



Research Article

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## Chlorosulfonation of Acetanilide to Obtain an Intermediate for the Preparation of a Sulfa Drug

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### ABSTRACT

Sulphonamides were the first effective chemotherapeutic agents employed systematically for the prevention and cure of bacterial infections in humans. They are called as wonder drugs of their times. Though their usage has been limited they are still being used for burns, bacterial infections in stomach. In the present work the yield of sulfathiazole was increased by using new modified method based on the available literature from which high yields with reduced time periods were successfully achieved. Sulfathiazole is prepared by Chlorosulfonation of Acetanilide to obtain an intermediate which is reacted with 2-aminothiazole. The samples of intermediate and 2-aminothiazole with ratios (3:1, 1:1, and 1:3) and with different acid acceptors named Pyridine, Sodium bicarbonate, Di-methyl aniline and Ammonium hydroxide are studied. The analysis was done by using IR spectroscopy in FT – IR which is found to be the best method for identification of samples.

**Keywords:** Acetanilide; Chlorsulfonation; FT-IR Spectroscopy; P-Acetamidobenzenesulfonylchloride; Pyridine; Sulfathiazole

### INTRODUCTION

Sulfonamides were the first effective chemotherapeutic agents employed systematically for the prevention and cure of bacterial infections in humans. They were classified as the first real “wonder” drug developed [1]. After the introduction of penicillin and other antibiotics, the popularity of sulfonamides decreased. However, they are still considered useful in certain therapeutic fields, especially in the case of ophthalmic infections as well as infections in the urinary and gastrointestinal tract. Sulfathiazole, (4-Amino-N-2-thiazolylbenzenesulfonamide), is clinically one of the most used. Sulfonamide is the basis of several groups of drugs. They are bacterio-static antibiotics that competitively inhibit conversion of *p*-amino benzoic acid to dihydropteroate, which bacteria need for folate synthesis and ultimately purine and DNA synthesis. For preparation of sulfathiazole [2-5] many methods are available in present day trend but many of the processes don't offer maximum efficiency. The main aim of the work is to develop a method which gives maximum yields with reduced time and cost efficient when compared to literature. These processes were divided into 3 steps for proper understanding where first step is chlorosulfonation [3] of acetanilide which results in an intermediate *p*-acetamidobenzenesulfonylchloride. In the present investigation it was found that proper mixture of acetanilide and chlorosulfonic acid is required for a good quality of intermediate. So a trial run was made at different temperatures up till 114°C till the best sample is obtained.

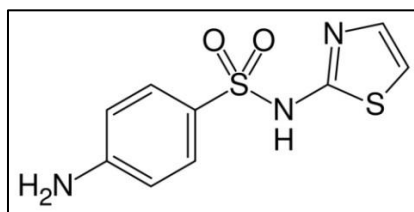


Figure 1: Structure of Sulfathiazole

Then the second step was preparation of sulfathiazole (Figure 1) from the obtained intermediate by varying the quantities of intermediate and amine and varying different acid acceptors like pyridine, etc.

The third step was recrystallization of sulfathiazole to obtain purer product. All the identification of samples was done using IR Spectroscopy with FT-IR [4].

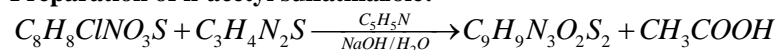
### Complete reaction of sulfathiazole

#### Chemical reactions for p-acetamidobenzenesulfonyl chloride:



Acetanilide + Chlorosulfonic acid p-acetamidobenzenesulfonylchloride

#### Preparation of n-acetyl sulfathiazole:



P-acetamido 2-Aminothiazole Sulfathiazole

benzenesulfonyl

Chloride

\*Acid acceptor - C<sub>5</sub>H<sub>5</sub>N

## PROCESS REACTION

### Material and methods

#### Materials and equipment:

Acetanilide (Hychem labs), Chlorosulfonic acid (Uvscientifics), P- acetamido benzene sulfonyl chloride (Virchow Laboratories, Hyderabad), 2-Amino thiazole (Hychem labs), Pyridine (Hychem labs), Sodium Bicarbonate, Ammonium Hydroxide. Di-methyl aniline, Sodium Hydroxide, Hydrochloric acid, Sulfathiazole (Hychem labs).

FTIR Spectrophotometer (SHIMADZU-1800), Melting point apparatus (Griffin), complete glass Reflux apparatus, heated magnetic stirrer with contact thermometer (Remmi) and oil bath with magnetic fish (Corning pc-351).

#### Synthesis:

**Chlorosulfonation of acetanilide (preparation of p-acetamidobenzenesulfonylchloride) [6]:** This is the first step of the processes where required amount of acetanilide is reacted with chlorosulfonic acid to obtain an intermediate called P-acetamidobenzenesulfonylchloride. This mixture is made to react in a reflux condenser for about 15-20 min where a semi-solid paste is obtained which is brown in color. This step was conducted at different temperatures from 98°C to 114°C because proper melting of acetanilide gave an outstanding output.

**Preparation of {4-Amino-N-(1, 3-thiazol-2-yl) benzene sulfonamide} [7,8]:** This is the second step of the process. 4-aminothiazole reacts with P- acetamidobenzenesulfonylchloride with different compositions and different acid acceptors pyridine, sodium bicarbonate, ammonium hydroxide and Di-methyl aniline were considered and refluxed for about 45 min at 95°C.

#### Acid acceptors:

Acid acceptance has long been a primary function for vapor degreasing solvent stabilizer systems. Acid acceptance provides for the neutralization and removal of hydrochloric acid (HCl) from the degreasing operation. Hydrochloric acid is formed if the solvent breaks down. The acid acceptor reacts with the HCl and removes it by forming insoluble compounds. The insoluble compounds are typically removed with the contaminated solvent.

**Re-crystallization of obtained Sulfa drug (Sulfathiazole) [9]:** To crude sulfathiazole ethyl alcohol is added and boiled below 78°C and cooled. The obtained re-crystallized product is primarily investigated using melting point apparatus and was observed that the product obtained has melted at 201- 202°C. Hence it was confirmed that the obtained product was Sulfathiazole which is compared to pure sulfathiazole [10] (IP Grade). This same process was applied for different compositions of 2-aminothiazole and P- acetamidobenzenesulfonylchloride for different acid acceptors [11] (3:1, 1:1, and 1:3). The obtained 12 samples were investigated using melting point apparatus and 3 best samples (one from each composition) were chosen and were further investigated using FTIR spectrophotometer for which results were reported.

**Analysis of the samples:** FTIR Spectrophotometer [12,13]: Standard and Sample preparation: Sample/KBr ratio: Thin pellets were prepared with known amount of sample and KBr. A pellet is much thicker than a liquid film, hence a low concentration of the sample is used, and too high concentration usually causes difficulties

obtaining clear pellets. The sample is then inserted on the thin glass film which is homogeneous and transparent. The sample is inserted in to the IR holder and the spectrum is made to run. The pure intermediate and sulfathiazole pellets were prepared at different concentrations 10 $\mu$ g, 20 $\mu$ g, 30 $\mu$ g and 40 $\mu$ g and also the samples were prepared in the same procedure.

## RESULTS AND DISCUSSION

The following melting point tests were carried out for each single sample obtained.

### Melting point test for p-acetamidobenzenesulfonylchloride

Five different samples operated at different temperatures ranging from 98°C- 114°C were synthesized and melting point test is performed for all the samples. Out of all the samples the one which is reacted at 114°C melted completely at 144°C during the test which is same as standard melting point temperature of P-acetamidobenzenesulfonylchloride. Hence it is found that reaction between acetanilide and chlorosulfonic acid is complete at 114°C and also at this sample gave maximum yield when compared to those at low temperatures. Thus the intermediate obtained from this sample is of good quality. Percent yield obtained for this particular sample of P-acetamidobenzenesulfonylchloride is 90.05 %. (Figure 3). Further this sample is selected for FT-IR identification.

Table 1: Yields of intermediate observed at varied temperatures of acetanilide

Sl.no	Varied temperatures for acetanilide Temp at (°C)	% yields obtained for Intermediate (re-crystallized)
1.	98	81.08
2.	102	82.63
3.	106	84.27
4.	110	86.59
5.	114	90.05

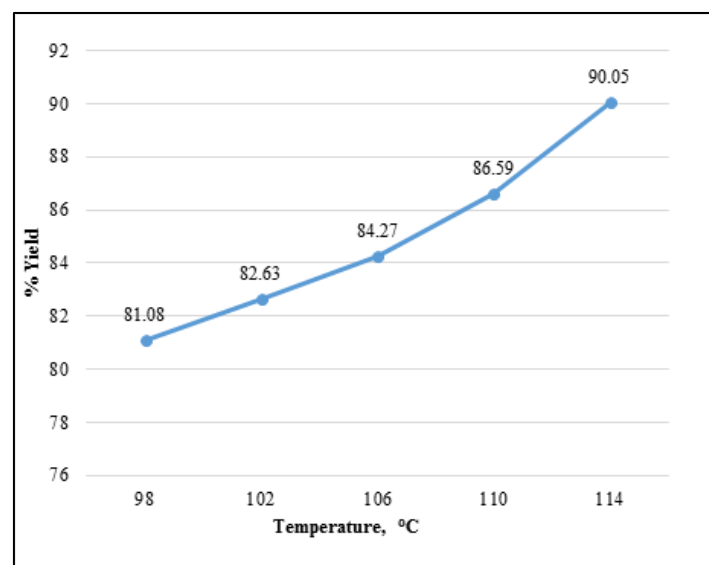


Figure 3: yields of Intermediate observed at varied temperatures

### Melting point test of Sulfathiazole (with 3:1, 1:1, 1:3 ratios of p-acetamidobenzenesulfonyl chloride to 2-Aminothiazole)

All the 12 samples were synthesized with different compositions of intermediate and 2-aminothiazole with different acid acceptors. Melting point test was performed for all the samples and the melting temperatures were noted and tabulated (Table 2). Standard sulfathiazole melts at 202°C. Based on the theoretical yield the weight of crude sulfathiazole is calculated then the product is re-crystallized and dried. The dried product is weighed and the percent yield is calculated. The yields of all the samples were calculated and tabulated (Table 3). Based on these findings 3 best samples (efficient melting at standard temperature and yield) one from each composition is selected (sample1, sample2, sample3) for further investigation. It was found that out of all samples pyridine proved to be the best acid acceptor. Therefore, the product obtained from these samples (with pyridine as acid acceptor) is of good quality.

Table 2: Melting points of different samples of Sulfathiazole

Acid acceptors	3:1 ratio	1:1 ratio	1:3 ratio
	Melting point observed (°C)		
Pyridine	201**	199	204**
Sodium bicarbonate	195	202**	195
Ammonium hydroxide	189	209	185
Di-methyl aniline	208	185	190

Table 3: Yields of Sulfathiazole samples

Acid acceptors	% Recovery		
	3:1(sample 1)	1:1(sample 2)	1:3(sample 3)
Pyridine	97.55*	94.56	91.93*
Sodium bicarbonate	94.8	95.71*	89.33
Ammonium hydroxide	92.38	93.06	87.38
Di-methyl aniline	94.26	94	88.03

**Determination of the selected samples by FT-IR spectrophotometer**

Best three selected samples are, Sample1: Here the (3:1 ratio) sample with acid acceptor pyridine gave good recovery (97.55%) and yield (91.814%). Sample2: Here the (1:1 ratio) sample with acid acceptor sodium-bicarbonate gave good recovery (95.71%) and yield (81.73%). Sample3: Here the (1:3 ratio) sample with acid acceptor pyridine gave good recovery (91.93%) and yield (68.9%).

**FT-IR for p-acetamidobenzenesulfonyl chloride [12]:**

FT-IR Spectra of standard p-acetamidobenzenesulfonylchloride: (Figures 4 and 5). The spectrum is observed for series of samples of concentrations 10µg, 20µg, 30µg, 40µg of pure p-acetamidobenzenesulfonylchloride and also the sample. Based on the peaks obtained from FTIR spectrophotometer calibration data is generated. The absorbance obtained for sample at 20µg is 0.601. The absorbance for standard sample of p-acetamidobenzenesulfonylchloride at 20µg is 0.621.

Table 4: Calibration data for Intermediate

Concentration (µg)	Absorbance (A)
10	0.315
20	0.621
30	0.823
40	0.988

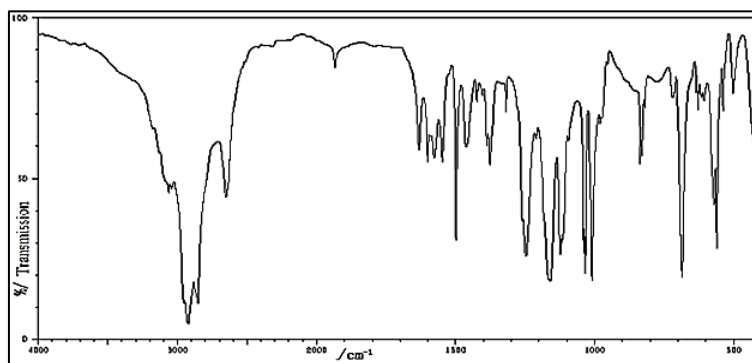


Figure 4: FT-IR Spectra of Standard Intermediate

It fits the accuracy Calibration graph for p-acetamidobenzenesulfonylchloride (Figure 6).

**FT-IR for sample 1(sulfathiazole with 3:1 ratio of intermediate to amine)**

FT-IR spectra of standard sulfathiazole: (Figure 7). The spectrum is observed for series of samples of concentrations 10µg, 20µg, 30µg, 40µg of standard sulfathiazole and calibration data was generated. Similarly, the sample is analyzed at wave length 480nm for 20µg sample, where absorbance obtained is 0.365, which is very near to the absorbance for standard sulfathiazole (0.387)

Calibration graph for pure sulfathiazole (Figure 8)

FT-IR for sample 1: Figure 9

FT-IR for sample 2: Figure 10

FT-IR for sample 3: Figure 11

Table 5: calibration data for sulfathiazole

Concentration ( $\mu\text{g}$ )	Absorbance(A)
10	0.102
20	0.387
30	0.657
40	0.844

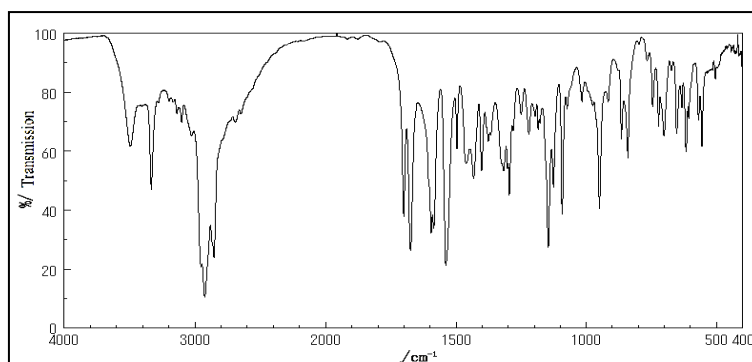


Fig 5: FT-IR spectra of sample (p-acetamidobenzenesulfonyl chloride)

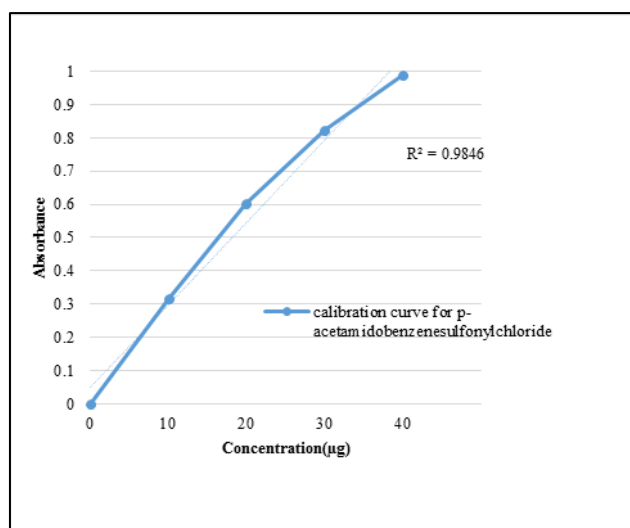


Figure 6: Calibration graph for p-acetamidobenzenesulfonyl chloride

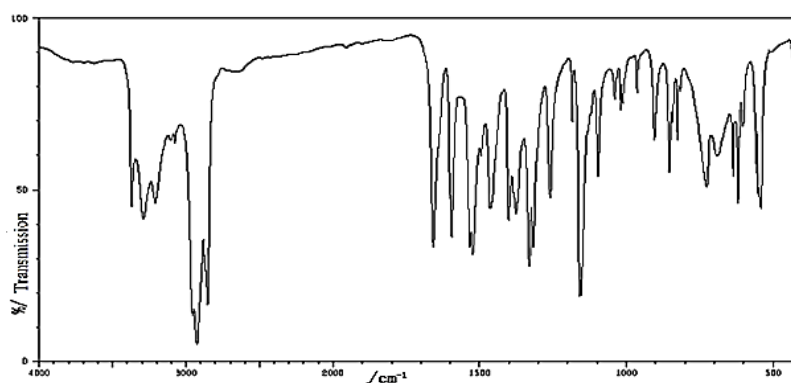


Figure 7: FT-IR spectra of standard sulfathiazole

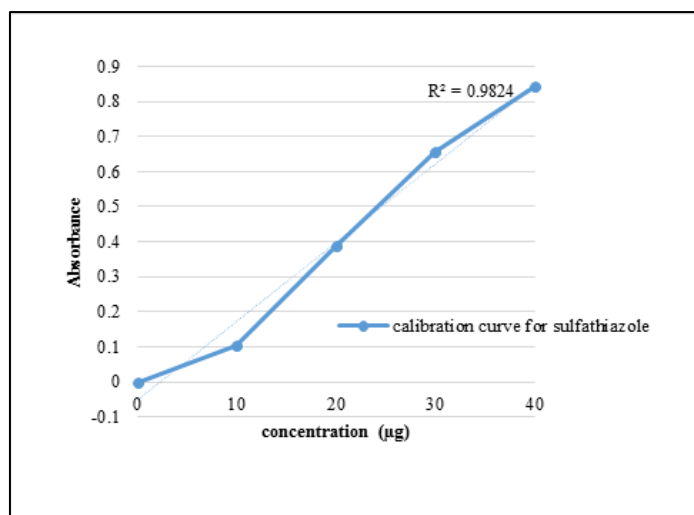


Figure 8: Calibration graph for pure sulfathiazole

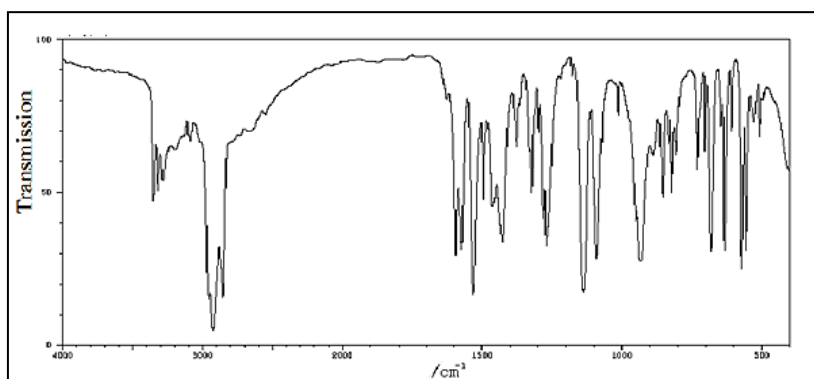


Figure 9: FT-IR for Sample 1(sulfathiazole with 3:1 ratio of intermediate to amine)

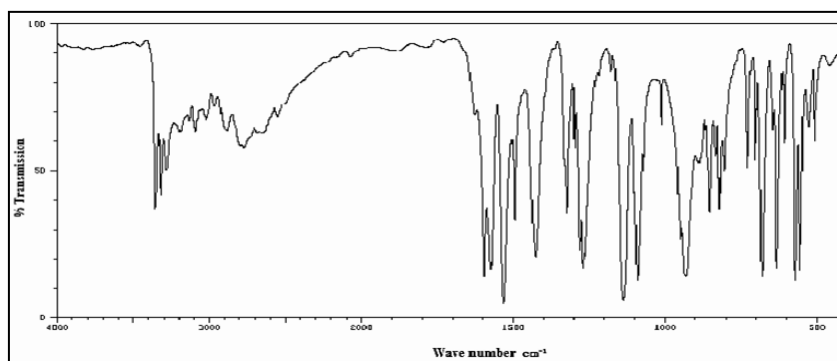


Figure 10: FT-IR for sample 2(sulfathiazole with 1:1 ratio of intermediate to amine)

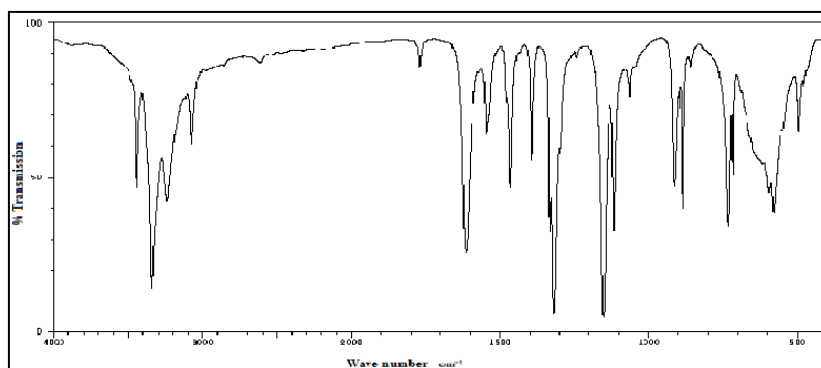


Figure 11: FT-IR for sample 3(sulfathiazole with 1:3 ratio of intermediate to amine)

## DISCUSSION

The identification test was performed for p-acetamidobenzenesulfonylchloride (intermediate) and three samples of sulfathiazole. The obtained graphs were compared to standard graphs. Functional groups were identified for all the samples at similar wave lengths to that of standard graphs and structures were identified.

In FT-IR results of p-acetamidobenzenesulfonylchloride and Sulfathiazole sample 1 peaks obtained were very close to standard data and resulted in appropriate structures, whereas in the other samples identified were appropriate but, disturbed peaks were observed to a higher extent due to impurities.

The calibration charts were plotted for standard p-acetamidobenzenesulfonylchloride and Sulfathiazole at different concentrations to corresponding absorbance. The absorbance at 20µg for the standard p-acetamidobenzenesulfonylchloride and Sulfathiazole were compared to the absorbance at 20µg for corresponding samples. This resulted in best quality of p-acetamidobenzenesulfonylchloride and sulfathiazole sample1 (with 3:1 ratio of intermediate to amine) when compared to other samples.  $R^2$  plotted for all the graphs showed that the method followed for experimentation gave maximum accuracy and best results.

**Table 6: Absorbance observed for pure sulfathiazole and other 3 samples at 20µg concentration**

Conc. of sulfathiazole (µg)	Absorbance(A) of pure sulfathiazole	Absorbance(A) of sample1	Absorbance(A) of sample2	Absorbance(A) of sample3
20	0.387	0.365	0.259	0.88

## CONCLUSIONS

Amongst the reaction ratios studied for sulfathiazole sample with 3:1 ratio of p acetamidobenzenesulfonylchloride to 2 Aminothiazole with pyridine as acid acceptor is proved to be best reactant ratio.

The process employed for experimentation proved to be an efficient and time saving process when compared to general processes as reported in the literature. Pyridine is the best acid acceptor as compared to other acid acceptors. Maximum percent yield obtained is 91.34%. FT-IR spectrum is a reliable technique for establishing the identity of sulfathiazole as well as the intermediate.

## ACKNOWLEDGEMENTS

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