MICROWAVE ASSISTED ORGANIC SYNTHESIS (MAOS) - A COMPARATIVE ACCOUNT

DISSERTATION

Submitted in partial fulfillment of the requirements provided for the award of Degree of

Master of Philosophy

In

CHEMISTRY

By

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Under the supervision of

Prof. Khaliquz Zaman Khan

DEPARTMENT OF CHEMISTRY
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Dedicated

To

My Parents

& Grand

Parents

University of Kashmir
Srinagar-190006
J&K, India

DEPARTMENT OF CHEMISTRY

CERTIFICATE FROM SUPERVISOR

This is to certify that the work presented in this dissertation entitled "*MICROWAVE ASSISTED ORGANIC SYNTHESIS (MAOS) – A COMPARATIVE ACCOUNT* " is original and has been carried out by **Ms. Ulfat Araf Jan** under my supervision. This piece of work is suitable for submission for the award of M.Phil Degree in Chemistry. It is further certified that the work has not been submitted in part or full for award of any degree in this or any other University.

(Prof. Khaliquz Zaman Khan)
Supervisor

DECLARATION

I hereby declare that the work incorporated in the present dissertation was carried out by me in the Department of Chemistry, University of Kashmir, Srinagar 190006. The entire work or any part of it has never been submitted before for any prize or degree anywhere.

(Ulfat Araf Jan)

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Microwave Assisted Organic Synthesis (MAOS)-Theoretical

1.1 Introduction

The focal point in chemical research now a days is the development of environmentally benign processes. Emphasis is on reduction in the amount of solvents, hazardous substances and more efficient use of energy. Microwave Assisted Organic Synthesis (MAOS) is one of the means to achieve this goal.

Electromagnetic radiations cover a wide range of frequencies or wavelength[1] as depicted in the following **table 1.1**.

Table 1.1

Spectral Region	**Wavelength(m)**	**Frequency Range(Hz)**
Gamma Rays	1×10^{-12}	3×10^{19}
X Rays	10^{-12}- 10×10^{-9}	3×10^{19}- 3×10^{16}
Vacuum Ultraviolet	10^{-9}-200×10^{-9}	3×10^{16}-1.5×10^{15}
Ultraviolet	200 - 400×10^{-9}	1.5×10^{15}-7.5×10^{14}
Visible	400 - 800×10^{-9}	7.5×10^{14}-3.8×10^{14}
Near infrared	0.8 - 2.5×10^{-6}	3.8×10^{14}-1×10^{14}
Mid infrared	2.5 - 50×10^{-6}	1×10^{-14}- 6×10^{-12}
Far infrared	50 - 300×10^{-6}	6×10^{12}- 1×10^{12}
MICROWAVES	**0.3×10^{-3}- 0.5**	**1×10^{12}- 6×10^{8}**
Radio waves	0.5 – 300	6×10^{8} - 1×10^{-6}

In the electromagnetic spectrum microwave radiation area is located between infrared and radio waves having a wave length in the range of 0.3mm to 0.5m corresponding to frequencies between 1×10^{12} – 6×10^{8} Hz (30GHz – 300MHz). In the laboratory microwave instruments generate the waves corresponding to a wave length of 12.2 cm and energy of 2450 MHz, as per the international convention so that any interference with telecommunication and radar equipment is minimized (**Figure 1.1**).

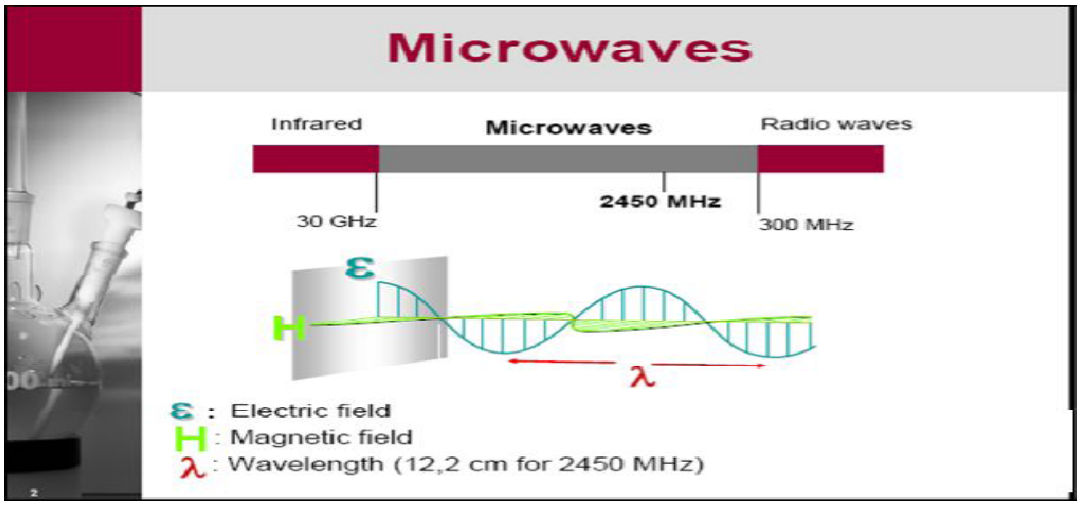


Figure 1.1: Range of frequencies of electromagnetic radiation

Microwaves are reflected by the metal surfaces but pass through paper, glass, chinaware and plastic ware. Hence these materials find extensive use as reaction vessels or utensils since microwaves are absorbed directly by the chemical species or food stuff without affecting the container. Microwaves penetrate several centimetres deep into the material to be heated because of a high penetration power and the dissipation of energy results in a quick and even rise in temperature of the substances.

1.2 Components of Microwave Oven

The microwave oven consists of the following components

- **Magnetron/Klystron**: It is a thermo ionic diode possessing an anode and a directly heated cathode. It emits the radiations over a narrow frequency range.
- **Wave guide**: It is a hollow tube of metal of rectangular cross-section with reflective walls to allow the transmission of microwaves from the magnetron to the microwave cavity.
- **Microwave cavity**: It is the internal space of the oven where the samples are placed for irradiation and usually contains a turn table to ensure that each sample experiences the same average heating. The cavity has reflective walls to prevent the leakage of microwaves as well as to increase the efficiency of the oven.
- **Mode stirrer**: A reflective fan shaped paddle to ensure that the microwaves are evenly distributed throughout the cavity.
- **Door interlocks**: These are safety devices in the door of the oven to prevent the door from being opened during microwave irradiations.
- **Exhaust fan**: This isolates and ventilates the oven to prevent acid fumes from attacking the electronic of the unit.

- **Time control**: This allows the time to be set for which the sample is to be irradiated.
- **Power control**: This allows the power level to be set before microwave irradiation of a sample is to be done.

A schematic diagram of a microwave oven is shown in **Figure 1.2**.

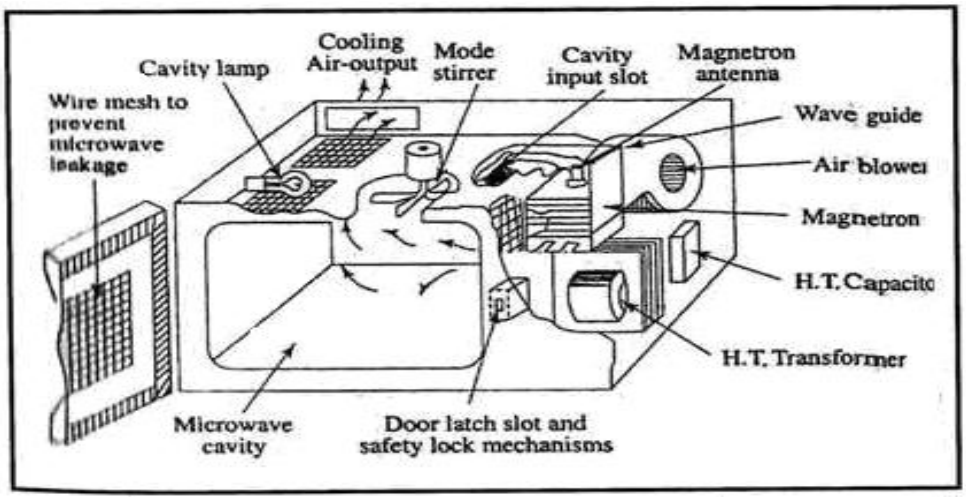


Figure 1.2: Cavity-type microwave oven

There are two types of microwave reactors, **Monomode** and **Multimode**[2] which are used now-a-days. The former gives focussed rays using an optical fibre or IR detector into a cavity inside which the reaction vessel is kept. In the latter, the distribution of electric field is not homogenous creating temperature gradients in different zones called as "hot spots". In addition, the multimode oven doesn't have any provision for accurate temperature measurements. The microwave oven used for cooking purposes is a multimode reactor. Moreover, for the reaction vessel to withstand high pressures, Teflon (polytetrafluoroethylene, PTFE) has been employed in the manufacture of reaction vessels and tubes that can withstand pressures up to 1500 psc. In spite of

reproducible results obtained using monomode ovens, the use of multimode ovens by chemists in research laboratories continues because it is economical and convenient to use.

1.3 Origin of Microwave Heating

Microwaves provide the only method of heating that does not involve thermal conduction. While as infrared or heat radiations get absorbed on the surface of a material. Microwaves penetrate several centimetres deep into it, carrying the electromagnetic energy to the core of the material. The heat generated in a sample on microwave exposure has mainly been attributed to the electric component of microwaves. The heat generation usually occurs by two mechanisms-dipolar polarization and ionic conduction.

1.3.1 Dipolar mechanism

Microwave heating of a solid or a liquid is related to the existence of an electric dipole in the molecule of the material. In water, for example, the dipole arises due to the different affinities of oxygen and hydrogen atoms for the available electron density and the angular shape of water molecule. As the electron density is concentrated more on the electronegative oxygen atom, the result is a net dipole moment for the water molecule.

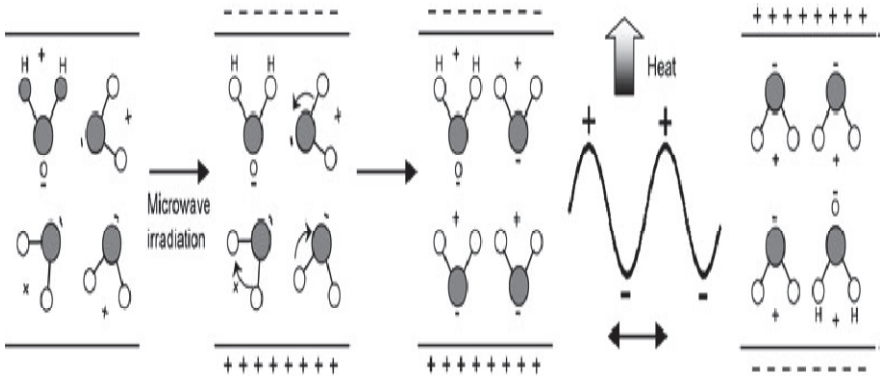


Figure 1.3a: Dipolar molecules try to align with oscillating field of microwaves

The heating effect generated in microwave oven is mainly due to the dielectric polarization that is orientation of a dipole with that of the applied field (**Figure 1.3a**). If the field is alternating, the dipole tends to align and realign itself with the applied field leading to thermal agitation which in turn produces heat.

1.3.2 Ionic conduction mechanism

In a solution containing ions or even an isolated ion, ions will move in a solution under the influence of an electric field resulting in expenditure of energy due to an increased collision rate converting the kinetic energy to heat energy, for example, if two samples containing distilled water and tap water are heated in a single mode microwave cavity at the same time and power level, the final temperature will be higher in the tap water sample. It has been found that the conductivity mechanism is much stronger than the dipolar mechanism with regard to the heat generation capacity[3] (**Figure 1.3b**).

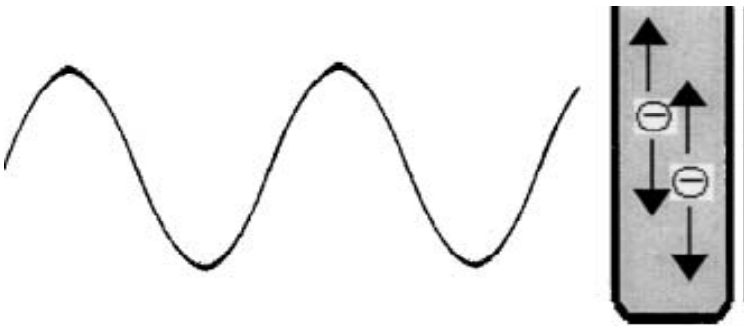


Figure 1.3b: Charged particles in a solution will follow the electric applied field. (Microwave heating by conduction mechanism)

1.4 Microwave penetration

In microwave heating, suitable frequencies for efficient heating and depth of penetration are in the frequency range between 50-5000 MHz. Special frequencies are allocated for industry, laboratory and medical use. These frequencies are 433.92

MHz, 915MHz and 5800MHz respectively. For most household microwave ovens, the frequency of 2450MHz is used with respect to the penetration depth and cooking speed.

Figure 1.4a shows the relationship between the penetration depth, degree of heating and frequencies of microwave radiations. As is evident from the graph, lower the frequency, deeper the penetration but a slower heating effect will result and higher the frequency, faster the heating speed but smaller the penetration depth.

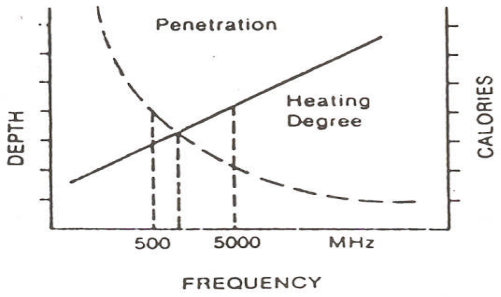


Figure 1.4a

As the microwave penetrates the material, power is lost in each successive layer of molecules as shown in **Figure 1.4b.** This is termed as "**penetration degree of depth**" and expressed as the point at which the microwaves are decreased to **37**% of their original strength. It is an inverse ratio of frequency. So, as the frequency is increased, the penetration depth decreases[4].

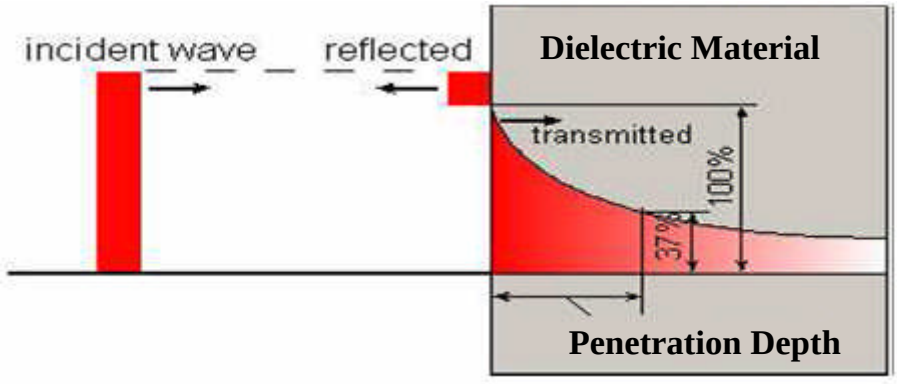


Figure 1.4b

1.5 Microwave Effect verses the Conventional Effect

Microwaves provide the only method of heating that does not use thermal conductions. Unlike infrared radiations adsorbed on the surface of the material, microwaves penetrate several centimetres deep and dissipate the electromagnetic energy carried by them to the heart of the material. Microwave dielectric heating is dependent on the ability of a polar solvent or reaction mixture to absorb microwave energy and convert it into heat.

Microwave differs from conventional heat sources in a way that the solvents or reactants are directly heated without heating the reaction vessel that is, there is an insitu generation of heat. The liquid or reaction mixture is often at a higher temperature than the vessel in which it is held and this in turn leads to an increase in the reaction rates and improvement in yield.

In conventional methods, the vessel gets heated first and heat gets transferred to the material by convection. As such the heat supplied is not homogeneously distributed. On the other hand, there is homogeneity of heat in case of microwave irradiation. It is more efficient in terms of the energy used and is consequently more rapid than conventional heat sources (**Figure 1.5a**).

Not only are microwaves sometimes able to reduce chemical reaction time from hours to minutes, but they are known to reduce side reactions, increase yield and improve reproducibility. Hence microwave synthesis has an edge over conventional synthesis in terms of time, yield and ease of work up, making it a technique worth an implement in organic synthesis[6,7]. Microwave assisted synthesis is particularly important for industrial synthesis as it saves time, power and leads to improved yields (**Figure 1.5b**).

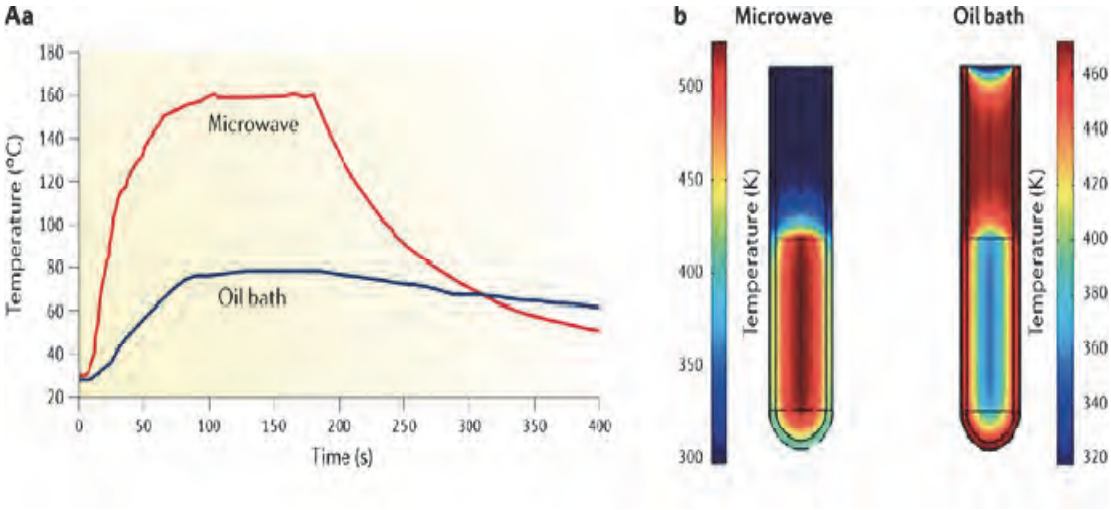


Figure 1.5a: Temperature profiles under microwave radiation and open vessel oil bath condition and temperature gradient 1 min. after heating. (Kappe and Dallinger 2006)[5]

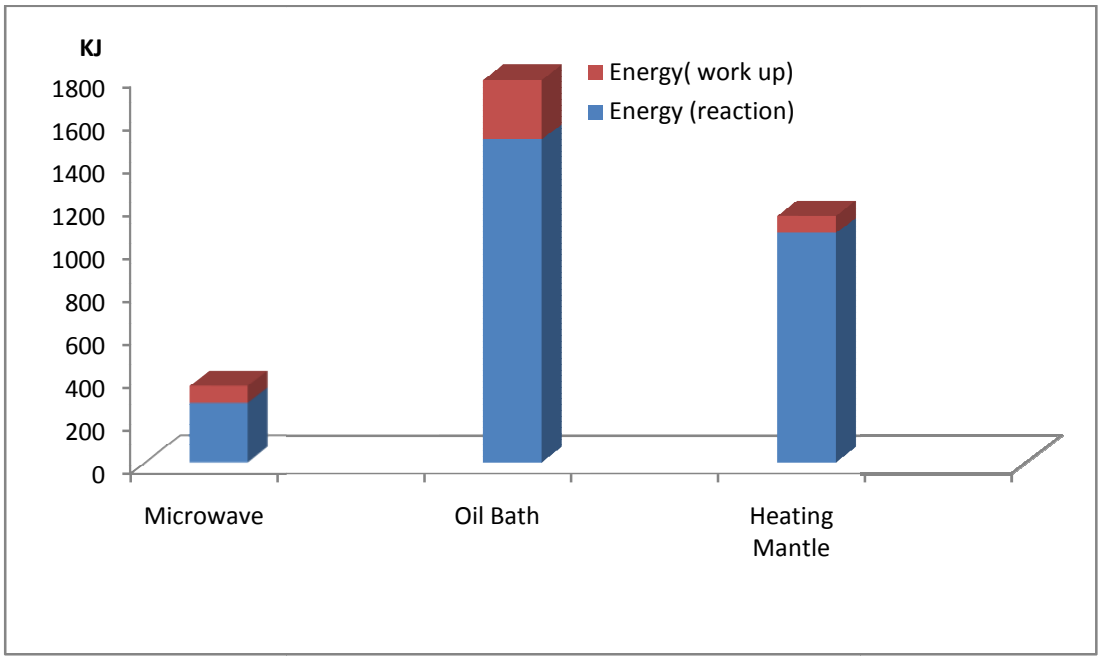


Figure 1.5b: Energy consumption of various heating methods

1.6 Merits and Demerits of Microwave Heating

1.6.1 Merits/ Advantages

1 Microwave assisted synthesis reduces the time of reaction substantially. Microwave enhancement may take several forms like reaction rates get accelerated, yield gets improved than the conventional counterparts and virtually no decomposition takes place during the drying of samples.

2 Microwaves form an essential aspect of green chemistry because of the solvent free technique. Reactants can be adsorbed on solid supports like clay, Montmorillonite, silica gel, alumina etc and then exposed to microwaves. This eco-friendly procedure minimizes the use of solvents leading to cleaner reaction and improved yields in addition to being safer. Ability to control the desired chemo, regio or stereoselectivity is possible using microwave assisted synthesis.

3 Microwave heating can be used with less operator interventions, improved safety and greater control over the reaction conditions as well as minimum sample contamination and loss.

4 Microwave reactions are eco-friendly and can be achieved under solvent free conditions[8-10].

5 The advantages of microwave are applicable to different disciplines of chemical research like drying of samples, melting of solid samples and a variety of organic and inorganic synthetic reactions.

1.6.2 Demerits/Disadvantages

Reactions requiring the use of dry nitrogen atmosphere, fuming substances or substances which may corrode the interior of the oven can not be conducted inside a domestic microwave oven.

1 There is a possibility that the higher temperature /superheating of the solvent in sealed vessels may encourage the decomposition of the desired product or may lead to the formation of thermodynamically stable product in preference to the kinetically favoured product.

2 Metals are reflective to microwaves and the radiations tend to bounce off them like the light from the mirror. Due to this, metals particles or metals have to be avoided inside the microwave oven because of an electric spark in the oven.

3 No classical vessels should be used except the ones specially designed for withstanding high pressures like Teflon tubes.

4 One of the major drawbacks of domestic microwave ovens is the power levels which significantly change from unit to unit.

1.7 Conclusions

Keeping in view the advantages of carrying out organic synthesis under microwave irradiations, the present work deals with the attempted microwave assisted synthesis of nitro aromatic compounds, which are precursors to a large variety of organic compounds and sugar osazones. These have also been prepared under conventional conditions and a comparative account has been given.

Chapter-2

Review of Literature

Review of literature

Lot of work is being done on Microwave Assisted Organic Synthesis resulting in the publications of thousands of papers and reviews every year. We are also engaged in our own humble way, for the last few years in exploiting the use of microwave energy in organic synthesis[11] and other areas[12].

Nitration of Aromatic Compounds

Nitration of aromatic compounds is a very useful reaction in organic synthesis. Nitro aromatic compounds are widely used in the synthesis of dyes, pharmaceuticals, perfumes plastics and explosives. Nitrophenols are important class of organic compounds which find wide applications in industry, agriculture and defence[13]. They are frequently used as intermediate in the manufacture of explosives, pharmaceuticals, pesticides, pigments and photographic chemicals[14-16]. 3-nitro-4-hydroxycoumarin possess antiallergic activity[17] and 7-hydroxy-coumarin have been found to possess antitumour activity against several human tumour cell lines[18] whereas 6-nitro-7-hydroxycoumarin along with 3,6,8-trinitro-7-hydroxycoumarin have been shown to be potent and selective anti-proliferative agents in a human melanoma cell line[19].

Nitration of aromatic compounds is one of the widely studied organic reactions. Pollution free processes are currently amongst important environmental concerns. Classical nitration usually requires use of excess of nitric acid with assistance of strong acids such as concentrated sulphuric acid and usually these reactions are not selective, suffer from low regioselectivity[20] and over nitration[21,22]. Formation of dinitro or polynitro compounds, oxidized products and unspecified resinous materials are the cause of environmental concern. Disposal of the large excess of mixed acids

and hazardous wastes and generation of nitrogen oxide fumes leading to the formation of excess acid adds to the environmental concerns. In order to overcome these problems alternative method using microwaves assisted synthetic routes have been developed for nitration of aromatic compounds.

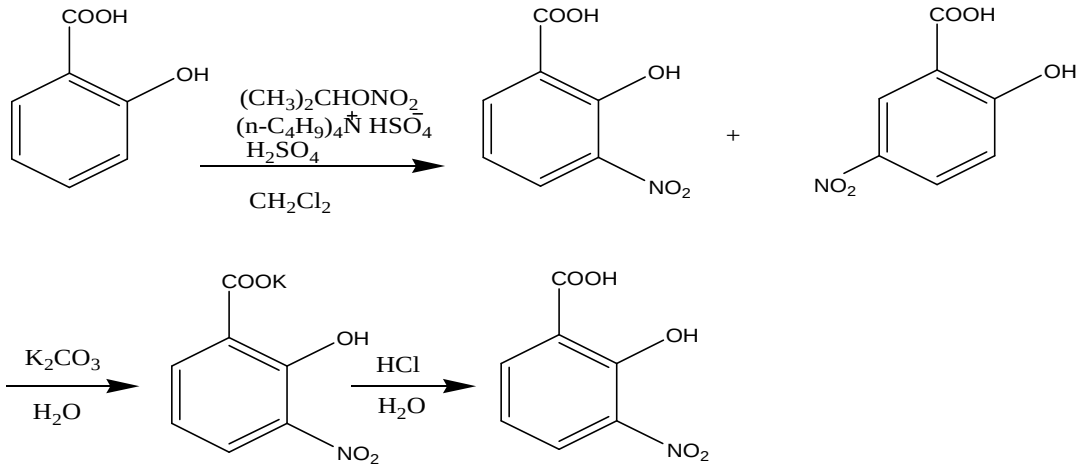
- Earlier reports on the nitration of aromatic compounds using microwave radiation include nitration of phenolic compounds by calcium nitrate and acetic acid[23]. This method is compatible with the Green chemistry approach because calcium salts as inorganic byproducts, can be useful as agrochemicals rather than waste chemicals. A novel dinitro secondary metabolite 2-nitro-4-2(-nitroethenyl) phenol from a marine source is prepared via accelerated microwave assisted nitration using mild reagents by ipso-substitution of a carboxy group by a nitro group[24]. Nitration of phenols has been carried by using various solid acids like p-TsOH, mono and trichloro acetic acid and heteropolyacids. Oxalic acid is considered as best solid acid for nitration of phenols in solid phase under microwave conditions[25].Phenol has been nitrated to mono nitrophenol and the ratio of ortho and para nitrophenols was found to be 4:6. Oxalic acid/$NaNO_3$ has been found to be an extremely powerful and efficient nitrating agent for phenols under simple conditions.
- Ritter *etal* have synthesized derivatives of pyridine like 2-methyl-Nitramino-3,5-dinitropyridine, isomeric 4-methyl-Nitramino-3,5-dinitropyridine, 2,6-bis-(methylnitramino)-3,5-dinitropyridine and 2,4,6-tris(methyl nitramino)-1,3,5-triazines using bismuth nitrate pentahydrate as an eco-friendly nitrating agent. These are used in high energy materials, pharmaceuticals and fertilizers[26].
- Smith *etal* have reported selective nitration of certain aromatic compounds using $N_2O_4/O_3/O_2$ mixtures[27].

- Joshi *etal*[28] have reported selective nitration of phenols and substituted phenols to the corresponding nitro compounds under mild condition in a liquid-liquid two phase system with dilute nitric acid (6 wt %) in the presence of a phase-transfer catalyst, namely Tetrabutylammonium bromide (TBAB). TBAB was found to be the most effective phase transfer catalyst in terms of conversion and selectivity. Experimental results have been accounted for, by a binary role of phase transfer catalyst in the system.
- Ganguly *etal*[29] have selectively nitrated the carbocyclic ring of 6-hydroxycoumarins and their O-methyl ethers in the presence of activating 4-methyl group in 2-Pyrone ring with Cerium(IV) Ammonium Nitrate (CAN) separately in acetic acid or acetonitrile and also under solvent free condition on Montmorillonite K-10 clay support under microwave irradiation. Acetonitrile has been found to be a better solvent for regioselective nitration than acetic acid. Use of CAN on Montmorillonite K-10 clay under microwave irradiation has been reported for the first time.
- Nitration of active phenolic compounds like resorcinol, quinol, cresol etc using copper nitrate trihydrate supported on zeolite H-Y as a nitrating reagent in solid phase has been achieved[30]. The reactions were performed under mild and heterogeneous conditions at optimum temperature and under microwave irradiations to get the products in moderate to excellent yields. Recently novel nitration systems comprising of nitric acid, trifloro acetic anhydride and zeolite H-beta have been reported by Smith[31] for the nitration of deactivated aromatic compounds, wherein he has demonstrated that mordenite and zeolite H-beta can play an important role in the selective mononitration of phenols. High para

selectivity is achieved, when acetyl or benzoyl nitrates are used along with nitric acid. Similarly the selective nitration of halobenzenes and toluene at para position using a nitrogen dioxide-oxygen-zeolite H-beta /H-Y system has also been achieved[32].

- Since known methods for ortho-nitration of phenolic compounds fail in the presence of electron withdrawing groups such as carboxylic acid, a new method that favours the desired ortho-nitration has recently been described in a patent[33]. Hummel *etal*[34] have reported a new method of nitration of salicylic acid. It involves phase-transfer catalysis and the use of 2-propylnitrate or sulphuric acid or tetrabutylammonium- hydrogen sulphate in dichloromethane or water and yielded a mixture of 3-nitro and 5-nitro isomers in the ratio of 56:44, where the 3-nitro isomer is claimed to precipitate exclusively from the reaction mixture. Among them 2-propylnitrate is safe and inexpensive nitrating agent and gives preferentially the 3-nitro isomer. Pure potassium 3-nitro salicylate has been crystallized and converted to 3-nitro salicylic acid in 30 % yield. 3-Nitro salicylic acid is a very useful synthetic intermediate for 3-amino salicylates and 3-aminosalicylamides, which are of wide interest and relevance in the synthesis of pharmaceutical and agrochemical products[35,36]. This procedure is highly regioselective method of nitration of salicylic acid at ortho position and this three step synthesis shown below is superior to all previous ones with respect to safety, yield, convenience and overall cost.

Scheme 2.1: Reaction showing synthesis of 3 nitro salicylic acid

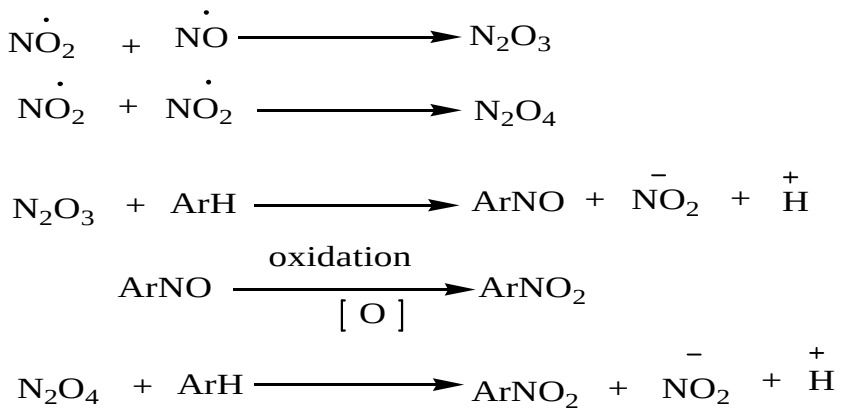


- A novel and safe method for nitration of phenols, anilines and other aromatic compounds have been reported by Saravari *etal*[37] where in alumina sulphuric acid (ASA) is an effective reagent for esterification and Beckmann rearrangement, is also good inorganic resin for nitration of aromatic compounds with magnesium nitrate hexahydrate as nitrating agent under simple and green conditions using water as solvent. The use of water makes this method compatible with the green chemistry approach. ASA can be readily prepared by reaction of acidic alumina with chlorosulphonic acid[38,39]. It is a white solid which can be stored for a long period of time without any decrease in its activity.
- Sathunuru *etal*[40] have studied the exclusive regioselective nitration with the Cerium (IV) Ammonium Nitrate (CAN)/$NaHCO_3$ reagent at the less hindered ortho site, in a series of hydroxy heterocycles with two different unsubstituted ortho positions. The advantage of this method is that neither dinitro nor oxidized products are obtained. The hydroxyl heterocycles include some derivatives of 7-hydroxcoumarin, sesmol, 2,3dihydrobenzo(b)furan-3-one, 6-hydroxy-1,3-benzoxthiol-2-one, 5-hydroxyindole and (5-isoxazolyl)phenols. Phenols which

contain a strong deactivating group such as nitro, cyano were not nitrated by the CAN/$NaHCO_3$ reagent.

- Yong-qiang Chen and Hong Jiang[41] have synthesized a novel nitrating reagent, Melamine nitrate (MN-melamine nitric acid complex) for the regioselective nitration of phenols to their corresponding o-nitro phenols with para toluene sulphonic acid as catalyst in good to excellent yields. The advantageous feature of this method is the easy separation of products by simple filtration. Ortho orientation relative to hydroxyl group and mono nitration of phenolic compounds was observed. For example 4-methoxy-2-nitrophenol was isolated in 96% yield by the nitration of 4-methoxy phenol in acetone solution. Similarily 3-nitro-1,2-benzene diol was obtained in 89% yield by the nitration of catechol under the same reaction conditions.
- Dugar *etal* [42] have studied the photochemical aromatic nitration of phenol and salicylic acid which was carried out in the presence of UV radiations and formation of products has been observed spectrometrically. The effect of various operating variables like pH, concentration of nitrite ion, formate ion, phenol and salicylic acid on the rate of reaction has also been observed. A tentative mechanism involving NO_2 radical has been proposed for photo chemical nitration of phenols and salicylic acid. The rate of reaction increases on increasing pH because N_2O_4 and N_2O_3 are easily generated, which are active species for photo nitration of aromatic systems as shown in the reaction scheme.

Scheme 2.2: Mechanism of photochemical aromatic nitration



- Selzer *etal*[43] have investigated the photo nitration of phenol by tetra nitro methane under visible light. Phenol has been used as a model aromatic molecule and TiO_2 as photocatalyst to carry out aromatic nitration in homogenous and heterogenous aqeous systems[44]. Photo chemically induced nitration of organic compound in the presence of nitrate and nitrite in ice water has also been reported[45]. A solvent free synthesis of para nitrostyrene derived from styrene and its substituted derivatives using "doped" clay reagents, clayfen and clayan have been reported by Varma and co workers[46].
- Nagaev *etal* have carried out direct N-nitration of bis(trifloro methyl) containing 2 azanorboranes[47]. Nitration of thiacalix arene using nitrosonium nitrate complex[48] and of (3,3) and (3,3,3) meta cyclophanes through space electronic between two or three benzene rings have also been reported[49]. Dagade *etal*[50] have carried out the vapour phase nitration of toluene using nitric acid and molecular modeling studies over beta zeolite.
- X.Yang and Chanjuan xi[51] have reported the cerium nitrate mediated nitration of N,N dialkyl anilines with $NaNO_2$ using water as solvent in good to excellent yields. The nitrating reaction proceeded smoothly and at ambient temperature.

This mild nitrating system needs neither acidic conditions nor organic solvents and is quite easy to handle. When various N,N-dialkyl anilines were used, ortho and para nitrated products were obtained in good yield and the later was always the major one.

- Samajdar *etal*[52] have reported the synthesis of several nitro compounds of biological significance in high yield by an excellent reagent Montmorillonite impregnated with bismuth nitrate. Similarly there are reports of the synthesis of various nitro aromatic compounds by a reagent Montmorillonite clay impregnated with anhydrous cupric nitrate termed as "claycop" [53] and various nitro phenols in moderate to high yield via nitration of phenols by antimony nitrate $Sb(NO_3)_3.5H_2O$ as an efficient nitrating reagent[54]. In the latter case reactions were carried out at room temperature by grinding equimolar amounts of phenolic compound and $Sb(NO_3)_3.5H_2O$ in an ice water bath. This method has advantage over other conventional methods like operational simplicity, good to high yields and use of non toxic and easily available catalyst.
- Synthesis of nitrophenols and substituted nitrophenols in moderate to high yield using a combination of $Mg(HSO_4)_2$ or $NaHSO_4.H_2O$, $NaNO_3$ and wet SiO_2 in dichloromethane at room temperature is also reported[55]. This method provides short reaction time, good yield, easy and clean workup and is highly selective and contamination by oxidation side products is also avoided. Moreover a new feature of this method is the heterogeneous nature of the reaction, which provides effective surface area for insitu generation of nitric acid in low concentration.
- N. Nowrouzi and M.Z. Jonaghani have reported the nitration of aromatic compounds under essentially neutral conditions by employing Ph_2PCl

(chlorodiphenyl phosphine) in the presence of iodine and silver nitrate[56]. This method minimizes waste, di and poly nitrated products as compared to conventional/traditional conditions and gives the corresponding mono nitro derivatives in good to excellent yields in dichloromethane at room temperature. Tertiarybutyl nitrate has been identified as a safe and chemoselective nitrating agent that provides preferentially mono nitration of phenolic substrates in the presence of potentially competitive functional groups by Koley *etal*[57]. It is proposed that the reaction proceeds through the formation of O-nitrosyl intermediate prior to C-nitration through homolysis and oxidation. This nitration method is compatible with tyrosine containing peptides on solid support in the synthesis of fluorogenic substrates for characterization of proteases.

- Kristovich *etal*[58] have reported the nitration of benza(a)pyrene by nitrogen dioxide adsorbed on the surface of thermally activated coal flyash and model aluminosilicate particles which led to the formation of nitro benzo(a)pyrene. This nitration of adsorbed poly aromatic hydrocarbons on coal flyash by reaction with nitrogen dioxide can occur in the smoke stack, but with the aging of the fly ash particles, the extent of the reaction gets diminished.
- The nitration of ortho xylene, phenol and toluene with 100% nitric acid adsorbed on various solid supported systems like MoO_3/SiO_2, WO_3/SiO_2, TiO_2/SiO_2 and $TiO_2/WO_3/SiO_2$ has also been reported[59]. Phenol and toluene were nitrated with yields higher than 90%, while nitration of ortho xylene was carried most effectively with 10% and 15% MoO_3/SiO_2 catalyst. These most active catalysts exhibited the para position selectivity of nitration.

- Synthesis of 1-(2-Nitroxyethyl nitramino)-2,4,6-trinitrobenzene, 1,3-bis(2-Nitroxyethyl nitramino)-2,4,6-trinitrobenzene and 1,3,5-tris(2-Nitroxyethyl nitramino)-2,4,6-trinitrobenzene by the nitration of 1-(2-hydroxyethyl amino)-2,4,6-trinitrobenzene, 1,3-bis(2-hydroxyethyl amino)-2,4,6-trinitrobenzene and 1,3,5-tris(2-hydroxyethyl amino)-2,4,6-trinitrobenzene respectively using bismuth nitrate pentahydrate (ecofriendly nitrating agent) in tetrahydrofuran adsorbed on silica gel under microwave irradiations have been achieved[60]
- Selective nitration of di-n-octyl-crown-6calix(4)arene with nitric acid under different conditions have been studied with LS-MS and ^{1}H and ^{13}C NMR spectroscopic techniques leading to the identification of expected isomeric nitro derivative[61].
- Nitration chemistry has been reviewed by Olah and co-workers[62] with strong emphasis on nitronium salt, of which nitronium tetrafluoroborate (NO_2BF_4) and nitronium hexafluorophosphate (NO_2PF_6) have been found to be the most effective nitrating agents.
- Various substituted 4-hydroxy-3-nitrocoumarins were synthesized by the nitration of the corresponding 4-hydroxycoumarins. All were found to possess antiallergic activity as measured by the homocytotropic antibody antigen induced passive cutaneous anaphylaxis reaction in the rat[17].
- Selective nitration of phenols with $Fe(NO_3)_3.9H_2O$ in the presence of nano-SiO_2 at room temperature in good to high yields and shorter reaction time have been carried out[63]. The reactions were performed in various solvents and the catalyst could be reused for several runs. The use of nano-SiO_2 as catalyst for the first time is an advantage of this method.

- Majid *etal*[64] have carried out the nitration of phenols and napthols regioselectively with sodium nitrate in the presence of $KHSO_4$ at 50 ^{0}c in high yield and the catalytic effects of some Keggin type heteropolyacids and polyoxometalates is also reported[65]. The catalytic amounts of heteropolyacids and polyoxometalates promoted mononitration of phenolic compounds using Iron(III) nitrate and bismuth(III) nitrate pentahydrate in dichloromethane at room temperature. Tungstophosphoric acid cesium salt in a heterogeneous phase, exhibited significant rate enhancement of reactions as well as ortho selectivity without over nitration and oxidation of products. Simple, rapid, clean and environmentally benign synthesis of aromatic nitro compounds by using inorganic nitrates as nitrating agents adsorbed on silica gel as a solid support has been carried out[66].
- Phenols have been nitrated regioselectively with NH_4NO_3 in presence of $KHSO_4$ as a catalyst in high yields[67].
- Khazaei *etal*[68] have reported the synthesis of nitrophenols in high yield via nitrosation-oxidation of phenols by 3-methyl-1-sulfonic acid imidazolium chloride (MSim)cl as a new bronsted acidic ionic liquid and $NaNO_2$, at room temperature. Insitu generation of nitric acid and a radical cation mechanism via the nitrous acid catalyzed pathway is applicable to phenol nitration using this reagent system.

Scheme 2.3: Proposed mechanism for the nitration of phenols

$$\overset{+}{H} + \overset{-}{NO_2} \longrightarrow HNO_2 \quad (1)$$

$$HNO_2 + 2\overset{+}{H} \longrightarrow \overset{+}{NO} + \overset{+}{H_3}O \quad (2)$$

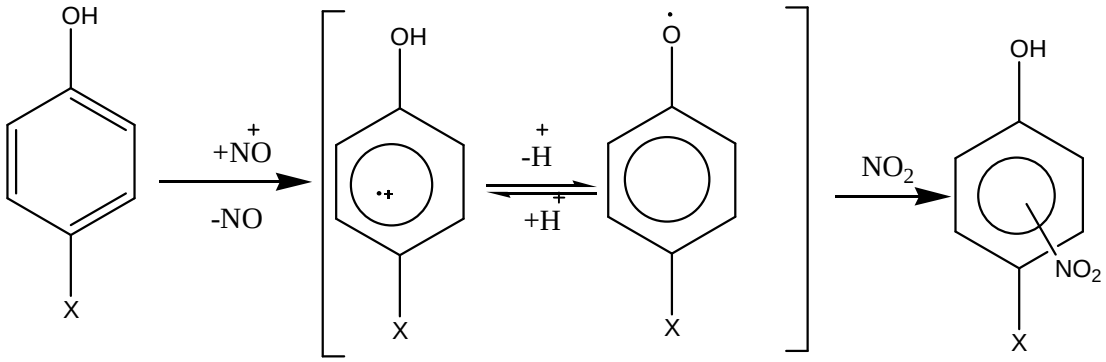
$$2HNO_2 \longrightarrow N_2O_3 + H_2O \quad (3)$$

$$N_2O_3 \longrightarrow NO + NO_2 \quad (4)$$

$$2NO_2 \longrightarrow N_2O_4 \quad (5)$$

$$2NO \longrightarrow N_2O_2 \quad (6)$$

$$N_2O_2 + O_2 \longrightarrow N_2O_4 \quad (7)$$



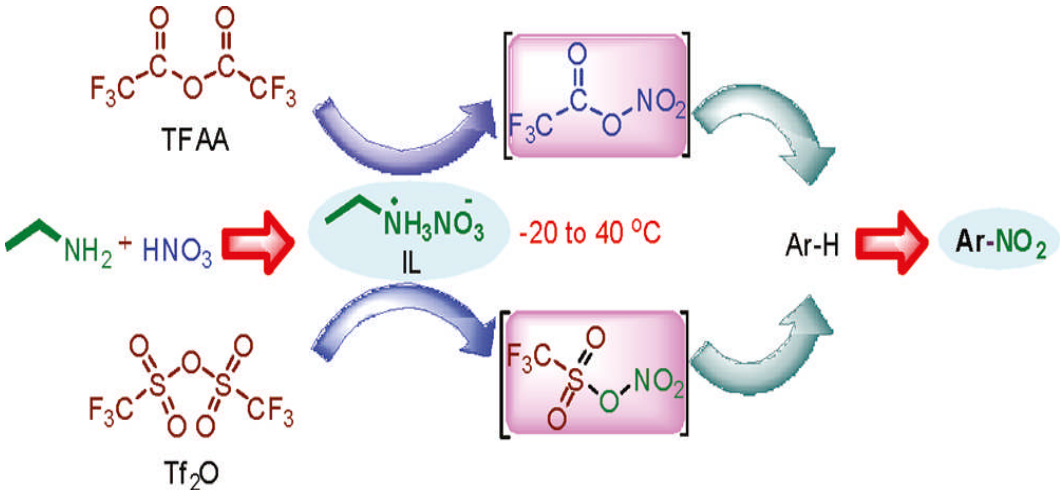
1 or 5 3, 4 or 6

Phenols were converted to para nitrophenols selectively by 3-methyl-1-sulfonic acid imidazolium chloride (3eq)/$NaNO_3$ (1eq) system. Moreover phenol nitrosation is rapid and yields almost entirely the para isomer which can be readily converted to para nitro phenol via a mild oxidation with nitric acid. This is a one pot reaction under mild conditions.

- Smith *etal*[69] have reported the regioselective mononitration of simple aromatic compounds in several different ionic liquids which are stable in air and moisture. Use of a mixture of nitric acid and acetic anhydride as a nitrating reagent gave rise

to enhanced reactivity and improved para selectivity for halobenzenes compared to those when carried out in a molecular solvent like CCl_4. In addition, the ionic liquid could be recovered easily and reused, which opens up the possibility of a more economic process.

- Selective nitration of phenols with sodium nitrate carried out in the presence of acidic ionic liquid 1-butyl-3-methyl imidazolium hydrogen sulphate (bmim)(HSO_4) at room temperature in good to high yields and short reaction time have been reported[70]. This method uses inexpensive and relatively non toxic acidic reagent. It has also been reported[71] that triflyl nitrate ($TfONO_2$) and trifluoroacetyl nitrate (CF_3COONO_2) generated in the EAN/Tf_2O and EAN/TFAA systems respectively via metathesis in the ethylammonium nitrate (EAN) ionic liquid as solvent are powerful electrophilic nitrating reagents for a wide variety of aromatic and heteroaromatic compounds. Comparative nitration experiments indicate that EAN/Tf_2O is superior to EAN/TFAA for the nitration of strongly deactivated systems.



Chapter-3

Microwave Assisted Synthesis of Nitro Aromatic Compounds

3.1 Introduction

Microwave Assisted Organic Synthesis (MAOS) has become an important tool in the hands of chemists for bringing up rapid valuable transformation or synthesis of organic and inorganic compounds. Many research papers have been put forward over the last decades on the application of Microwave technology in organic synthesis[72].Some of the advantages include remarkable decrease in reaction time, lesser number of by-products and excellent yield as compared to conventional heating methods.

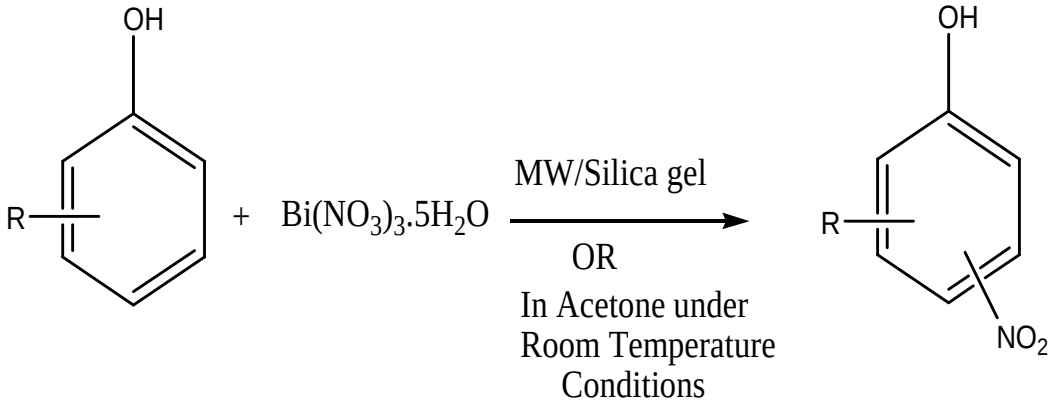
Recently this method has been exploited in multistep-total synthesis[73,74] and drug discovery/designing[75]. It has attracted great deal of interest in Pharmaceutical industry, Polymer synthesis[76, 77], Material science[78,79], Nanotechnology[80], Biochemical process[81] and Combinatorial Chemistry. MAOS has an immense potential for the development of new reaction conditions especially environmentally benign ones.

Nitration of aromatic compounds is one of the most studied organic reactions[82,83] as nitrated products are important intermediates for the synthesis of pharmaceuticals, perfumes, plastics and dyes. Nitrophenols are important class of organic compounds which have been discussed in chapter **2**.

Classical nitration usually requires use of excess of nitric acid in combination with other strong acids and suffers from low regioselectivity[20], over nitration[21,22] and is not environment friendly. To overcome this problem, alternative methods using different nitrating agents and microwave assisted synthesis have been developed for nitration of aromatic compounds. This has not only helped in overcoming the problems such as

low yield, low selectivity and elimination of volatile organic solvents but has also made the entire process eco-friendly.

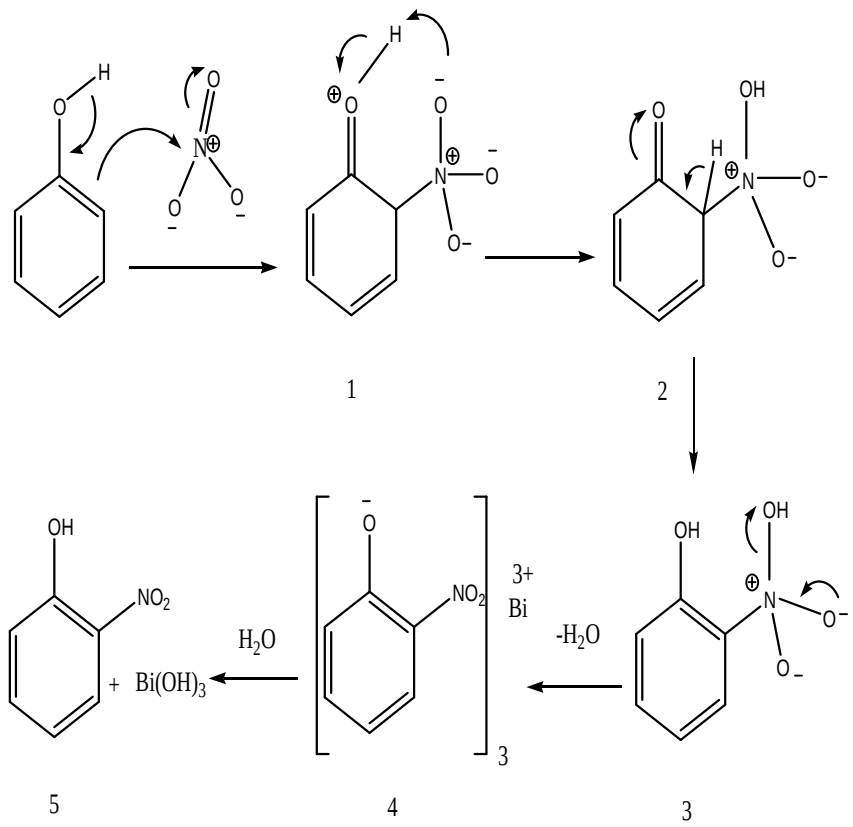
An alternative method for nitration of phenolic aromatic compounds is by using bismuth nitrate pentahydrate as a nitrating agent. It is an inorganic catalyst which is adsorbed on silica gel and nitration is carried out through microwave irradiation in an eco-friendly way without using solvents and hazardous substances. A general **Scheme I** for the synthesis of aromatic nitro compounds using bismuth nitrate pentahydrate is given below.



R = -H, -OH, -CH_3, -COOH or fused aromatic ring.

Scheme-I

The proposed mechanism involved in the reaction of phenolic substrate with bismuth nitrate pentahydrate involving initial interation between nitrate ion and the aromatic ring followed by dehydration as is depicted below (**Scheme-II**).



Scheme-II

3.2 Importance of the present work

Since the concept of green chemistry is gaining momentum in the field of organic synthesis[84], emphasis is being laid to devise new methods and procedures for synthesizing potentially important compounds in an eco-friendly environment. Keeping into consideration the enormous pharmacological potential of nitro aromatic compounds, it is of utmost importance that their synthesis should be achieved by simple, effective and a time saving methodologies.

Much work has been done on the synthesis of nitro aromatic compounds under classical conditions, as well as under microwave conditions. The latter has blossomed

as an eco-friendly procedure with the advantage of improved yield, easy work-up and considerable shortening of reaction times. Several nitro aromatic compounds have been synthesized under microwave irradiations under solvent free conditions and enhancement in yield and time reduction has been reported [52,53].

In this background, we also report here the microwave assisted synthesis of nitro aromatic compounds with the advantage of improved yields and shortened reaction times. This efficient eco-friendly procedure provides a green chemistry approach for the synthesis of nitro aromatic compounds.

3.3 Results and discussion

3.3.1 General study

For the convenient synthesis of nitro aromatic compounds, phenol and a range of other aromatic substituted phenolic compounds like resorcinol, cresol, salicylic acid and oxygen containing heterocycles like 4-hydroxycoumarin, 7-hydroxycoumarin were treated with bismuth nitrate pentahydrate. Reactions were carried out under solvent free conditions (silica gel used as solid support) in the molar ratio of 1: 2 taken in an open vessel and irradiated in a multimode oven at the corresponding power and time as shown in **table 3.1**. Optimum irradiation times were precisely achieved but the reaction was carried out with intervals of 30 seconds in order to avoid decomposition of product due to rapid rise in the temperature. Progresses of the reactions were monitored periodically with the help of thin layer chromatography. The problems encountered while performing the reactions under conventional conditions were easily over come by solvent free technique and the yield obtained was almost quantitative.

This clearly indicates that microwaves do not affect the mechanism of a reaction but the procedure is governed by the same laws as in classical chemistry. However enhanced effects result because there is an insitu generation of heat in case of microwave irradiation and an indirect conventional heat transfer in case of classical procedure.

3.3.2 Comparative study

A comparison of microwave assisted synthesis of nitro aromatic compounds from aromatic phenolic compounds with those carried out under conventional conditions has been drawn in **table 3.2**.The reactions were irradiated from seconds to minutes depending upon the substrate used and a power level of 25% -100% to monitor an exact comparison in terms of yield and time.

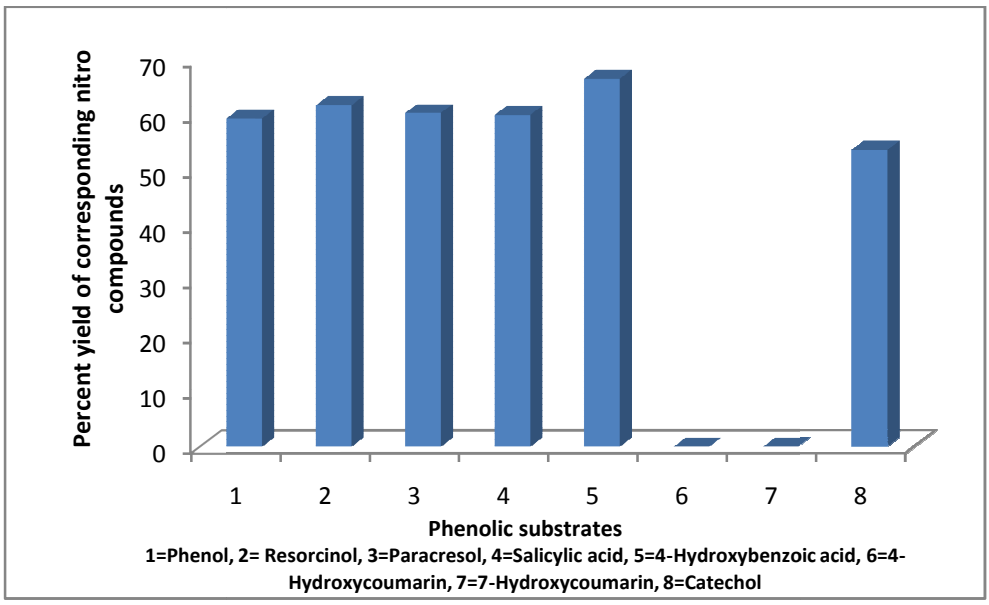


Figure 3.1: Plot of percent yield of the corresponding nitro aromatic compound vs the phenolic substrates with 2:1 molar ratio of bismuth nitrate pentahydrate and phenolic substrate under thermal conditions.

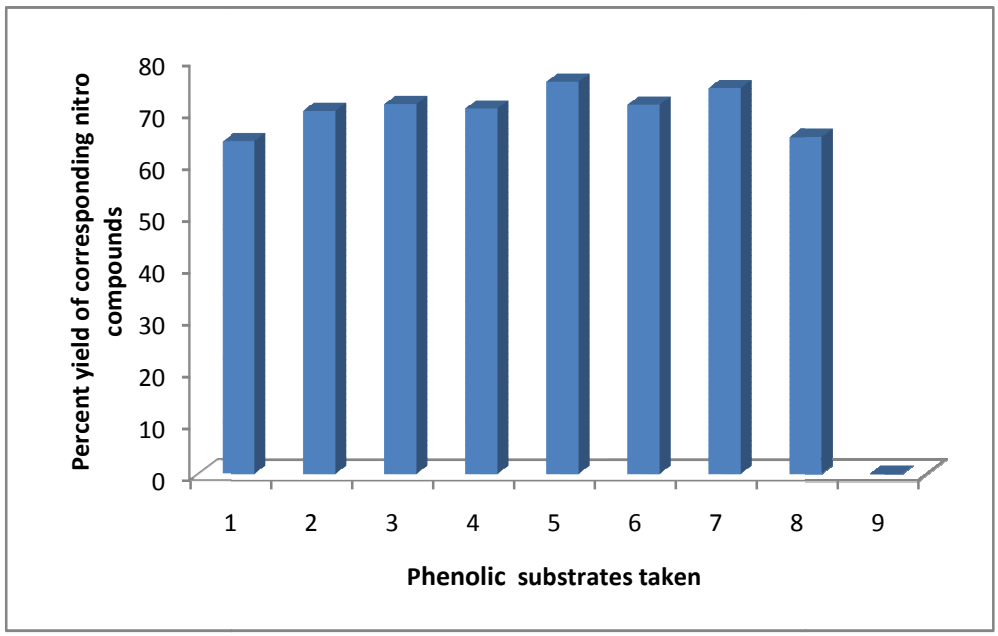


Figure 3.2: Plot of percent yield of the corresponding nitro aromatic compound vs the phenolic substrates with 2:1 molar ratio of bismuth nitrate pentahydrate and phenolic substrate under microwave irradiation conditions.

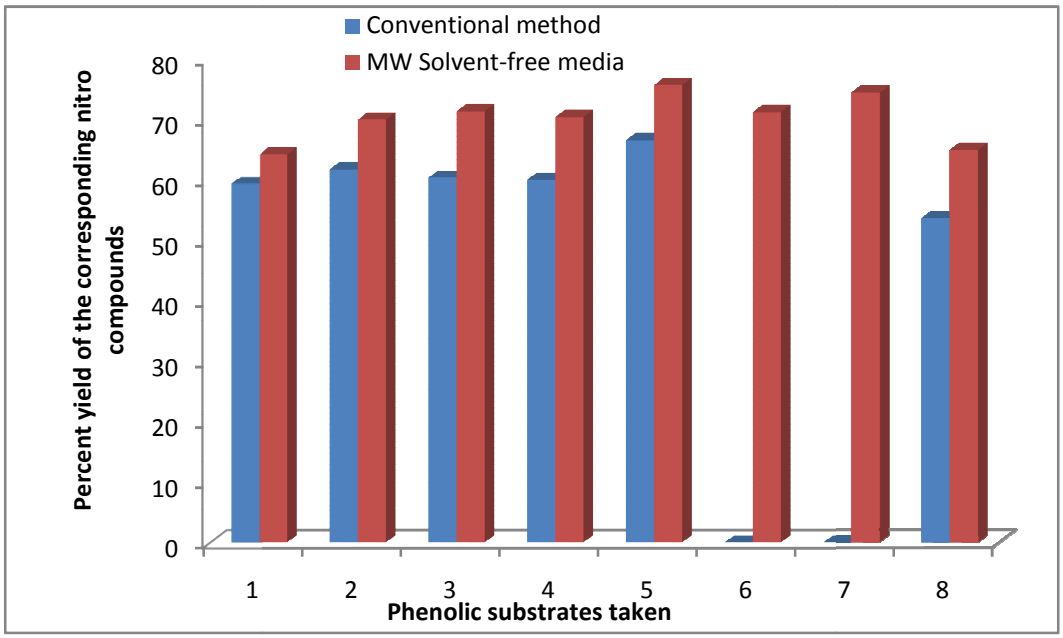


Figure 3.3: Clubbed graph showing the comparative account of % yield of nitro aromatic compounds from bismuth nitrate and corresponding phenolic substrates taken in a 2:1 molar ratio under two different conditions.

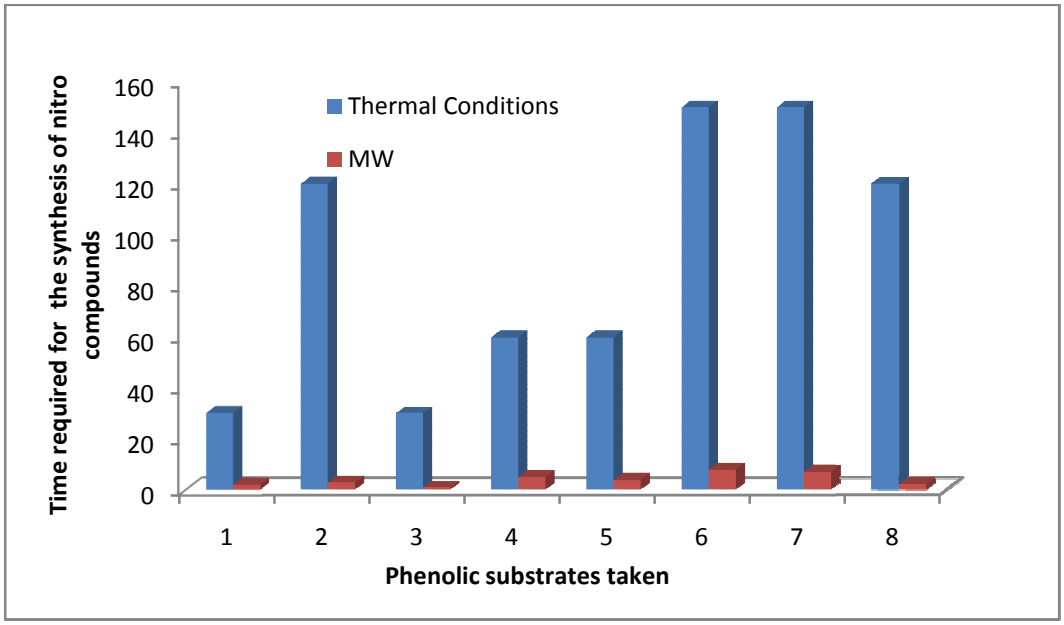


Figure 3.4: Clubbed graph showing the comparative account of time required for the synthesis of nitro aromatic compounds from bismuth nitrate and corresponding phenolic substrates taken in a 2:1 molar ratio under two different conditions.

Table 3.1: Solid-state nitration of phenolic substrates with bismuth nitrate pentahydrate adsorbed on silica gel under microwave conditions.

S.No.	Substrate	Product	Microwave irradiations	
			Time (minutes)	% Yield
1	Phenol	4-nitrophenol	2	64.24
2	Resorcinol	2-nitroresorcinol	3	70.09
3	Para Cresol	2-nitro Paracresol	1	71.42
4	Salicylic acid	3-nitro Salicylic acid	5	70.51
5	4-hydroxybenoic acid	3-nitro-hydroxybenzoic acid	4	75.75
6	4-hydroxycoumarin	3-nitro-4-hydroxycoumarin	8	71.31
7	7-hydroxycoumarin	6-nitro-7-hydroxycoumarin	7	74.45
8	Catechol	3-nitro Catechol	2	64.97

Table 3.2: Nitration of phenolic substrates with bismuth nitrate pentahydrate in acetone under thermal conditions.

S.No.	Substrate	Product	Room Temperature	
			Time (minutes)	% Yield
1	Phenol	4-nitrophenol	30	59.4
2	Resorcinol	2-nitro-1,3-benzenediol	120	61.86
3	Para Cresol	2-nitro Paracresol	30	60.42
4	Salicylic acid	3-nitro Salicylic acid	60	60.06
5	4-hydroxybenoic acid	3-nitro-hydroxybenzoic acid	60	66.66
6	4-hydroxycoumarin	3nitro-4-hydroxycoumarin	No reaction	0
7	7-hydroxycoumarin	6-nitro-7-hydroxycoumarin	"	"
8	Catechol	3-nitro Catechol	120	53.67

3.4 General procedure for the synthesis of nitro aromatic compounds

3.4.1 Under microwave irradiations (solvent free conditions)

Phenolic aromatic compounds and the bismuth nitrate pentahydrate in 1:2 molar ratio were adsorbed on silica-gel (60-120 mesh) by grinding in a mortar and pestle and irradiated under the microwave oven for the time indicated in **table 3.1**. After cooling, the solid mixture was treated with dichloromethane and then filtered. The filtrate upon concentration or solvent evaporation (removal of solvent) gave the product which was crystallized from an appropriate solvent.

3.4.2 Under conventional conditions (room temperature)

A mixture of bismuth nitrate pentahydrate and phenolic aromatic compounds were dissolved in 30 ml of acetone in the molar ratio of 2:1 and the reaction mixture was continuously stirred in a 250ml stopped conical flask for varying period of time. The insoluble residue was filtered, because of heterogeneous nature of the reaction medium and the solvent was removed. The solid thus obtained was crystallized from the appropriate solvent.

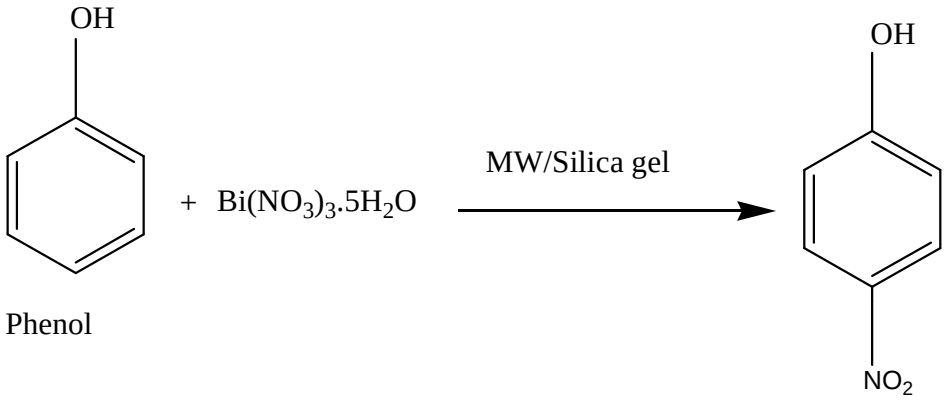
3.5 Experimental

3.5.1 General study

The melting points were taken in open capillaries using electro thermal method on a *Labotech/Perfit* instrument and are uncorrected. Infrared spectra were recorded on a *Perkin Elmer 2000-FT* spectrometer. Ultra-violet spectra were measured in DMSO (spectral grade) as the solvent on a *Schimadzu UV-1650 PC* UV/Visible spectrophotometer. All the solvents and chemicals used were of AR grade. All the reactions were carried out in a multimode *Sharp Carousel*^{TM} microwave oven.

3.6 Reaction of bismuth nitrate pentahydrate with various phenolic substrates.

1 Reaction with phenol



Phenol

Para Nitrophenol

A) Under microwave conditions (solvent free)

A mixture of bismuth nitrate pentahydrate (0.5gms) and phenol (0.25gms) was adsorbed on silica gel by grinding in a mortar and pestle and irradiated in the microwave oven for 2 minutes at medium power. The mixture after cooling was treated with dichloromethane and filtered. The filtrate upon concentration and work up yielded the product. The product was crystallized with chloroform solvent.

Yield=0.239gms

B) Under thermal conditions.

A mixture of bismuth nitrate pentrate hydrate (0.5gms) and phenol (0.25gms) in 30 ml of acetone was continuously stirred in a 250ml stopped conical flask for 30 minutes at room temperature. The mixture was filtered and the filtrate was concentrated, dried and yellow crystals of nitrophenol were obtained and crystallized from chloroform for further purification.

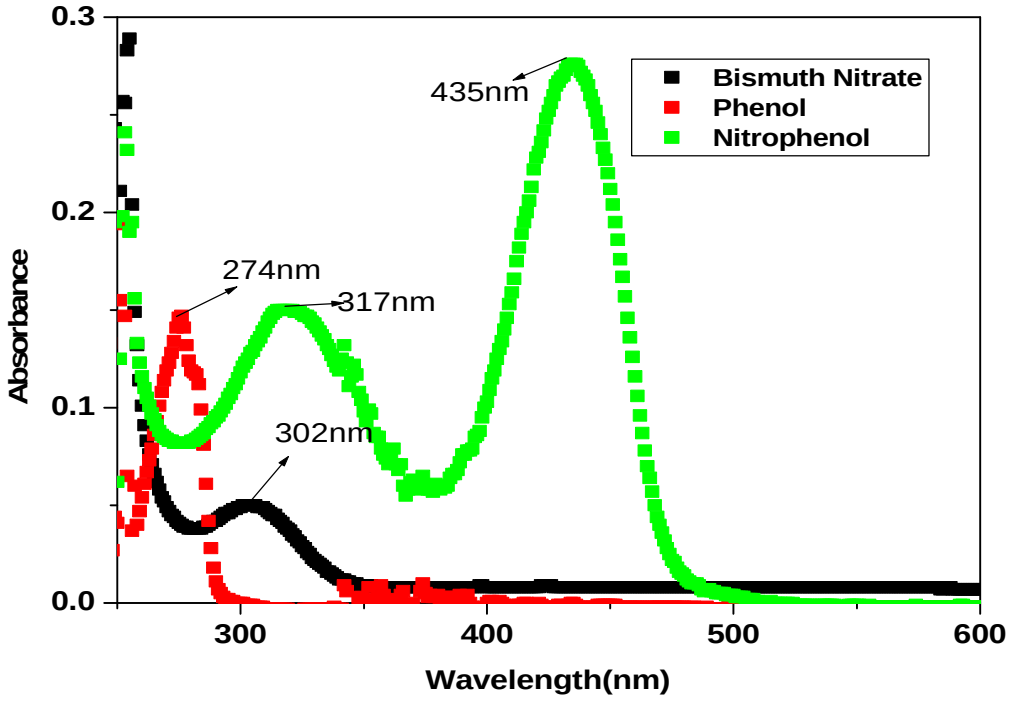
Yield=0.221gms

Spectral data

4-Nitrophenol: Yellow powder, Melting point-112-114^{0}C,

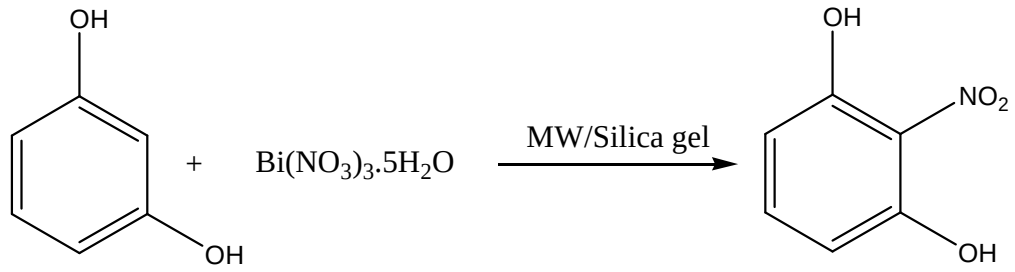
IR (KBr) cm^{-1}: 3331, 1614, 1592, 1500, 1346.

UV/Visible plot of 4-Nitrophenol



The data was identified with those reported in literature for 4-nitrophenol[36].

2 Reaction with resorcinol.



1,3-benzenediol

2-nitro-1,3-benzenediol

A) Under microwave conditions (solvent free)

A mixture of bismuth nitrate pentahydrate (1gm) and resorcinol (0.5gms) was adsorbed on silica gel by grinding in a mortar and pestle and irradiated in the microwave oven for 3 minutes at medium power. The mixture was treated with dichloromethane and filtered. Upon concentration and work up, the product was obtained and was crystallized with benzene solvent.

Yield=0.497gms

B) Under thermal conditions.

A mixture of bismuth nitrate pentratehydrate (0.5gms) and resorcinol (0.25gms) in 30ml of acetone was continuously stirred in a 250ml stopped conical flask for 2 hours at room temperature. The mixture was filtered and the filtrate was concentrated, dried and yellow crystals of nitroresorcinol were obtained and crystallized from benzene for further purification.

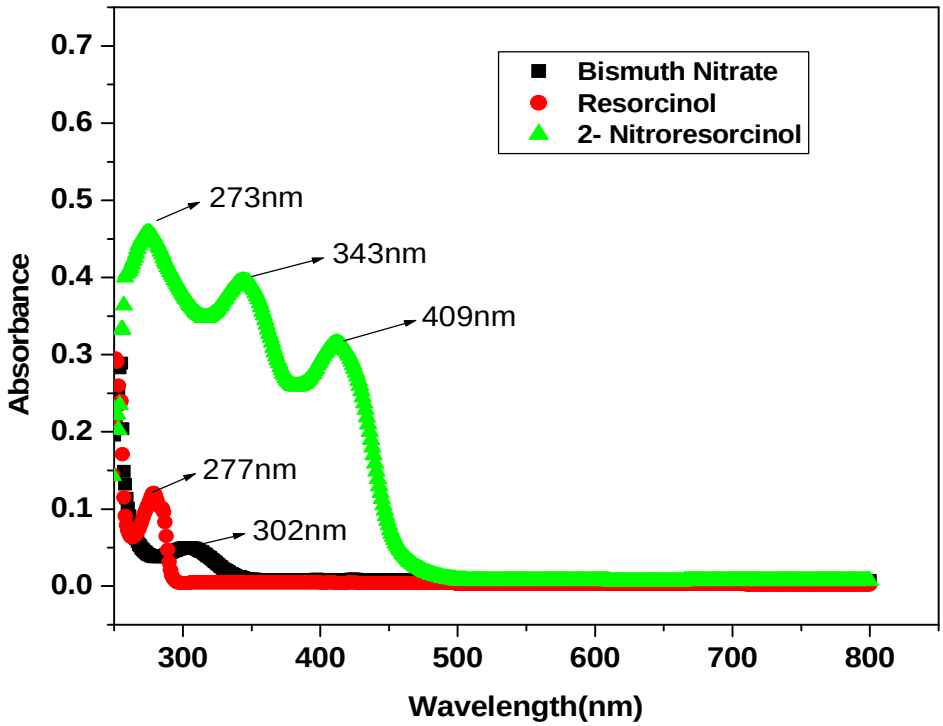
Yield=0.219gms

Spectral data

Yellow powder, Melting point 82-84^{0}C.

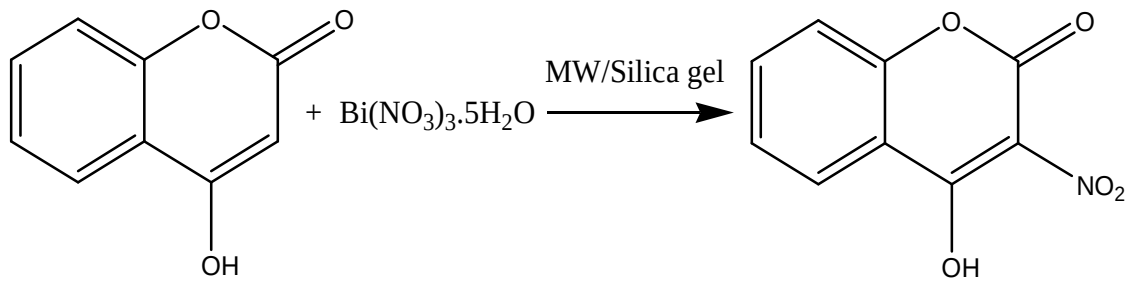
IR (KBr) cm^{-1}: 3388, 3300, 1628, 1592, 1525, 1511, 1444, 1327, 1284.

UV/Visible plot of 2-Nitroresorcinol



The data was identified with those reported in literature for 2-nitro-1, 3-benzenediol[54].

3 Reaction with 4-hydroxycoumarin.



4-hydroxycoumarin 3-nitro-4-hydroxycoumarin

A) Under thermal conditions

A mixture of bismuth nitrate pentahydrate (0.5gms) and 4-hydroxycoumarin (0.25gms) in 30 ml of acetone was continuously stirred in a 250ml stopped conical flask was for 70 hours at room temperature. No reaction was observed.

B) Under microwave conditions (solvent free)

A mixture of bismuth nitrate pentahydrate (1gm) and 4-hydroxycoumarin (0.5gms) was adsorbed on silica gel by grinding in a mortar and pestle and irradiated in the microwave oven for 8 minutes at medium power. The mixture was treated with dichloromethane and filtered. Upon concentration and work up, yielded the product and crystallized with chloroform solvent.

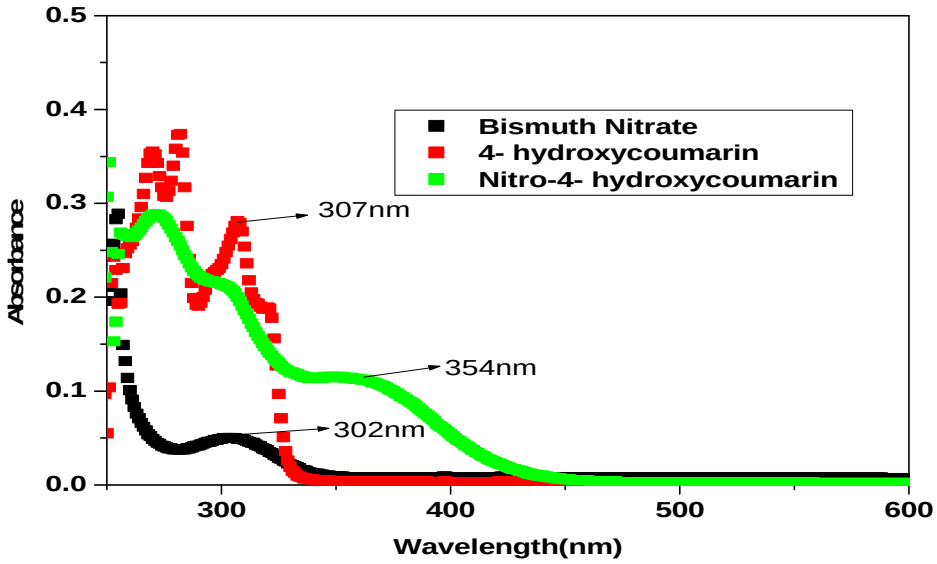
Yield=0.455gms

Spectral data

3-Nitro-4-hydroxycoumarin. Melting point 175-176^{0}C.

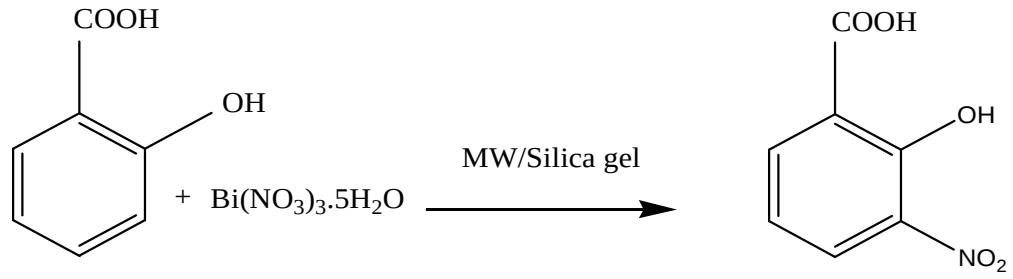
IR (KBr) cm^{-1}: 3440, 1740, 1620, 1550, 1360.

UV/Visible plot of 3-Nitro-4-hydroxycoumarin



The data was identified with those reported in literature for 3-nitro-4-hydroxycoumarin[17,28].

4 Reaction with salicylic acid.



Salicylic acid 3-Nitro Salicylic acid

A) Under microwave conditions (solvent free)

A mixture of bismuth nitrate pentahydrate (1gm) and salicylic acid (0.5gms) was adsorbed on silica gel by grinding in a mortar and pestle and irradiated in the microwave oven for 5 minutes at high power. The mixture was treated with dichloromethane and filtered. Upon concentration and work up, yielded the product and crystallized with benzene solvent.

Yield=0.471gms

B) Under thermal conditions

A mixture of bismuth nitrate pentratehydrate (0.5gms) and salicylic acid (0.25gms) in 30 ml of acetone was continuously stirred in a 250ml stopped conical flask for 1 hour at room temperature. The mixture was filtered and the filtrate was concentrated, dried and crystallized from benzene for the further purification.

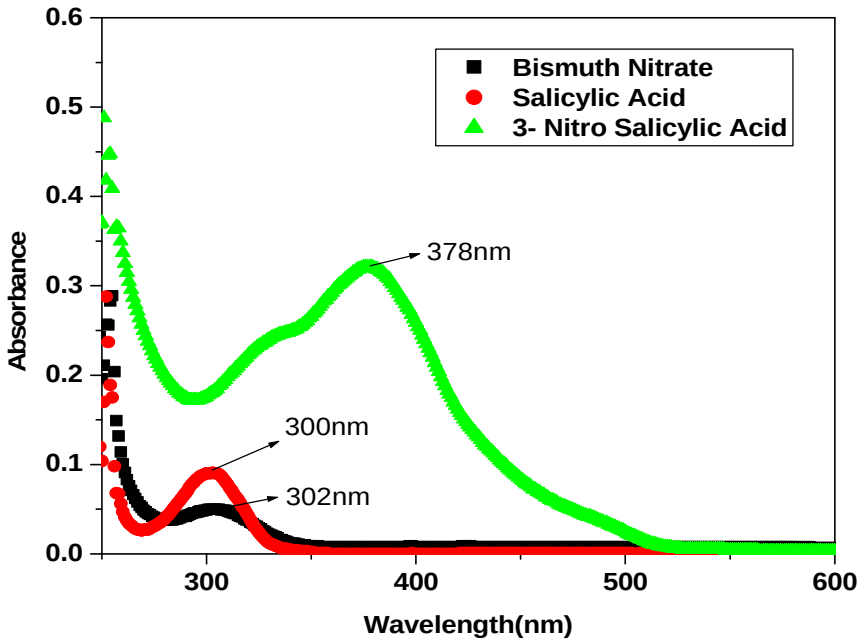
Yield=0.2gms

Spectral data

Melting point: 123^0C.

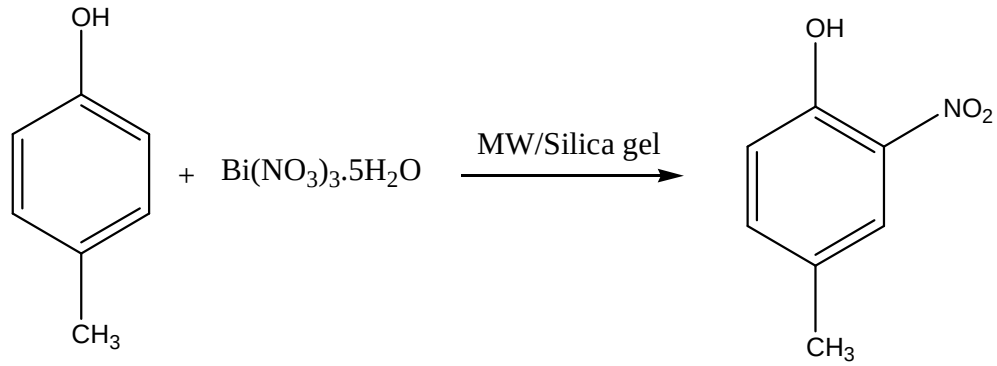
IR (neat) cm^{-1}: 3096, 2824, 2548, 1667, 1596, 1519, 1441, 1357, 1251, 1130, 1097, 900,848, 771, 743, 693, 597.

UV/Visible plot of 3-Nitro Salicylic acid



The data was identified with those reported in literature for 3-nitro salicylic acid[33].

5 Reaction with Para Cresol



Para Cresol

2-Nitro Para Cresol

A) Under microwave conditions (solvent free)

A mixture of bismuth nitrate pentahydrate (0.5gms) and para cresol (0.25gms) was adsorbed on silica gel by grinding in a mortar and pestle and irradiated in the microwave oven for 1 minute at medium power. The mixture was treated with

dichloromethane and upon work up, yielded the product, which upon crystallization with benzene resulted in a yellow product.

Yield=0.25gms

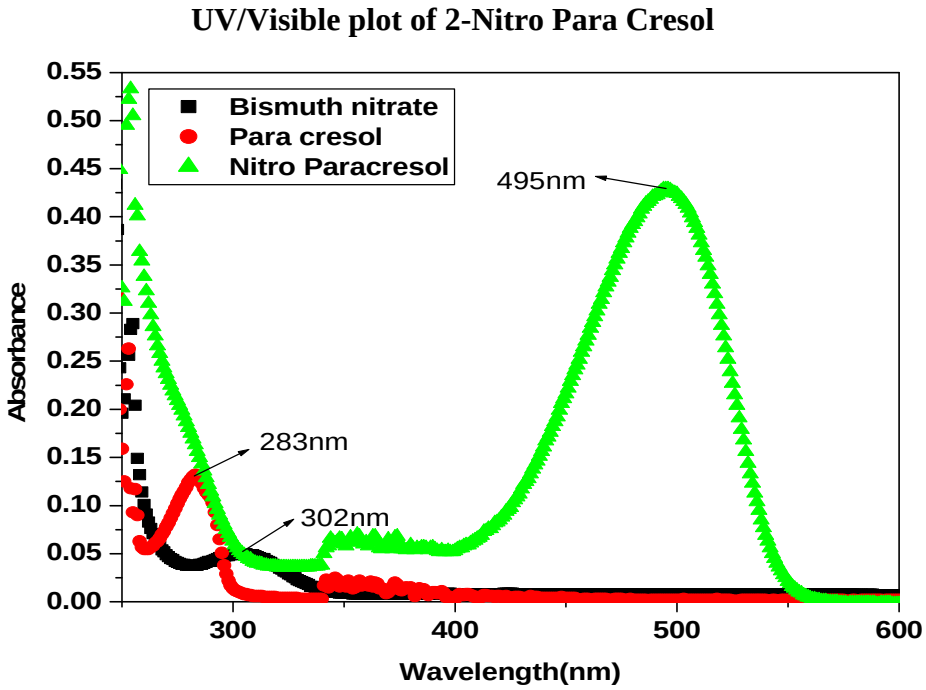
B) Under thermal conditions

A mixture of bismuth nitrate pentahydrate (0.5gms) and para cresol (0.25gms) in 30 ml of acetone was continuously stirred in a 250ml stopped conical flask for 30 minutes at room temperature. The mixture was filtered and the filtrate was concentrated, dried and yellow crystals of nitro para-cresol were obtained and crystallized from benzene for further purification.

Yield=0.215gms

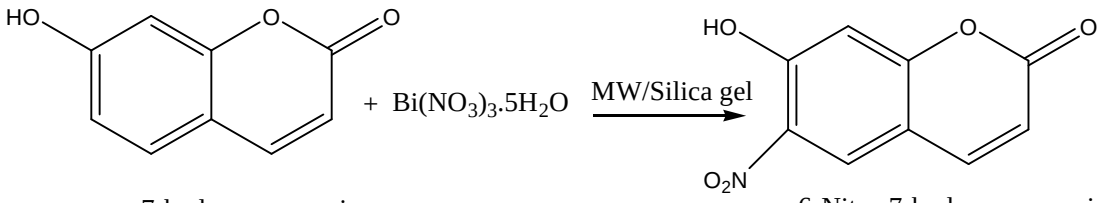
Spectral data

Melting point: 33-34^{0}C.



The data was identified with those reported in literature for 2-nitro paracresol[40].

6 Reaction with 7-hydroxycoumarin.



7-hydroxycoumarin 6-Nitro-7-hydroxycoumarin

A) Under thermal conditions.

A mixture of bismuth nitrate pentahydrate (0.5gms) and 7-hydroxycoumarin (0.25gms) in 30 ml of acetone was continuously stirred in a 250ml stopped conical flask for 60 hours at room temperature. No reaction was observed.

B) Under microwave conditions (solvent free)

A mixture of bismuth nitrate pentahydrate (0.5gms) and 7-hydroxycoumarin (0.25gms) was adsorbed on silica gel by grinding in a mortar and pestle and irradiated in the microwave oven for 7 minutes at medium power. The mixture was treated with dichloromethane and filtered. Upon concentration and work up, yielded the product which upon crystallization with chloroform solvent resulted in a bright yellow product.

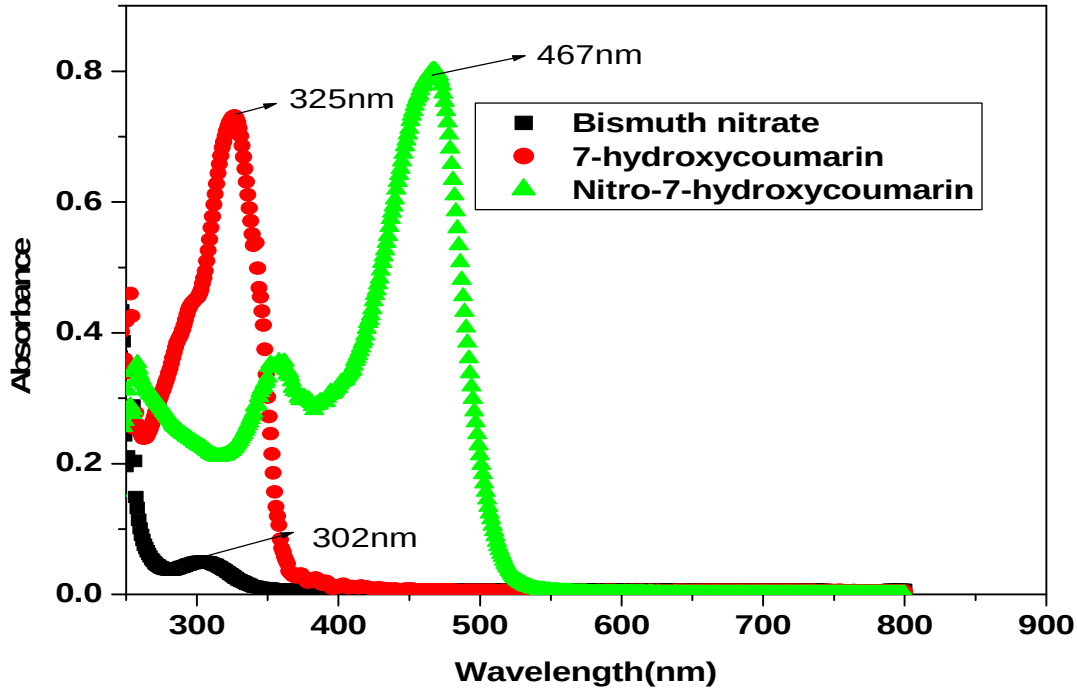
Yield=0.475gms

Spectral data

Yellow needles.

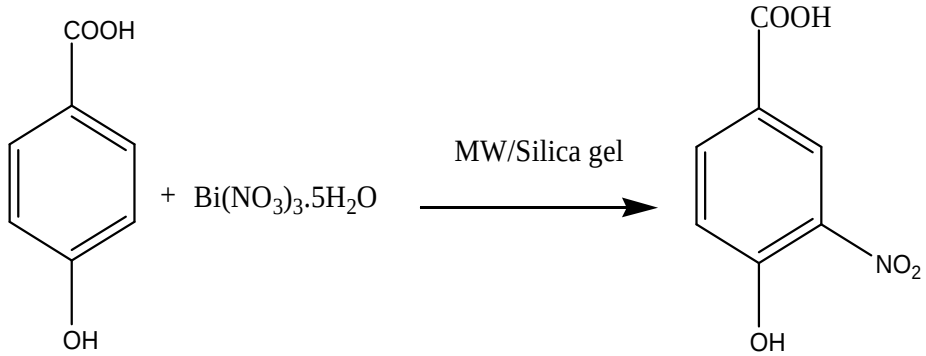
Melting point: 229^0c

UV/Visible plot of 6-Nitro-7-hydroxycoumarin



The data was identified with those reported in literature for 6-nitro-7-hydroxycoumarin[39].

7 Reaction with 4-hydroxybenzoic acid.



4-hydroxybenzoic acid

4-hydroxy-3-nitrobenzoic acid

A) Under microwave conditions (solvent free)

A mixture of bismuth nitrate pentahydrate (0.5gms) and 4-hydroxybenzoic acid (0.25gms) was adsorbed on silica gel by grinding in a mortar and pestle and irradiated in the microwave oven for 4 minutes at medium power. The mixture was treated with dichloromethane and filtered out. The filterate upon concentration and work up, yielded the product which was crystallized with benzene solvent.

Yield=0.25gms

B) Under thermal conditions

A mixture of bismuth nitrate pentratehydrate (0.5gms) and 4-hydroxybenzoic acid (0.25gms) in 30 ml of acetone was continuously stirred in a 250ml stopped conical flask for 1 hour at room temperature. The mixture was filtered and the filtrate was concentrated, dried and yellow crystals of 4-hydroxy-3-nitrobenzoic acid were obtained and crystallized from benzene for further purification.

Yield=0.22gms

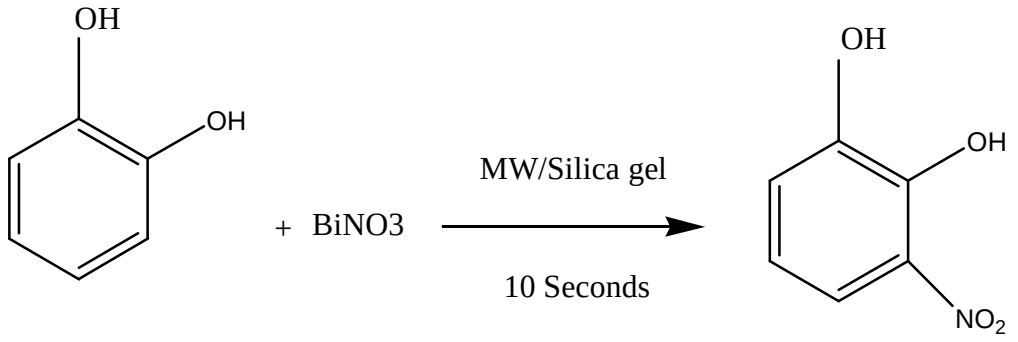
Spectral data

Melting point: 180-183^{0}C

IR (KBr) cm^{-1}: 3309, 3089, 2842, 1627, 1539, 1434, 1342.

The data was identified with those reported in literature for 4-hydroxy-3-nitrobenzoic acid[36].

8 Reaction with Catechol



Catechol

3 Nitro Catechol

A) Under microwave conditions (solvent free)

A mixture of bismuth nitrate pentahydrate (0.5gms) and catechol (0.25gms) was adsorbed on silica gel by grinding in a mortar and pestle and irradiated in the microwave oven for 2 minutes at medium high power. The mixture was treated with dichloromethane and filtered. Upon concentration and work up yielded the product which upon crystallization with benzene solvent resulted in a yellow product.

Yield=0.23gms

B) Under thermal conditions

A mixture of bismuth nitrate pentratehydrate (0.5gms) and catechol (0.25gms) in 30 ml of acetone was continuously stirred in a 250ml stopped conical flask for 2 hours at room temperature. The mixture was filtered and the filtrate was concentrated, dried and yellow crystals of nitro catechol were obtained and crystallized from benzene for further purification.

Yield=0.19gms

Spectral data

Melting point: 130-131^{0}C

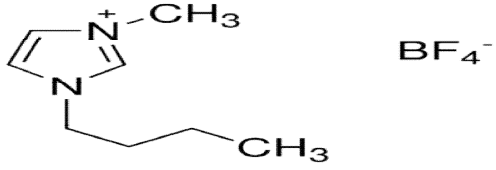
The data was identified with those reported in literature for 3-nitrocatechol

3.7 Reaction in ionic liquid 1-butyl-3-methylimmidazolium tetrafloroborate.

3.7.1 Introduction

The ambient temperature ionic liquids especially those based on 1,3-dialkylimidazolium cations have gained considerable interest as promising alternative green solvents in organic synthesis[85]. These ionic liquids have several interesting properties such as excellent chemical and thermal stability, non-volatility, non-coordinating nature, good solvating capability, wide liquid range and ease of recycling. Furthermore, their hydrophobicities/hydrophilicities can be tuned by appropriate modification of the cation or anion[85-86]. Therefore, room temperature ionic liquids have found wide uses in catalytic and non-catalytic reactions[87-88]. In addition, the synthesis of task-specific ionic liquids, which have a functional group in their framework, may expand the application of ionic liquids in organic chemistry[89-91]. Due to their unique properties such as non-volatility and reusability, acidic ionic liquids have been successfully used in many organic reactions[90-94].

During the nitration of phenols, concentrated nitric acid or mixed acids are always associated with the formation of some di-nitro compounds, oxidized products, and unspecified resinous compounds. In most of the cases, the typical yield of the direct nitration never exceeds 60% because of the side reactions mentioned above. These limitations make the existing processes uneconomical. Therefore, it is worthwhile to consider an alternative highly selective nitration process. Nitration was therefore carried out by using a mild nitrating agent- bismuth nitrate pentahydrate in 1-butyl-3-methylimidazolium tetrafloroborate([bmim][BF_4]) as an acidic ionic liquid as shown below.

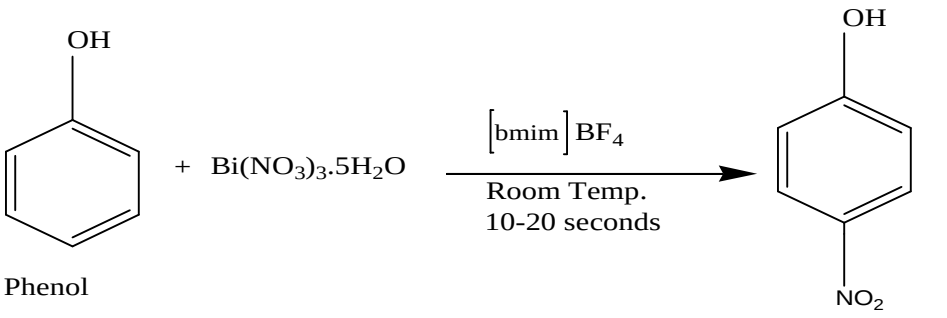


3.7.2 Procedure for the Mono-Nitration of Phenol using [bmim][BF_4]/Bi(NO_3)$_3$ System

A mixture of compounds consisting of phenol (0.05g) and Bi(NO_3)$_3$ (0.05g) in 1.5ml of [bmim][BF_4] was added in a beaker with stirring, at room temperature. After completion of the reaction, as monitored by thin layer chromatography, the reaction mixture was extracted with ethyl acetate (15ml), the resulting mixture was filtered, and the solvent was evaporated. The residue was crystallized with benzene and the product obtained was para-nitrophenol.

Yield=0.041gms

% Yield=82



Phenol

Para Nitrophenol

Spectral data

4-Nitrophenol: Yellow powder, Melting point-112-114^{0}C. (lit.mp=114^{0}c)

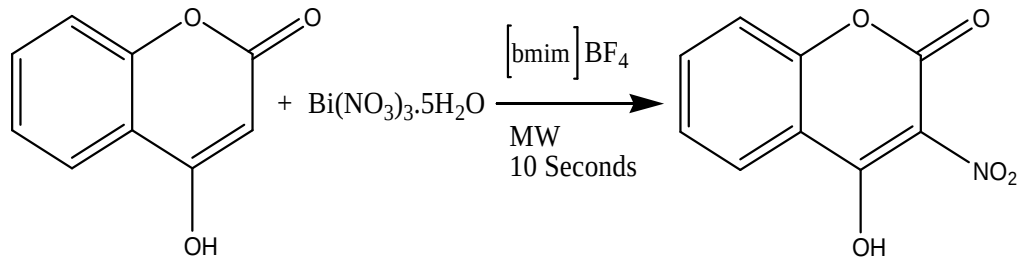
IR (KBr) cm^{-1}: 3331, 1614, 1592, 1500, 1346.

3.7.3 Procedure for the nitration of 4-hydroxycoumarin using [bmim][BF_4]/Bi(NO_3)$_3$ System

A mixture of compounds consisting of 4-hydroxycoumarin (0.05g) and $Bi(NO_3)_3$ (0.05g) in 2ml [bmim][BF_4] ionic liquid was added in a beaker and irradiated in a microwave oven for 10 seconds at medium low power during which the reaction reached to completion as monitored by thin layer chromatography. The reaction mixture was extracted with ethyl acetate (15ml). After some time, the resulting mixture was filtered and the solvent was evaporated. The residue was crystallized with chloroform and the product obtained was identified as 3-nitro-4-hydroxycoumarin.

Yield=0.039gms

% Yield=78



4-hydroxycoumarin 3-nitro-4-hydroxycoumarin

Spectral data

3-Nitro-4-hydroxycoumarin. Melting point 175-176^{0}C. (lit. m.p=177^{0}c)

IR (KBr) cm^{-1}: 3440, 1740, 1620, 1550, 1360.

3.7.4 Results and discussion

We also carried out nitration of phenolic aromatic compounds in 1-butyl-3-methylimmadiazolium tetrafloroborate by using bismuth nitrate pentahydrate as a mild nitrating agent and the results obtained were good in comparison to the reaction carried out in organic solvent (acetone) or in solid support (silica gel) in terms of yield and time because of interesting properties associated with them as discussed in **4.7.1**.

Furthermore para product is formed exclusively because the nature of ionic liquid affects the regioselectivity of nitration.

3.8 Conclusions

Nitro aromatic compounds have been prepared with improved yield under solvent free microwave conditions in minimum time than reported so far in literature. This novel method is simple, efficient and the usage of solvent-free conditions makes it an eco-friendly procedure. Moreover, the use of easily accessible domestic microwave oven makes the procedure more convenient.

We have also reported a mild and efficient method for the nitration of phenols by using bismuth nitrate pentahydrate as nitrating agent in the presence of acidic ionic liquid 1-butyl-3-methylimmidazolium tetrafloroborate in good yields, faster rate and better para-selectivity.

Chapter-4

Preparation of Osazones

4.1 Introduction

The word carbohydrates was coined during the nineteenth century to describe a family of compounds with the general formula $C_n(H_2O)_n$ (hydrates of carbon). But the term is now modified and broadened and now includes polyhydroxy aldehydes, ketones, alcohols, acids and their simple derivatives as well as their polymers. Carbohydrates is the most abundant group of compounds in nature which comprise 50% of dry biomass on earth. They perform a wide range of functions and exist in more diverse forms than any other group of natural products. They provide structure to biological material, play an important role in molecular recognition and metabolic energy storage. Carbohydrates are also major constituents of diverse natural products like antibiotics (Streptomycin and Puromycin containing amino sugars), nucleic acids (carbohydrate-containing polymers) that control the biosynthesis of proteins and are responsible for the transfer of genetic information. Carbohydrates are also the basis of many important industries like food, textiles, pharmaceutical and cosmetic industry.

4.2 Classification of carbohydrates

Carbohydrates can be classified into main two groups:

1 Simple carbohydrates - containing only carbohydrates in their structure.

2 Complex carbohydrates - contain carbohydrates covalently bound to lipids and proteins.

Based on their molecular size, simple carbohydrates can be divided into three major groups, monosaccharides, oligosaccharides and polysaccharides. The term saccharide means “sugar like” and includes lowers members of carbohydrates like monosaccharides and oligosaccharides. Monosaccharides are the lower members of

carbohydrates which can not be degraded by hydrolysis to smaller carbohydrate molecules. They constitute the building blocks of higher carbohydrates. Oligosaccharides and polysaccharides are polymers of monosaccharides joined by acetal-type linkages. Oligosaccharides contain two to ten monosaccharide units while as polysaccharides contain more than ten units. Both oligosaccharides and polysaccharides can be hydrolyzed to their corresponding monosaccharides or monosaccharide derivatives.

Complex carbohydrates include complex glycosides, carbohydrate antibiotics, nucleic acids, glycoproteins, proteoglycans, peptidoglycans, lipopolysaccharides and glycolipids.

4.3 Formation of Osazones

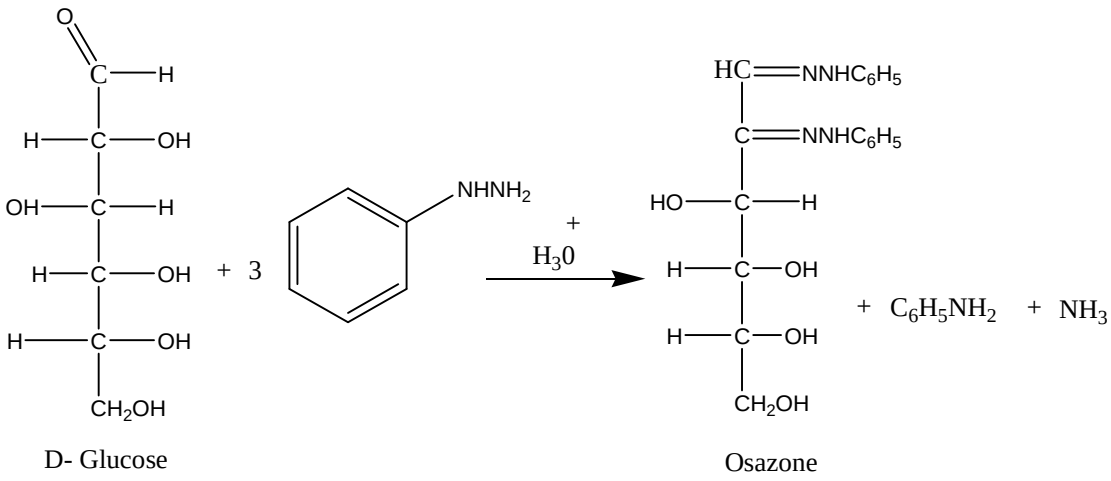
Carbohydrates being polyfunctional in nature participate in a multitude of chemical and biochemical reactions, making them ideal scaffolds for a wide range of invitro and invivo applications. One such reaction is their interaction with phenylhydrazine. But phenylhydrazine reaction is only given by monosaccharides and certain oligosaccharides to give corresponding osazones[95]. The name osazone is derived from "ose" for the sugar moiety and "azone" from the hydrazine residue. Osazone formation was first introduced by the famous German chemist Emil Fischer[96] who used this reaction to differentiate between the monosaccharides where stereochemistry differed by only one chiral carbon[97,98]. In addition osazone formation is still one of the most important test for identification of mono and disaccharides.

In general mono and oligosaccharides have the tendency to form syrups and don't easily crystallise which made their purification and identification difficult. Emil

Fisher converted them into water insoluble, sharp melting, yellow crystalline osazones by treating them with phenylhydrazine. Osazones possess characteristic crystalline forms when observed under the microscope. For example glucose gives broomstick shaped crystals whereas those of maltose are sunflower shaped. Less than 5 mg of sugar is needed for this purpose.

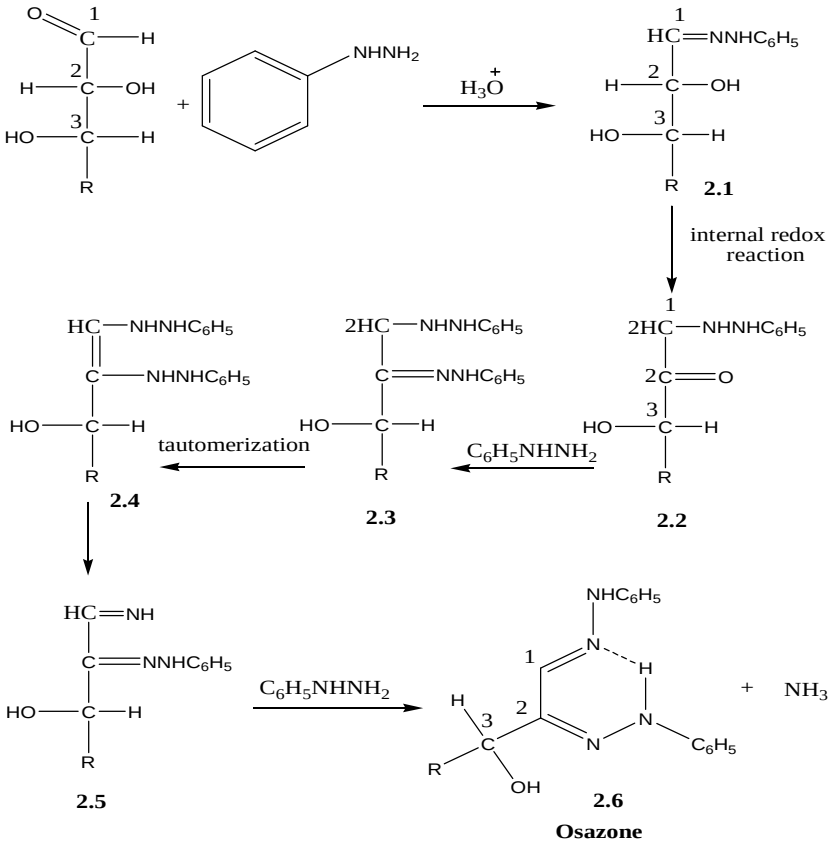
In the identification of a sugar, the unknown osazone may be compared with the one prepared simultaneously from known sugars or with photomicrographs of osazones of different sugars. By observing the crystal form of the osazone under the low power ordinary microscope, a particular sugar may be tentatively identified. Further confirmation is desirable from melting point determinations or from the study of optical properties.

Monosaccharides or oligosaccharides that have an aldehyde or ketone carbonyl group either free or in equilibrium with a hemiacetal, will react with phenylhydrazine to form bright yellow, crystalline osazones. The reactions involved are shown in **Scheme I**.



Scheme I: Osazone Formation

The accepted mechanism (**Scheme II**) for the reaction is shown in figure 2. Following the formation of the phenylhydrazone **2.1**, there is an internal oxidation-reduction reaction that involves the tautomeric migration of two hydrogens from C-2 to the hydrazone moiety to give the carbonyl product **2.2**. The newly formed carbonyl group condenses with a second equivalent of phenyl hydrazine to give **2.3** which undergoes subsequent tautomerization to **2.4**. Following the 1,4-elimination of aniline, which produces **2.5**, a third equivalent of phenyl hydrazine condenses with the imine group to give the osazone **2.6** and ammonia. The formation of the intramolecular hydrogen bond in **2.6** prevents another internal oxidation-reduction sequence between the secondary alcohol at C-3 and the hydrazone group at C-2 and the introduction of a third phenylhydrazine unit.



Scheme II: Mechanism of osazone formation

Although the time taken for osazone formation may be used to make qualitative distinctions among the different mono and oligosaccharides. Osazones of monosaccharides (glucose & fructose) are formed in 15 minutes and have the same crystal shape needles under the microscope. While as the reducing disaccharides (maltose & lactose) are formed after a longer time (60-90 minutes) and crystals appear slowly after cooling and can be distinguished under the microscope.

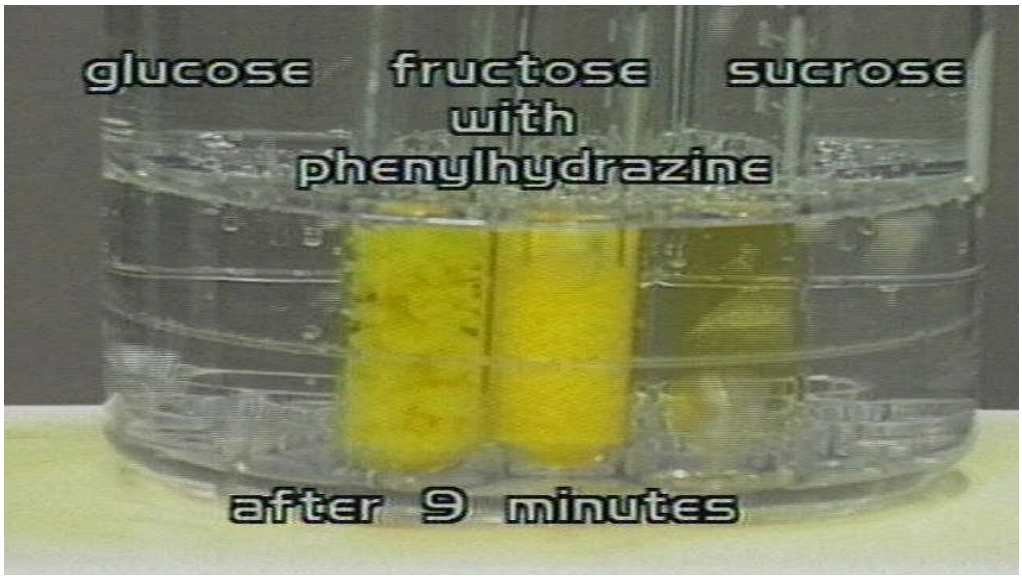


Figure 4.1: Formation of osazones

4.4 Comparative study

A comparison of microwave assisted synthesis of osazones from sugars with those carried out under conventional conditions has been drawn in **table 4.1**.The reaction mixtures were irradiated from seconds to minutes depending upon the substrate used and a power level of 25% -100% to monitor an exact comparison in terms of yield and time.

4.5 Experimental

(**General study**)

The melting points were taken in open capillaries using electro thermal method on a *Labotech/Perfit* instrument and are uncorrected. Photographs depicting shape of osazones were taken on *Labomed TCM 400* microscope. All the solvents and chemicals used were of AR grade. All the reactions were carried out in a multimode Sharp Carousel^{TM} microwave oven.

4.6 General procedure for the synthesis of osazones

4.6.1 Under microwave irradiations

To a solution of 0.3g of sugar in 3ml of water, 0.5 ml phenylhydrazine and two drops of glacial acetic acid were added in a Teflon tube. The mixture was irradiated in a multimode oven at different power levels and time durations as shown in **table 4.1**, until the yellow or orange coloured osazones got separated out which were filtered, washed with cold water and crystallized from hot water or 60% alcohol.

4.6.2 Under conventional conditions

To a solution of 0.3g of sugar in 3ml of water, 0.5 ml phenylhydrazine and two drops of glacial acetic acid were added in a boiling tube. The reaction mixture was shaken and kept in a boiling water bath for different time durations, until the yellow or orange coloured osazones got separated out (**table 4.1**). The precipitate was filtered, washed with cold water and crystallized from hot water or 60% alcohol.

Table 4.1: Comparison of results under microwave and conventional method for the preparation of osazones.

S. No.	Substrate	Conventional		Microwave		Melting point (^{0}C)
		Time (minutes)	% Yield	Time (seconds)	% Yield	
1	D-Fructose	2	80	30	90	205
2	D-Xylose	7	87	30	88	164
3	D-Galactose	20	87	60	94	201
4	D-Glucose	4	84	45	90	205
5	D-Mannose	0.5	93	10	99	205
6	Maltose	60	73	150	78	206
7	D-Lactose	90	70	90	74	200

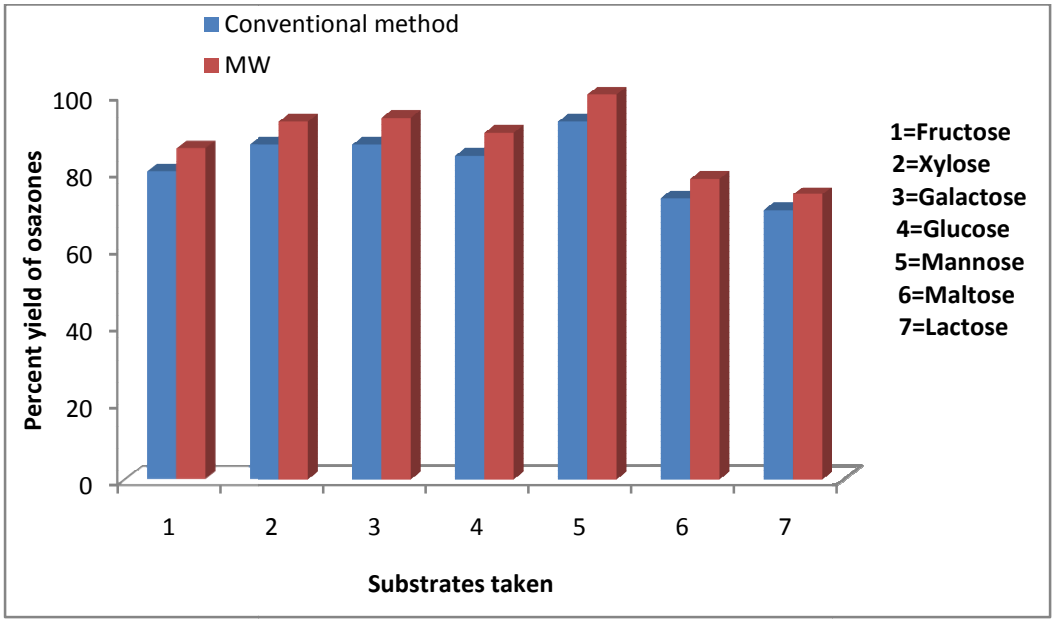


Figure 4.2: Clubbed graph showing the comparative account of % yield of osazones under two different conditions.

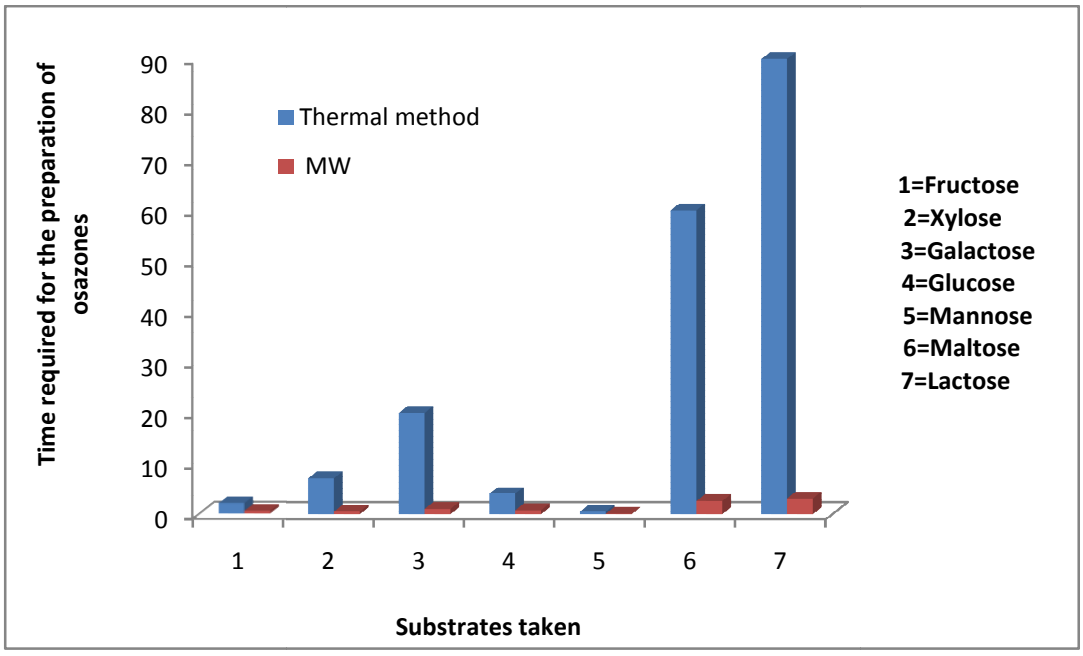


Figure 4.3: Clubbed graph showing the comparative account for time required for the preparation of osazones under two different conditions.

Reactions of sugars with phenylhydrazine to form osazones were carried out in a multimode domestic microwave oven at different power levels and for different time durations. Therefore, in order to obtain best possible results we took different reaction mixtures for each of the substrate having equal concentration of reactants and irradiated at medium low, medium, medium high and high power with variable reaction time.

Table 4.2: Percent yield and time required for the preparation of osazone of xylose under different power levels.

Power level	**Time (seconds)**	**% Yield**
Medium low	150	82
Medium	60	86
Medium high	**45**	**88**
High	30	84

Conclusion: The best possible result for the formation of xylose osazone is at medium high power with 88% yield and time required is 45 seconds.

Table 4.3: Percent yield and time required for the preparation of osazone of glucose under different power levels.

Power level	Time(seconds)	% Yield
Medium low	135	82
Medium	60	84
Medium high	60	90
High	**45**	**96**

Conclusion: The best possible result for the formation of glucose osazone is at high power with 96 % yield and time required is 45 seconds.

Table 4.4: Percent yield and time required for the preparation of osazone of fructose under different power levels.

Power level	Time(seconds)	% Yield
Medium low	75	86
Medium	60	88
Medium high	**45**	**90**
High	30	88

Conclusion: The best possible result for the formation of fructose osazone is at high power with 90 % yield and time required is 45 seconds.

Table 4.5: Percent yield and time required for the preparation of osazone of mannose under different power levels.

Power level	Time (seconds)	% Yield
Medium low	20	92
Medium	15	99
Medium high	**15**	**94**
High	10	90

Conclusion: The best possible result for the formation of mannose osazone is at medium power with 99 % yield and time required is 15 seconds.

Table 4.6: Percent yield and time required for the preparation of osazone of galactose under different power levels.

Power level	Time (seconds)	% Yield
Medium low	180	92
Medium	**120**	**94**
Medium high	70	90
High	60	88

Conclusion: The best possible result for the formation of galactose osazone is at medium power with 94 % yield and time required is 120 seconds.

Table 4.7: Percent yield and time required for the preparation of osazone of maltose under different power levels.

Power level	Time (seconds)	% Yield
Medium low	600	72
Medium	370	74
Medium high	**240**	**78**
High	130	76

Conclusion: The best possible result for the formation of maltose osazone is at medium high power with 78 % yield and time required is 240 seconds.

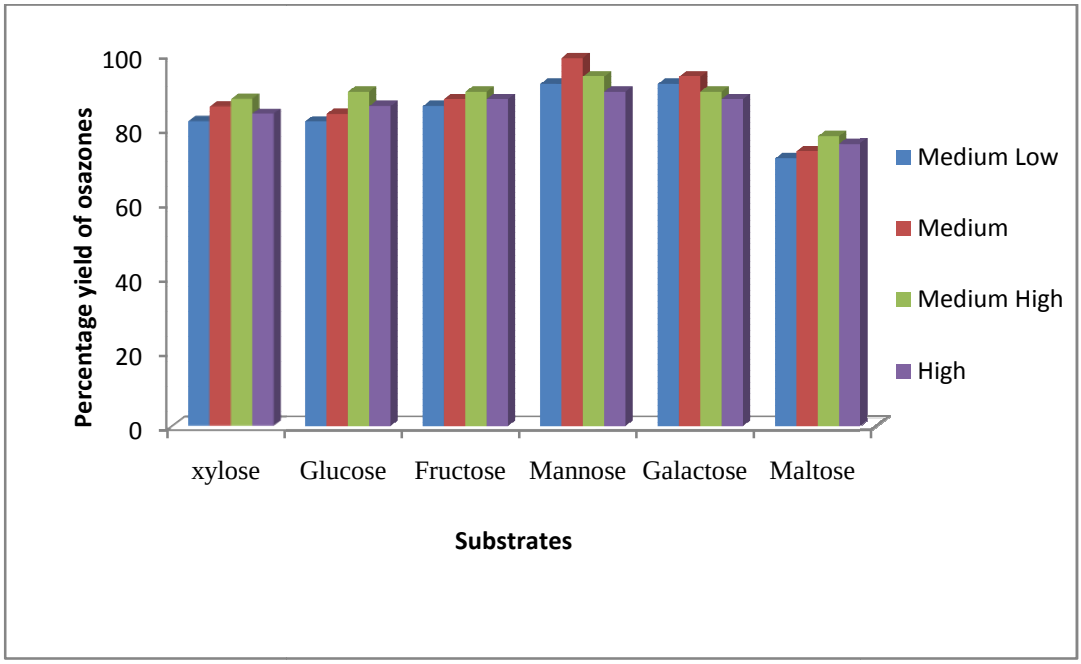


Figure 4.4: Clubbed graph showing the comparative account of % Yield of osazones at different power levels. (Table 2, 3, 4, 5, 6, 7)

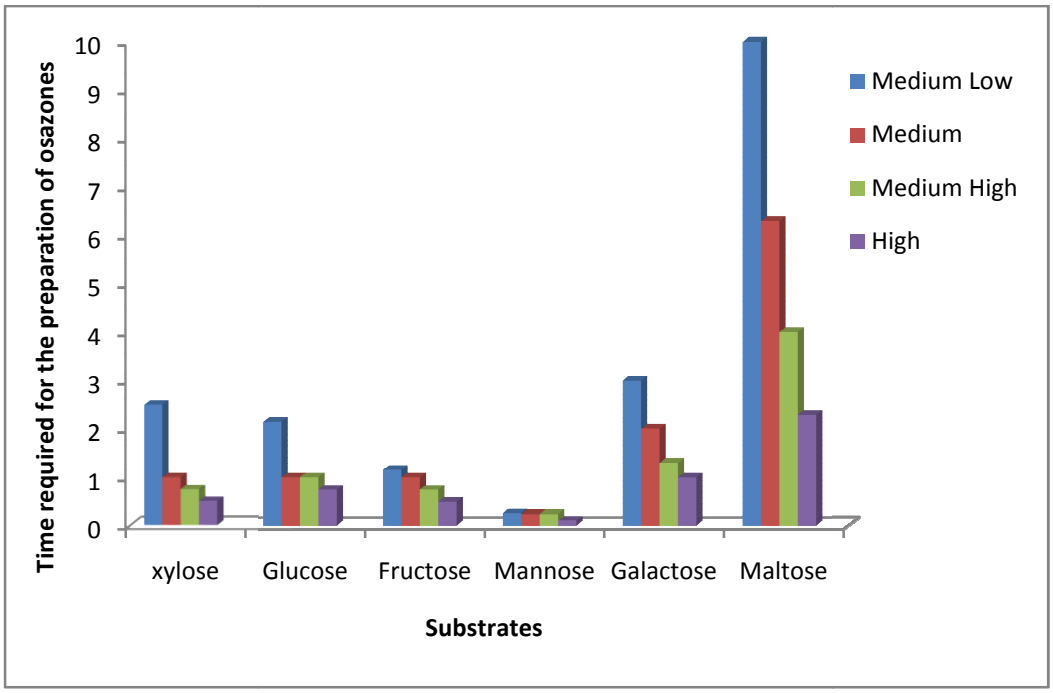


Figure 4.5: Clubbed graph showing the comparative account of time required for the preparation of osazones at different power levels. (Table 2, 3, 4, 5, 6, 7)

4.7 The photographs taken for various osazones are shown below

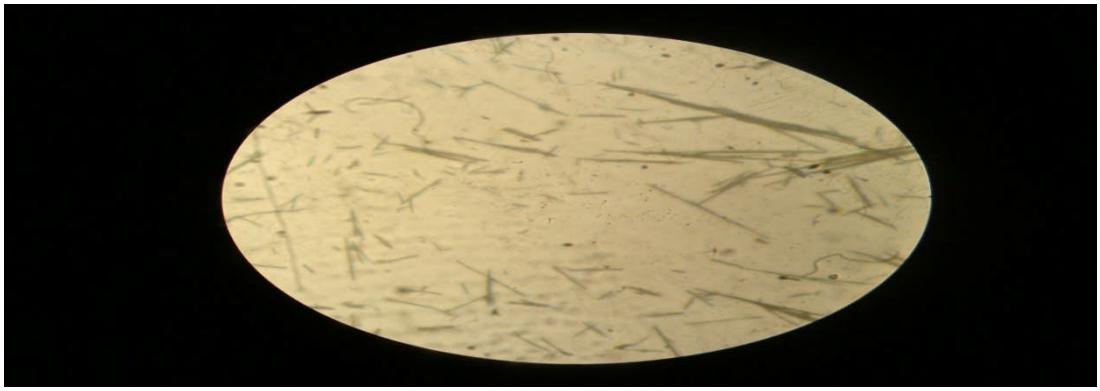


Figure 4.7.1: Photograph showing needle shaped osazone of Glucose

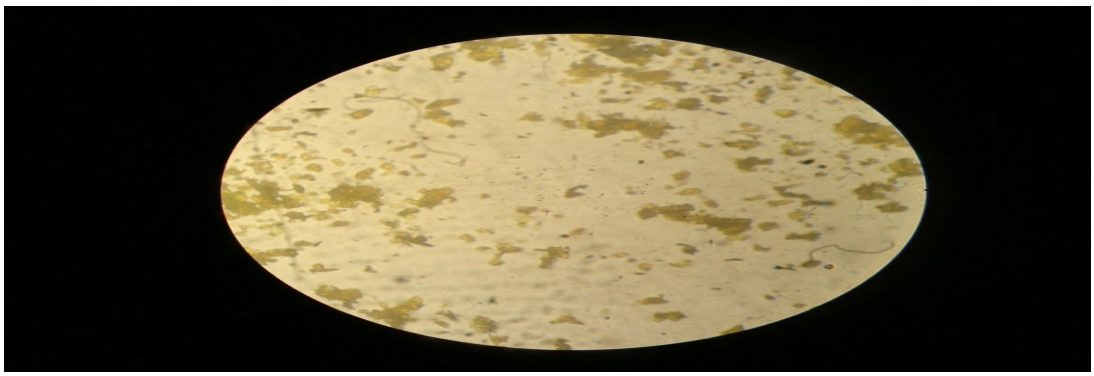


Figure 4.7.2: Photograph showing powder shaped osazone of Maltose

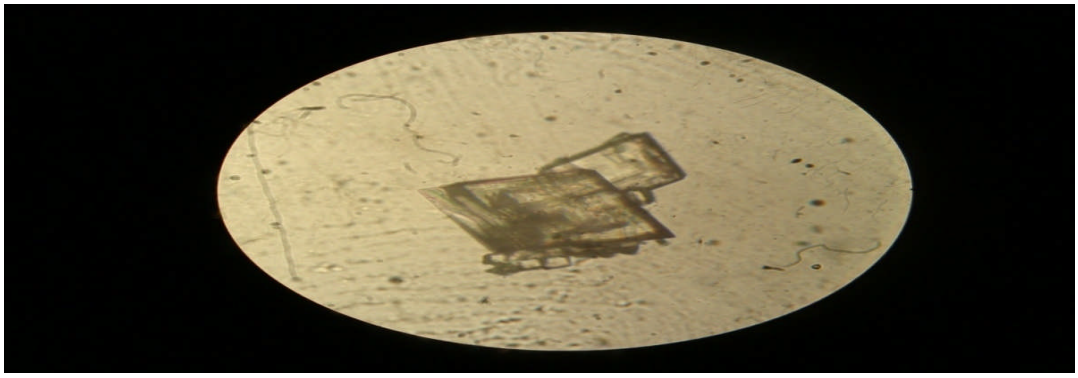


Figure 4.7.3: Photograph showing square shaped osazone of Galactose

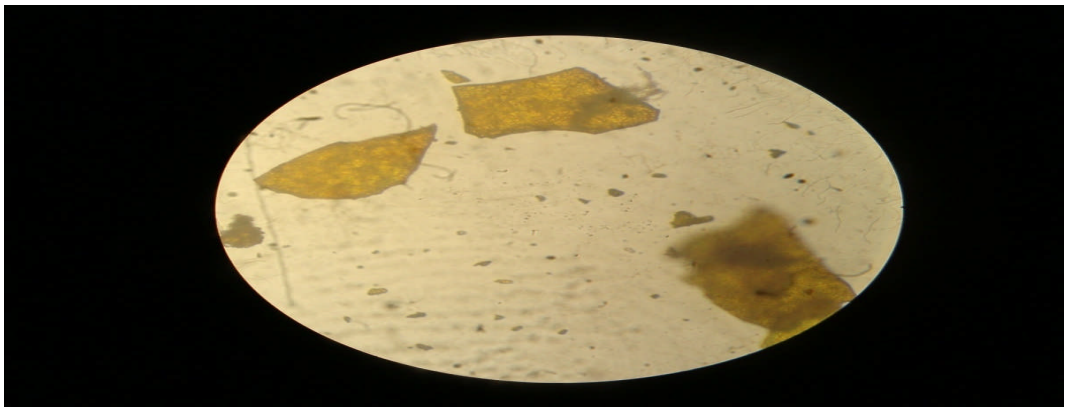


Figure 4.7.4: Photograph showing polygon shaped osazone of Lactose

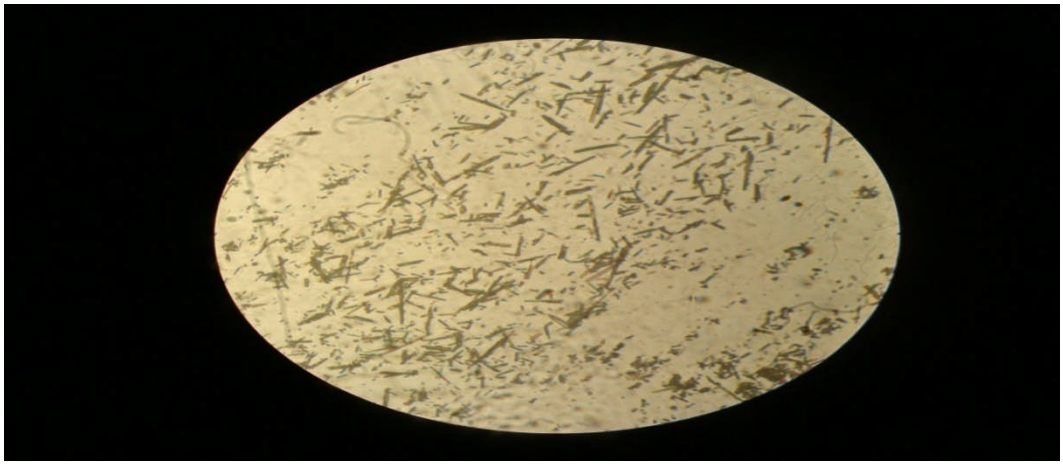


Figure 4.7.5: Photograph showing cylinder shaped osazone of Mannose

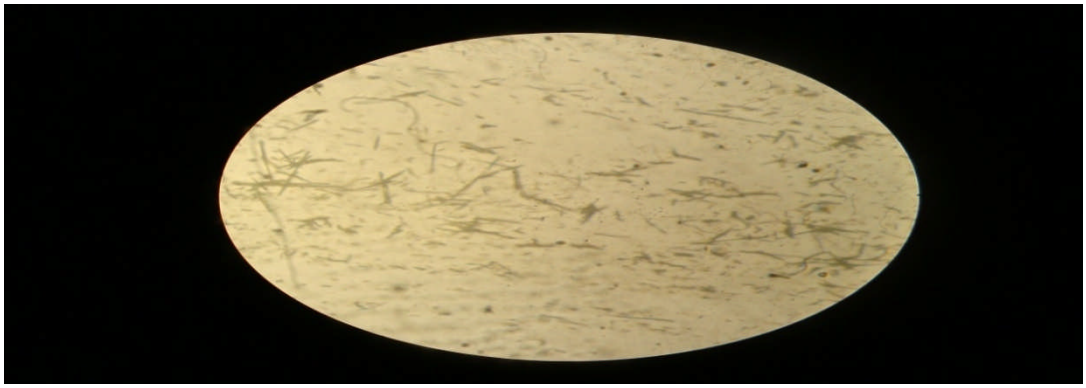


Figure 4.7.6: Photograph showing needle shaped osazone of Fructose

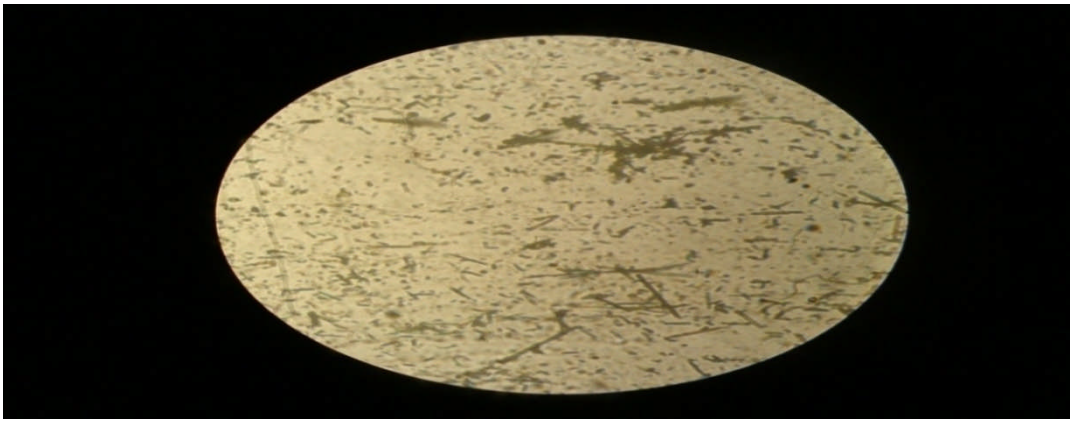


Figure 4.7.7: Photograph showing needle shaped osazone of Xylose

The shapes observed for these osazones were identified with those already reported in literature[99].

4.8 Conclusions

Laboratory preparation of osazones was a tedious and time consuming process. So reactions were carried out between different sugars and phenylhydrazine under microwave conditions and a comparative account was made with improvement in yield and shortening of reaction time. Thus our efforts standardized the procedure feasible for routine laboratory tests.

Chapter-5

Main Highlights of the Present Work

1 Microwave technology proves to be an efficient and alternative green tool for the synthesis of organic compounds.

2 A novel green chemistry approach using microwave heating over conventional is proposed for the synthesis of nitro aromatic compounds.

3 A mild nitrating system bismuth nitrate pentahydrate is used instead of strong nitrating systems such as nitric acid, for the nitration of phenolic aromatic compounds.

4 Synthesis of nitro aromatic compounds has also been achieved using ionic liquid 1-butyl-3-methylimmadiazolium tetrafloroborate, as an alternative green tool for the synthesis of nitro aromatic compounds.

5 Preparation of osazones under microwave and thermal conditions and a comparative account made in terms of time and yield which standardized the procedure for routine laboratory tests.

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