COMPARISONS IN THE SYNTHESIS OF SODIUM SULFACETAMIDE BY REFLUX AND ULTRASONIC IRRADIATION METHODS.

Takudzwa. C. Chiwoneso, Nyashadzashe Mhlanga, Tafadzwa. L. Chisoko, Terrence Mushayavanhu, Cornelius Munyoro.

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Abstract

To synthesize sodium sulfacetamide, 4 routes of synthesis were established in this study where route 1 was the reflux of 4-aminobenzenesulfanomide (sulfanilamide) and acetic anhydride. A major step in this route involved the synthesis of N-{(4-aminophenyl)sulfonyl} acetamide (sulfacetamide) and purifying it by the use of liquid chromatography (***using*** chromatography column PTFE stopcock, length 300mm, diameter 32mm, joint 24/29, made in Xinhua, China). Confirmation of sulfacetamide that was primarily synthesized in route 1 and all other routes was by thermal capillary method (M.P N-{(4-aminophenyl)sulfonyl} acetamide 182 – 184°C). The sulfacetamide formed in route 1 was then refluxed with 20% NaOH to finally form sodium sulfacetamide. Route 2 was the alkylation of 4-aminobenzenesulfonyl chloride by reflux with acetamide in the presence of 22.5% NaOH. Both 4-aminobenzenesulfonyl chloride and acetamide were dissolved before reflux (M.P C6H6ClNO2S = estimate 170 ±30°C, acetamide = 81°C). The reflux in this route resulted directly in the formation of sulfacetamide which was confirmed and further refluxed exactly as in route 1 to form the target molecule sodium sulfacetamide. Route 3 and 4 employed the use of ultrasonic irradiation, a new technique in organic synthesis that is eco friendly, time conservative and high yield favorable (Li et al. 2015). Route 3 involved the ultrasonication of sulfanilamide and acetic anhydride in the presence of 22.5% NaOH. The same UI equipment (BV 2L, 20-40 rpm, Ultrasonic power 1.2kw, max voltage 220V, made in China) used for route 3 was used as well for route 4 which reacted 4-aminobenzenesulfonyl chloride and acetic anhydride to obtain sulfacetamide which was reacted with 77% NaOH exactly as in route 3 to obtain the final product sodium sulfacetamide. Sodium sulfacetamide products from all routes were examined for purity and confirmation by use of TLC (CHCL3 : CH3OH : NH4OH = 3:6:1 v/v) before the results were used to add speculation room for production analysis.

Keywords:

4-aminobenzenesulfanomide, N-{(4-aminophenyl)sulfonyl} acetamide sulfacetamide, 4-aminobenzenesulfanoyl chloride, N1,N4-diacetyl-sulfanilamide-d4, acetic anhydride, acetamide, reflux, ultrasonic irradiation (UI) . Active Pharmaceutical Ingredient (API), Sodium sulfacetamide,

Statements and Declaration

All authors involved in this manuscript have no conflicts of interest and all contents have been agreed on and there are no financial interests to mention. This work is also not under any review

in any other platform or publication.

Introduction

Over 50 Million people in the US alone are affected by acne annually, globally acne is in the top 10 list of the most prevalent diseases (Tan and Bhate 2015), and conveniently sodium sulfacetamide is one of the most utilized Active Pharmaceutical Ingredient for this tragedy. Not limited to acne, sodium sulfacetamide is used also in the treatment of urinary tract and eye problems. It is important for such a drug to be manufactured and produced in bulk and at the same time be readily available for all patients especially those without flexible financial capabilities. Sodium sulfacetamide is an antibacterial organic salt of IUPAC name sodium;acetyl-(4- aminophenyl)sulfonylazanide that is mostly used to treat skin, oral and urinary tract infections(Roychowdhury et al. 2010). It is also used as eye drops in the treatment of conjunctivitis, trachoma and other eye related conditions. The most common method in the synthesis of sodium sulfacetamide involves a series of reflux reactions including addition of acetic anhydride to sulfanilamide(4-aminobenzenesulfanomide) to form N1,N4-diacetyl-sulfanilamide-d4 and sodium;acetyl-(4- aminophenyl)sulfonylazanide which are hydrolyzed in the presence of NaOH to form N-{(4-aminophenyl)sulfonyl} acetamide (sulfacetamide). The N-{(4-aminophenyl)sulfonyl} acetamide is then refluxed under sodium hydroxide to form the target molecule, sodium sulfacetamide(Vardanyan and Hruby 2006). Besides being fatigue packed, synthesis by reflux method is slow and the reaction is by all means conducted in moderately warm to hot conditions to speed up the rate of reactions. In this article 4 possible routes in the synthesis of sodium sulfacetamide were conducted. Routes 1 employed the use of reflux reaction of 4 -aminobenzenesulfanomide (sulfanilamide) with acetic anhydride, route 2 was the reflux of 4-aminobenzenesulfonyl chloride with acetamide. The methodology used in both the reflux routes were also used in routes 3 and 4 but with the use of ultrasonic irradiation under normal room temperature to attain the target molecules. Basic synthesis of sodium sulfacetamide consists of 2 main stages, preparation or synthesis of a sulfacetamide and its hydrolysis to finally form the salt, sodium sulfacetamide hence all routes in this article followed this synthetic procedure.

Route 1: Reflux of 4-aminobenzenesulfanomide with acetic anhydride.
Route 2 : Reflux of 4-aminobenzenesulfonyl chloride with acetamide.
Route 3 : Ultrasonic irradiation of 4-aminobenzenesulfanomide with acetic anhydride.
Route 4 : Ultrasonic irradiation of 4-aminobenzenesulfanomide with acetamide

Route 1: Reflux 4-aminobenzenesulfanomide with acetic anhydride.

Materials and Methods

Preparation of sulfacetamide

Materials	Specifications	Amount	Mole	Mole Ratio
Sulfanilamide	-	17,2g	0,1	1
Acetic anhydride	-	13,6ml	0.14	1,4
NaOH	22,5%	22ml	0.11	1.1
NaOH	77%	12.5ml	0.19	1.9
HCl	10%	8 ml	-	-

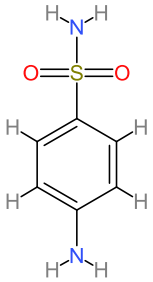
In preparation of sulfacetamide, 17.2g sulfanilamide was weighed and refluxed with 22ml of 22.5% NaOH in a 3 necked flask equipped with a magnetic stirrer and a thermometer. This reaction was maintained at a temperature of about 45-60°C, also the reaction was stirred throughout to increase the rate of the reaction. The main reason of this initial step was to dissolve the solid sulfanilamide which is pretty soluble in NaOH (solubility of sulfanilamide in sodium hydroxide n.d.), this automatically meant that the next step was due when all the solid sulfanilamide had dissolved. It took 25 minutes to completely dissolve all 17.2g sulfanilamide.

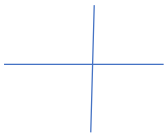
The next stage was the synthesis of sulfacetamide from sulfanilamide. Drops of acetic anhydride and 77% NaOH were added to the dissolved sulfanilamide reaction in turns, at specified and constant time interval differences. At first 3.6ml acetic anhydride was added then 2.5ml of 77% NaOH was added after 5 minutes in turn followed by 2.5ml acetic anhydride then again 2.5ml of the NaOH still after 5 minutes until all 13.6ml acetic anhydride and 12.5ml 77% NaOH were added. By adding dropwise, all the reagents were allowed to fully react and avoid the production of the unwanted product as different concentrations of NaOH were used throughout this reaction implying that any fabrication of NaOH concentration at any stage would lead to a different direction of the reaction. When adding NaOH and acetyl anhydride the pH was kept highly basic, that is 12 -14 as a lower pH would have favored production of a lower yield. Temperature was maintained at 45 - 60°C and stirring was never stopped again to increase the rate of reaction. Still in the 3 necked flask the reaction was allowed to propagate for 30 minutes before being transferred to a beaker where 20ml of water was added gradually to avoid a sudden drop of temperature as a sharp decrease in temperature would have affected the maintained pH (Barron, Ashton, and Geary 2019). Prior the reduction of pH to 7, the reaction occurred as in fig1.1. After the temperature had dropped to room temperature, the solution in the beaker was immersed in ice for at 90 minutes.

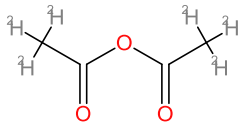
$$sulfanilamide + acetic \quad anhydride \xrightarrow[reflux\ 45-60°C]{NaOH\ pH\ 7} sulfanilamide + dIacylated\ sulfanilamide + sodium\ sulfacetamide$$

Fig1.1

Chemical structures of Products (Sulfanilamide + acetic anhydride)



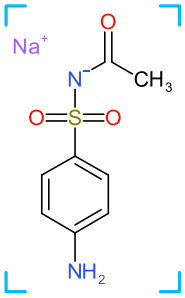


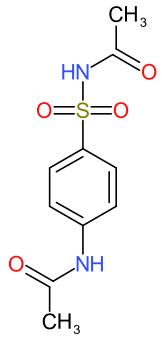


+ acetic anhydride

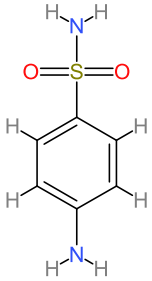
+ sulfanilamide

(target molecule)





(impurity)



(impurity)

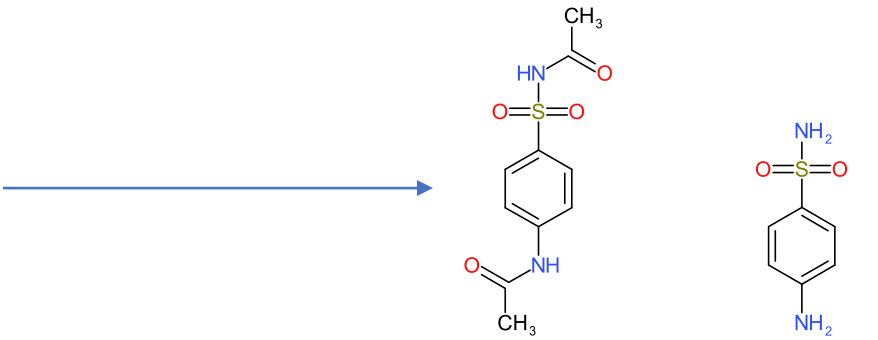
Fig1.2

After 90 minutes a solid precipitate had formed to which it was relevant to note that after reflux the solution contained three compounds, Fig1.2, unreacted sulfanilamide, diacylated sulfanilamide and the sodium sulfacetamide which was the target compound, sulfacetamide (Ahmad, Ahmad, and Usmanghani 1994). The solid was collected by suction and ice water was used to wash in the solid that was left or stuck when conducting the filtration. Besides efforts of eliminating the unreacted sulfanilamide from the solution, there was need to increase the percentage yield of sulfacetamide (monoacetylated compound) by hydrolyzing the diacylated sulfanilamide which was already in the system. Also, in order to eliminate sulfanilamide and unwanted impurities from the previous reactions, the filtration solution (the solid precipitate with ice water) had to undergo selective deacetylation of the disubstituted compound (Cysewski et al. 2021), which was therefore the next stage of the procedure.

The collected 3 compound solution, of sulfanilamide, N1,N4-Diacetylsulfanilamide and sodium sulfacetamide, still in the beaker was treated by concentrated HCl maintained at a pH of not less than 4 and not higher than 5, Fig1.3. Whenever the pH went under 4, dilute NaOH was added to raise the pH and concentrated HCl was added dropwise to attain the required pH range whenever it exceeded 5. This stage was complete when a solid precipitate was formed and the process was synchronous to the hydrolysis of both the diacylated sulfanilamide and sodium sulfacetamide to form N1, N4 – Diacetylsulfanilamide and sulfanilamide. Fig1.3. This stage of reaction summed up to just 20 minutes.

$$\xrightarrow[HCl]{pH4-5} N1, N4 - diacylated\ sulfanilamide + sulfanilamide$$

Fig1.3



(diacylated sulfanilamide) (sulfanilamide)

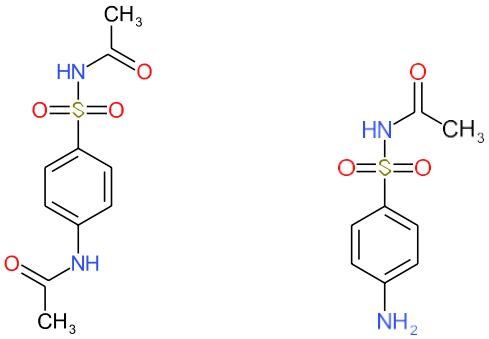
Fig 1.4

To this beaker Fig.1.4, 10% HCl was added while stirring until a solid was formed, prior the addition of 10% HCl, dilute NaOH was also added dropwise to maintain a pH of at most 5. The dissolved solid particles contained the remainder of the diacylated compound and possible impurities. The undissolved solution was sulfacetamide which could not dissolve in acidic conditions due to its weak acidity(ACCURATE CALCULATION OF PK A OF SULFACETAMIDE USING HIGH-LEVEL AB INITIO CALCULATIONS n.d.), therefore through suction the liquid was disposed out of the system and the liquid solution was taken to the next stage of the reaction which was equivalent to purification or elimination of impurities in the preparation of sodium sulfacetamide.

$$\xrightarrow[10\%\ HCl]{a\ few\ minutes} N1,N4-diacylated\ sulfanilamide + sulfacetamide$$

fig 1.5

Chemical structures of compounds after addition of 10% HCl



Diacylated sulfanilamide sulfacetamide

Fig1.6

The liquid solution as in ***Fig1.6*** was allowed to settle for 30 minutes undisturbed before filtration

to eliminate undissolved solid particles in the solution. The remaining solution was yellow in color and activated charcoal was applied to decolorize the solution (Jr 1989), at room temperature. At this point the pH was low due to the presence of the 10% HCl in the solution hence 40% NaOH was added to raise and maintain the pH at 5. Besides the selective de-acylation of N1,N4-diacetyl-sulfanilamide-d4 , NaOH also reacted with the HCl neutralizing the solution at the same time forming sulfacetamide which illuminated as a precipitate that was obtained through suction.

The solid sulfacetamide obtained was dried for 1 hour in an oven at 105 to 115°C to purify it from the HCl and water through evaporation before it was weighed. Weight after drying was 10.20 g. Swiftly after recording the final weight, a capillary was used to extract a small amount of the final product and directed to a heating bath for melting point confirmation. The first liquid droplet in the capillary tube was noted at 179 °C and all product had melted at 183°C, this result was used to conclude that the product was indeed sulfacetamide (No Title n.d.).

Structure of sulfacetamide

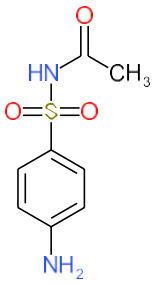


fig1.7

Preparation of Sodium sulfacetamide

The prepared sulfacetamide ***Fig1.7***, was then used in the preparation of sodium sulfacetamide, and 20% sodium hydroxide was employed to facilitate this synthesis. The now synthesized sulfacetamide was placed in a beaker and a few drops of water were added just to make the compound wet. The wetted solution was heated to a temperature of 80 – 90 °C. Drops of 20%NaOH were added to maintain the pH at 7 – 8. While heating, apparatus for column chromatography were prepared with silica as stationary phase. After heating for 1 hour the mixture dissolved and at this point sodium sulfacetamide was formed however it contained some impurities hence quickly just prior dissolving, the filtration solution was employed into the prepared column chromatography. Sodium sulfacetamide being a salt was eluted first (Teledyne Isco Inc. 2010) and collected in the beaker. The collected solution, now in a beaker was immersed into an ice bath to form a solid sodium sulfacetamide solution. ***Fig1.8***. To eliminate water, the solid solution was placed in an oven and heated for 1 hour at 105 -115°C.

Sodium sulfacetamide

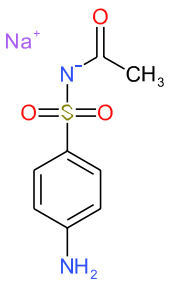


Fig1.8

Results

After 1 hour of drying, the sodium sulfacetamide was weighed and 7.90g were noted. Yield was calculated on the basis that 0.1 mol sulfacetamide was used and the molecular weight of sodium sulfacetamide which equal 236 as in the equation below:

$$percentage\ yield = \frac{final\ weight}{\text{relative molecular mass}} \times 100\%$$

$$\frac{7.90}{(236\ \times 0.1)} \times 100\%$$

$$= 33.47\%$$

Route 2: Reflux of 4-aminobenzenesulfunoyl chloride with acetamide

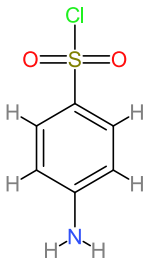
Route 2 took advantage of the fact that the sulfacetamide, as is a sulfonamide can be also be prepared by a direct alkylation of a sulfonyl halide (sulfonyl n.d.).

Preparation of sulfacetamide
Materials and Methods

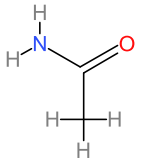
Materials	Specifications	Amount
4-aminobenzenesulfunoyl chloride	-	19.2 g
Acetamide	-	20g
NaOH	22.5%	12.5ml
NaOH	20%	10mL

19.2g solid 4-aminobenzenesulfunoyl chloride was weighed and subjected into a three necked flask equipped also with a thermometer immersed on one of the openings and a regular glass stopper on the other. Also in the flask was a magnetic stirrer to speed up the reaction. The 4-aminobenzenesulfunoyl chloride in the flask was gradually heated, duration for complete melting was timed and the whole solution dissolved after about 1 hour of stable heating at 150 – 165°C. The compound was dissolved to attain ease of reaction, 4-aminobenzenesulfunoyl chloride could have simply been dissolved in water but this was not executed as sulfonyl halides would be hydrolyzed by water to a corresponding acid (Corbu and Cossy 2012), in this case 4-aminobenzesulfonyl acid. Once the whole compound had dissolved, temperature was re-adjusted and maintained at 110 -120°C.

Just when solid 4-aminobenzenesulfunoyl chloride had melted, 5g acetamide was weighed into a beaker and was heated using a heat gun at 78 – 83 °C until the weighted 5g had all dissolved (Acetamide | CH3CONH2 - PubChem n.d.). Just prior the addition of acetic acid, 2.5ml NaOH was added dropwise in a time frame of 30 minutes. The chemical structures of the initiating reagents are as in ***fig 1.9*** below



4-aminobenzesulfonyl chloride



acetamide

Fig1.9

The reagents in fig 1.9 were allowed to propagate at a temperature maintained at 60 -70°C with NaOH as a catalyst. The reaction between 2-aminobenzenesulfonyl chloride produces HCl that when added to the system reacts with the catalyst NaOH to form a salt, NaCl. Besides being a catalyst that removes HCl from the reaction favoring the forward reaction, NaOH also neutralizes the reaction mixture. However the catalytic effect of NaOH in speeding up the reaction is extremely insignificant in comparison with other catalysts in organic synthesis. The quantity of water produced during neutralization is extremely small and hence easily evaporated out of the reaction system just upon formation.
The reaction proceeded as in the equation in fig 2.1

$$4-aminobenzene\ sulfonyl\ chloride + \text{acetamide} \xrightarrow{NaOH} Sulfacetamide$$

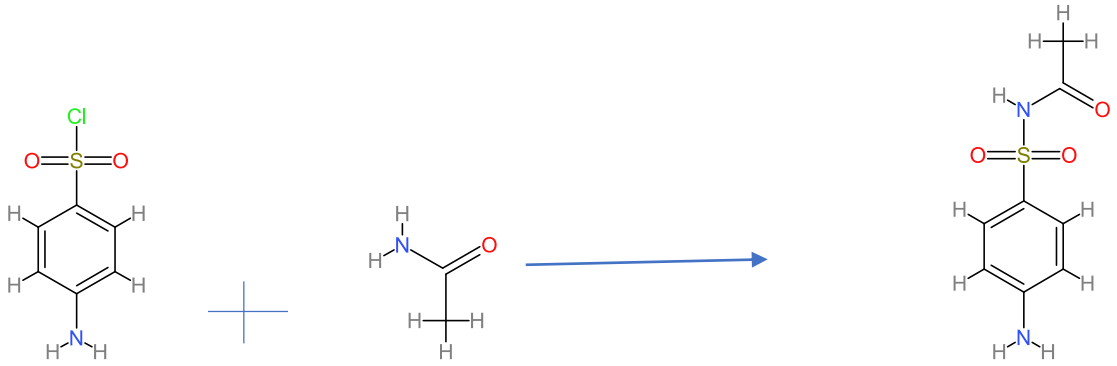


Fig2.1

The above reaction was almost complete after approximately 4hours 30 minutes. Before the reaction had ceased completely 5 more grammes of liquid acetamide were added to the reaction mixture followed by 2.5ml of NaOH again dropwise in a time frame of 30 minutes. This stage was repeated until all 20g of acetamide and 10ml NaOH were completely applied to the reaction system. The 2nd application took approximately 5hrs 20 minutes, the 3rd and 4th took 4hrs 30 minutes and 3hrs 20 minutes respectively. The product in the receiving flask was collected and 1st cooled to room temperature before immersion into ice until a white solid was formed. The solid precipitate was immediately transferred into an oven and left to dry at 105 -115°C for 1.5 hours.
A tiny amount of the solid was obtained by use of melting point capillaries and was examined for melting point, the first liquid droplet was again noticed at 179°C and all contents had dissolved at 183°C confirming identity to be sulfacetamide, **fig2.2**. The solid sulfacetamide was then weighed and recorded to be 15.1g.

structure of sulfacetamide

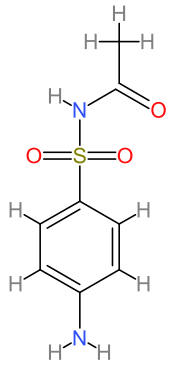
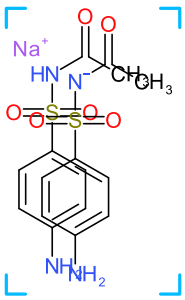


fig 2.2

Preparation of sodium sulfacetamide

The sulfacetamide synthesized in the above reaction now in a beaker was then wetted just by a few drops of water before 20% NaOH was added. At a temperature of 80 - 90°C, the reaction was allowed to propagate for 1 hour 45 minutes before it was immersed in an ice bath until solid hydrated sodium sulfacetamide was formed. To eliminate water the solid compound was let to dry in an oven at 105 -115°C, it took almost 2,5 hours for this compound to completely dry. The product was finally weighed and a pleasing 13.4 g were recorded.

$$sulfacetamide \xrightarrow{20\%\ NaOH} sodium\ sulfacetamide$$



Results

Percentage yield was again calculated on the basis that sodium sulfacetamide has a relative molecular mass of 236 and 0.1 mol sulfacetamide was used in its synthesis.

$$\text{Percentage yield} = \frac{13.4}{(236\ \times 0.1)} \times 100\%$$

56.78 %

Route 3: Ultrasonic irradiation of 4-aminobenzenesulfanomide with acetic anhydride

Preparation of sulfacetamide
Materials and Methods

Materials	Specifications	Amount	Mole	Mole Ratio
Sulfanilamide	-	17,2g	0,1	1
Acetic anhydride	-	13,6ml	0.14	1,4
NaOH	22,5%	22ml	0.11	1.1
NaOH	77%	12.5ml	0.19	1.9
HCl	10%	8 ml	-	-

At room temperature, 17.2g of sulfanilamide was weighed into a jacketed glass beaker and 22ml of 22.5% NaOH was added, the mixture was set for ultrasonic irradiation. All the solid sulfanilamide particles had dissolved within 5 mins of exposure to ultrasonic irradiation which is basically the initial step for the preparation of sulfacetamide for the synthesis of sodium sulfacetamide.

Next, 13.6 ml acetic anhydride was gently added to the reaction mixture followed by 12.5 ml NaOH, unlike route 1 where turns and time intervals were considered during a similar process, these reagents were added all in one go, acetic anhydride then 77 % NaOH respectively. Still at room temperature under UI the solution in the jacketed beaker was allowed to propagate as in the equation in ***fig 2.3*** below.

$$Sulfanilamide + acetic\ anhydride \xrightarrow{NaoH} sulfanilamide + diacylated\ sulfanilamide + sodium\ sulfacetamide$$

Fig2.3

It took approximately 20 minutes for this stage of the reaction to be complete. Products of the reaction contained as in **fig 1.2**, the target molecule sodium sulfacetamide at the highest proportion, sulfanilamide and the diacylated sulfanilamide **fig 2.4**. Despite the sodium sulfacetamide at the present stage of the reaction that was at the highest proportion, the reaction mixture did not only have too many impurities but also considering the starting reagents, the

yield would have been too low if harvested at this stage.

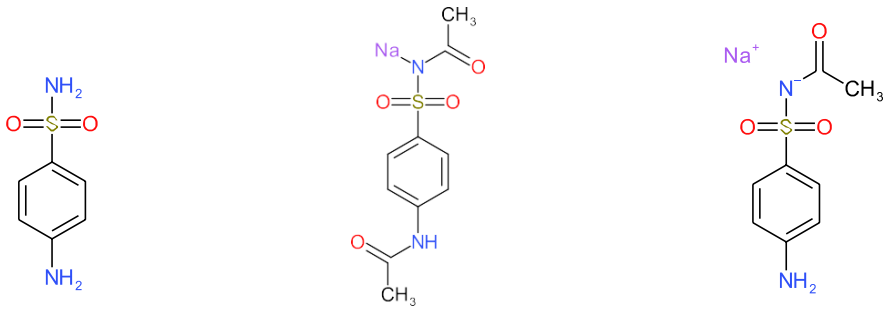


fig 2.4

The solution **fig 2.4** was transferred from the jacketed beaker into an ice water bath for about 5 - 10 minutes, in this beaker the unreacted sulfanilamide existed as a liquid whilst the other 2 components of the system were solid and were obtained from the mixture by filtration.

Back in the jacketed beaker, the solid filtration contents were contained and 10% HCl was added and ultrasonic irradiation was set to proceed for 30 mins before the reaction mixture turned into a faint yellowish solid of which the color was treated with activated carbon (Alkhatib 2018) to finally obtain a white solid, sulfacetamide. The reaction propagated as **fig 2.5** below

$$\xrightarrow{10\%HCl} sulfacetamide$$

fig2.5

The sulfacetamide formed was set in an oven at a temperature of 105 – 115 °C for 1.5 hours for complete drying and was weighed afterwards to obtain a recorded value of 13.1g. Again for confirmation, a capillary tubule was employed and a pinch of the solid sulfacetamide was examined for melting point, the first droplet was noted exactly at 180°C, all contents in the capillary having dissolved at 184°C and this gave enough confidence to conclude that the product at hand was definitely sulfacetamide.

<u>Preparation of sodium sulfacetamide route 3</u>

A few drops of water were added to wet the sulfacetamide again in the jacketed beaker at room temperature, this was eventually followed by the addition of 7.4 ml of 20% NaOH. The reaction took place under UI for about 15 minutes. Soon after Ultrasonic Irradiation, the liquid solution was allowed to go through liquid chromatography with silica gel to eliminate all possible impurities. Sodium sulfacetamide that was formed was eluted first still because of its properties mentioned in route 1. The collected liquid solution was dried at 105 -115°C for 1,5 hours and a weighed, 12.6g of product was obtained.

$$sulfacetamide \xrightarrow{20\%\ NaOH} sodium\ sulfacetamide$$

fig2.6

Results

$$\text{Percentage yield} = \frac{12.6}{(236 \times 0.1)} \times 100\%$$

$$= \ 53.39\%$$

Route 4 Ultrasonic irradiation of 4-aminobenzenesulfonyl chloride with acetamide

Preparation of sulfacetamide
Materials and reagents

Materials	Specifications	Amount
4-aminobenzenesulfunoyl chloride	-	19.2 g
Acetamide	-	20g
NaOH	22.5%	12.5ml
NaOH	20%	10Ml

At room temperature 19.2g 4-aminobenzenesulfunoyl chloride, was added into a jacketed beaker accompanied by 20g melted acetamide, the reagents were employed to ultrasonic irradiation in the presence of 22.5 % NaOH (12.5 ml) with the same catalytic roles as in route 2,

$$4 - aminobenezenesulfonyl\ chloride + acetamide \xrightarrow{NaOH} sulfacetamide$$

Fig2.7

The reaction in fig 2.7 above was complete in about 1hr 45 minutes and produced sulfacetamide which was transferred to a beaker immersed in water bath for 30 minutes. The solid sulfacetamide was dried for 1.5 hours at 105 -115 °C before being weighed. 16.1g of weight was obtained. After weighing, the melting point of this product was verified still by using a capillary tubule for melting point and the result was qualified to conclude identity of the compound to be sulfacetamide.

Preparation of sodium sulfacetamide

10ml of 20% NaOH was applied to the sulfacetamide again in the jacketed beaker at room temperature, ultrasonic irradiation was allowed to commence as directed by the reaction in **fig 2.8** for 25 minutes.

$$sulfacetamide \xrightarrow{20\%\ NaOH} sodium\ sulfacetamide$$

Fig2.8

The sodium sulfacetamide was allowed to dry still applying the same conditions of 105 -115°C in an oven but for 2.5 hours as this sample appeared to be more in weight that in other synthetic routes, 1- 3 mentioned before, and being weighed to obtain 14.3g as final weight.

Results

$$\text{Percentage yield} = \frac{14.3}{(236 \times 0.1)} \times 100\%$$

$$= 60.59\%$$

Thin Layer Chromatography

TLC was introduced in order to verify the product, sodium sulfacetamide as well as to estimate the degree of impurities (Rf 1992) hence all products of routes 1 – 4 were subjected to TLC under the same conditions that is silica gel stationary phase and CHCL3 : CH3OH : NH4OH = 3:6:1 v/v as mobile phase (Sweeny 1972).

Summary of TLC observation

	Route 1	Route 2	Route 3	Route 4
Sodium sulfacetamide	Positive	Positive	Positive	Positive
Impurity	Positive	Negative	Negative	Negative
Detected impurity	Sulfanilamide	-	-	-

Production Analysis

In order to evaluate the benefits of the synthetic routes in the synthesis of this Active Pharmaceutical Ingredient, a production analysis was established based on the time, yield and costs of reagents employed from start to end of the synthetic procedure. Other factors had need to be also considered such as electricity as route 3 and 4 were reassessed in South Africa where there was massive loadshedding in the time frame of this research(Guide 2019). Production analysis is important as can always assist manufacturers to innovate more reliable, accurate as

well as cost effective strategies to execute in respective pharmaceutical plants and research areas.(Žagar and Mihelič 2022).

Accountable time was summed up in minutes and divided by 60 to give an estimate of the number of hours spent in each experiment, percentage yield was also calculated per experiment and averaged to be out of 20 for flexible tallying. Lastly different online chemical shops in China (Pinduoduo), India (I buy Chemikals) and several others in the USA were consulted to find an average cost of each and every reagent used. Accountable data considered for production analysis in this study are summarized in the graph below, fig 3.1, with route 2 having utilized more time of over 19 accountable hours, route 4 with the highest percentage yield and the lowest cost of reagents

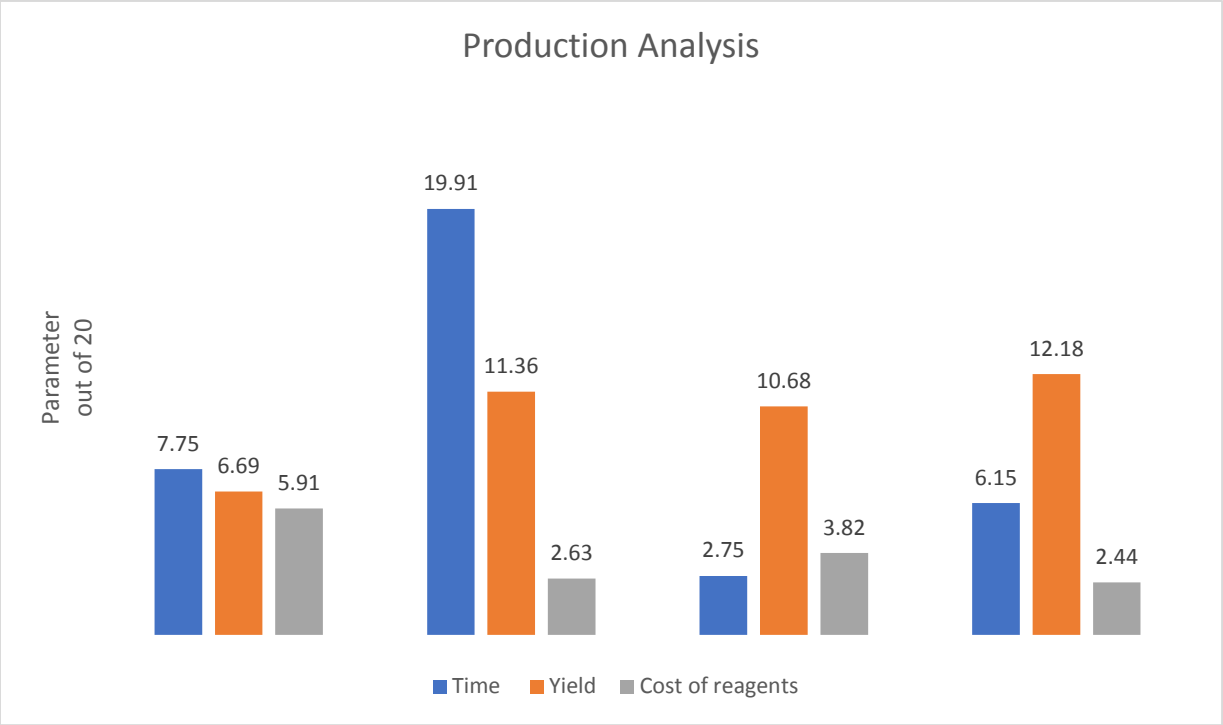


Fig3.1

Conclusion

Sodium sulfacetamide was synthesized by 4 distinct routes, reflux of 4-aminobenzenesulfanomide with acetic anhydride (route 1), reflux of 4-aminobenzenesulfonyl chloride (route 2) and the application of ultrasonic irradiation to both routes as routes 3 and 4 respectively.

Route 1 made use of lots of time, resources and energy. It produced a low yield with an impurity. Route 2 utilized more time than route 1, however there was much higher yield harvested in route 2 than route 1. In addition, route 2 was cheaper to operate in terms of reagents used. Route 3 was

the least time consuming, purity immaculate and also more environment friendly. Route 4 produced the highest yield of all the routes, was the easiest and cheapest to perform despite utilizing more time than route 3 and containing and HCl impurity was however eliminated by intensive heating. Route 4 was the most beneficial synthetic route besides it having attained more time than route 3. synthesis of sodium sulfacetamide by alkylation of 4-aminobenzenesulfonyl chloride by use of ultrasonic irradiation is an effective method in the synthesis of the API in question.

Ultrasonic irradiation was most effective method in the synthesis of sodium sulfacetamide and it greatly outweighed reflux in all factors analyzed in this article and also synthesis of sodium sulfacetamide by alkylation of 4-aminobenzenesulfonyl chloride by use of ultrasonic irradiation is an effective method in the synthesis of the API in question.

Discussion

Advancements in the synthesis of sodium sulfacetamide should eliminate time and energy consumption and at the same time promote maximization of yield and purity. As important as this API is, it is important to note that it is readily available at an affordable price about USD10 in the United States (Committee 2020).

Synthesis of sodium sulfacetamide by reflux of 4-aminobenzenesulfanomide and acetic anhydride is a common synthetic method mostly in educational setup. It is however unfortunate that the route always brings low yield as each stage contained a notable amount of unreacted product that was recorded as impurities and in addition these products are generally unstable chemical components. Each stage in this reaction was important and had to be executed with enough care as any alter in either pH and temperature could have largely affected the final product in terms of both quality and yield. In conducting a synthesis of sodium sulfacetamide by reflux it is important to maintain a stable temperature but it is always difficult to do so as almost every stage required immersing of a product into an ice bath after heating, however the best solution was monitoring a gradual decrease of temperature by allowing the hot solution to cool down on its own at room temperature which is again a time-consuming process.

Route 2 was unsafe to operate as the HCl that was emitted in this reaction was in gaseous state which affects the environment by influencing either acid rain and photochemical smog among other factors (HCl n.d.). Also the HCl gas omitted would affect operating personnel through a number of factors not limited to total blindness (Service 2002). For this method to be considered for implementation, more efficient catalysts would need to be employed, catalyst that would not add more unnecessary work in terms of purifying the system.

Ultrasonic irradiation generally gives solutions to reflux reactions in terms of purity, environmental friendliness as well as time consumption (B9780128207925000044 n.d.). Synthesis by route 3 was efficient in saving time and producing a very much pure product but the method like route 1 involved a lot of procedures which would then give room for product distortion if a mistake would have been made at any point of the synthesis.

Route 4 promoted the feasibility of alkylation by ultrasonic irradiation to which in this study

reduced the time spent throughout the reaction, in comparison with route 2 by almost 60%. The time taken to perform both route 2 and 3 could have further been reduced if temperature was increased, this can be achieved by employing new UI equipment that provide heating options. The HCl impurity in route 4 was obtained as the UI was conducted at room temperature and hence the HCl was contained in the reaction system as a liquid hence still conduction of this alkylation reaction at a higher temperature totally eliminates such a fault.
Synthesis of sodium sulfacetamide through alkylation by the use of ultrasonic irradiation is an easy, cost effective, environmental friendly and high yield propagating method that is worth employing in the synthesis of a medicine of such high demand.

Acknowledgement

Great appreciation in this research is owed to Professor Sun Jianbo, School of Traditional Chinese Pharmacy for supervision of this research and Pharmacy student class of 2019 for all forms of support and encouragement to make this project viable.

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