# A SIMPLE AND ECONOMICAL METHOD FOR THE SYNTHESIS OF INTERMEDIATES OF CEFAZOLIN

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**Abstract :** A simple convenient method of synthesis of 2-mercapto-5-methyl-1,3,4-thiadiazole (MMTD) is described. Hydrazine hydrate, ethyl acetate and carbon disulphide were used as the starting materials and transformed into the target molecule in three steps. MMTD was later converted into 7-Amino-3-{[(5-methyl-1,3,4-thiadiazole-2-yl)thio]methyl}-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, a main drug intermediate of cefazolin.

## Introduction

Few drug manufacturing companies in worldwide have the ability to produce all the range of basic chemicals needed for their key drug reqirements because of availability of expensive chemicals as well as tideous method of synthesis of various drug intermediates. The best that many others can expect to do in the next decade is the ability to select and produce its own basic chemicals requirements available from local inexpensive raw materials. These measureses will results in a considerable increase in the value added and reduce dependence on imports. A major goal has yet to be achieved but has been our objective is to find out some convenient chemical conversion with drug intermediates required for the therapeutically useful antibiotic cefazolin (1).

The literature does not appear to have a record of simplest and convenient method of synthesis of 2-mercapto-5-methyl-1,3,4-thiadiazole (MMTD), however many alternative methods were known (2,3). We here by report the simplest and cost effective method of synthesis of one of the major intermediate known as 2-mercapto-5-methyl-1,3,4-thiadiazole (MMTD) followed by other important drug intermediate of cefazolin known as 7-amino-3-{[(5-methyl-1,3,4-thiadiazol-2yl)thio]methyl}-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (4).

## Result & Discussion

A possible synthetic route of MMTD synthesis would involved the synthesis of acetic hydrazide from a starting material already containing two nitrogen atoms. We found hydrazine hydrate as the most suitable source for nitrogen atoms and carbon disulphide as the other similar source for two sulphur atoms along with one carbon atom as present in MMTD. Thus, the ring closure of a salt of

dithiocarbazoic acid leads to the formation of required MMTD. The ethyl acetate was converted into acetic hydrazide by condensation with hydrazine hydrate which on further reaction with carbon disulphide gave the potassium salt of acetyl dithiocabazate and finally the cyclization of this salt gave the required final product MMTD in good yield. Various other attempts to the ring closure of potassium salt of acetyl dithiocarbazate using either concentrated hydrochloric acid, or thionyl chloride or iodine-potassium iodide solution have been failed to give the desired product MMTD. The cyclization was either too poor or unsuccessful in the hot dilute sulphric acid but gave excellent yield with cold concentrated sulphruic acid (Scheme-I).

7-Amono-3-{[(5-methyl-1,3,4-thiadiazol-2-yl)thio]methyl}-8-oxo-5-thia-1azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid was synthesised by simple conversion of 7-aminocephalosporanic acid (7-ACA) into its soluble aqueous salts followed by condensation with soluble aqueous MMTD as shown in Scheme II.

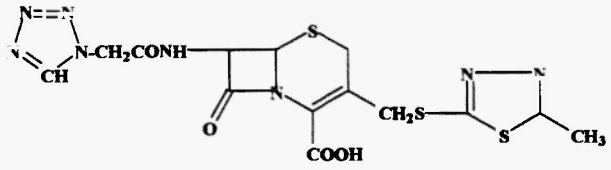
**Experimental Section**

Melting and boiling points are uncorrected. UV spectra were recorded on Beckmann DU-64 spectrometer. HPLC were recorded on Shimadzu LC-4A liquid chromatograph using with C-18 coloum. Mass spectra were recorded on JEOL JMS-D 300 spectrometer. A Perkin-Elemer 783 IR spectrometer was used for recording IR spectra in KBr pellets and a Hitachi 60 MHz R-600 NMR spectrometer was used for measuring $^1$H-NMR spectra (solvent $CD_3OD$, $D_2O$; internal standard tetramethyl silane).

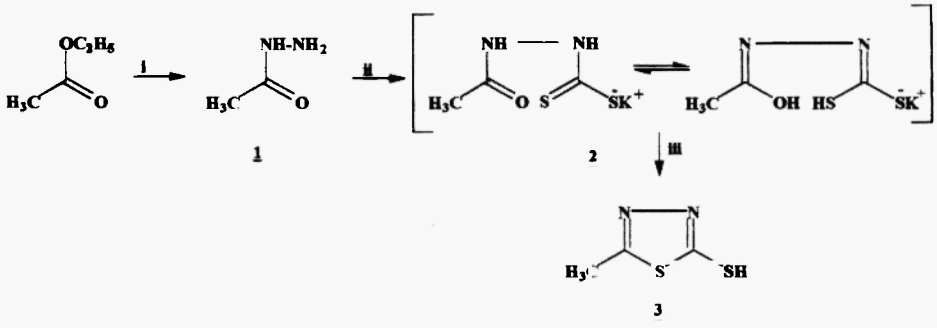
**Acetic hydrazide (1).** A solution of hydrazine hydrate (26g, 99%, 0.51mol) containing ethanol (10 ml) and ethyl acetate (65 ml) was stirred and warmed slightly in order to make a clear solution. After 10 minutes, the mixture was refluxed with stirring for 2h at 80-90° C. The excess solvents including ethanol,ethyl acetate, water and hydrazine hydrate were removed completely under vacuum distillation. The remaining solution was allowed to cool to 0-5° C in which solid acetic hydrazide separated out which could be kept as such for the second step of the reaction. Yield ( 36.82 g), mp 65- 68° C.

**Potassium acetyl dithiocarbazide (2).** A solution of potassium hydroxide (34g) in ethanol (60 ml) was added into acetic hydrazide (36.82g, 0.497 mol) and the solution was kept below 0° C in which carbon disulphide (45g, 0.592 mol) was added dropwise under stirring. The solution was kept at 0-5° C for 2-3 hours in order to allow the complete separation of potassium acetyl dithiocarbazide. The yellow solid crystalline salt was filtered at pump, washed with acetone (3x40 ml), dried and kept as such for the next step of the reaction without further purication. Yield. 65.04 g.

**2-Mercapto-5-methyl-1,3,4-thiadiazole (MMTD) (3).** Potassium acetyl dithiocarbazide (65.04g, 0.345 mol) was added in portions to a well stirred cold concentrated sulphuric acid (180 ml, sp gr. 1.84)

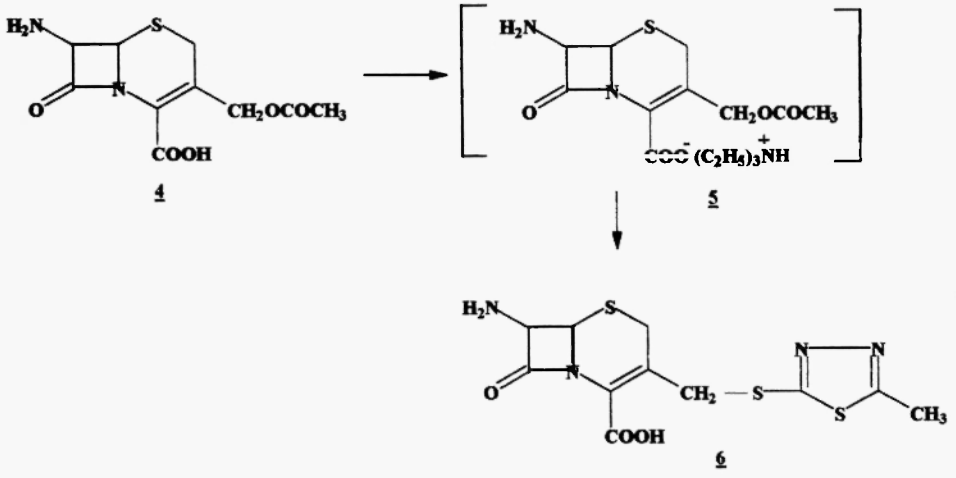


**Cefazolin**



i = $H_2N\ NH_2.H_2O$; ii = $CS_2$, KOH; iii = $H_2SO_4$

**Scheme I**



**Scheme II**

and the mixture was vigorously stirred for 90 minutes at 10° C. The crushed ice or cold water at 0-5° C was added slowly by which the crude MMTD separated out from the solution. The crude MMTD was filtered at the pump, washed with cold water and partially dried at room temperature.

**Purification of crude MMTD.** The crude MMTD as obtained above was dissolved in sodium hydroxide (11.65g) solution containing active carbon (0.4g) at 10° C. After 15 min the solution was filtered at the pump and pure MMTD was allowed to separate out at pH 2.0 with hydrochloric acid, filtered at pump, washed with water and dried. Yield 37.72 g , mp. 183-184° C, assay >98 %, water content 0.68%, UV : $\lambda_{max}$ 308 nm in methanol , 330 nm in acetone, transmittance: 92.1% in 2% w/v in methanol at 400nm, TLC : Rf. 0.46 (methanol : chloroform :: 1 : 9, v/v). HPLC: A single peak on a Lichrosphere-RP18 column (E. Merck, Germany). Mobile phase : 85:15 (v/v) acetonitrile : buffer 3.6 (U.S.P.); Flow rate : 0.5 ml / min; Abs : 310 nm. Mass spectrum: m/z 132($M^+$). IR(KBr) ν ($cm^{-1}$) : 3051, 1552, 1450, 1269, 1198, 741, 622. $^1$H NMR, $CD_3OD$ ($C_3H_3N_2S_2Na$) δ: 2.54 (s, 3H, $-CH_3$).

**7-Amino-3-{[(5-methyl-1,3.4-thiadiazol-2yl)thio]methyl}-8-oxo-5-thia-1-azabicyclo[4.2.0] oct-2-ene-2-carboxylic acid (6)**

7-Aminocephalosporanic acid (**4**) (7-ACA) (30g, 0.11 mol), sodium sulphite (4g) was dissolved in water (30ml) containing triethylamine (25g, 0.247 mol). This solution was stirred at 67-70° C with 2-mercapto-5-methyl-1,3,4-thiadiazole (16g, 0.121 mol). The reaction mixture was cooled to 40° C after 90 min. Sodium dithionite (2g) was added into the solution and pH of the solution was adjusted to 6.0 with 20% sulphuric acid. After 30 min, the pH of the solution was finally adjusted to 4.0-4.2. The precipitated product was filtered at pump after 60 minutes at 30° C, washed with water (3x100 ml) followed by acetone (2x50 ml) and dried. Yield 27.5g, mp. 202-205° C (dec.), assay >96%, transmittance 80% in 2% w/v in sodium bicarbonate solution. A single peak was obtained on HPLC using C-18 column (E. Merck, Germany). Mobile phase : 85:15 (v/v) acetonitrile : buffer 3.6 (U.S.P.); Flow rate : 0.5 ml / min; Abs : 310 nm. Mass spectrum: m/z 344($M^+$). IR(KBr) ν ($cm^{-1}$) : 3540, 3159, 3001, 2616, 2052, 1803, 1619, 1547, 1411, 1344, 1110, 1055, 797. $^1$H NMR, $CD_3OD$ + $D_2O$ ($C_{11}H_{11}N_4O_3S_3Na$) δ: 2.75 (s, 3H), 3.60 (m, 2H), 4.05 (m, 2H), 5.05 (d, 1H), 5.40 (d, 1H).

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