Nature of Invention: Chemical molecule and synthesis route

Applicant: Chimique Inc

Inventors: 1. Lokesh Yadav

2. Sujal Jain

3. Anisurya Jana

Chemical Formula: $C_7H_8ClN_3O_4S_2$

Chemical Name: 6-Chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide (Hydrochlorothiazide)

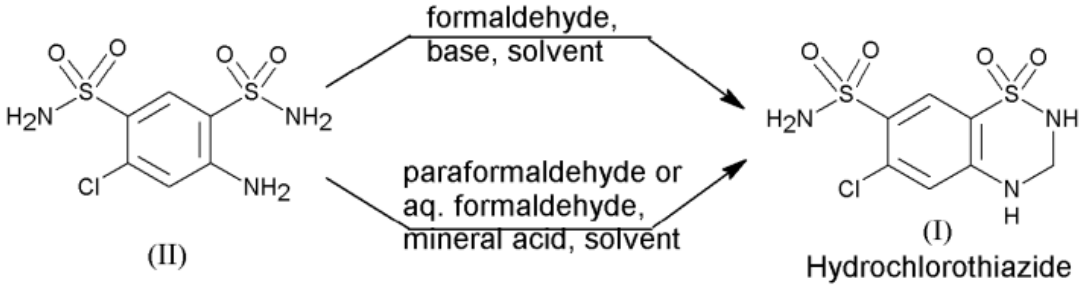
Chemical synthesis routes:

Raw Materials –

1. 5-chloro-2,4-disulfamyl-aniline (II)
2. Formaldehyde
3. Alkali metal hydroxide
4. Solvent (from THF, dioxane, di-ethylene glycol, methanol and water or mixture)
5. liq. Ammonia
6. sodium hydroxide
7. Activated carbon
8. Diethylene glycol
9. Diethyl ether

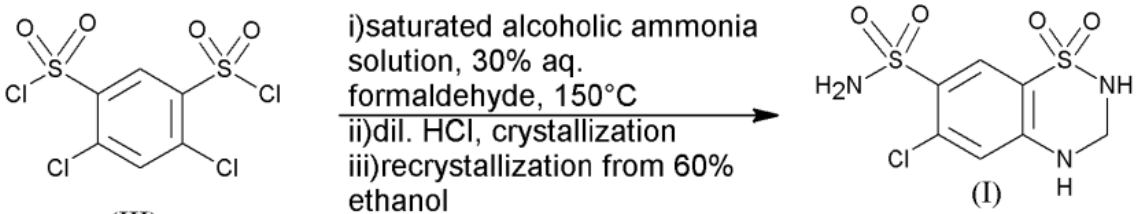
Reaction steps –

1. The process involves reacting 5-chloro-2,4-disulfamyl-aniline (II) or its salt with aldehyde such as formaldehyde in the absence or presence of a base and a solvent. The base is alkali metal hydroxide and the solvent is selected from THF, dioxane, di-ethylene glycol, methanol and water or mixtures thereof.



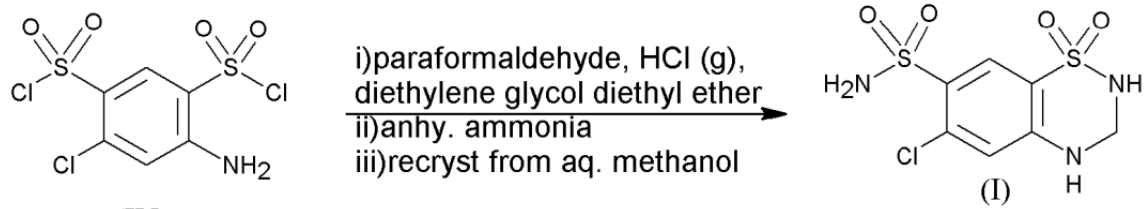
2. In other method, 5-chloro-2,4-disulfamyl-aniline (II) is reacted with paraformaldehyde in the presence of a mineral acid and a solvent. The mineral acid is selected from hydrochloric acid, hydrobromic acid and sulfuric acid. Hydrochlorothiazide obtained is recrystallized from water. However, the yield obtained by this process is only 46.3% which makes the process less attractive at an industrial scale. Moreover repeating this experiment, it is found that it results in the formation of dimer impurity along with Hydrochlorothiazide which is difficult to remove by con ventional purification methods.

3. The process involves reacting 4,6-dichloro-benzene-1,3-disulfonic acid dichloride (III) with 30% aq. formaldehyde in the presence of saturated alcoholic ammonia solution at 150°C. The solvent is distilled off and residue obtained is acidified with dil. HCL The oily reaction product crystallizes on standing in a refrigerator. The product is further charcoalized in 60% ethanol and then recrystallized from the same solvent.



(III) (I) Hydrochlorothiazide

4. The process involves reacting 5-chloro-aniline 2,4-disulfonyl chloride (IV) with paraformaldehyde in the presence of HCl gas in diethylene glycol diethyl ether to give an intermediate which is further reacted with an anhydrous ammonia to give solid product which is further purified by recrystallization from aqueous methanol to give pure Hydrochlorothiazide.



(IV) (I) Hydrochlorothiazide

(a) Preparation of Hydrochlorothiazide

5-chloro-2,4-disulfamyl aniline (25 g) was heated with paraformaldehyde (2.98 g) in water at reflux temperature for 1 to 2 hours. The reaction mixture was cooled to 15°C to 30°C. The precipitated solid was filtered and washed with water (50mlx2) and suck dried. The product

hydrochlorothiazide is obtained as white wet cake. The solid is dried in hot air oven to give Hydrochlorothiazide (24.0g)

Yield: 92%

Dimer content: 0.47%
Purity (by HPLC): ~99.0%

(b) Purification of Hydrochlorothiazide

Hydrochlorothiazide wet cake (33.0 g) obtained in step (a) was suspended in a mixture of liq. Ammonia: water (1:1) (125 ml). 50% sodium hydroxide solution was added to the reaction mixture to get clear solution. Activated carbon (0.5 g) was added and stirred for 15 to 20 min at 20°C to 25°C. The reaction mixture was filtered through hyflobed. The pH of filtrate was adjusted to about 4 to about 10 by adding 5N HCl (140 ml). Resulting solid was filtered, washed with water (50 ml) and suck dried. The solid was dried in hot-air oven at about 60°C to about 65°C for 12 to 14 hours to give pure Hydrochlorothiazide as white crystalline (20.0g).

Yield: 80.0%

Purity (by HPLC): 99.9%

Dimer content: Not detected

Trimer content: Not detected

X-ray diffraction pattern: 12.8, 16.5, 18.6, 19.0, 20.8, 21.3, 24.5, 27.8, 28.7, 33.3,

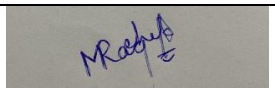
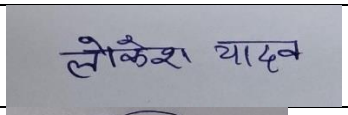
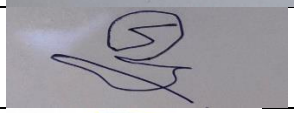
References:

1.Patent (WO 2009/150497 Al)

2. Patent (WO 2023/161490 A1)

List the contributions of each author:

- Author 1 and 4 carried out the literature search.
- Authors 1, 2 and 3 found the reaction steps, product yield, necessary separation steps to achieve desired product purity.

Name	Roll No	Signature
Mehek Agarwal	220646	
Lokesh Yadav	220594	
Sujal Jain	221100	
Anisurya Jana	220152	
Ram Aggarwal	220864