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Application of Continuous Flow Chemistry in Organic Synthesis

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ABSTRACT- Continuous flow organic synthesis is one of the Enabling techniques; it is a promising method in drug discovery. Flow methodology has an edge over pre-existing batch methodologies. Organic transformations spanning from liquid –liquid to solid-liquid-gas systems has shown to benefit the production as the reaction conditions established in a micro reactor need not be re-optimized for scaling up.
Index Terms- words or phrases in alphabetical order, separated by commas. Keywords are used to retrieve documents in an information system such as an online journal or a search engine. (Mention 4-5 keywords)

I. INTRODUCTION

Flow chemistry is a discipline in synthetic organic chemistry that uses a continuous stream of different reagents, which are introduced by pumps and mixed in a continuous reactor, such as a plug flow reactor (PFR) or continuous-stirred tank reactor (CSTR) .Compared to conventional batch processing methods , flow method has several advantages such as enhanced mass and heat transfer, improved safety, increased reaction efficiency, reduced waste, better scalability, and improved reproducibility.

Advantage of flow process over Batch process is By virtue of very short residence time in flow micro reactors; short-lived highly reactive intermediates can be rapidly generated and transferred to another location in the flow system for use in subsequent reactions before they decompose. On the basis of such a feature of flow micro reactors

As a consequence, flow chemistry allows for precise control over reaction conditions and enables real-time monitoring and analysis of reaction kinetics, resulting in high-quality products and streamlined processes.

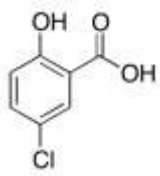
Continuous flow organic synthesis of compounds is performed by first synthesizing of the raw materials which is described in the route of synthesis section followed by purification of raw materials and addition of reagents this is a sustainable way of manufacturing

1) Purity of raw Materials
2) Synthesis
3) Chlorination & Condensation
4) Reaction Flow
5) Recovery of solvents
6) Recovery & Re-use of by products
7) Commercial advantage
8) Comparative research on solvents
9) Environmental Factors

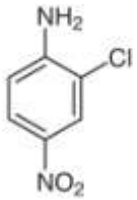
II. PURIFICATION OF RAW MATERIALS

DESCRIPTION OF RAW MATERIALS

CHEMICAL NAME : 5-CHLOROSALICYLIC ACID
MOLECULAR FORMULA: $C_7\ H_5\ ClO_3$
MOLECULAR WEIGHT: 172.56 G/MOL
STRUCTURAL FORMULA:



CHEMICAL NAME : 2-CHLORO 4-NITROANALINE
MOLECULAR FORMULA:$C_6H_5ClN_2O_2$
MOLECULAR WEIGHT:172.56 G/MOL
STRUCTURAL FORMULA:



- PURITY OF RAW MATERIALS IS TESTED WITH THE HELP OF GAS CHROMATOGRAPHY THE APPARATUS USED FOR TESTING IS DISPLAYED BELOW

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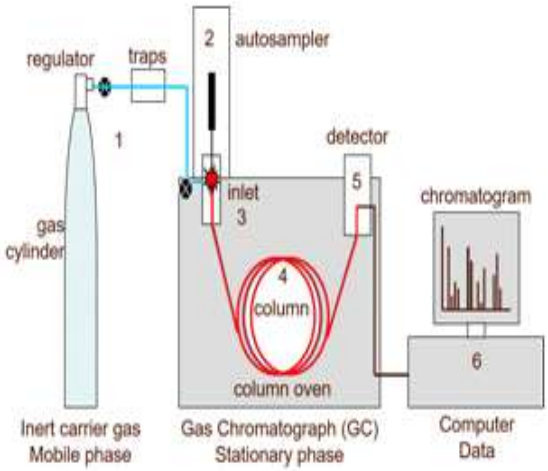

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PREPARATION OF 5-CHLOROSALICYLIC ACID GC

TEST SOLUTION

TO 1.0 G OF THE SUBSTANCE TO BE EXAMINED ADD 15 ML OF WATER, BOIL FOR 2 MIN, COOL, FILTER THROUGH A MEMBRANE FILTER (NOMINAL PORE SIZE: 0.45 µM), WASH THE FILTER AND DILUTE THE COMBINED FILTRATE AND WASHINGS TO 20.0 ML WITH WATER.

REFERENCE SOLUTION

DISSOLVE 30 MG OF 5-CHLOROSALICYLIC ACID IN 20 ML OF METHANOL AND DILUTE TO 100.0 ML WITH WATER. DILUTE 1.0 ML OF THE SOLUTION TO 100.0 ML WITH WATER.

TO 10.0 ML OF THE TEST SOLUTION AND TO 10.0 ML OF THE REFERENCE SOLUTION ADD SEPARATELY 0.1 ML OF FERRIC CHLORIDE SOLUTION. ANY VIOLET COLOUR IN THE TEST SOLUTION IS NOT MORE INTENSE THAN THAT IN THE REFERENCE SOLUTION (60 PPM).

PREPARATION OF 2-CHLORO 4-NITROANALINE GC

TEST SOLUTION

TO 0.250 G OF THE SUBSTANCE TO BE EXAMINED ADD 5 ML OF METHANOL, HEAT TO BOILING, COOL, ADD 45 ML OF 1 M HYDROCHLORIC ACID, HEAT AGAIN TO BOILING, COOL, AND FILTER AND DILUTE THE FILTRATE TO 50.0 ML WITH 1 M HYDROCHLORIC ACID.

REFERENCE SOLUTION

DISSOLVE 50 MG OF 2-CHLORO-4-NITROANILINE IN METHANOL AND DILUTE TO 100.0 ML WITH THE SAME SOLVENT. DILUTE 1.0 ML OF THE SOLUTION TO 100.0 ML WITH METHANOL. DILUTE 2.0 ML OF THIS SOLUTION TO 20.0 ML WITH 1 M HYDROCHLORIC ACID.

TO 10.0 ML OF THE TEST SOLUTION AND TO 10.0 ML OF THE REFERENCE SOLUTION ADD SEPARATELY 0.5 ML OF A 5 G/L SOLUTION OF SODIUM NITRITE AND ALLOW TO STAND FOR 3 MIN. ADD 1 ML OF A 20 G/L SOLUTION OF AMMONIUM SULPHAMATE, SHAKE, ALLOW TO STAND FOR 3 MIN AND ADD 1 ML OF A 5 G/L SOLUTION OF NAPHTHYLETHYLENEDIAMINE DIHYDROCHLORIDE. ANY PINKISH-VIOLET COLOUR IN THE TEST SOLUTION IS NOT MORE INTENSE THAN THAT IN THE REFERENCE SOLUTION (100 PPM).

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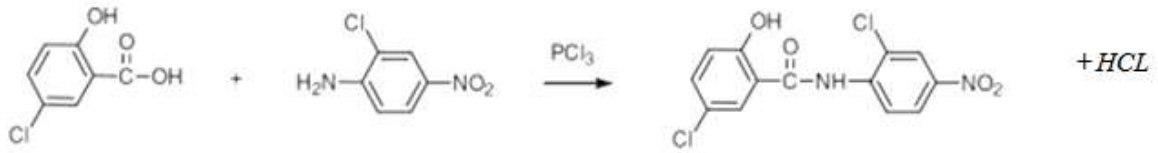
III. FLOW OF SYNTHESIS

ROUTE OF SYNTHESIS

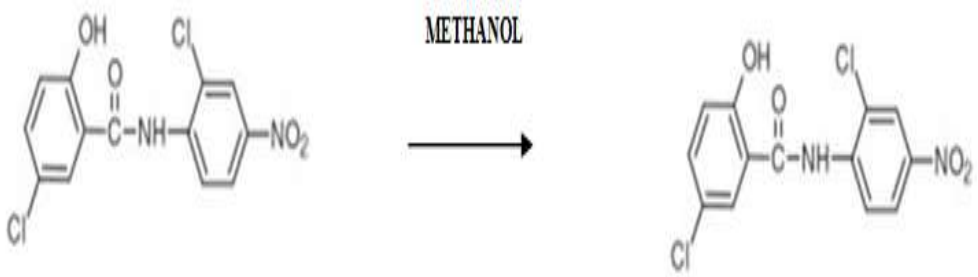


5-CHLORO SALICYLIC ACID	2-CHLORO-4-NITROANILINE	NICLOSAMIDE	HYDROCHLORIC ACID
M.WT:172. 55	M.WT:172.55	M.WT:327. 119	M.WT:36.46

IV. REACTION FLOW

1. TAKE 25 GMS OF 5-CLOROR SALICYLIC ACID AND ADD 200 ML OF TOLUENE WITH 30 GMS OF OCPNA (2-CHLORO 4- NITRO ANILINE) CHARGE THE MIXTURE INTO A 4-NECK RBF AT 30 ° C
2. STIR THE MIXTURE FOR 10 MINUTES AND OBSERVE THE COLOUR OF THE MIXTURE FOR YELLOW
3. IF THE COLOUR IS YELLOW CONTINUE TO STEP 4 ELSE REPEAT STEP 2
4. SLOWLY HEAT THE RM TO 50 ° - 55 ° C
5. SLOWLY ADD 2 GMS OF PCL_3 TO THE RBF WITH THE SUPPORT OF A ADDITIONAL FUNNEL TO THE REACTION MIXTURE
6. RETAIN THE RM FOR 30 MIN AT 50 °C
7. AFTER COMPLETION OF PCL_3 ADDITION SLOWLY RAISE THE TEMPERATURE TO 100 ° C
8. MAINTAIN THE TEMPERATURE AT 100 ° C FOR 10 HOURS WHILE STIRRING THE MIXTURE CONTINUOUSLY MONITOR TEMPERATURE FOR EVERY 30 MIN
9. AFTER 10 HOURS CHECK TLC WITH UV CHAMBER IF IT COMPLIES THEN COOL THE MIXTURE TO 70 °C
10. ONCE THE RM HAS REACHED THE DESIRED TEMPERATURE OF 70 ° C DISTIL TOLUENE USING A VACUUM PUMP
11. ONCE TOLUENE IS COMPLETELY DISTILLED OUT COOL THE RM TO 30 – 35 ° C
12. AT 30 ° C ADD 200 ML OF METHANOL TO THE NICLOSAMIDE TECH
13. HEAT THE RM TO 60 ° C
14. MAINTAIN THE TEMPERATURE OF 60 ° C FOR 60 MINUTES
15. FURTHER COOL THE RM TO 30-35 ° C
16. FILTER THE RM AND DRY IN HOT OVEN

V. PURIFICATION FLOW



Niclosamide Tech Pure Niclosamide

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VI. RECOVERY AND RE-USE OF SOLVENTS AND BY PRODUCTS

HCL IS A BYPRODUCT OBTAINED IN THE REACTION WHICH CAN BE RECOVERED BY DILUTING IT WITH THE HCL WITH WATER AND PASSING IT THROUGH A SERIES OF SCRUBBERS THAT SEPARATES THE CHLORINE AND HYDROGEN

$$HCL\uparrow + H2O \xrightarrow{\text{SCRUBBING}} HCL$$

MOTHER LIQUID OBTAINED FROM THE REACTION FLOW IS DISTILLED WHERE METHANOL CAN BE RECOVERED AND REUSED FOR FURTHER REACTIONS.

$$\text{MOTHER LIQUID} \xrightarrow{\text{DISTILLATION}} \text{METHANOL}$$

REACTION MASS IS DISTILLED OUT IN A HIGHLY CLOSED ENVIRONMENT TO SEPARATE TOLUENE, THIS RECOVERED SOLVENT FOR FURTHER USE IN ANOTHER REACTIONS.

$$\text{REACTION MASS} \xrightarrow{\text{DISTILLATION}} \text{TOLUENE}$$

VII. COMPARATIVE ANALYSIS OF SOLVENTS FOR PURIFICATION

- SEVERAL METHODS OF PURIFICATION ARE BEING TRIED OUT USING ETHANOL, ACETONE, ACETO NITIRILE AND METHANOL BUT THE HIGHEST PURITY AND COMMERCIAL ADVANTAGE LIES IN USING METHANOL AS IT IS A POLAR SOLVENT AND IS AVAILABLE AT COMPETITIVE PRICES.
- THE RESULTS OF THE ABOVE OBSERVATIONS ARE TABULATED AS FOLLOWS

S.NO	Name of Solvent	Chemical Formula	Commercial Viability	Purity Achieved
1	Methanol	CH_3OH	yes	In Range
2	Ethyl Acetate	$C_4\ H_8\ O_2$	No	Not in range
3	Acetone	C_3H_6O	No	Not in range
4	Acetonitrile	$CH_3\ CN$	No	Not in range

VIII. ENVIRONMENTAL FACTOR

- DISTILLATION IS CARRIED OUT IN CLOSED FACILITY WHERE NO VAPORS SHALL ESCAPE TO THE ENVIRONMENT
- IF ANY ORGANIC RESIDUES ARE OBTAINED CEMENT INDUSTRIES CAN USE IT AS BOILER FUEL POLLUTION EQUIPMENTS LIKE MECHANICAL DUST COLLECTOR /CYCLONE DUST COLLECTOR / BAG FILTER AND THE TRACES IF ANY CHIMNEY IS 110 FT HIGH
- HCL GAS IS NOT RELEASED IN TO THE ATMOSPHERE BUT THEY ARE PROCESSED TO BE REUSED WHICH CONTRIBUTES A GREAT EXTENT TO THE ENVIRONMENT

IX. CONCLUSION

Continuous flow organic synthesis is one of the Enabling techniques; it is a promising method in drug discovery. Flow methodology has an edge over pre-existing batch methodologies. Organic transformations spanning from liquid –liquid to solid-liquid-gas systems has shown to benefit the production as the reaction conditions established in a micro reactor need not be re-optimized for scaling up. On experimenting different solvents for purification it is found Methanol is the best solvent as it can be safely recovered and re used for further reactions without causing any harm to the environment. It is also easily available and commercially viable option. If any miscellaneous waste is formed it can be used as a boiler fuel as mentioned in the section eight of the paper.

ACKNOWLEDGMENT

I DEDICATE MY WORK TO MY BELOVED PARENTS

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