GREEN SYNTHESIS OF SUBSTITUTED PHENYL ACETIC ACIDS

DISSERTATION

Submitted In Partial Fulfilment Of

The Degree of MSc. (Organic Chemistry)

By

PRIYANKA MANJUNATH NAIK

To

School Of Chemical Sciences

Goa University

Goa 403206

APRIL 2020

STATEMENT

I hereby declare that the matter presented in this dissertation entitled, **"Green Synthesis Of Substituted Phenyl acetic Acids"** is based on the results of investigations carried out by me in the School of Chemical Sciences, Goa University under the supervision of **Ms. Siddhali V. Girkar**, School of Chemical Sciences, Goa University and the same has not been submitted elsewhere for the award of a degree or diploma.

Priyanka Manjunath Naik

CH-18-053

MSc. Part-II

Organic Chemistry

Date :

Place : School Of Chemical Sciences, Goa University

Goa , 403206

CERTIFICATE

This is to certify that the dissertation entitled, **"Green Synthesis Of Substituted Phenyl acetic Acids"** is a bonafide work carried out by **Miss. Priyanka Manjunath Naik** under my supervision in partial fulfilment of the requirement for the award of the degree of Master of Science in Chemistry at the School of Chemical Sciences, Goa University.

Ms. Siddhali V. Girkar

Project Supervisor

School Of Chemical Sciences

Goa University

CERTIFICATE

This is to certify that the dissertation entitled, **"Green Synthesis Of Substituted Phenyl acetic acids"** is a bonafide work carried out by **Ms. Priyanka Manjunath Naik**, under the supervision of **Miss. Siddhali V. Girkar** for the award of the degree of Master of Science in Chemistry at the School of Chemical Sciences , Goa University.

Prof. V. S. Nadkarni

Dean ,

School of Chemical Sciences

Goa University

ACKNOWLEDGEMENT

It gives me immense pleasure to present my dissertation topic **"Green synthesis of substituted Phenyl acetic acids".**

I express my gratitude and sincere thanks to my project guide **Ms. Siddhali V. Girkar,** Assistant Professor, School of Chemical Sciences, Goa University, for her valuable guidance, suggestions and help extended during my dissertation without which dissertation would have not been successfully completed.

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I would also like to thank **Mr. Prajyot Chari** for recording the IR spectra of my compounds.

My deep sense of gratitude goes to all my friends and my batch mates who have shared their thoughts and for their support and co-operation all the way through my dissertation work.

Last but not the least I wish to thank my parents for their moral support and financial assistance, without whom, I would have not been able to pursue my studies. Their encouragement has given me a lot of confidence during the project work as it could successfully reach to completion.

Above all, I owe it to God the Almighty for being with me always.

ABBREVATIONS

GENERAL ABBREVATIONS

MEASUREMENT

Aq - Aqueous

Eqiv - Equivalent

Fig. - Figure

Min - Minutes

Mmole - Millimole

M,p. - Melting point

r.t - Room temperature

°C - Degree Celsius

mL - Millilitre

g. - Grams

TECHNIQUES

TLC - Thin Layer Chromatography

IR - Infra red

cm^{-1} - Frequency in wave number

SOLVENTS

EtOH - Ethyl Alcohol

NaOH - Sodium Hydroxide

H_2O_2 - Hydrogen Peroxide

H_2O - Water

GENERAL REMARK

- IR spectra were recorded on a Shimazdu FTIR-spectrophotometer (solid-KBr pellets).
- All the melting points were measured by normal Thiels tube method and are corrected.
- Distilled solvents used in all cases.
- Commercial reagents were used without further purification.
- All solvents and reagents were purified and dried by standard techniques.
- All the reactions were monitored by Thin Layer Chromatography (TLC) on silica gel (13% $CaSO_4$ as binder).
- Room temperature = 25-30°C.

CONTENTS

INTRODUCTION

INTRODUCTION:

Phenyl acetic acid is an organic compound which contains a phenyl functional group and a carboxylic acid functional group. It has many applications, due to its nice odour it is used in perfumes. It is used in Pencillin G production and diclofenac production.

Phenyl acetic acids are very important compounds as they are showing wide range of biological activity i.e antibacterial, analgesic, virucidal, prostaglandin synthetase response, plant growth regulator, etc. They are used as important intermediates in the syntheses of benzamido and phenylacetamido phenyl benzoxazole derivatives; N-(aryl/heteroaryl acetyl) amino acid esters; caprolactams, benzodioxinones, imidazoles, N-(propynyl) aryl acetamides, phenyl furanone , halobenzyl isoquinolines, estradiene and estratriene and anticancer calcium channel blockers.[1]

Substituted phenyl acetic acids can be prepared from different conventional and green methods. A key theme recently implemented is the development of more environmentally benign synthetic reactions. This approach involves the development of non-thermal, catalyst and solvent-free processes, as well as the identifying of solvents and catalysts that can be recovered and subsequently re-used.[2]

All phenyl acetic acids have been synthesized by[1]

(1) Rhodium catalyzed carbonylation.
(2) Hydrogenation of Mandelic acid derivatives to the corresponding phenyl acetic acid derivatives catalysed by Pd/C.
(3) Carbonylation of benzyl choride in the presence of water soluble complex [$PdCl_2$ $\{PPh_2(m\text{-}C_6H_4SO_3Na)\}_2$] and surfactants under two phase conditions.
(4) Microwave induced Willgerodt-Kindler reactions of styrenes.
(5) Production of phenyl acetic acid by liquid phase oxidation of acetophenone with sulphur in the presence of aqueous ammonia.

Although , all these methods have some limitations such as long reaction times, hazardous reaction conditions and use of microwave ovens which are not commonly available in all the research laboratories. Therefore in view of the above said limitations and their pharmaceutical and biological importance, there is a need to develop a new and efficient method for the synthesis of biologically active phenyl acetic acids under mild and eco friendly reaction conditions.[1]

Most of the methods of synthesis of phenyl acetic acids proceed through the formation of **thiomorpholides.**

Thiomorpholides are carboxylic acid derivatives that have recently become very important functional group in organic synthesis and medicinal chemistry. In particular, thioamides have proven useful as building blocks for the synthesis of numerous biologically relevant heterocylic scaffolds. Thioamides exhibit many interesting properties, for example typically the thioamide -NH is a stronger hydrogen donor and the sulphur a weaker hydrogen bond acceptor than the corresponding amide. In addition, when compared to amides and formamides, thioamides possess different bond lengths and bond rotation characteristics and these unique properties have been exploited in both medical chemistry (including peptidomimetics) and polymer chemistry applications.[2]

LITERATURE REVIEW

LITERATURE REVIEW:

The green synthesis of substituted phenyl acetic acids occur via three steps:

Step 1- Synthesis of acetophenone.

Step 2- Formation of thiomorpholide.

Step 3- Hydrolysis of thiomorpholide to yield phenyl acetic acid.

SYNTHESIS OF ACETOPHENONES

METHOD 1-Synthesis of Acetophenones by direct acylation of phenols and naphthol derivatives in a mixture of Graphite and methanesulfonic acid[3]

The o-hydroxyaryl ketones are versatile intermediates in the synthesis of xanthones, chromanones, flavones, pharmaceutical compounds and low-molecular weight mesogens among others. Although the Fries rearrangement of acyloxy benzenes or naphthalenes provides useful routes to these compounds , more than a stoichiometric amount of $AlCl_3$ is required because the acid is trapped by the products. An alternative method is direct acylation of phenol and naphthol derivatives. These reactions have been carried out by using more than a stoichiometric amount of $AlCl_3$; treatment of the aluminium residue has sometimes induced environmental problems and the drastic reaction conditions have caused some severe side reactions.

Furthermore, acid chlorides and acid anhydrides are commonly used as acylating reagents in these reactions. These reagents are usually prepared from carboxylic acids and therefore, it would be desirable if the acylations could be carried out by using carboxylic acids directly as acylating agents.

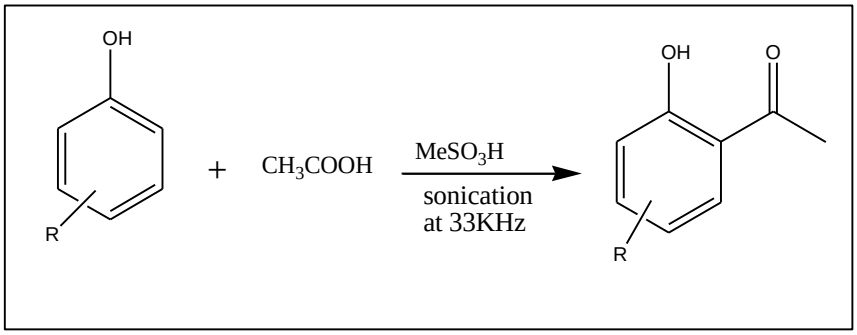
The most important objective is to adapt classical processes so that pollution effects are kept to minimum with both a reduction in energy and consumption of raw materials. In this respect, dry media reactions are promising and a new approach has been undertaken using graphite chemistry.

Graphite has an exceptional ability to adsorb organic molecules and it once used can be recycled.

Methanesulfonic acid is used as green catalyst due to its high acid strength (pKa=-1.9) and low molecular weight (96.0g/mol).It is easy to handle and can be recycled. It is less corrosive and toxic than other mineral acids.

METHOD 2- *Synthesis of o-hydroxy ketone under ultrasound condition*[4]

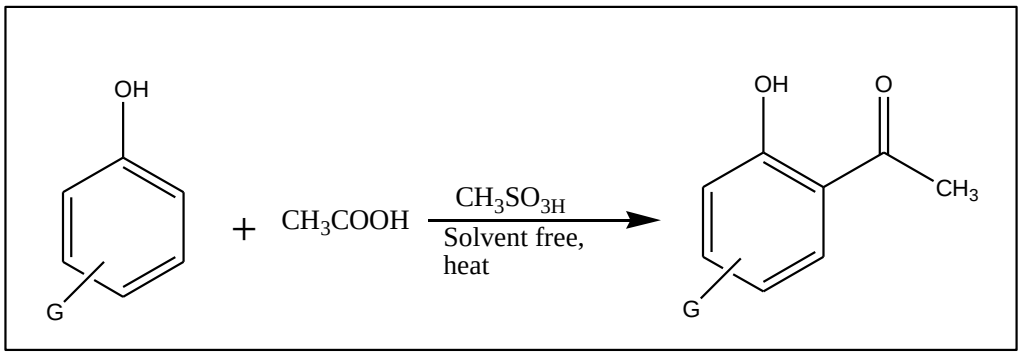
In recent years ultrasound reactions attracted attention of most of the researchers due to reactions are fast, carried out solvent free and use of non-conventional heating.



Methane sulphonic acid has high acid strength and biodegradable acid. We use its high acid strength in ortho acylation of phenol under sonochemical conditions.

METHOD 3-*Solvent free direct ortho C-acylation of phenolic systems by methanesulfonic acid as catalyst*[10]

Hossein Naeimi et. Al (2011) reported that direct C-acylation of phenolic systems under solvent free condition can be done by using methanesulfonic acid as catalyst.



SYNTHESIS OF THIOMORPHOLIDES

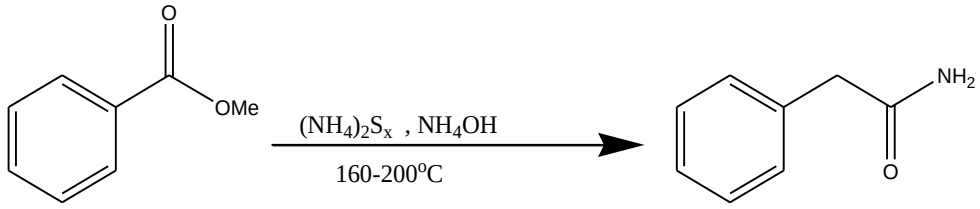
After the synthesis of starting material i.e. acetophenone, second step is the synthesis of thioacetamides.

Thioamides are traditionally prepared by thionation of the corresponding amides using phosphorus pentasulfide or the Lawesson reagent. Other protocols that have been developed for thioamide synthesis include the thiolysis of nitriles (or iminium salts), a Friedal-Crafts type of reaction of thiocyanates and the thiocylation of amines.[2]

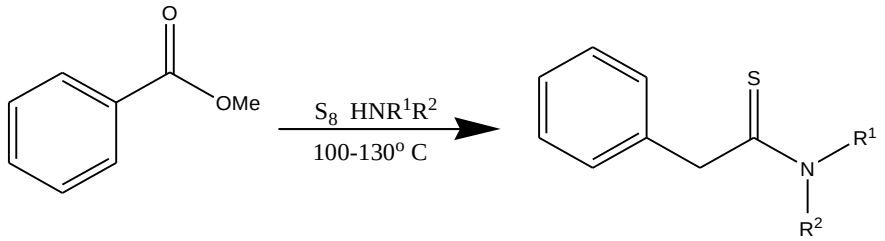
The Willgerodt-Kindler reaction was first described by Conrad Willgerodt in 1887 and involves the oxidation/rearrangement of ketones to form a terminal amide or the ammonium salt of the corresponding carboxylic acid. This synthetic transformation was traditionally performed using ammonium polysulfide, however in 1923, Karl Kindler reported a

modification of this reaction, which involved the use of elemental (S_8) and secondary amine, such as morpholine under thermal conditions to afford the thioamide derivative.[2]

The Willgerodt Reaction [2]



The Kindler Modification[2]

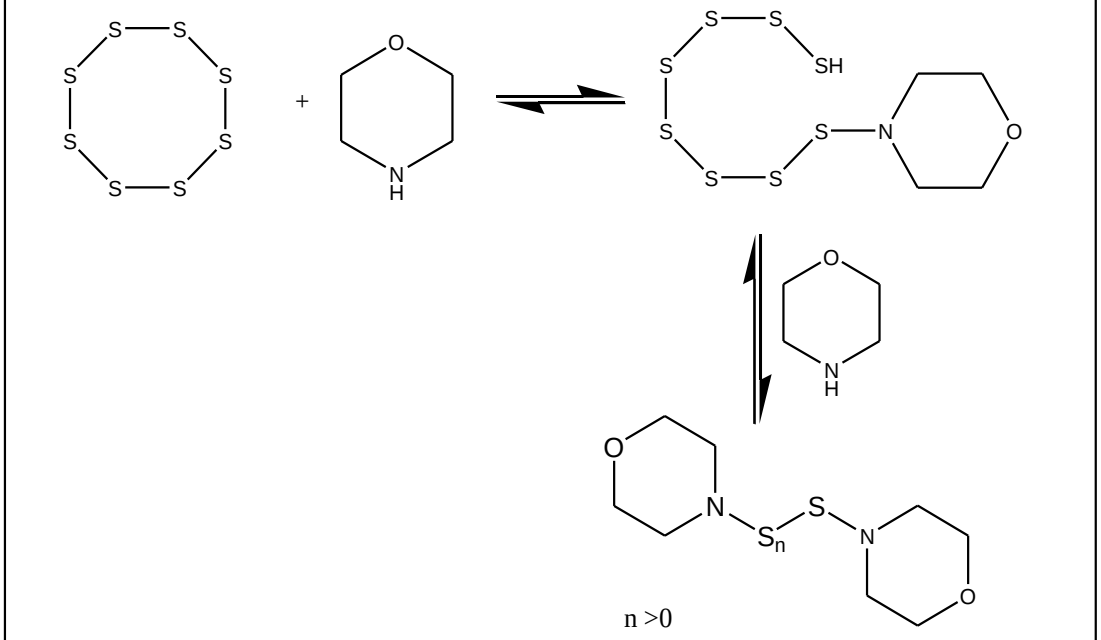


Today Willgerodt-Kindler reaction can be classified as one-pot, 3 component process for the synthesis of synthetically useful (thio)amides.

The Willgerodt-Kindler reaction involves the reaction of an aldone (aldehyde or ketone), sulphur and primary or secondary amine to yield chiefly a thioamide derivative. When carried out using an aryl alkyl ketone, this reaction can be considered as an autoredox system, whereby the ketone is reduced and subsequent oxidation at the terminal carbon atom takes place.

The reaction details were originally investigated using acetophenone, but the studies were subsequently extended to include propiophenone, butyraphenone and valerophenone. It was observed however, that the longer the carbon chain is, the less effective the carbonyl migration process is and lower yields are obtained. It is now typically considered that the ideal alkyl chain length for the Willgerodt-Kindler reaction with ketones is no greater than two or three carbon atoms long.

Amino-sulphur species playing a role as catalyst in enamine isomerisation during the Willgerodt-Kindler reaction



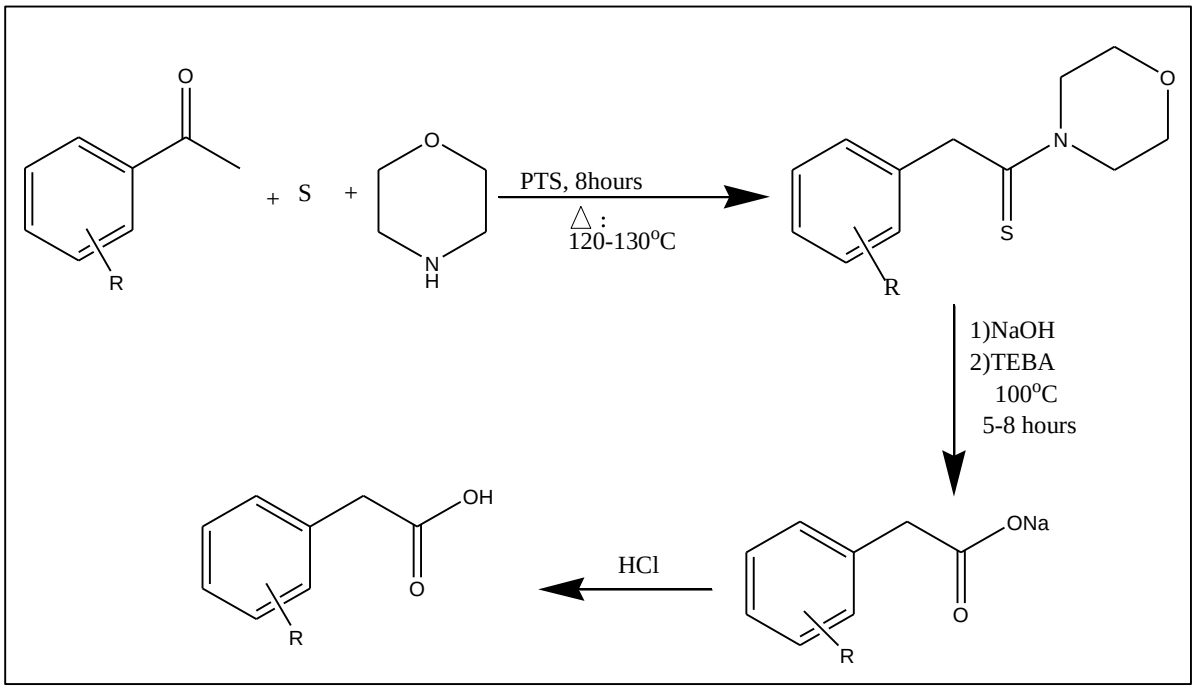
Role of sulphur-It has been proposed that amino-sulfur species is responsible for promoting the ketone isomerisation that facilitates the migration of the carbonyl group along a methylene chain in the Willgerodt-Kindler reaction. Carmack and co-workers identified that in the presence of a suitable ketone and secondary amine, sulphur could be introduced into the reaction mixture in any number of forms. The sulfur sources that proved successful in inducing isomerisation of the ketone during the Willgerodt-Kindler reaction included elemental rhombic sulphur(S_8), sulphur polysulfides and polythiosulfenamides. Another important consideration is that the sulphide ion must be able to re-capture the eliminated morpholino-sulfur functionality so that the enamine re-formation can take place and active forms of the amino-sulfur catalyst are regenerated.[2]

Under Willgerodt-Kindler conditions, when the enamine reaches the terminal methyl group during isomerisation of enamino/imino species is irreversibly oxidised to afford the thioamide. It has been proposed that the presence of extra hydrogens on the methyl group of the enamine allows this oxidation to proceed in the presence of an amino-sulfur species.[2]

Role of Morpholine (amines)-Morpholine is used in these transformations as it is considered to be much less susceptible to oxidation than other amines in the presence of sulphur. It has been shown that a wide range of amines can be applied in the Willgerodt-Kindler reaction. Both primary and secondary amines are effective; including morpholine, pyrrolidine and anilines, however tertiary amines do not participate in the Willgerodt-Kindler reaction due to its inability to isomerise the ketone functionality. [2]

METHOD 1- *Conventional method*[12]

M.Mujahid Alam & Srinivas R. Adapa (2003) reported a facile synthesis of Phenyl acetic acids via Willgerodt-Kindler reaction under PTC condition. The reaction proceeds efficiently by using triethyl benzyl ammonium chloride(TEBA) as phase transfer catalyst. The reaction is superior with regards to its simplicity, selectivity, reaction time and yield.

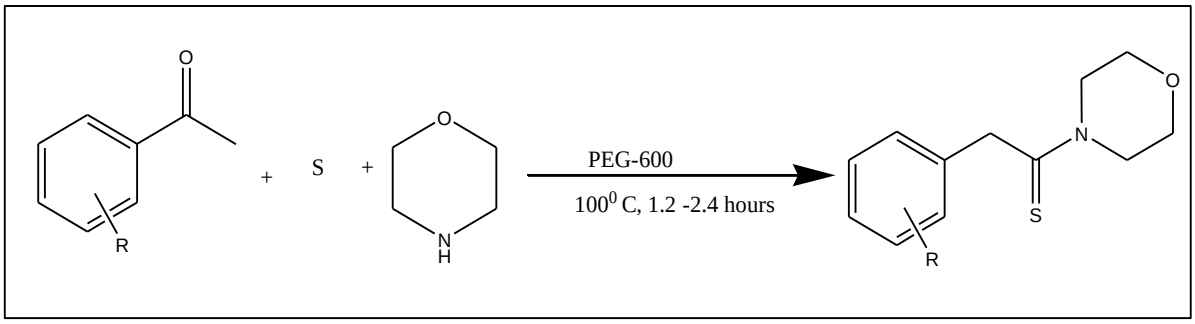


The green Willgerodt-Kindler reactions: A key theme recently implemented in many research groups is the development of more environmentally benign synthetic reactions that improve on well established protocols. This approach involves the development of non-thermal, catalyst and solvent free processes, as well as the identification of solvents and catalysts that can be recovered and subsequently re-used.

METHOD 2- *Uncatalyzed synthesis of thiomorpholide using polyethylene glycol as green reaction media*[5]

Shrikant S. Gawande, Babasaheb P. Bandgar, Prasad D. Kadam and Shailesh S. Sable (2010) reported a modified Willgerodt-Kindler reaction in the catalyst free synthesis of thiomorpholides using the solvent PEG-600.This reaction process was complete in 1-3 hours at 100˚C and afforded the products in high yields, with the reaction medium able to be recovered and used for subsequent reactions.

Polyethylene glycol-600 was used as an efficient and recyclable solvent for the one-pot three component condensation reactions of aryl alkyl ketones, sulphur and morpholine to produce the corresponding thiomorpholide.



Simultaneously, the effect of using the solvent at different temperatures were also studied during the formation of thiomorpholide.

Table: Synthesis of thiomorpholide at different temperatures

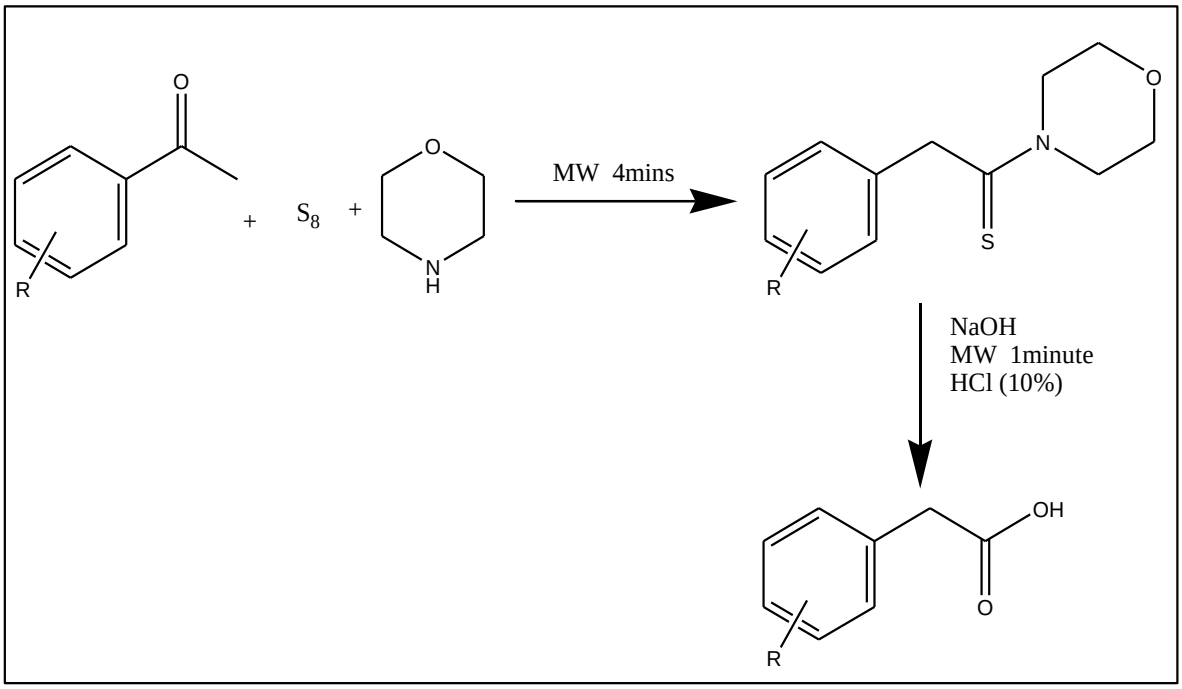
Entry	Solvent	Temperature (˚C)	Time (hours)	Yield (%)
1.	PEG-600	35	24	2
2.	PEG-600	75	5	78
3.	PEG-600	100	1.2	96

From the above table it was concluded that the reaction did not proceed when reaction temperature was 35˚C. However, obtained results were low even after long reaction times(24hrs).However at elevated temperatures (75-100˚C) using PEG-600 gave better results in terms of yield and reaction time. Hence, the condition of entry 3, in the above table were the optimised reaction condition.

In classical Willgerodt-Kindler reaction, morpholine was generally used in large excess as a solvent as well as a reactant. The use f PEG-600 as a solvent minimizes the quantity of morpholine in the reaction. This is because of the activation of ketones by PEG-600.

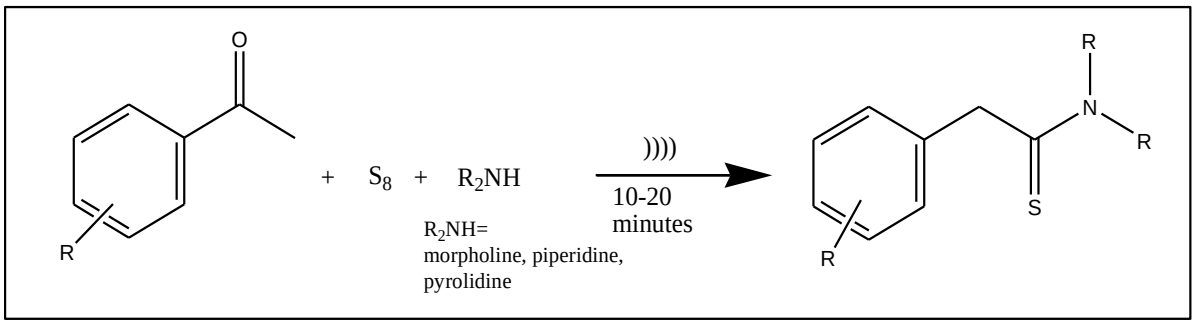
METHOD 3-*Microwave assisted rapid hydrolysis and preparation of thioamides by Willgerodt-Kindler reaction.*[6]

Firouz Matloubi Moghaddam & Mohammad Ghaffarzadeh (2001) reported the two-step conversion of ketones to carboxylic acids, whereby during this reaction process, Aldehydes and aryl ketones were efficiently transformed to thioamides with the same number of carbon atoms via Willgerodt-Kindler reaction and the thioamides obtained were hydrolyzed to corresponding carboxylic acids with microwave dielectric heating in one minute. Both reactions were fast and the yields were also excellent.



METHOD 4-*Ultrasound mediated Willgerodt-Kindler reaction: Non-thermal synthesis of thioacetamides*[7]

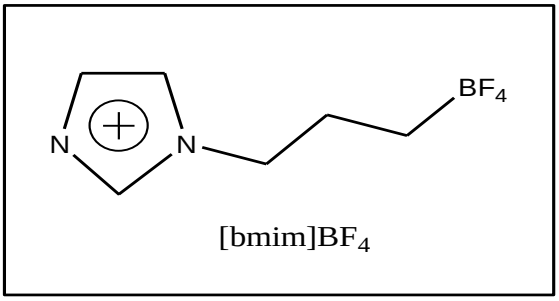
Ultrasound radiations have in recent years, demonstrated an ability to increase the selectivity and reactivity of several synthetic processes. Mohammed M. Mojtahedi, Tooba Alishiri & M. Saeed Abaee (2011) reported a non-thermal, ultrasound-mediated Willgerodt-Kindler reaction whereby a range of functionalised acetophenones could be converted to the corresponding thioamides in high yields in less than 25minutes at ambient temperatures.



The reaction completes within a few minutes, yields are relatively high, no solvent or extra additive is required during the course of the reaction and the method is environmentally safer.

METHOD 5- *Green protocol for Willgerodt-Kindler transformation using [bmim]BF_4 ionic medium*[8]

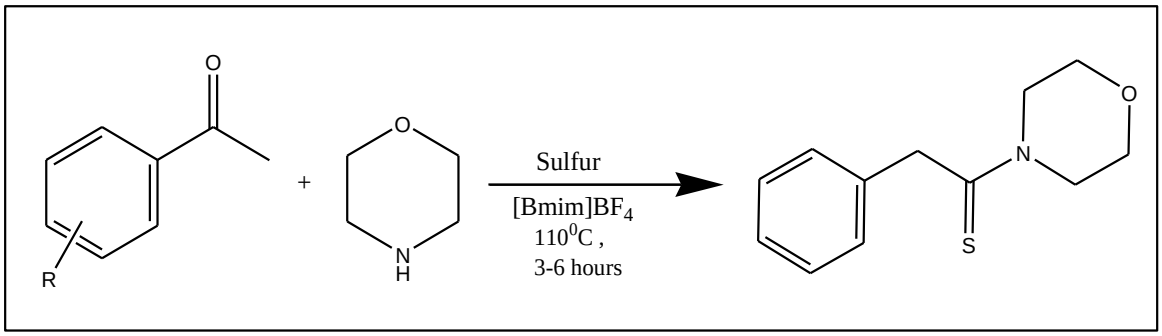
The Willgerodt-Kindler reaction of ketones run in ionic liquids was reported by J.S. Yadav and co-workers (2007). Aryl alkyl ketones react with morpholine in the presence of sulphur in air and moisture stable ionic liquid 1-butyl-3-methylimidazolium tetrafluoroborate [bmim]BF_4 to produce the corresponding thiomorpholides in high yields following a simple extraction with diethyl ether.



[bmim]BF_4

Chemical structure of ionic liquid

The use of recyclable ionic liquids makes this process quite simple, more convenient and environmentally friendly.



The notable features of this reaction are high conversions, operational simplicity, enhanced reaction rates, cleaner reaction reaction profiles and ease of isolation of products.

One limitation of this method, the use of ionic liquids as solvents is that the cost is usually expensive and they are difficult to use on an industrial scale.

HYDROLYSIS OF THIOMORPHOLIDES TO YIELD THE PHENYL ACETIC ACID[9]

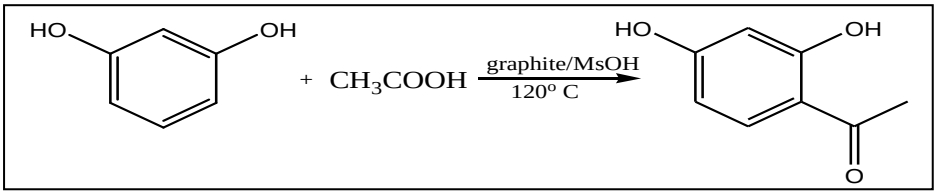
After the formation of thiomorpholides, hydrolysis of thiomorpholide has to be done to achieve the target molecules that is corresponding phenyl acetic acids. The hydrolysis of thiomorpholide is done by refluxing sodium hydroxide solution for 10 hours followed by acidification with conc.HCl and extraction with ether and followed by crystallisation from ethanol yielding the target molecule.

PRESENT WORK

PRESENT WORK

Synthesis of acetophenones

METHOD-1: Synthesis of acetophenones by direct acylation of phenols using graphite and MsOH.

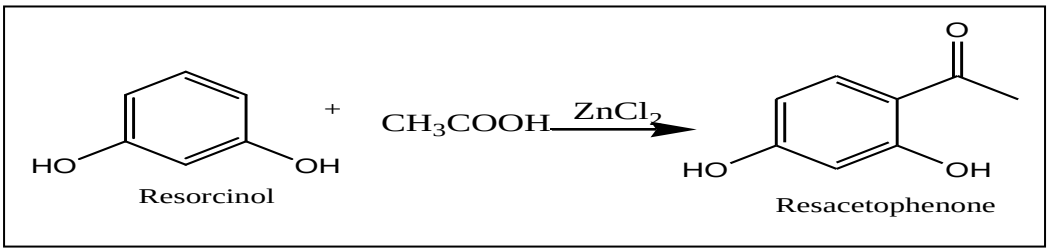


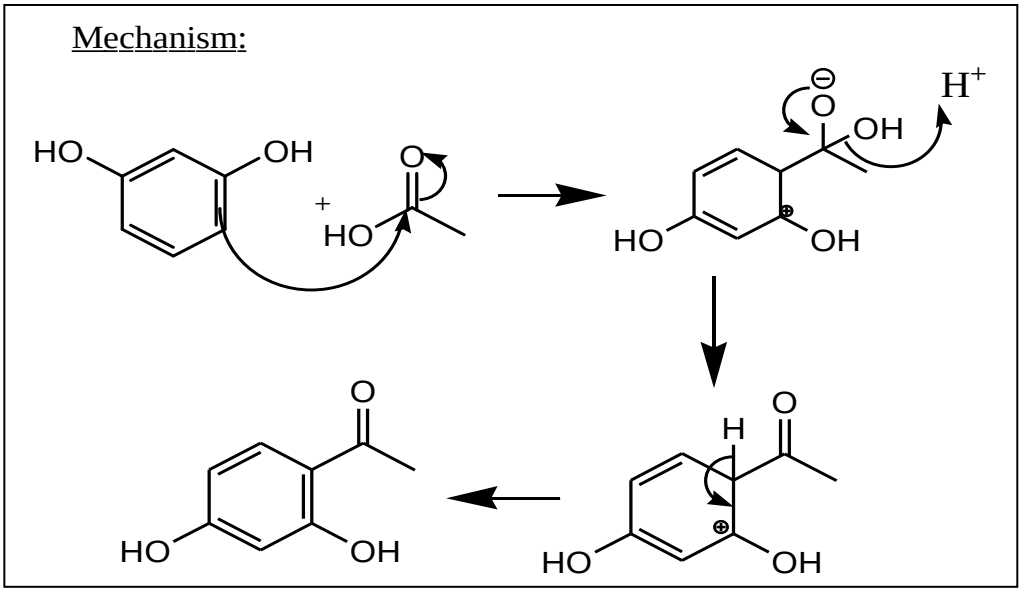
This method of synthesizing acetophenones was also used to synthesize acetophenones of the following phenols, such as from 4-Bromophenol, 4-Nitrophenol, 4-Aminophenol, but no product was obtained.

The advantage of this method is that the graphite used can be reused.

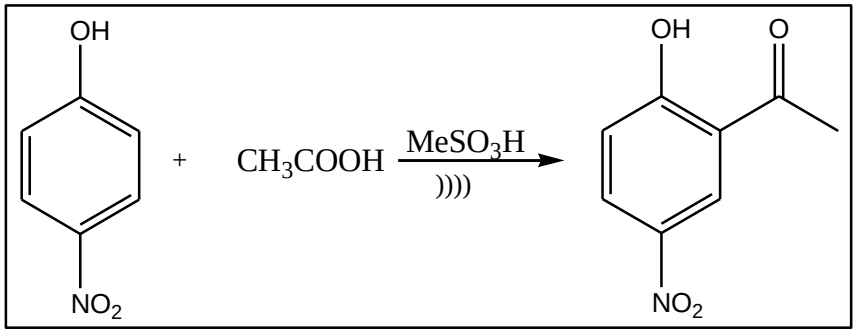
METHOD-2: Conventional method to synthesize resactophenone using zinc chloride.

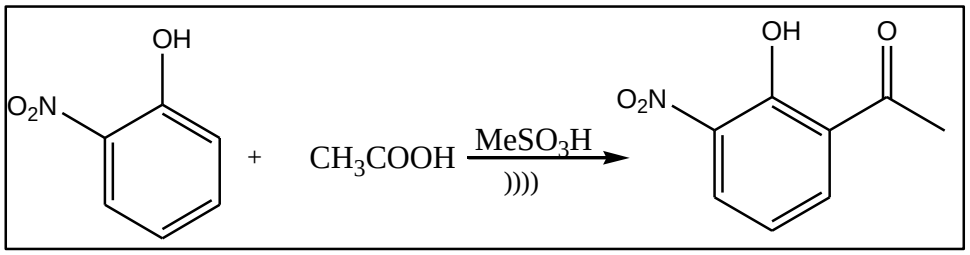
In this method resorcinol is converted into reacetophenone in the presence of zinc chloride.





METHOD-3: Synthesis of o-hydroxy acetophenone by sonication method using substituted phenol. Acetic acid and methane sulfonic acid.

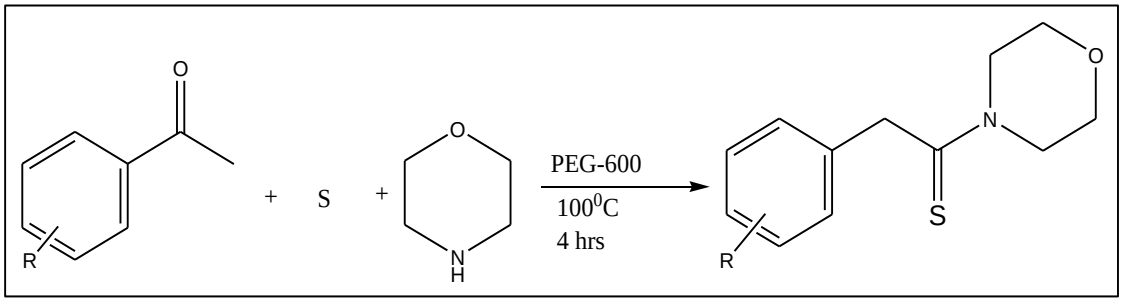


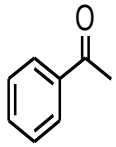
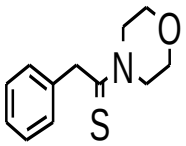
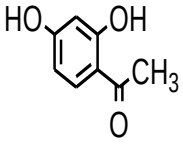
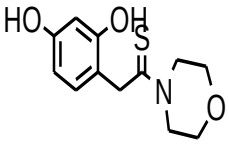
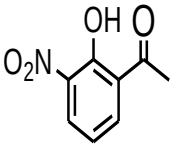
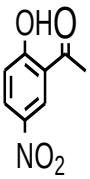
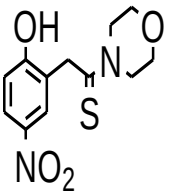
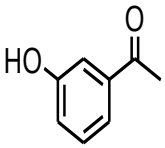
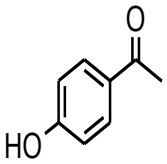
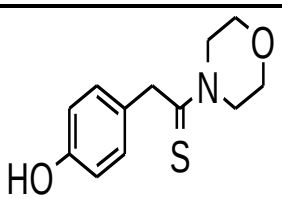
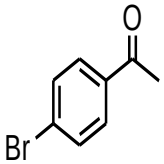


Synthesis of thiomorpholide from the acetophenones

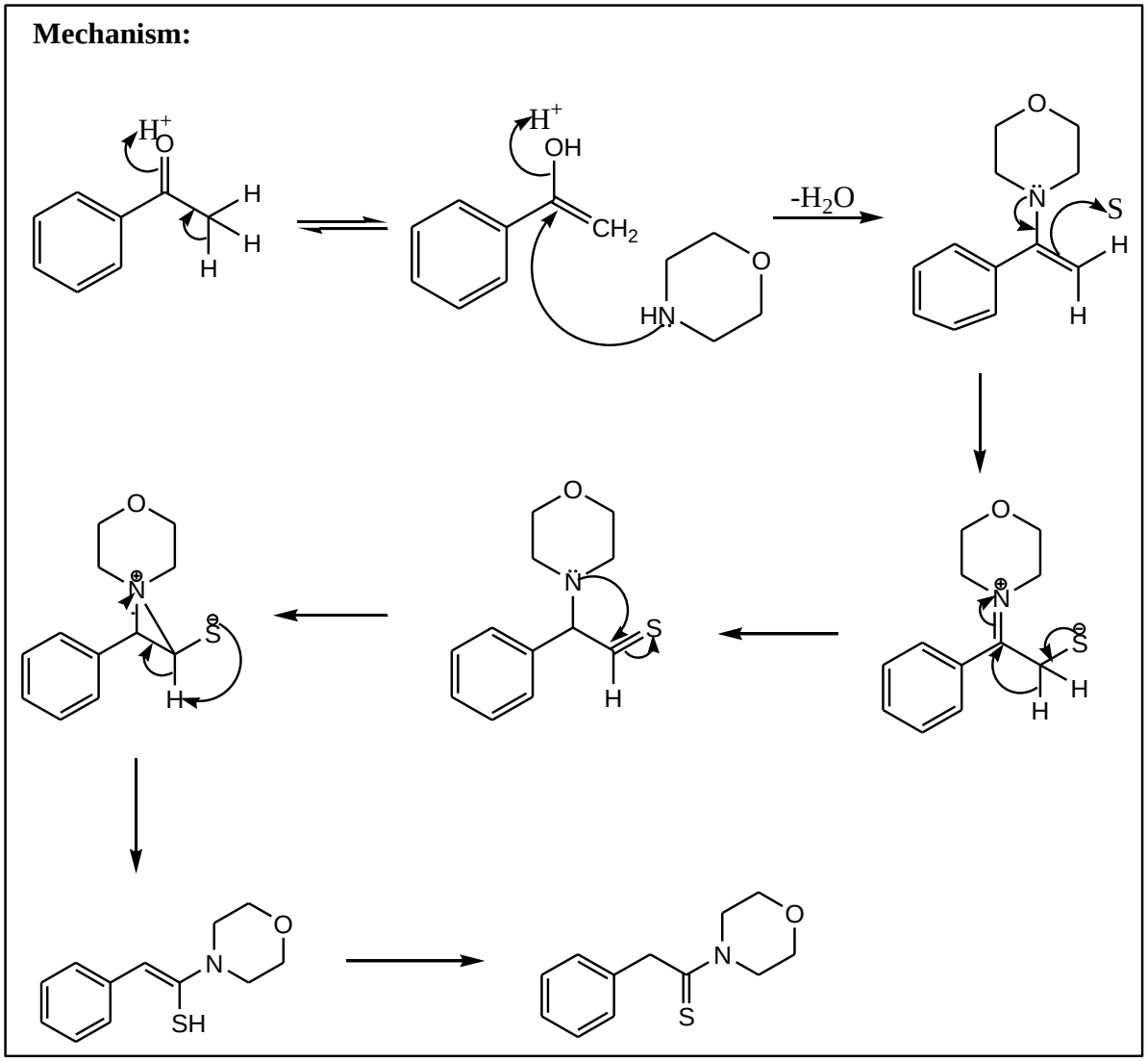
After the synthesis of the different substituted acetophenones, the next step to synthesize the target molecule is conversion of the acetophenones to its corresponding thiomorpholide.

A green method by using PEG-600 was employed to synthesize the corresponding thiomorpholide.(Willgerodt-Kindler reaction).



Reactant	Product	Time (h)	Yield (%)
		5 h	72.10 %
		5 h	56 %
	No product obtained	5 h	–
		5 h	67 %
	No product obtained	5 h	–
		5 h	72 %
	No product obtained	5 h	–

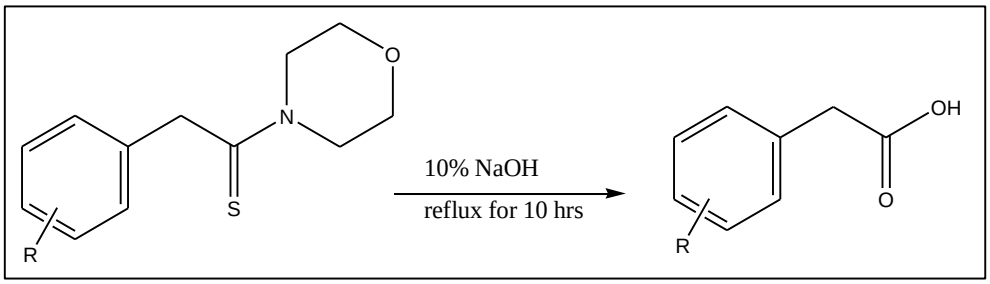
Mechanism:

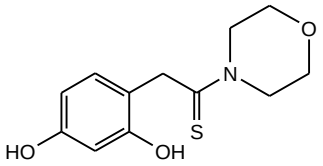
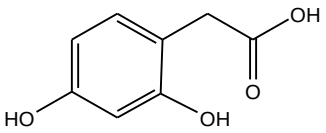
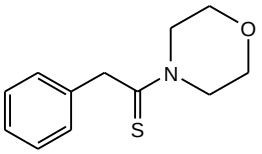
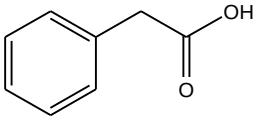
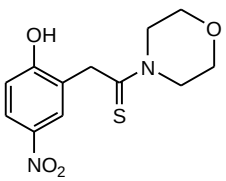
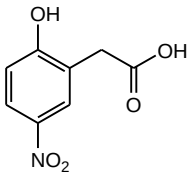
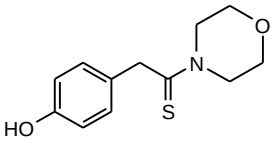
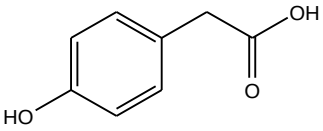


The completion of the reaction was monitored by Thin layer chromatography using hexane-ethyl acetate.

Hydrolysis of the thiomorpholides to yield the corresponding phenyl acetic acids.

After the formation of thiomorpholide, hydrolysis of it was done using 10% alcoholic NaOH for 9 hours followed by acidification of it with conc.HCl and extraction with ether and subsequent drying over anhydrous magnesium sulphate, wherein the solvent evaporates to yield the target molecule i.e. substituted phenyl acetic acid.



Substrate	Product	Time (h)
		10h
		10h
		10h
		10h

The purity of the formed product was monitored by TLC and recording IR spectra.

EXPERIMENTAL WORK

EXPERIMENTAL WORK

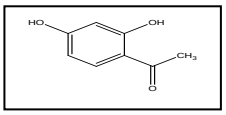
Melting points were recorded in open capillary tubes. The IR spectra are recorded on a SHIMADZU-FT-IR spectrophotometer.

STEP-1: Procedures for synthesis of acetophenones.

METHOD-1-Conventional Method

1-(2, 4-dihydroxyphenyl)ethan-1-one

In a beaker (7.5g, 55.01mmoles) of anhydrous zinc chloride was dissolved with the help of heat in (7.5 mL,124.8 mmole) of glacialacetic acid, which had been placed



in 250 mL beaker. To this hot mixture (about 40°C), (5g, 45.4 mmoles) of resorcinol was added with constant stirring. The solution was heated on an sand bath until it just began to boil (152°C). The flame was removed and the reaction was allowed to complete itself at a temperature not in excess of 159°C. After standing on the sand bath without further heating for 20minutes the solution was diluted with a mixture of 1:1 HCl. The dark red solution was then placed in an ice bath and cooled till the temperature came to 5°C. The resulting precipitate was filtered using Buckner funnel and washed free from Zn salt with 1:3 HCl three times. The orange-yellow precipitate after recrystallisation melted at 141°C.

GREEN METHODS

METHOD-2: Synthesis of acetophenones by direct acylation of phenols using graphite and methanesulfonic acid.

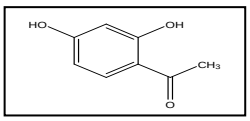
General procedure for preparation of substituted acetophenones by graphite method.

Mixture of graphite and methane sulfonic acid was taken in a 100 ml round bottom flask and was heated at 120°C in an oil bath, to that carboxylic acid and derivatives of phenols were added. And the reaction mixture was stirred for about 3 hours, then the whole mixture was poured in water (2×25ml), and and extracted with DCM (2×25ml). Further it was washed with a solution of $NaHCO_3$ (5%, 2×30ml) and dried over $CaCl_2$ and concentrated. The obtained residue is further recrystallised with ethanol and purity of the formed product was monitored by TLC.

1-(2,4-dihydroxyphenyl)ethan-1-one

In a 100 ml round bottom flask, 1g of graphite, methane sulfonic acid 94.41ml, 68.19mmoles)

glacial acetic acid (0.54ml, 9.47 mmole) and resorcinol (1g, 9mmoles)



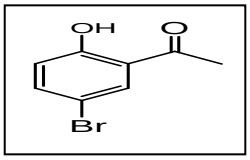
were heated in an oil bath at 120°C for about 3 hours. On further

workup and recrystallisation from ethanol yielded the desired product.. The purity of the formed product was monitored by TLC and melting point.

Melting point =142°C (reported)

1-(5-bromo-2-hydroxyphenyl) ethanone

In a 100 ml round bottom flask, 0.5g of graphite, MsOH (2.81ml, 0.043 mole), glacial acetic acid (0.32ml, 5.6 mmole**)** and 4-bromophenol **(1g,** 2.6mmole) were heated



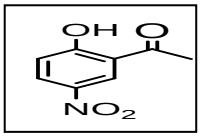
in an oil bath at 120°C for about 3 hours and proceeded with further workup.

On extraction of the organic layer with DCM and when sodium sulphate

anhydrous was added to it to remove moisture; it was observed that the sodium sulphate dissolved in the solution and further on evaporation of the organic layer, no product was obtained.

1-(2-hydroxy-5-nitrophenyl)ethanone

In a 100ml round bottom flask, 0.71g of graphite, MsOH



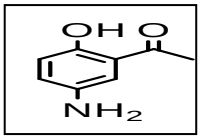
(3.5ml, 0.053 mmole), glacial acetic acid (2.05ml, 7.19 mmole) and

4-nitrophenol (1g, 35 mmole) were heated in an oil bath at 120°C for about

3 hours, then the whole mixture was poured in water (2 × 25ml) and extracted with DCM and proceeded with further workup. It was observed that on evaporation of the organic layer no product was obtained.

1-(5-amino-2-hydroxyphenyl)ethan-1-one

In a 100ml round bottom flask, 0.9g of graphite, MsOH (4.45ml, 0.068 mole),



glacial acetic acid (0.5 ml, 9.15 mmoles) and 4-aminophenol (1g, 9 mmole)

were heated in an oil bath at 120°C for about 3 hours. It was observed that on

further workup, while evaporating the organic layer, no product was formed.

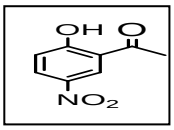
METHOD-3: Synthesis of o-hydroxy ketnes by sonication method

General procedure

A mixture of 5mmole of substituted phenol, 1ml of glacial acetic acid and 0.5mmole of MsOH was taken in a 50ml round bottom flask and was subjected to sonication for 5 minutes.The completion of the reaction was monitored by TLC. Once the reaction was complete, the reaction mixture was poured in water (10ml) and extracted using DCM. On evaporation of the organic layer, the product was obtained which was purified by recrystallisation with ethanol.

This method of synthesizing substituted acetophenones was applied for the following phenols:

1-(2-hydroxy-5-nitrophenyl)ethanone

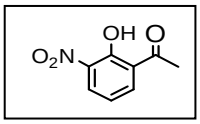


Mixture of 4-nitrophenol (10g, 0.071mmole),MsOH (0.46 ml, 0.071mol),

glacial acetic acid (14.37 ml) on sonication for 30 minutes and further workup

yielded 1-(2-hydroxy-5-nitrophenyl)ethanone.

1-(2-hydroxy-3-nitrophenyl)ethanone

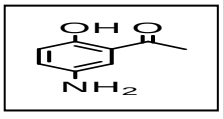


Mixture of 4-nitrophenol (10g, 0.071mmole),MsOH (0.46 ml, 0.071mol)

,glacial acetic acid (14.37 ml) on sonication for 30 minutes and further workup

yielded 1-(2-hydroxy-3-nitrophenyl)ethanone.

1-(5-amino-2-hydroxyphenyl)ethan-1-one

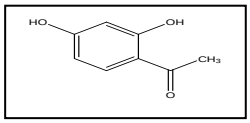


Mixture of 4-Aminophenol (10g, 0.097mol), MsOH (0.58ml, 9.17mmole),

Glacial acetic acid (18.34ml), on sonication for 30minutes, did not dissolve

the reagents. So, the reaction mixture was kept for sonication for more 30 minutes. On extraction with organic layer, no product was formed. So the mixture was kept aside in refrigerator overnight. But the next day, it was observed that a sticky type product was obtained and hence was not investigated further.

1-(2,4-dihydroxyphenyl)ethan-1-one



Mixture of resorcinol (0.55g, 5mmole), MsOH (0.032ml , 0.5mmole),

Glacial acetic acid (1ml), on sonication for 20 minutes and extraction using

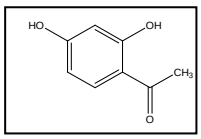
DCM, did not yield 1-(2,4-dihydroxyphenyl)ethan-1-one.

METHOD-4: Solvent-free direct ortho C-acylation of phenolic systems by MsOH acid as catalyst

General procedure for acylation of phenols

In a 50ml round bottom flask equipped with a reflux condenser, a mixture of substituted phenol (1.4mmole), acetic acid (8mmole) and MsOH (0.52mmole) was heated for about 10 minutes at reflux in an oil bath. The completion of the reaction was monitored by TLC and the mixture was cooled to room temperature and dissolved in DCM (10ml) and water (20ml).After the organic phase was extracted (EtOAc 3×5 ml), it was transferred to a separating funnel and washed with aqueous $NaHCO_3$ (2 ×20ml) and water (3×50ml), dried over anhydrous magnesium sulphate , filtered and evaporated.

1-(2,4-dihydroxyphenyl)ethan-1-one



The above procedure was used to synthesize 1-(2,4-dihydroxyphenyl)

ethan-1-one. It was observed that, the organic layer (ethyl acetate layer)

could not be evaporated to yield the desired product.and hence this was not investigated further.

Procedure for synthesis of thiomorpholides and its subsequent hydrolysis

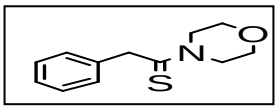
Synthesis of thiomorpholide using polyethylene glycol as green reaction media

General procedure:

In a 50ml round bottom flask, a mixture of acetophenone(4mmole), sulphur(4mmol) and morpholine (4mmole) in PEG-600 (2ml) was mixed and stirred at 100°C for 4 hours. The contents of the reaction flask was then poured into cold water. Solid product which separates out, was filtered using Buckner funnel, washed with water and dried. The crude product was

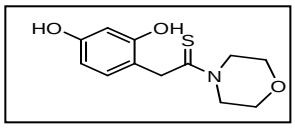
recrystallised using ethanol. The completion of the reaction was monitored by TLC using hexane-ethyl acetate.

1-(morpholin-4-yl)-2-phenylethane-1-thione



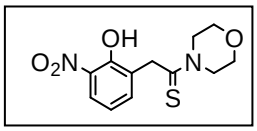
A mixture of acetophenone(0.48ml, 4mmole), sulphur (0.12g, 4mmole), morpholin (0.34ml, 2mmole) and PEG-600 were refluxed in a round bottom flask for 4 hours. This on further workup yielded 1-(morpholin-4-yl)-2-phenylethane-1-thione.

2-(2,4-dihydroxyphenyl)-1-(morpholin-4-yl)ethane-1-thione



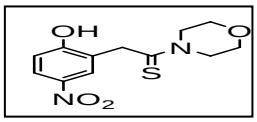
A mixture of resacetophenone(0.6g, 4mmole), sulphur (0.12g, 4mmole), Morpholin (0.34ml, 4mmole) and PEG-600 were refluxed for 4 hours and on further workup yielded the desired product.

2-(2-hydroxy-3-nitrophenyl)-1-(morpholin-4-yl)ethane-1-thione



A mixture of 1-(2-hydroxy-3-nitrophenyl)ethan-1-one (0.7g, 4mmole), Sulphur (0.12g, 4mmole), morpholine (0.34ml, 4mmole) and PEG-600 were refluxed for 4 hours. This on further workup with water formed a sticky emulsion type product. Hence, not investigated further.

2-(2-hydroxy-5-nitrophenyl)-1-(morpholin-4-yl)ethan-1-thione

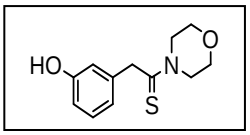


A mixture of 1-(2-hydroxy-5-nitrophenyl)ethan-1-one (0.7g, 4mmole) Sulphur (0.12g, 4mmole), morpholine (0.34ml, 4mmole) and PEG-600 were refluxed for 4 hours. On further workup it yielded 2-(2-hydroxy-5-nitrophenyl)-1-(morpholin-4-yl)ethan-1-thione.

2-(3-hydroxyphenyl)-1-(morpholin-4-yl)ethane-1-thione

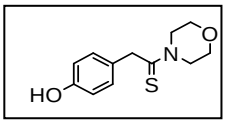
A mixture of m-hydroxyacetophenone (0.54g, 4mmole), sulphur(0.12g, 4mmol), morpholine (0.34ml, 4mmole) and PEG-600 were refluxed for 4 hours.

It was observed that on workup with water, no product separated out. Hence, it was kept aside overnight in refrigerator.But, even the next day there was no formation of any solid.



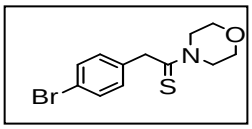
2-(4-hydroxyphenyl)-1-(morpholin-4-yl)ethane-1-thione

A mixture of p-hydroxyacetophenone (0.54g, 4mmole), sulphur (0.12g, 4mmole), morpholine (0.34ml, 4mmole) and PEG-600 were refluxed for 4 hours.On further workup with water, the solid product was obtained, which was recrystallised and whose purity was monitored by TLC.



2-(4-bromophenyl)-1-(morpholin-4-yl)ethan-1-thione

A mixture of p-bromoacetophenone(0.79g , 4mmol), sulphur (0.12g, 4mmole), morpholine (0.34ml, 4mmole) nad PEG-600 were refuxed for 4 hours.



It was observed, on workup with water, no solid was separated out. This, on even keeping aside for overnight gave no changes.

STEP-3: Hydrolysis of the thiomorpholides

General procedure for hydrolysis of the thiomorpholides to yield the corresponding phenyl acetic acid:

The thiomorpholide was refluxed for 9 hours with alc.NaOH (10%). The reaction mixture was diluted with water and acidified with conc.HCl. It was further cooled and extracted using diethyl ether. The oganic layer was dried over anhydrous magnesium sulphate and the ether was evaporated. The residual desired product was recrystallised from water. The purity of the formed product was monitored by TLC and recording the IR spectra.

Using this hydrolysis procedure, four substituted phenyl acetic acids were synthesized..

SPECTRAL ATTACHMENTS

SPECTRAL ATTACHMENTS:

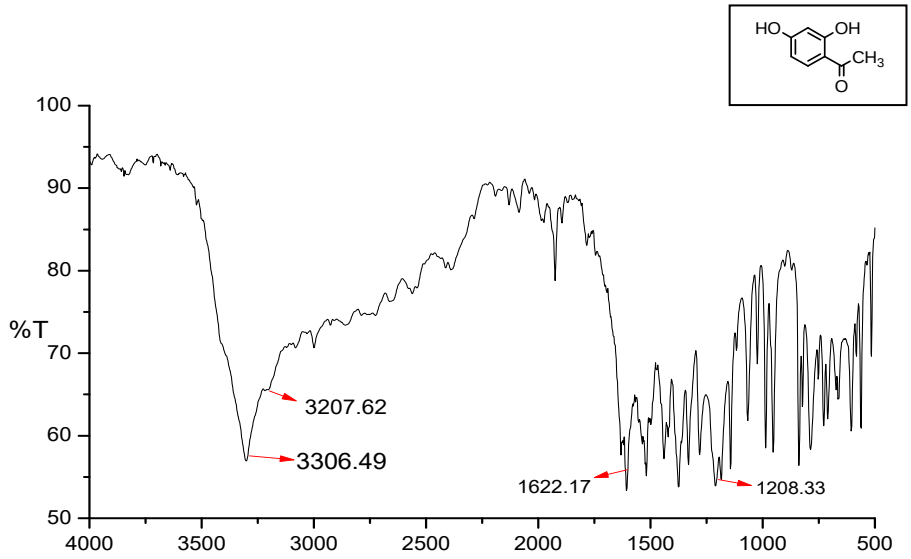


Fig.1. IR spectra of 1-(2,4-dihydroxyphenyl)ethan-1-one

(Green method)

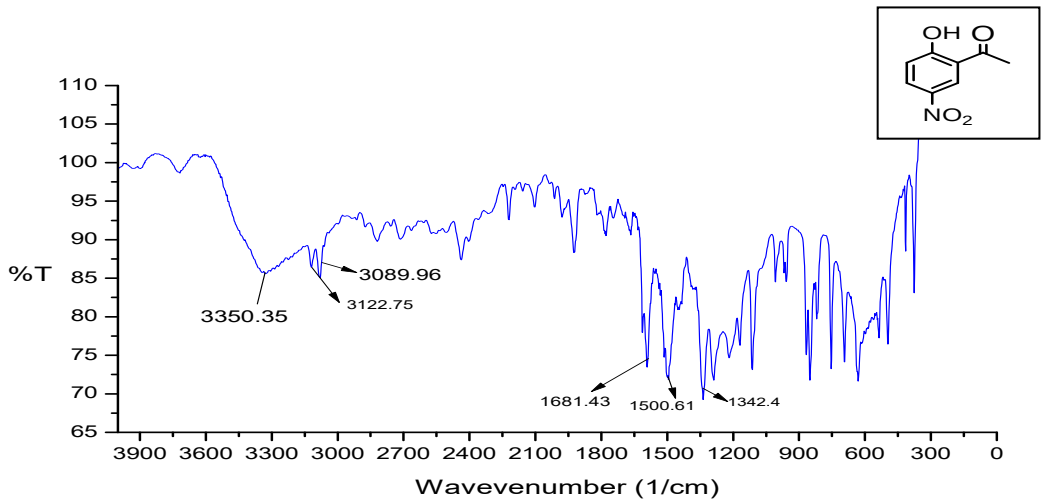


Fig.2. IR spectra of 1-(2-Hydroxy-5-nitrophenyl)ethanone

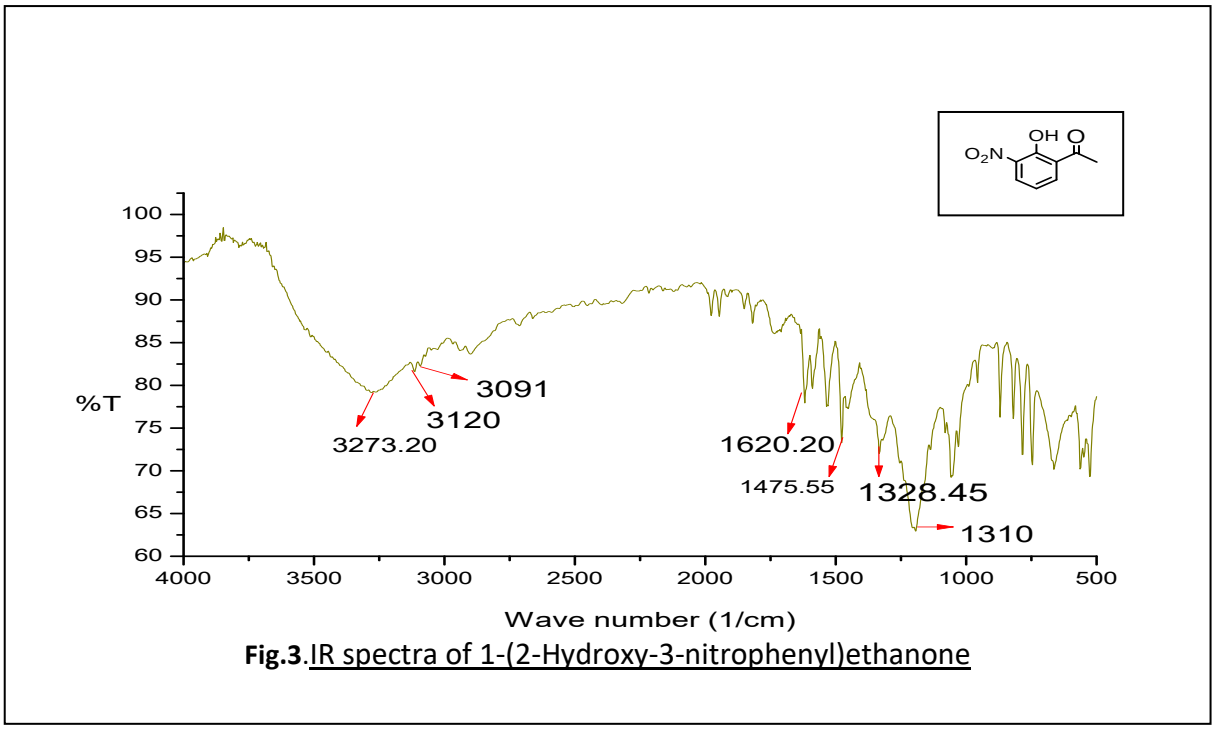


Fig.3.IR spectra of 1-(2-Hydroxy-3-nitrophenyl)ethanone

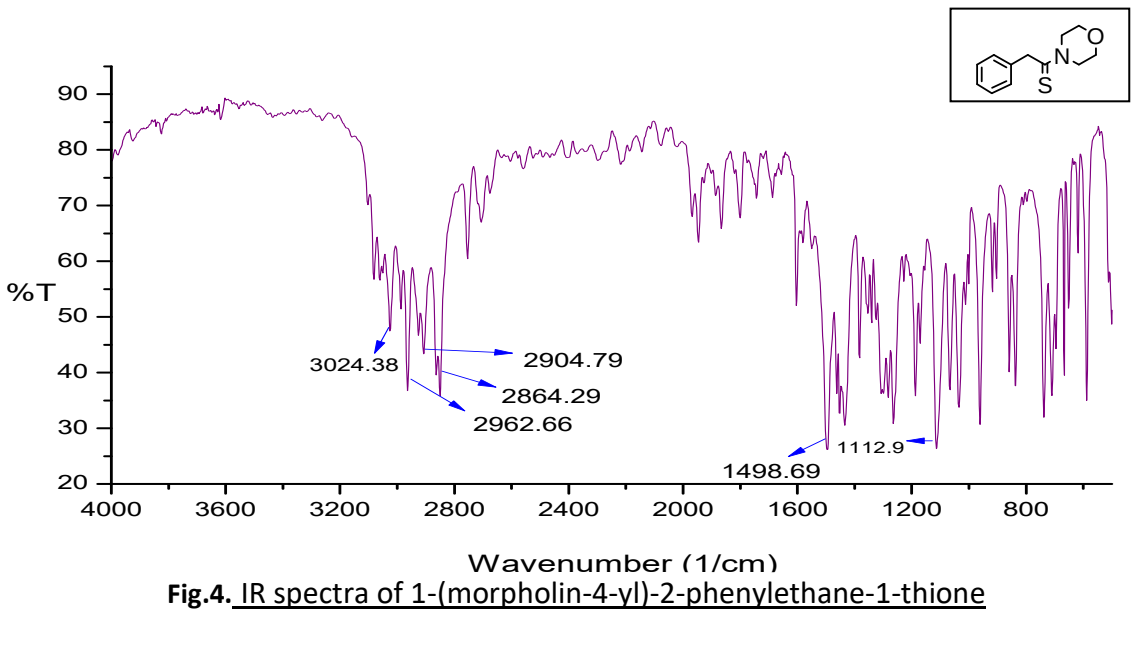


Fig.4. IR spectra of 1-(morpholin-4-yl)-2-phenylethane-1-thione

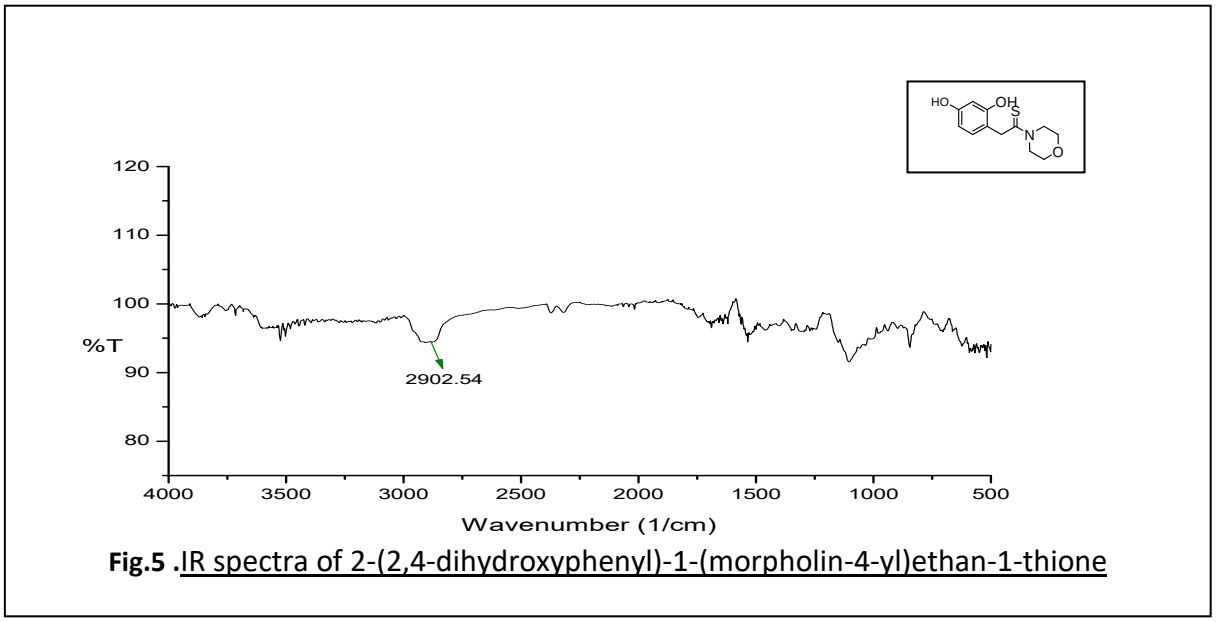
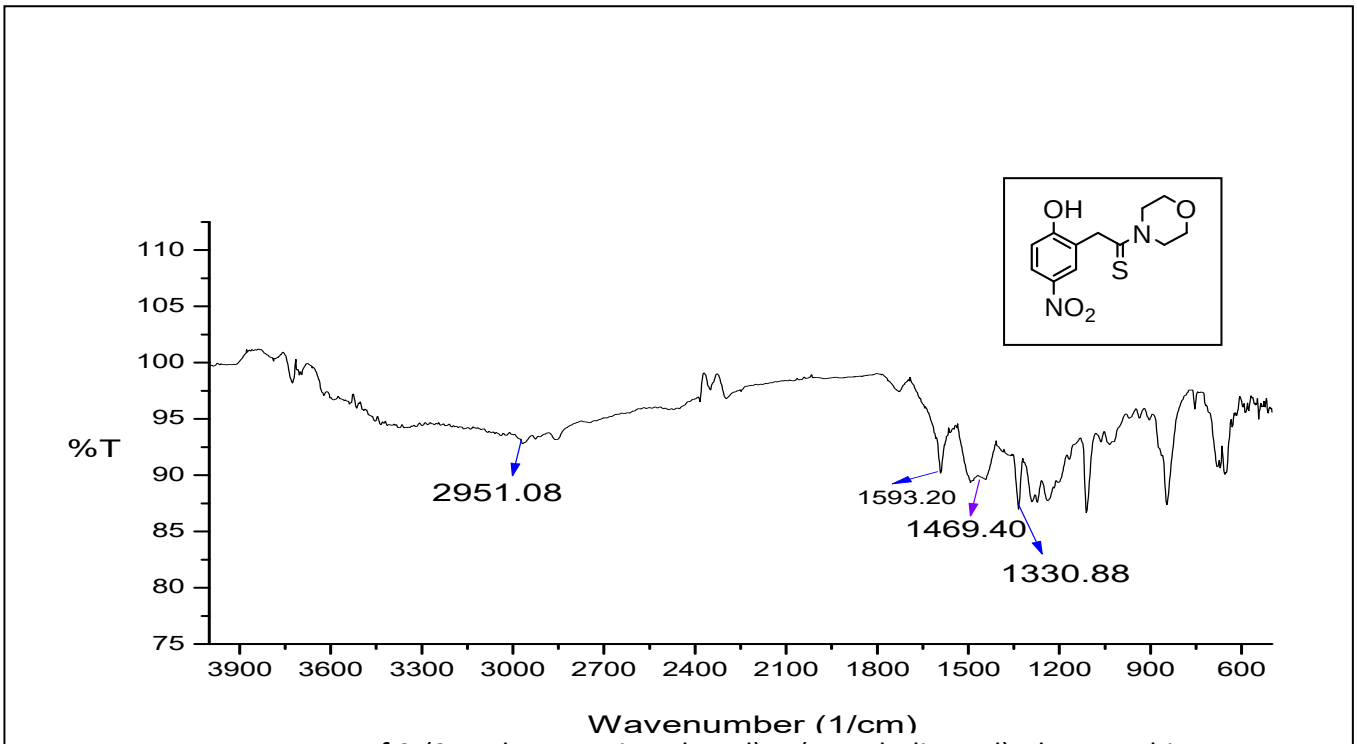


Fig.5 .IR spectra of 2-(2,4-dihydroxyphenyl)-1-(morpholin-4-yl)ethan-1-thione



Fi g.6. . IR spectra of 2-(2-Hydroxy-5-nitrophenyl)-1-(morpholin-4-yl)ethane-1-thione

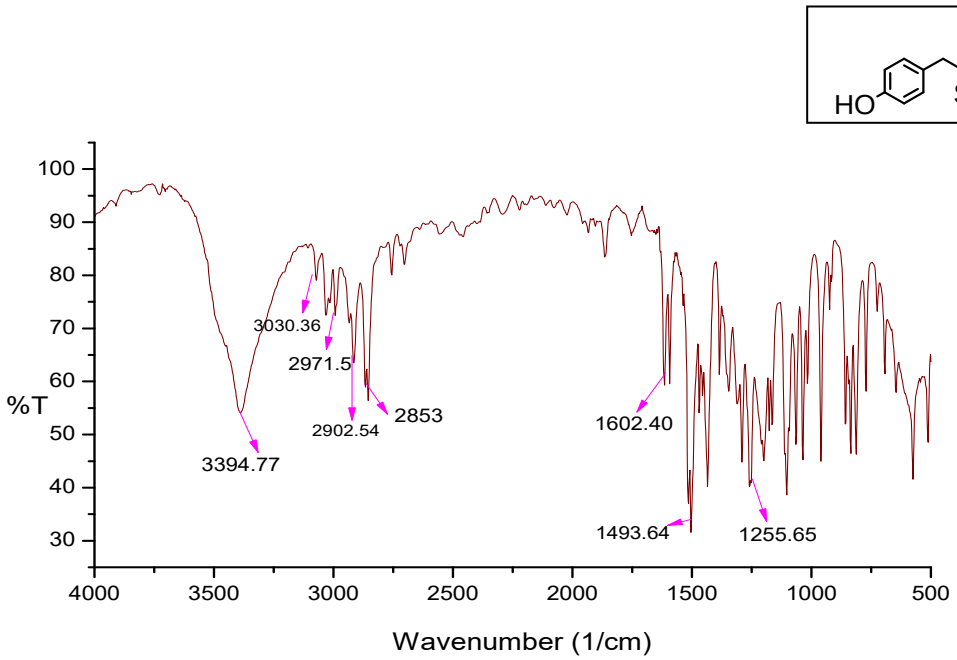


Fig.7 . IR spectra of 2-(4-Hydroxyphenyl)-1-(morpholin-4-yl)ethan-1-thione

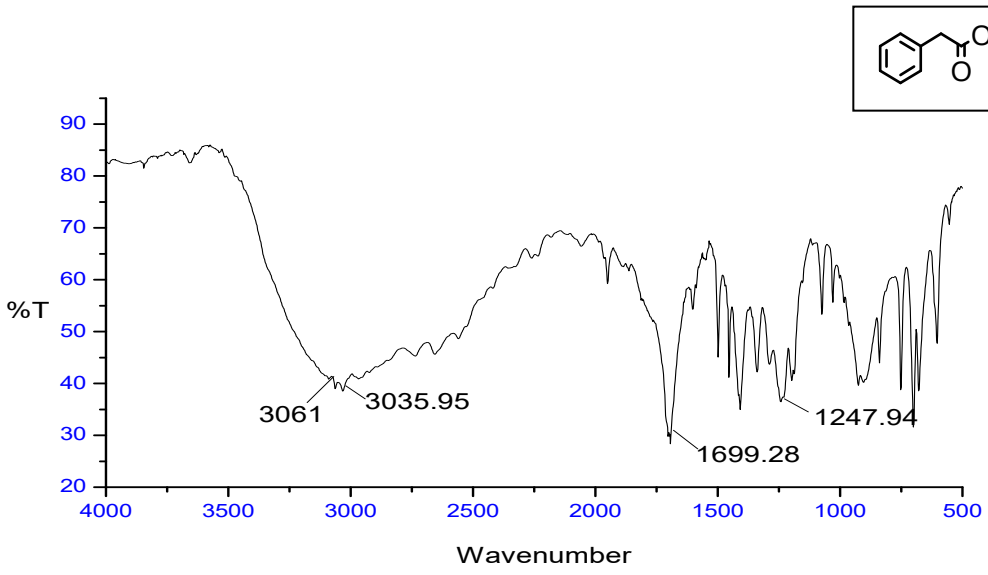


Fig.8. IR spectra of phenyl acetic acid

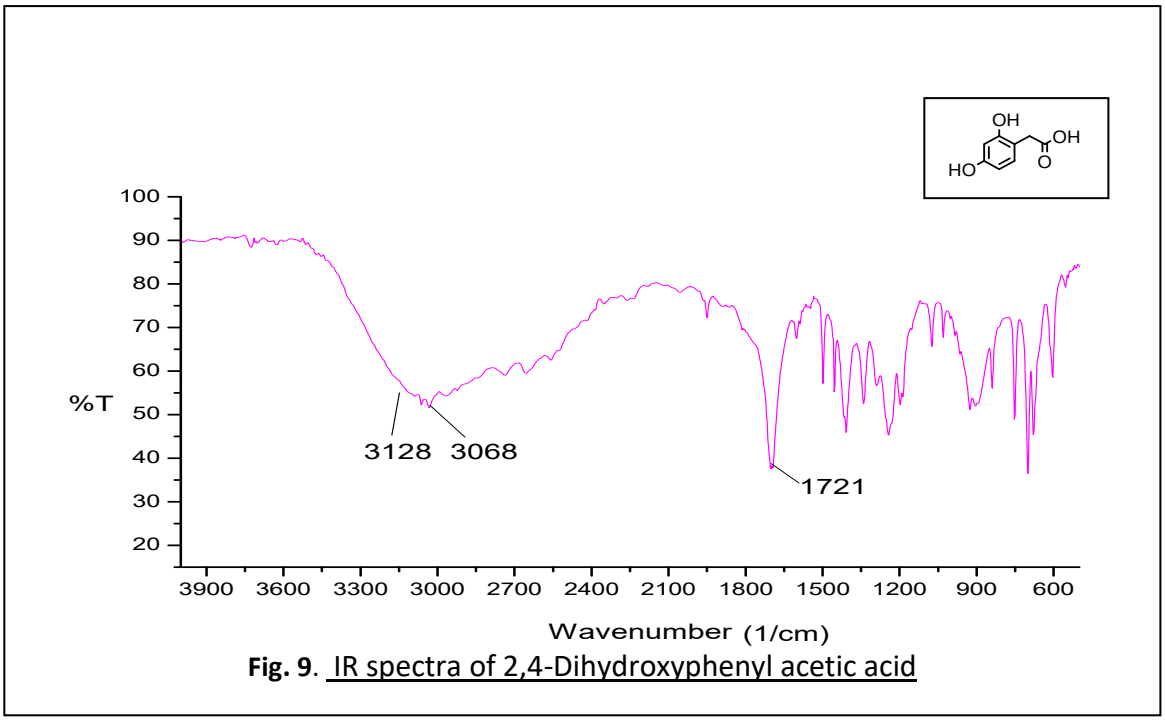


Fig. 9. IR spectra of 2,4-Dihydroxyphenyl acetic acid

RESULTS AND DISCUSSION

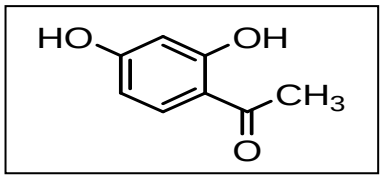
RESULTS AND DISCUSSION:

To synthesize substituted phenyl acetic acids, the first step was to prepare different substituted acetophenones by using different phenols and glacial acetic acid.

An environmentally friendly approach was used to minimize the pollution effects or to eliminate the use of any hazardous chemical.

By Graphite method

1-(2,4-dihydroxyphenyl)ethan-1-one



Yield : 85.5 %

Nature :Orange-yellow solid

Melting point : 142°C (reported)

IR spectral details (KBr), cm^{-1}: 3306.49 (ortho OH), 3207.62 (para OH), 1622.17 (C=O) and 1208.33 (C-O strectch). **[Fig.1]**

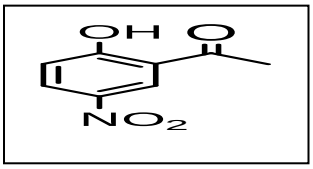
In the preparation of 1-(2,4-dihydroxyphenyl)ethan-1-one, comparison was made by extracting the product using three different organic solvents .i.e. dichloromethane, ethyl acetate and diethyl ether. It was observed that, dichloromethane gave good yield with high purity and ethyl acetate the extraction process was too time consuming due to high boiling point of ethyl acetate and also gave poor yield.

The graphite method was also applied to synthesize acetophenones from phenols such as 4-Bromophenol, 4-Nitrophenol and 4-Aminophenol. But in all the cases no product was formed and was not investigated further. One of the remarkable advantage of this method is that the used graphite could be easily recovered from the reaction mixture by washing with DCM.

By Sonication method

Using sonication method , two acetophenones were synthesized.

1-(2-hydroxy-5-nitrophenyl)ethan-1-one



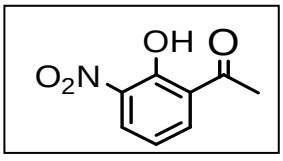
Yield : 61.4 %

Nature: Pale white solid

Melting point : 122°C

IR spectral details (KBr), cm^{-1} : 3350.35 (OH stretch), 1681.43 (carbonyl, C=O), 1500.61 & 13424 (NO_2 stretching bands) and 3122.75 & 3089.96 (due to C-H stretch). **[Fig.3]**

1-(2-hydroxy-3-notrophenyl)ethan-1-one



Yield : 73.42 %

Nature : Green solid

Melting point : 62°C

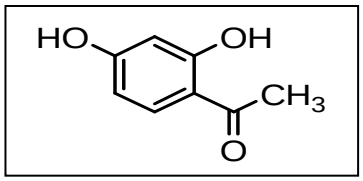
IR spectral details (KBr), cm^{-1}: 3273.2 (OH stretch), 3120 & 3091 (C-H stretch of alkane), 1310 (C-O of carbonyl), 1328 &1475.55 (NO_2 stretching bands) and 1620.20 (C=O, ketone).**[Fig. 2]**

This method was also used to synthesize acetophenones from 4-Aminophenol and resorcinol.

In the case of 4-Aminophenol , it was observed that a sticky residue was obtained whereas in the case of resorcinol no residual matter was obtained at all on extraction and further evaporation of the organic layer.

Conventional method

This method was used to synthesize resacetophenone using $ZnCl_2$ (Lewis acid).



Yield : 74.05 %

Nature: orange- yellow solid

Melting point: 141°C.

Solvent-free method using MsOH

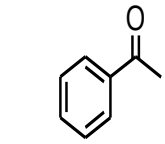
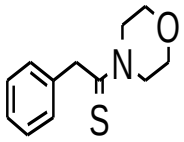
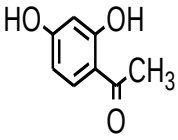
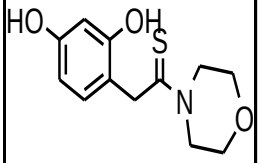
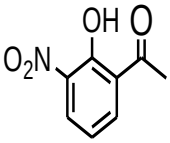
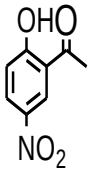
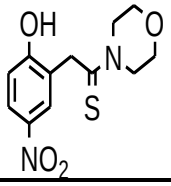
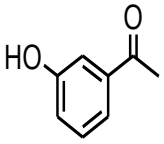
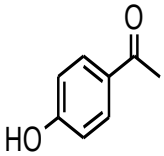
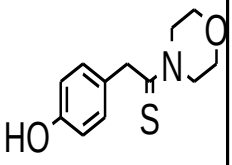
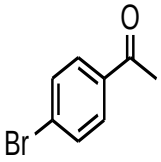
Using this method, an attempt was made to synthesize 1-(2,4-dihydroxyphenyl)ethan-1-one. But unfortunately, it was observed that the product could not be isolated from the organic layer and when attempts were made to do so, it lead to the formation of emulsion.

Second step to synthesize substituted phenyl acetic acid was converting the acetophenones to its corresponding thiomorpholides.

The acetophenones which were synthesized in the first step and also some commercially available acetophenones were taken to proceed with thiomorpholide synthesis.

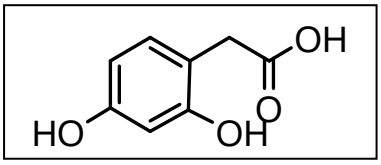
A green method using Polytehylene glycol-600 was employed to proceed with the second step .i.e., synthesis of thiomorpholides.

Polyethylene glycol-600 is an efficient and recyclable solvent with minimal environmental pollution and simple work-up procedure. The PEG-600 helps in activation of ketones.

Reactant	Product	Yield	Time	Melting point	Nature
		72.10 %	5 h	63^0 C	Yellow solid
		56%	5 h	75^0 C	Pale yellow solid
	No product obtained	–	5 h	–	Sticky emulsion type residue
		67%	5 h	145^0 C	Greenish yellow solid
	No product obtained	–	5 h	–	Emulsion type residue
		72%	5 h	120^0 C	Grey solid
	No product obtained.	–	5 h	–	No solid separated out on adding water

The third and the final step to synthesize the target molecule was hydrolysis of the prepared thiomorpholides.

2-(2,4-dihydroxyphenyl) acetic acid

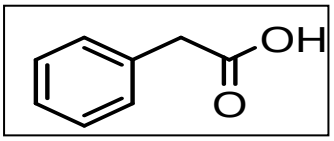


Yield : 76.8%

Nature : light yellow solid with sweet odour.

IR spectral details (KBr), cm^{-1}: 3128 (OH stretch of alcohol), 3068 (OH stretch of acid) and 1721 (C=O of acid).**]Fig.9].**

Phenyl acetic cid

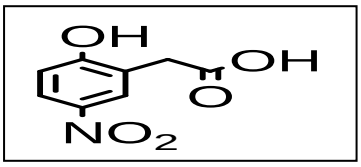


Yield : 84.41%

Nature : White solid with perfume like odour.

IR spectral details (KBr), cm^{-1}: 3035.95 & 38.863 (OH stretching bands), 1699.28 (C=O), 1247.94 (C-O band).**]Fig.8].**

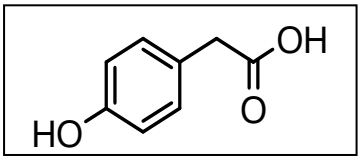
2-(2-hydroxy-5-nitrophenyl)acetic acid



Yield : 73.9%

Nature : Pale green solid

2-(4-hydroxyphenyl)acetic acid



Yield : 81.7%

Nature : Greyish white solid with perfume odour.

CONCLUSION

CONCLUSION:

The entire dissertation is based on green and environmentally friendly approach to synthesize the desired target molecule .i.e., substituted phenylacetic acid.

Firstly, to prepare the starting material .i.e., substituted acetophenone, the methods employed were graphite method, conventional and sonication method.

The **graphite method** is a simple method, the reaction time is also short and the work-up procedure is efficient and most importantly, the yield obtained is of high purity.

Conventional method, though gave sufficient yield, one drawback of this method was the use of Lewis acid which can cause environmental problems.

Sonication method, is a short and efficient method to synthesize substituted acetophenones, using methane sulfonic acid, which gives high yiels in a short period of time and is is also free from pollution. The MsOH acid used is biodegradable forming sulphate and CO_2 and due to its high strength it is used to catalyze this organic reaction.

Secondly, the method employed to convert the acetophenones to its corresponding thiomorpholides was by using Polyethylene glycol-600 (based o Willgerodt-Kindler reaction).

It is observed that, this method gave high conversions, enhanced the reaction rates, operational simplicity and also the workup procedure was very much efficient.

And finally hydrolysis of these thiomorpholides, gave the corresponding desired phenyl acetic acid with characteristic perfume like odour.

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