abstract the proton on the nitrogen to give intermediate (**1c-1**), and then gives amino-azo-vinylchloride (**1c-2**) by substitution and following cyclization of **1c-2** gives 1,2,3-triazole as shown in Figure 5.

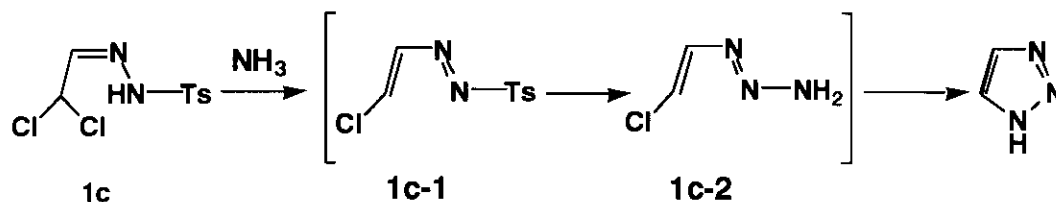


Figure 5.

However, under the strongly basic conditions hydrolysis of dichloroacetaldehyde tosylhydrazone should proceed preferentially prior to the abstraction of the proton on the nitrogen atom because we found tosylhydrazine as a by-product. Furthermore, the strongly basic conditions increase anionic in reaction system, which should also decrease the polarization of the O-S bond to afford the N-S bond tight and therefore the substitution of ammonia for the tosyl group makes more difficult.

1,2,3-Triazole can be purified by distillation but the separation of it from a large amount of by-products derived from tosyl group is difficult because toluenesulfonic acid, and also 1,2,3-triazole are freely soluble in water and hence the selective extraction of 1,2,3-triazole from the reaction mixture prior to isolation and purification of 1,2,3-triazole by distillation is difficult. In order to decrease the amount of the by-product derived from the tosyl group, we tried to use mesylhydrazine instead of tosylhydrazine. Dichloroacetaldehyde mesylhydrazone has been unknown but was easily made by the reaction of the aldehyde according to the described method in a literature.<sup>13</sup> The reaction conditions and results are summarized in Table 3.

Table 3. Preparation of 1-substituted 1,2,3-triazole by using mesylhydrazine.

**1c'**

**Ms: Methanesulfonyl**

**R**

**3a** H

**3b** benzyl

**3c** phenyl

**3d** NH<sub>2</sub>

Run No.	<b>1c'</b> (mM)	RNH <sub>2</sub> R	MeOH (mM)	MeOH (mL)	Temp. (°C)	Time (h)	Product	Yield of <b>3</b> (%)
1	4.88	benzyl	15.94	12	0	4	<b>3b</b>	60
2	4.88	phenyl	15.94	12	0	3	<b>3c</b>	85
3	4.88	NH <sub>2</sub>	15.94	12	25	3	<b>3d</b>	64

As a result, 1,2,3-triazole derivatives could be obtained in almost the same yields with those by the reaction with **1c**.

## EXPERIMENTAL

### Synthesis of 2,2-dichloroacetaldehyde tosylhydrazone(**1c**).

This compound(**1c**) was prepared according to the method described in the literature<sup>13</sup> from dichloroacetaldehyde and tosylhydrazine except the reaction time and after standing overnight in a refrigerator and then the reaction mixture was filtrated. The isolated **1c** was dried under reduced pressure at 40 °C.

Yield of **1c** was 75%. mp 122.5-123 °C (*lit.*,<sup>13</sup> mp 123 °C)

### Synthesis of 2,2-dichloroacetaldehyde mesylhydrazone(**1c'**)

To a solution of 4.87 g (44.22 mmol) of mesylhydrazine in 50 mL of propionic acid was added 5.00 g (44.27 mmol) of dichloroacetaldehyde below 0 °C. The stirring was kept for 1 h at the same temperature. The resulting crystals were isolated by filtration, washed with toluene and dried under reduced pressure. 9.07 g of the compound (**1c'**) was obtained in 71.8 % yield. mp 132-135 °C. <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) δ ppm= 3.14(3H, s), 6.21(1H, d, J=7.33 Hz), 7.26(1H, d, J=7.33 Hz), 7.96(1H, s).

A typical procedure for the synthesis of 1,2,3-triazole (**3a**) by the reaction with **1c**

To a solution of ammonia (8.9 g, 523 mmol) in methanol (40 mL) under ice cooling, 4.4 g (15.7 mmol) of the compound (**1c**) in methanol (60 mL) was added slowly and then the reaction mixture was kept stirring at 22 °C for 9 h, the reaction mixture was filtrated to remove ammonium chloride and the filtrate was concentrated to be chromatographed on silica gel with 50% ethyl acetate-hexane to give 0.81 g (11.7 mmol) of 1,2,3-triazole (**3a**) in 74.8 % yield as colorless oil ; bp 208-210 °C (*lit.*,<sup>8</sup> bp 208-210 °C), <sup>1</sup>H-NMR(400 MHz, CDCl<sub>3</sub>) δ ppm= 7.83(2H, s), 15.33(1H, s).

**A typical procedure for the synthesis of 1-benzyl-1,2,3-triazole(3b) by the reaction with 1c**

To a solution of benzylamine (1.92 g, 18 mmol) and triethylamine (3.33 g, 33 mmol) in 20 mL of methanol under ice-cooling, 4.2 g (15 mmol) of the compound (**1c**) in 30 mL of methanol was added slowly and then the reaction mixture was kept stirring at 40 °C for 4 h, the reaction mixture was filtrated to removed the salt and the filtrate was concentrated and chromatographed with 50% ethyl acetate-hexane to give 1.26 g of **3b** in 52.8 % yield, as colorless crystals; mp 63-64 °C (*lit.*,<sup>8</sup> mp 61 °C), <sup>1</sup>H-NMR(400 MHz, CDCl<sub>3</sub>) δ ppm=5.54(2H, s), 7.24-7.38(5H, m), 7.50(1H, d, J=0.98 Hz), 7.68(1H, d, J=0.98 Hz).

**A typical procedure for the synthesis of 1-phenyl-1,2,3-triazole(3c) by the reaction with 1c**

To a solution of aniline (1.67 g, 18 mmol) and triethylamine (3.33 g, 33 mmol) in 20 mL of methanol under ice cooling, 4.2 g (15 mmol) of the compound (**1c**) in 30 mL of methanol was added slowly and then the reaction mixture was kept stirring at 40 °C for 4 h, the reaction mixture was filtrated to remove the salt and the filtrate was concentrated and chromatographed with 50% ethyl acetate-hexane to give 1.61 g of **3c** in 74 % yield as colorless crystals; mp 60-61 °C (*lit.*,<sup>14</sup> mp 55-56 °C), <sup>1</sup>H-NMR(400 MHz, CDCl<sub>3</sub>) δ ppm= 7.42-7.46(1H, m), 7.50-7.54(2H, m), 7.72-7.75(2H, m), 7.84(1H, d, J=0.98 Hz), 8.03(1H, d, J=0.98 Hz).

**A typical procedure for the synthesis of 1-amino-1,2,3-triazole(3d) by the reaction with 1c**

To a solution of hydrazine hydrate (2.45 g, 18 mmol) in 20 mL of methanol under ice-cooling, 4.2 g (15 mmol) of the compound (**1c**) in 30 mL of methanol was added as powder portion over a period of 5 min and then the reaction mixture was kept stirring at 40 °C for 4 h, the reaction mixture was filtrated to remove the salt and the filtrate was concentrated and chromatographed with 50% ethyl acetate-hexane to

give 0.95 g of **3d** in 75 % yield as colorless crystals; mp 48-49°C (*lit.*,<sup>15</sup> mp 49-51°C), <sup>1</sup>H-NMR(400 MHz, CDCl<sub>3</sub>) δ ppm= 5.73(2H, s), 7.59(1H, s), 7.62(1H, s).

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