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Synthesis of Bromo Acid by Solvent and Catalyst-Free Reaction

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Abstract:- Chemistry is an extremely significant field of study. In the pharmaceutical industry chemistry plays an important role in formulating the drug. Nowadays , when a drug is to be synthesized everyone is looking towards the simple and non-tedious chemical reaction which can be done by using less use of materials, In the past decades, the approach of making organic reactions sustainable and innovative , various new methodologies by making it solvents or catalysts-free and applying alternative energy sources such as microwaves, sonication, conventional and room temperature heating conditions, mechanochemical mixing, and high-speed ball milling are becoming popular. All are approaching towards the Green Chemistry method which provides "Green" paths for different synthetic routes using non-hazardous solvents and environmental- friendly chemicals. By application of this approach the synthesis of bromo acids has been done using the sonication process.

Keywords: *Bromo Acid, Sonication, Green Chemistry, IR Spectroscopy.*

I. INTRODUCTION

A solvent-free reaction may be carried out by using the reactants alone or incorporating them with other safe catalyst to attain high degree of stereoselectivity in the product, to reduce the by-product and to maximize the rate of reaction. Solvent-less technology has many advantages from the viewpoint of both academy and industry. Two of twelve principles of "Green Chemistry" are "use of safer solvent and reactions condition" and to "prevent waste" and both these principles are directly met by eliminating a reaction medium. Solvent-free and/or solvent-less protocol is frequently exhibiting remarkable rate of acceleration due to the increased reaction conditions with some of them occurring under ambient situation i.e., at room temperature, microwave irradiation, ball milling etc**.**

➢ *Objectives:*

The main objectives of our research project are:

- To design a catalyst-free and solvent-free system to synthesize 3-bromo benzoic acid
- To implement and promote green chemistry
- To find out the novelty of the synthesized method
- To understand the chemistry of the desired product
- Selection of the correct reaction method by trial-and-error systems

➢ *Catalyst Free Organic Synthesis:*

Catalysts usually promote faster chemical reactions and for some reactions the desired selectivity (regioselectivity or chemo selectivity) can be obtained using specific selective sites of them. Conventional catalysts/additives are usually associated with higher costs, toxicity, and non-reusability and thereby generating more wastes. From the green chemistry perspectives, significant efforts have been made to improve overall applicability of catalytic substances from suitable modifications and/or innovation of new kinds of catalysts with multiple benefits. However, the most useful way for designing an organic reaction protocol without the aid of a catalyst. Catalyst-free synthetic processes provide benefits to get rid of toxicity and wastes related with using these catalysts. Hence, designing of catalyst-free synthetic processes to improvise toward safe, cost-effective, waste-free, simple, and sustainable environment. It is often observed that suitably selected starting materials can undergo self-catalysis in suitable solvents (preferably in aqueous or aqueous ethanolic medium) in many conditions and/or the solvents can also yield catalytic benefits to certain reaction processes from their unique inherent properties. Reactions can also be promoted by using simple conventional heating in the presence or absence of solvent(s), and by the applications of microwave irradiation, ultrasound irradiation and mechanochemical mixings.

➢ *Solvent Free Organic Synthesis:*

Solvent-free synthesis is an alternative method to traditional solution-based synthesis. Solvent-free synthesis has various advantages over the traditional method of

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synthesis and that it is a type of green chemistry where little or no solvents are used and environmentally friendly chemicals are used. The advantages of solvent-free reactions are:

- Economic (cost saving, save money on solvent)
- Not necessary to collect, purify, recycle, and remove solvent after completion of reaction.
- Due to more availability of reactants, the reaction rate is generally high.
- Environmentally friendly
- Decreased of energy consumption
- Large reduction in batch size volume (reactor size) and capital investment.

➢ *Sonicator:*

Sonication is the process of applying sound energy to agitate particles in a liquid. Ultrasonic frequencies greater than 20 kHz is used; therefore the process is also known as ultrasonication. Sonication can be done using either an ultrasonic bath or an ultrasonic probe (sonicator) which converts an electrical signal into a physical vibration to break substances apart. This interference can mix solutions, accelerate the dissolution of a solid into a liquid, such as sugar into water, and remove dissolved gas from liquids.

- *Sonication Process:*

During sonication, cycles of pressure form thousands of microscopic vacuum bubbles in the solution. The bubbles collapse into the solution in a process known as cavitation. This causes powerful waves of vibration that release an extensive energy force in the cavitation field, which disrupts molecular interactions such as interactions between molecules of water, separates clumps of particles, and facilitates mixing. The energy from sound waves creates resistance in the solution, which creates heat. To stop a sample from heating up and degrading, keep it on ice before, during and after sonication.

Fig 1 Sonication Process

- *Green Aspects of Sonication Process:*

Ultrasound- Assisted organic synthesis is applied in many organic synthetic routes with advantages such as-

✓ High efficiency
✓ Low waste
✓ Low energy requirements
✓ Ability to disperse reagent in small particles and accelerate reactions

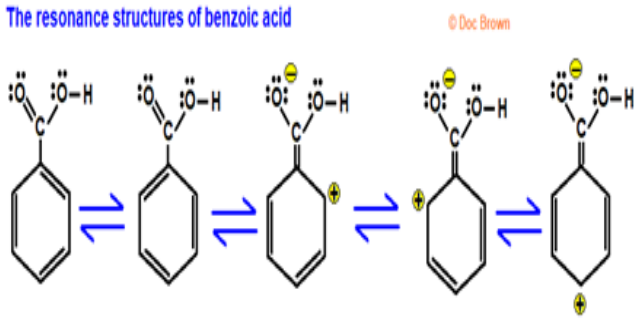
Sonication chemistry enhances or promotes chemical reactions and mass transfer and offers the advantage for shorter reaction cycles, cheaper reagents, and less physical conditions. Existing literature on sonication chemical reacting systems is chemistry-intensive. Applications of this novel method provides a means of reaction in environmentally friendly and pollution prevention which seem almost unlimited and is rapidly growing area.

- *Experimental Details:*

✓ *Requirements:* Conical flask, Glass rod, Spatula, Beaker, Butter paper, Weighing machine, funnel, Whatmann filter paper, Sonicator
✓ *Chemicals:* Benzoic acid LR, Benzoic acid extra pure, Bromine liquid, KBrO3, Acetic acid, Ethanol, NaOH, conc. HNO3, AgNO3 solution, Na metal

II. PRINCIPLE

The reaction of benzoic acid to m-bromobenzoic acid/ 3-bromo benzoic acid occurs through electrophilic substitution reaction means the replacement of any of the atoms of a parent compound by an electrophile. Electrophiles are electron loving species i.e.; they always attack at the region of maximum electron density. If we draw the structure of benzoic acid, we will find that the pi electrons of carbonyl group of COOH is in conjugation (alternate single and double bonds) with the pi electrons of the benzene ring. As a result, the pi electrons are delocalized (they move from their original positions) resulting into a number of structures which are in equilibrium with each other. In each of these structures, either the ortho carbon or the para carbon acquires a positive charge. It is only the meta carbon that does not acquire positive charge. That is, electron density always remains maximum at the meta position. So, it is quite natural that electrophile will always attack at the meta position. Therefore, electrophilic substitution in benzoic acid always occurs at the meta position.



➢ *General Reaction of Converting α- Carboxylic Acid to Bromo Derivative*

- *Hell-Volhard-Zelinsky Reaction:*

Treatment of carboxylic acid with bromine and a catalytic amount of phosphorus leads to the selective α-bromination.

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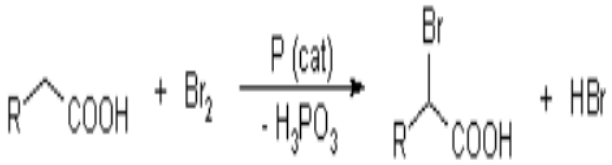
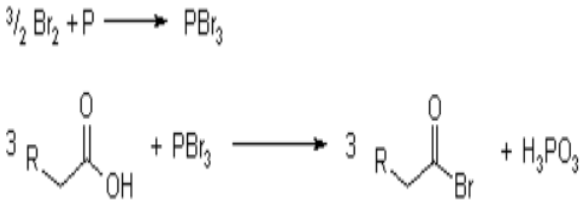
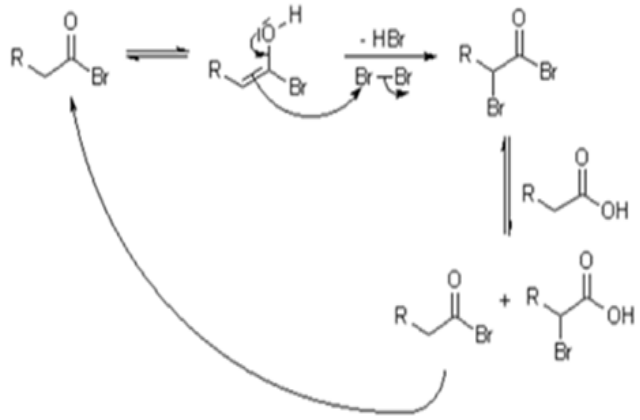


- *Mechanism of the Hell-Volhard-Zelinsky Reaction:*

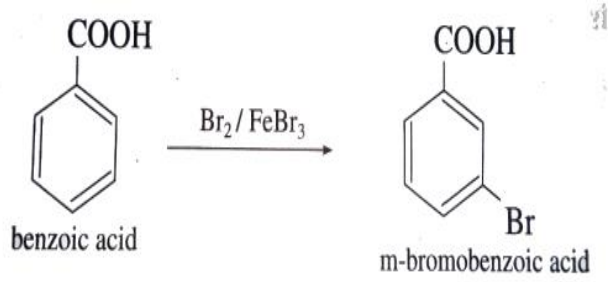
Phosphorus reacts with bromine to give phosphorus tribromide, and this converts the carboxylic acid into an acyl bromide.



An acyl bromide can readily exist in the enol form, and this tautomer is rapidly brominated at the α-carbon. The mono brominated compound is much less nucleophilic, so the reaction stops at this stage. This acyl intermediate compound can undergo bromide exchange with unreacted carboxylic acid via the anhydride, which allows the catalytic cycle to continue until the conversion is complete.



➢ *General Reaction of Converting Benzoic Acid to 3-Bromo Benzoic Acid:*



- Synthesis of m-bromo benzoic acid/ 3-bromo benzoic acid takes place by reaction benzoic acid with Br2 and FeBr3 as a catalyst.
- As discuss earlier, the substitution of bromine at the meta position occurs via electrophilic reaction.
- The role of FeBr3 is to give the meta substituted bromo benzoic acid.

➢ *Hazards of Bromine use:*

- May be harmful if swallowed.
- Causes severe skin burns and eye damage.
- Fatal if inhaled.

➢ *Precaution Taken During Handling of Bromine:*

- Do not breathe fume/gas/mist/vapours/spray.
- Avoid release to the environment.
- Wear protective gloves/protective clothing/eye protection/face protection.
- Wear respiratory protection.

➢ *Scheme 1:*

1.5 gm of Benzoic Acid LR + 5 ml of Bromine was taken in a beaker and the reaction was carried out in an open system. The beaker was placed in a Sonicator. Time Cycle for the reaction to completion was 1 hr 20 min. At 30 min, white small crystals were started to form at inside the walls of the beaker and water was added almost 2/4 th of the beaker and heated for 15 min on Sonicator. After completion of cycle, white solid crystals were formed and allowed to settle down and filtered. Solid crystals were separated and dried in hot air oven for 30 min at 80**°C.** Pale orange coloured product was obtained. Qualitative tests were performed on the crystals for detection of functional groups.

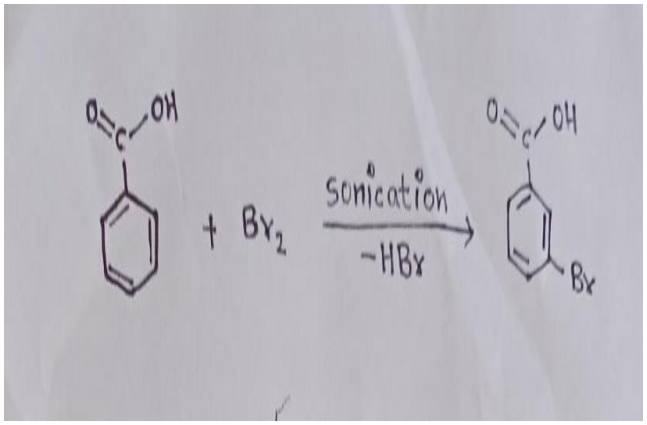


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Table 1 Preliminary Tests and Physical Evaluation for Scheme 1

TESTS	OBSERVATION	INFERENCE
1.Colour	Colourless: solids	Aromatic acids may be present
2.Odour	Pleasant odour	Aromatic hydrocarbon present
3. Solubility behavior: 0.1 gm of solid + 3ml of solvent. Shake thoroughly. If the sample does not dissolve, warm gently and cool again to room temperature before assessing the solubility	Insoluble in water But dissolves readily in 2N NaOH	Acidic compounds like phenols, carboxylic acids, acid anhydrides may be present
4. Heating on a copper gauze	Sooty flame	Aromatic compound containing more than 4 carbon atoms
5. Heating in a dry test tube	Compound melts/sublimes	Benzoic acid present
6. Action of potassium permanganate: Dissolve 0.2 gm solid in 2 ml of water then add few drops of neutral KMnO4 solution to it.	Decolorization	Unsaturated compounds present

- *Elemental Analysis:*

It is a qualitative analysis of an unknown organic sample consists of detection of chemical composition i.e., Elements present the organic sample. Carbon and hydrogen are main constituents. In addition to this samples contain sulphur, nitrogen, halogens which can be detected by sodium fusion test, which is also known as Lessaignen's test.

✓ *Lessaignen's Test:*

In this test the elements in the organic sample are converted into ionizable inorganic substances so that ionic tests can be done for their detection.

Table 2 Lessaignen's Test

TEST	OBSERVATION	INFERENCE
Test for halogen: a) Silver Nitrate test: 2 ml of sodium extract is boiled with 1 ml of conc. HNO3, the mixture is cooled and AgNO3 solution is added	No yellow ppt	Br absent

✓ *Detection of Functional Group:*

Table 3 Tests for Carboxylic Groups

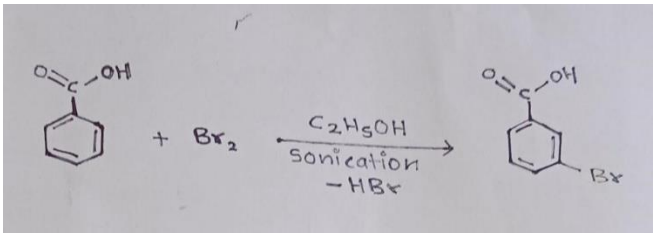
TESTS	OBSERVATION	INFERENCE
1) Take 0.2gm of compound + 2ml of NaHCO3	Strong evolution of CO2	-COOH group is present
2) Ester test: 0.2 gm of compound + 2ml conc. H2SO4 warm and add one or two drops of ethyl alcohol	Fragrant smell	-COOH group present
3) Neutral Test Solution: 0.5 gm of compound+ 1 ml water + phenolphthalein solution + ammonia solution till just alkaline. Now boil to remove excess of NH3.Complete removal to be tested through litmus paper, cool and few drops of aqueous FeCl3	A buff colored ppt	Benzoic acid present

▪ *Conclusion:*

As the required elemental group i.e., Bromine is not detected from the performed tests, this scheme fails to give the bromo derivative of benzoic acid.

➢ *Scheme 2:*

2 gm of Benzoic Acid + 5 ml of Bromine + 10 ml of ethanol in beaker was taken and placed on Sonicator. Time cycle required for completion of reaction is 1 hr 10 min. As crystals were not seen in the beaker addition of 15ml of distilled water + 5 ml of ethanol was done to see whether the crystals are forming or not Again, placed on Sonicator for 30 min. No crystals were obtained.



• *Conclusion:*

As not product was obtained, this scheme fails.

Fig 2 Scheme 2

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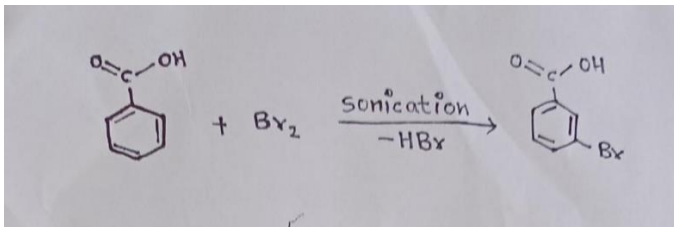
Table 4 Preliminary Tests and Physical Evaluation for Scheme 2

TESTS	OBSERVATION	INFERENCE
1.Colour	Colourless: solids	Aromatic acids may be present
2.Odour	Pleasant odour	Aromatic hydrocarbon present
3.Solubility behavior: 0.1 gm of solid + 3ml of solvent. Shake thoroughly. If the sample does not dissolve, warm gently and cool again to room temperature before assessing the solubility	Insoluble in water But dissolves readily in 2N NaOH	Acidic compounds like phenols, carboxylic acids, acid anhydrides may be present
4.Heating on a copper gauze	Sooty flame	Aromatic compound containing more than 4 carbon atoms
5.Heating in a dry test tube	Compound melts/sublimes	Benzoic acid present
6.Action of potassium permanganate: Dissolve 0.2 gm solid in 2 ml of water then add few drops of neutral KMnO4 solution to it.	Decolorization	Unsaturated compounds

➢ *Scheme 3:*

1.5 gm of benzoic acid + 5 ml of bromine was taken in a conical flask and closed with the cotton plug to avoid escape of bromine vapours. Conical flask was kept on Sonicator. Time cycle required for completion of reaction was 5 hr 30 min. Intermittent shaking of flask was taken place during the process. After completion of process the product obtained was filtered and separated. Solid crystals were separated and dried in hot air oven for 30 min at 80**℃.** Qualitative tests were performed on the crystals for detection of functional groups.



- *Lessaignen's Test:*

In this test the elements in the organic sample are converted into ionizable inorganic substances so that ionic tests can be done for their detection.

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Table 5 Lessaignen's Test

TEST	OBSERVATION	INFERENCE
Test for halogen: A) Silver Nitrate test: 2 ml of sodium extract is boiled with 1 ml of conc. HNO3, the mixture is cooled and AgNO3 solution is added	Yellow ppt	Br present
B) Chlorine water test: I f a yellow ppt is obtained in test (A) then 1 ml of sodium extract id acidified with 1 ml of dilute H2SO4 and 1 ml of CCL4 is added to it. A strong Cl2 water is added drop wise with shaking	The organic layer turns brown or reddish brown	Br present

- *Detection of Functional Group:*

Table 6 Tests for Carboxylic Groups

TESTS	OBSERVATION	INFERENCE
1) Take 0.2gm of compound + 2ml of NaHCO3	Strong evolution of CO2	-COOH group is present
2) Ester test: 0.2 gm of compound + 2ml conc. H2SO4 warm and add one or two drops of ethyl alcohol	Fragrant smell	-COOH group present
3) Neutral Test Solution: 0.5 gm of compound+ 1 ml water + phenolphthalein solution + ammonia solution till just alkaline. Now boil to remove excess of NH3.Complete removal to be tested through litmus paper, cool and few drops of aqueous FeCl3	A buff colored ppt	Benzoic acid present

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✓ *Conclusion:*

From the above tests performed it is concluded that the groups required in the desired product is confirmed. So this scheme passes for the bromo derivative of benzoic acid.

For more conformation of product FTIR is done for the compound.

➢ *Infrared Spectroscopy:*

Infrared spectroscopy is widely used in industry as well as in research. IR is most useful in providing information about the presence or absence of specific functional groups. Entire IR region is divided into group frequency region and fingerprint region. Range of group frequency is 4000-1500 cm-1 while that of finger print region is 1500-400 cm^{-1}usually contains a very complicated series of absorptions, frequently overlapping each other, mainly due to all kinds of bending or stretching vibrations. In group frequency region, the peaks corresponding to different functional groups can be observed. According to corresponding peaks, functional group can be determined. Each atom of the molecule is connected by bond and each bond requires different IR region so characteristic peaks are observed. This region of IR spectrum is called as finger print region of the molecule. It can be determined by characteristic peaks. Small differences in structure & constitution of molecule can result in significant changes in the peaks in this region. Hence this region helps to identify an unknown compound. The position and magnitudes of peaks in the spectrum is compared with profiles of pure compounds stored Identification is done based on position of absorption bands in the spectrum.

➢ *FTIR Spectra:*

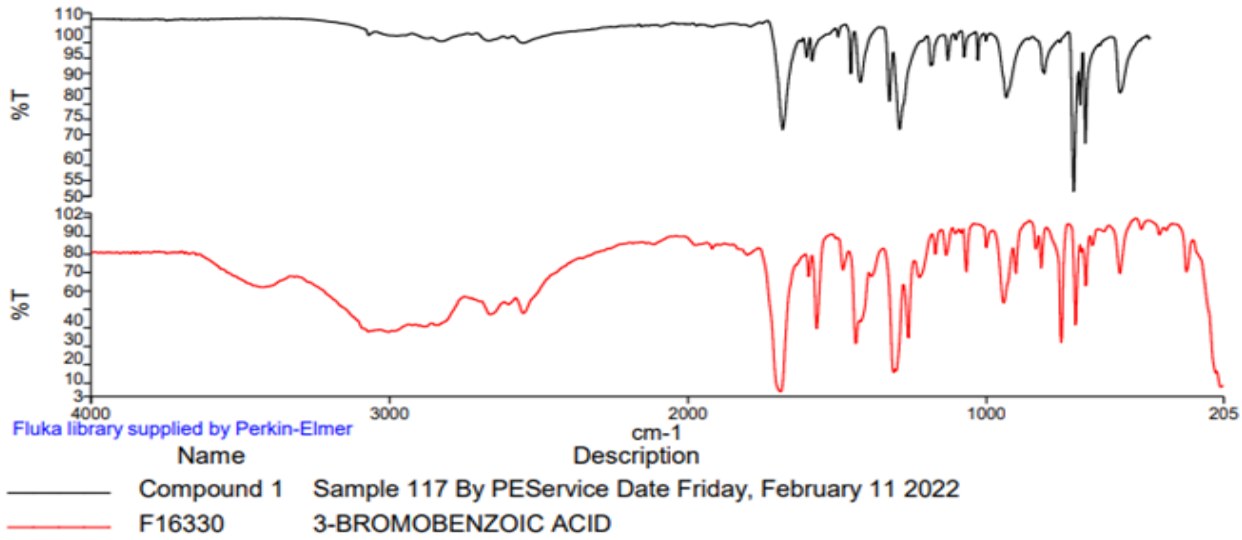

Fig 3 FTIR Spectra

➢ *IR Interpretation:*

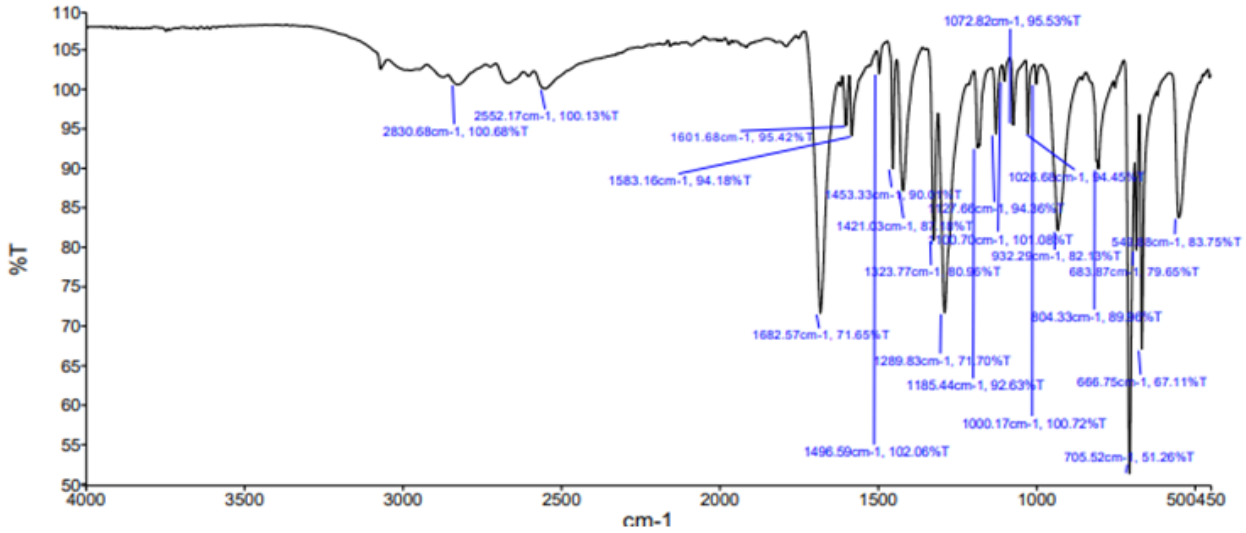

Fig 4 Spectrum Graph

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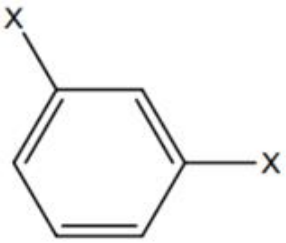
Table 7 IR Interpretation

FUNCTIONAL GROUP	NORAMAL FREQUENCY RANGE (cm^{-1})	OBSERVED FREQENCY RANGE	APPERANCE OF PEAK/INTENSITY	WHY SHIFT IN FREQUENCY RANGE
C=O of Carboxylic acid	1730 - 1700	1682.57	strong	Because of OH (E.W.G) attached to carbonyl group
OH of carboxylic acid	3300-2400	2830.68	medium	Intramolecular hydrogen bonding
C-H stretching of aromatic ring	3100 - 3000	Between 3500 and 3000	small	-
C=C of aromatic ring	1600-1475	1583.16	Weak-medium	-
C -Br	690-515	705.52	strong	Due to stretching vibrations

From the above IR Spectrum graph, we have got the IR frequency of **705.52 cm-1** which is of **Meta Disubstituted Aromatic Compound.**



meta disubstituted aromatic — 680-725, 750-810, 880-900 (sometimes)

By above IR interpretation data, it is now clear that the IR spectra of the groups containing in the product obtained is confirm. Therefore, we concluded that the 3-bromo benzoic acid is obtained.

➢ *Scheme 4:*

10.6 ml of Acetic Acid + 4g of KBrO3 + 6 ml of Bromine was taken in a conical flask and closed with the cotton plug to avoid escape of bromine vapours. This conical flask was placed on sonicator. Time cycle for completion of the reaction was 7 hrs Intermittent shaking of flask was taken place during the process. After completion of process the product obtained was filtered and separated. Solid crystals were separated and dried in hot air oven for 30 min at 80**℃** Qualitative tests were performed on the crystals for detection of functional groups.

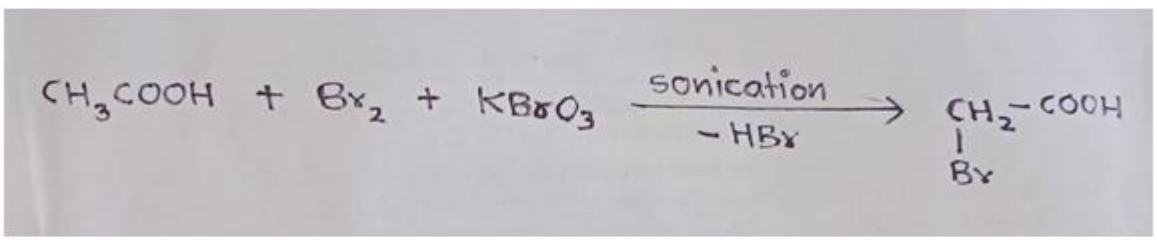


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Table 8 Preliminary Tests and Physical Evaluation for Scheme 4

TEST	OBSERVATION	INFERENCE
1.Colour	Colourless solid	Aliphatic carboxylic acids may be present
2.Heating in a clean dry test tube: small quantity of the given sample (solid) is heated in a clean, dry test tube, first gently and then strongly.	Sharp melting	Pure organic compound may be present
3.Solubility: Take about 0.1 g of solid sample in a test tube and treat it with about 3 ml of the solvent. Shake well. Warm if necessary and cool to room temperature and observe.	Soluble in water - acidic	Carboxylic acid may be present
4.Heating on a copper gauze: Take a small copper foil and heat it in the flame. Place 0.2 g if solid on it and heat in the flame.	Non sooty flame	Aliphatic compound

- *Lessaigne's Test:*

Table 9 Lessaigne's Test

TEST	OBSERVATION	INFERENCE
Test for halogen: b) Silver Nitrate test: 2 ml of sodium extract is boiled with 1 ml of conc. HNO3, the mixture is cooled and AgNO3 solution is added	No yellow ppt	Br absent

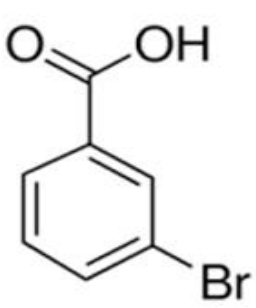
✓ *Conclusion:*

As bromine is not confirm through this test, this scheme fails to give the desired Product.

III. RESULT & DISCUSSION

From the 4 schemes performed, only 3rd scheme was successful for giving the desired product i.e., 3-bromo benzoic acid. After confirmation physical & chemical properties of 3- bromo benzoic acid was determined and reported.

➢ *Compound:*



- *Name* - 3-bromo benzoic acid
- *Synonyms* - m-bromo benzoic acid
- *Molecular Formula* - C7H5BrO2
- *Molecular Weight* - 201.017
- *Melting Point*- 155 – 158 °C
- *Appearance (Form)* - Powder or crystals
- *Appearance (Colour)* - White to yellow
- *Solubility* - Insoluble in water Soluble in methanol

➢ *Application*

- As test solute in the determination of acidity constants by capillary zone electrophoresis.
- As internal standard to study the retention mechanisms of an unmodified and a hydroxylated polystyrene-divinylbenzene polymer by solid-phase extraction.
- In synthesis of N-(1,1-dimethyl-2-hydroxyethyl)-3-bromobenzamide.

IV. CONCLUSION

Various schemes were performed reacting the various reagents at different volumes and different techniques. From the above results, the scheme 3 was only successful to give the product 3-bromo benzoic acid. Once the product was obtained, firstly the preliminary tests and functional group detection test was done to confirm the groups present in the structure. For final confirmation Infrared Spectroscopy was done on the product by which we came to conclusion that the desired product was obtained. As our main aim was to synthesize product by solvent and catalyst free, scheme 3 is best fit for these results and successful. The schemes performed follow the principles given in the green chemistry and the techniques used was by sonication. By the trial-and-error system, new method of synthesizing the product is formed which is novel and there is no evidence of this in any literature. The conclusion of this project is that the 3-bromo benzoic acid is synthesize by solvent and catalyst free reaction which is Novel and a Green Method.

REFERENCES

[1]. Ouellette, Robert J. (2014). Organic Chemistry || Electrophilic Aromatic Substitution., (), 417-451. Available form: https://doi.org/10.1016/B978-0-12-800780-8.00013-9

[2]. Dagani MJ, Barda HJ, Benya TJ, Sanders DC. Bromine compounds. Ullmann's encyclopedia of industrial chemistry. 2000 Jun 15. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1002/14356007.a04_405

[3]. Martínez RF, Cravotto G, Cintas P. Organic Sonochemistry: A Chemist's Timely Perspective on Mechanisms and Reactivity. the Journal of Organic Chemistry. 2021 Jun 22;86(20):13833-56. Available from: https://dx.doi.org/10.1021%2Facs.joc.1c00805

[4]. Puri S, Kaur B, Parmar A, Kumar H. Applications of ultrasound in organic synthesis-a green approach. Current Organic Chemistry. 2013 Aug 1;17(16):1790-828. Available from: http://dx.doi.org/10.2174/13852728113179990018

[5]. Crawford DE. Solvent-free sonochemistry: Sonochemical organic synthesis in the absence of a liquid medium. Beilstein journal of organic chemistry. 2017 Sep 4;13(1):1850-6. Available From: https://doi.org/10.3762/bjoc.13.179

[6]. Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University), Prof. Steven Farmer (Sonoma State University), Layne Morsch (University of Illinois Springfield).Alpha Bromination of Carboxylic Acids [Internet]. 2021 [cited 2022 May 7]. Available from: https://chem.libretexts.org/@go/page/36415

[7]. Dr.K.R.Mahadik, Dr.S.H.Bhosale:A Handbook of Practical Chemistry Inorganic and Organic Chemistry. Nirali Prakashan Publishers & Distributers, Thirteen Edition, May 2016

[8]. Donald L. Pavia, Gary M. Lampman, George S. Kriz, James R. Vyvyan: Introduction to Spectroscopy. Cengage Learning, Fifth Edition,2015

[9]. MERCK | INDIA – SIGMA-ALDRICH, 3-Bromobenzoicacid. Available from: https://www. Sigmaaldrich.Com/IN/ en/product/aldrich/186295

[10]. PubChem [Internet]. Bethesda (MD): National Library of Medicine (US), National Center for Biotechnology Information; 2004-. PubChem Compound Summary for CID 11456, 3-Bromobenzoic acid; [cited 2022 May 7]. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/3-Bromobenzoic-acid

[11]. APPLICATIONS OF IR SPECTROSCOPY: Pharma Tutor, 22 March 2010 Available From: https://www. pharmatutor.org/pharma-analysis/analytical-aspects-of-infra-redspectroscopy-ir/application-ir-spectrophotometry