MICROWAVE ASSISTED FRIES AND CLAISEN REARRANGEMENTS

DISSERTATION

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

Master of Philosophy
In
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By

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This dissertation is dedicated to my family for their love, endless support and encouragement.

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CERTIFICATE FROM SUPERVISOR

This is to certify that the work presented in this dissertation entitled *"MICROWAVE ASSISTED FRIES AND CLAISEN REARRANGEMENTS"* is original and has been carried out by **Ms. Fozia Ashraf** 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.

(Fozia Ashraf)

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“Instead of preparing a cup of tea in the microwave while waiting for a convention reaction to reach completion, why not put the reaction vessel in microwave instead!!!!”

1.1 Introduction

If the source materials and products fail to withstand the usually long reaction times at high temperatures and decompose, the yield is invariably reduced. In addition to this the production of large amount of waste means that it is unacceptable from both economic and environmental standpoint, therefore green technologies are looking for alternative ways to allow clean and efficient chemical synthesis. It is against this background that the microwave technology has increasingly developed into a powerful alternative that can be applied to a wide spectrum of organic synthesis.

Microwave-assisted synthesis is set to change organic chemistry for good. The technology is generally applicable to synthesis in medicinal and combinatorial chemistry, and compared to conventional methods, offers enhanced speed, reproducibility and scalability. This technique solves many of the challenges currently faced by pharmaceutical chemists and todays easy-to-use instrumentation, integrated robotics, and verified synthetic methods are designed to provide a complete lab solution.

In the electromagnetic spectrum, microwave region is located between infrared and radio frequencies with wavelength ranging from 1cm to 1m corresponding to the frequencies of 30 GHz to 300 MHz. However, some wavelengths in this region are employed for radar and telecommunication. So in order to avoid any disruption, only limited wavelengths with frequency of 2.45 GHz corresponding to a wavelength of 12.2 cm have been allocated to industrial and domestic microwave ovens by the international convention.

1.2 Components and features of Microwave oven

A schematic diagram of a microwave reactor is shown in **figure 1.1**

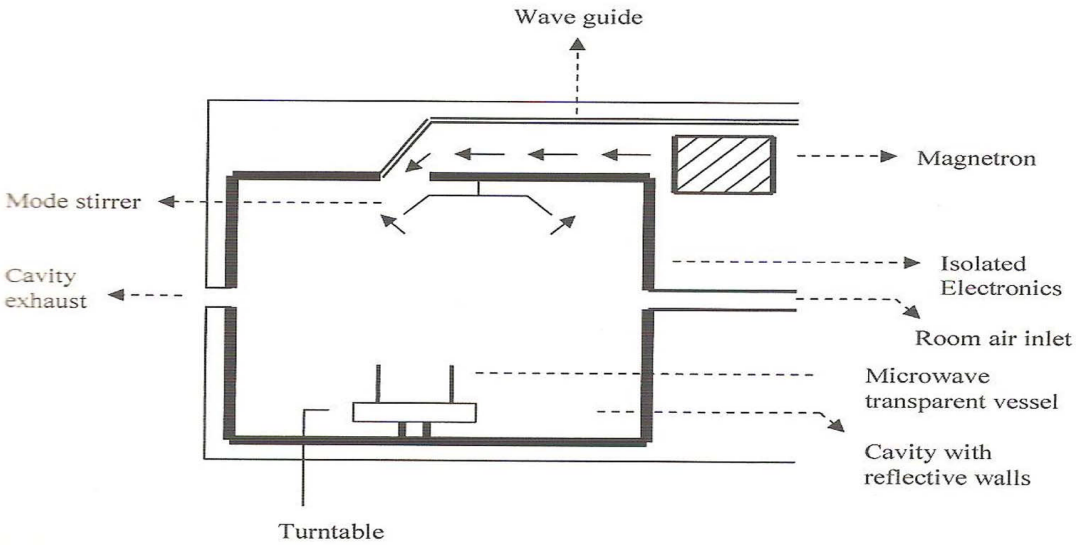


Figure 1.1: Cavity-type microwave oven

The microwave oven consists of the following components:

Magnetron/Klystron that emits the microwave radiations over a narrow frequency range, **Wave guide** to allow the transmission of microwaves from the magnetron to the microwave cavity, **Microwave cavity** where the samples are placed for irradiation, **Mode stirrer** a reflective fan shaped paddle to ensure that the microwaves are evenly distributed throughout the cavity, **Door interlocks** to prevent the door from being opened during microwave irradiations, **Exhaust fan** to isolates and ventilates the oven, **Time control and Power control** that allows the time and power level to be set for which the sample is to be irradiated.

Monomode and **Multimode**[1] are the two types of microwave reactors used nowadays. The former gives focused rays using an optical fiber or IR detector into a cavity inside which the reaction vessel is kept and the bottom few centimeters of the vessel get exposed to microwaves where as the upper region remains cool. 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 measurement. The microwave oven used for cooking purposes is a multimode reactor. In spite of reproducible results obtained

using monomode ovens, the use of multimode ovens by chemists in research laboratories continues because of convenience and economical benefit.

1.3 Mechanism 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 centimeters 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 usually 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.

The heating effect generated in microwave-assisted organic transformations is mainly due to the dielectric polarization, that is orientation of a dipole with that of the applied field (**figure 1.2(a)**).

Figure 1.2(a): Dipolar molecules try to align with oscillating field of microwaves.

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. This effect can be explained as follows:

The polar molecules, in the absence of an electric field, will have a random arrangement. This chaotic order with greater entropy will be the natural, lowest energy configuration for the assembly of molecules (**figure 1.2(b)**). When placed in a

strong electric field for sometime, these polar molecules will tend to align themselves parallel to this field (**figure 1.2(c)**). This new arrangement of molecules will therefore be higher in energy because of decrease in entropy and can be thought of as storing potential energy due to application of electric field. If the direction of applied field is changed slowly, the polar molecules will also rotate and try to keep themselves aligned with the field (**figure 1.2(d)**). If the direction of the field is changed more quickly, some of the molecules may not be able to remain in alignment with the direction of applied field. The molecules may try hard to remain in parallel with the field but keep colliding with other molecules. The potential energy stored in changing the molecular alignment no longer matches the applied field. This excess energy is transformed into kinetic energy on collision between the molecules and this effect gives rise to microwave heating[2].

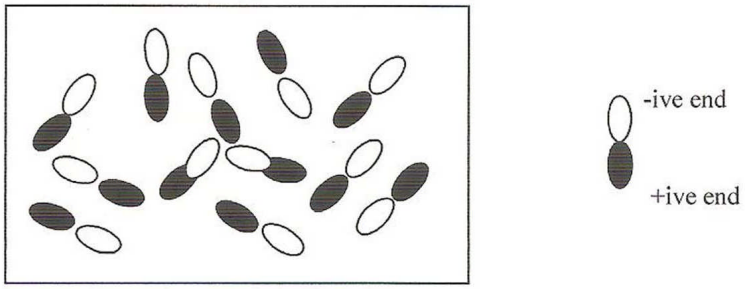


Figure 1.2(b): Dipoles in absence of an electric field

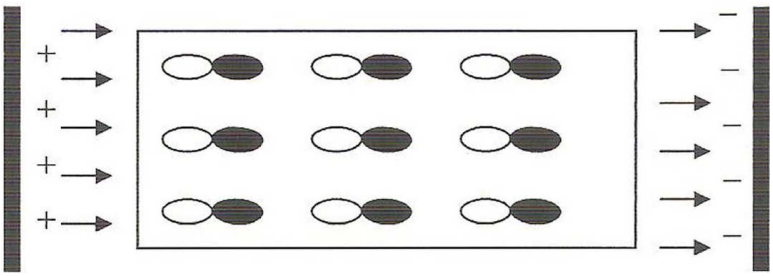


Figure 1.2(c): Dipoles in presence of an electric field

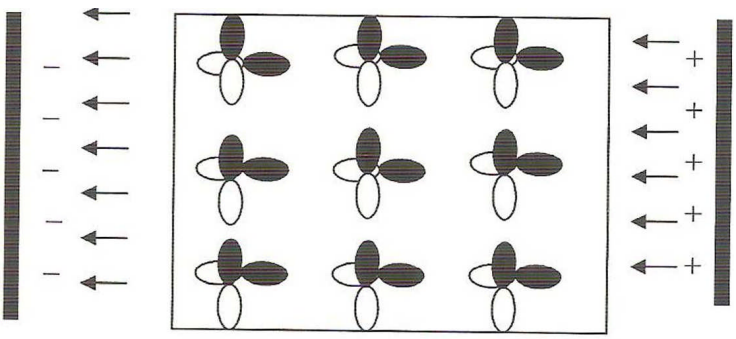


Figure 1.2(d): Dipoles rotating in case of changing electric field

It is noteworthy that if the electric field changes direction very rapidly, the polar molecules will not have the time to react to the changing field and will remain randomly oriented and consequently at these microwave frequencies, they will be unable to interact with the applied field and no heat will get generated[3].

A variable power output is achieved by switching the magnetron on and off according to a duty cycle. The exposure of a molecule to this alternating current inverses the electric field at each alteration, with a subsequent tendency for dipoles to move together to follow the field. Such a characteristic changing field induces stirring and friction of the molecules which appears as internal homogenous heat[3]. In fact, the heating or cooking of food in the microwave ovens is because of the dipolar polarization of water molecules present in the food. Other biological molecules in food are too large to be able to rotate.

1.3.2 Ionic conduction mechanism

Ionic conduction also contributes to microwave heating if ions are involved in the sample. When ions move through the solution under the applied field, heat is generated by frictional losses, which depends on the size, charge and conductivity of the ions, converting the kinetic energy to heat.

1.4 Microwave effect verses the conventional effect

Microwave heating is different from conventional heating in many respects. The mechanism behind Microwave heating is quite different from conventional heating. Points enlisted in **Table 1.1**, differ the microwave heating from conventional heating.

Table 1.1: Difference between conventional and microwave assisted heating

S. No.	Conventional	Microwave
1	Heating of reaction mixture proceeds from a surface, usually inside surface of reaction vessels.	Heating of reaction mixture proceeds directly from the bulk of mixture.
2	The vessel should be in physical contact with surface of heating source (e.g. mantle, oil bath, steam bath etc.).	No need of physical contact of reaction mixture with the surface of heating source, while vessel is kept in microwave cavities.
3	Heating source is either thermal or electrical.	Electromagnetic waves are source of heating.
4	Heating mechanism involve-conduction.	Heating mechanism involve-dielectric polarization and conduction.
5	Transfer of energy occurs from the wall, surface of vessel, to the mixture and eventually to reacting species.	The core mixture is heated directly while surface (vessel wall) is source of loss of heat.
6	In conventional heating, the highest temperature (for a open vessels) that can be achieved is limited by boiling point of particular mixture.	In microwave, the temperature of mixture can be raised more than its boiling point i.e. superheating take place.
7	Heating rate is less	Heating rate is several fold high.

1.5 Microwave- assisted organic synthesis (MAOS)

Microwave technology has been implemented in organic chemistry since 1980's[4-6]. This slow uptake of the technology has mainly been attributed to the lack of

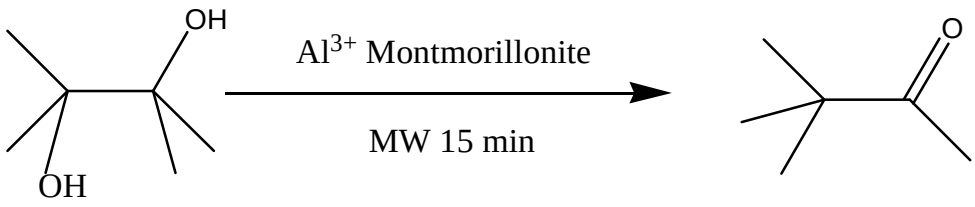
controllability, reproducibility and safety aspects associated with domestic microwave ovens and generally a low understanding of the basics of microwave dielectric heating and other effects associated with it. However, since 1990's, due to commercial availability of the microwave oven especially designed for organic synthesis, shorter reaction times and the solvent-free procedures coupled with the principles of green chemistry, the number of microwave based publications has increased multifold[7-11]. The use of microwaves on organic synthesis was first reported independently in 1986 by Giguere and Gedye *etal*. Since then, microwave assisted organic synthesis has blossomed into a useful technique and accelerations have been observed on a wide range of reactions.

Control of the desired selectivity (chemo, region, stereo and enantioselectivity) is the most important objective in organic synthesis[12].The application of microwave irradiation involves the modification of the reactivity as well as selectivity in relation to conventional heating[13-15].

1.5.1 Microwave-assisted rearrangement reactions

1.5.1.1 Pinacol-pinacolone rearrangement

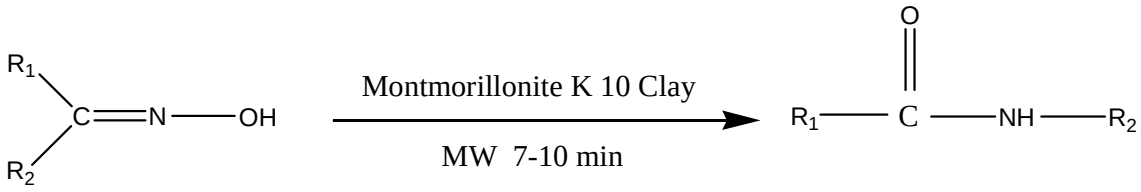
A solvent-free Pinacol-pinacolone rearrangement using microwave irradiation has been achieved involving the irradiation of the gem-diols with Al^{3+}-montmorillonite K-10 clay for 15 minutes to afford the rearrangement product in excellent yields. These results are compared to conventional heating in an oil bath where the reaction times are too long (15hours)[16].



98-99%

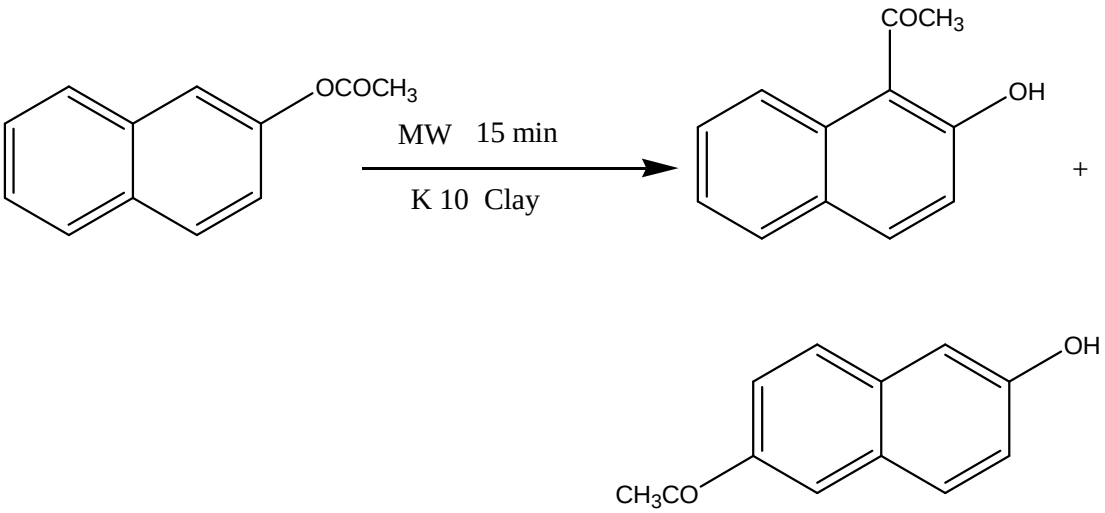
1.5.1.2 Beckmann rearrangement

The Beckmann rearrangement of ketoximes with montmorilonite K-10 clay in dry media in good yields has been reported[17].



1.5.1.3 Fries rearrangement

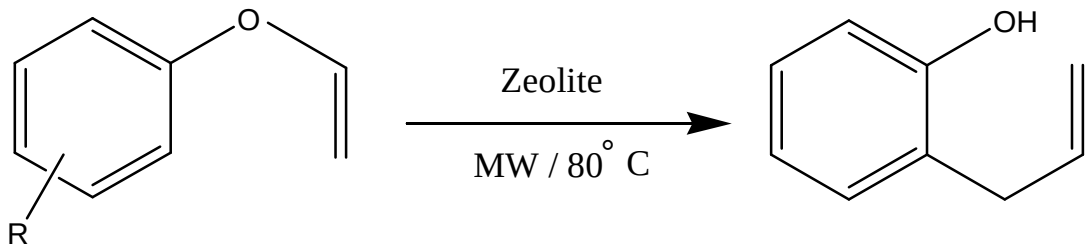
A solvent less Fries rearrangement using microwave irradiation has been achieved involving the irradiation of the ester with K-10 montmorilonite for 5-10 minutes to give the rearranged product in excellent yields[18].



1.5.1.4 Claisen rearrangement

Claisen rearrangement of allyl aryl ethers has been achieved over various zeolites under microwave activation and solvent-free conditions at 80°C. The reaction gives *ortho*-rearranged product selectively instead of expected further cyclised

dihydrobenzofuran derivative and thus represents a step forward from conventional technique[19].

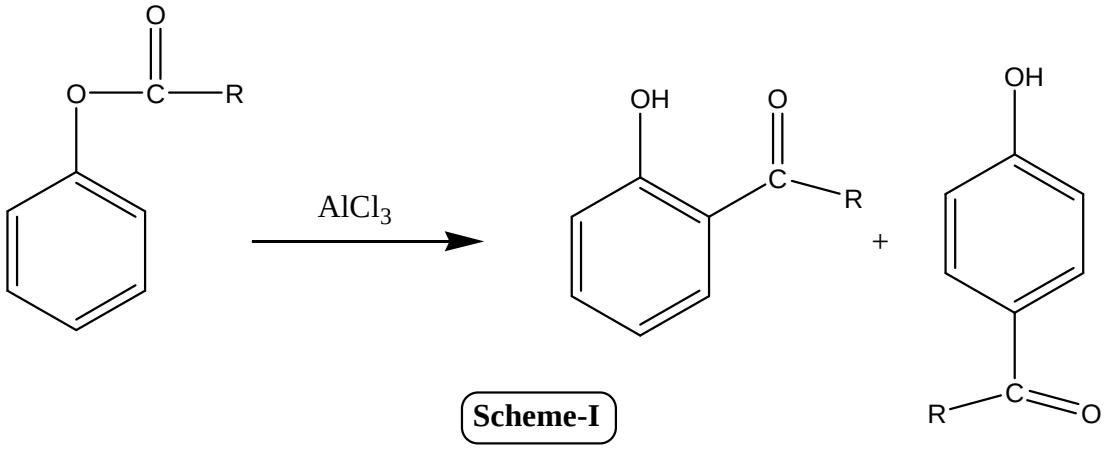


1.6 Conclusions

In view of the advantages associated with MAOS, we have attempted synthesis of acyl and allyl phenols, via Fries and Claisen rearrangements respectively. These compounds are important from synthesis viewpoint and are also versatile intermediates in the synthesis of large variety of organic compounds.

Fries rearrangement

The Fries rearrangement, named after the German chemist Karl Theophil Fries is an extremely useful reaction involving conversion of phenyl esters to *ortho* or *para* hydroxyketones, or a mixture of both, by treatment with aluminium chloride (**Scheme-I**). It involves migration of an acyl group of phenyl ester to benzene ring resulting in the formation of acyl phenols.



Scheme-I

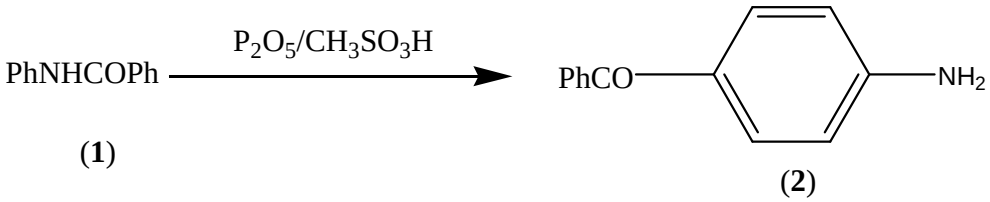
These acyl phenols are useful organic coumpounds and versatile intermediates in the synthesis of biologically active naphthoquinones, flavonoids, pesticides, photographic agents and uv adsorbents[20-22].

A second method available for the synthesis of similar compounds is the Friedle-Craft acylation, in which a phenol, or an ether of phenol, is condensed with an acid chloride or acid anhydride in the presence of aluminium chloride. Inspite of the fact that Fries reaction requires two steps – the preparation of ester and then its rearrangement to the hydroxyketones – as compared to the single step in the Friedle-Craft acylation, it is usually preferred for the preparation of phenolic ketones. The yields are ordinarily better and the experimental procedure does not have to be modified greatly to adapt it to a variety of esters.

As an alternative to aluminium chloride, other Lewis acids such as boron trifluoride or strong protic acids such as hydrogen fluoride can also be used. In order to avoid use of these highly corrosive and environmentally hazardous catalysts altogether, efforts are on to find alternative catalysts, some of which are described below:

- A silica-supported Zirconium based solid acid (ZS)[23] has been used as catalyst for the Fries rearrangement of phenyl acetate. The catalyst showed a higher phenyl acetate conversion activity and a much higher selectivity for *ortho*-hyroxyacetophenone than strongly acidic Zeolite catalysts. The high activity for phenyl acetate conversion with the supported catalyst may be attributed to the high degree of dispersion of the catalytically active component over the surface of the support. The catalytic properties were influenced significantly by pretreatment temperature. The activity for the phenyl acetate conversion over zirconium based solid acid catalyst decreased dramatically with the increase in pretreatment temperature. If the catalyst was treated at 340^{o}C, the phenyl acetate conversion activity decreased to about 7.8% as compared to 18.6 and 11.4% at 110 and 170^{o}C respectively. The deactivation of the catalyst may result from the decomposition of the active component on the surface of the support.
- The use of methane sulphonic acid (MSA) as catalyst in the Fries rearrangement is well known[24-29]. Usually it is used both as catalyst and solvent and *ortho* isomer is the major product. Commarieu *etal*[30] have optimized Fries rearrangement of phenyl acetate for paracetamol synthesis using a strong, stable and biodegradable methane sulphonic acid, to give *para*-hydroxyacetophenone with high conversion and selectivity (upto 92% of *para*-isomer and 8% of *ortho*-isomer at 100% conversion).
- Halogen and alkylhalogen aluminate(III) ionic melts are very much fascinating owing to their remarkable lewis acidity, which prompted researchers to try Fries rearrangement in such systems. Lewis acidity of such ionic melts is a function of the mole fraction of $AlCl_3$ present. Fries rearrangement was reported for the first time in 1-butyl-3-methyl imidazolium chloroaluminate, $[BMIm]^+ Al_2Cl_7$[31]. Substancial rate enhancement, good yields and high selectivity through temperature control are the salient features observed in this system. One of the interesting properties possessed by this system is the wide range of lewis acidity attainable, variation of which can be brought about by changing the molar ratio of the two components, that is the organic halide and $AlCl_3$[32] .

❖ The Fries rearrangement of acetanilide has been reported over zeolite catalysts at 280°C with 50% conversion[33]. Recently a Fries type rearrangement of anilides by using strong bases via an anionic rearrangement has also been reported[34]. Kaboudin *etal*[35] have reported Fries rearrangement of anilides (**1**) using a mixture of P_2O_5 in methane sulphonic acid (1:7) as an efficient reagent for the selective synthesis of para-aminoarylketones (**2**) (**Scheme-II**).

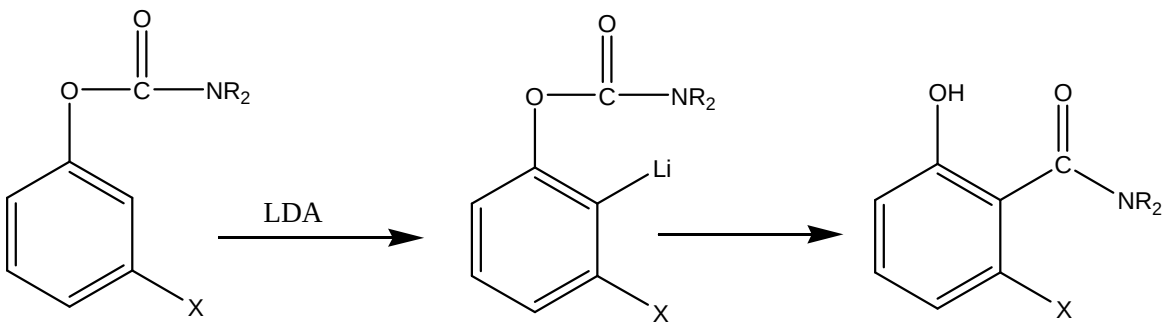


(**1**) (**2**)

Scheme-II

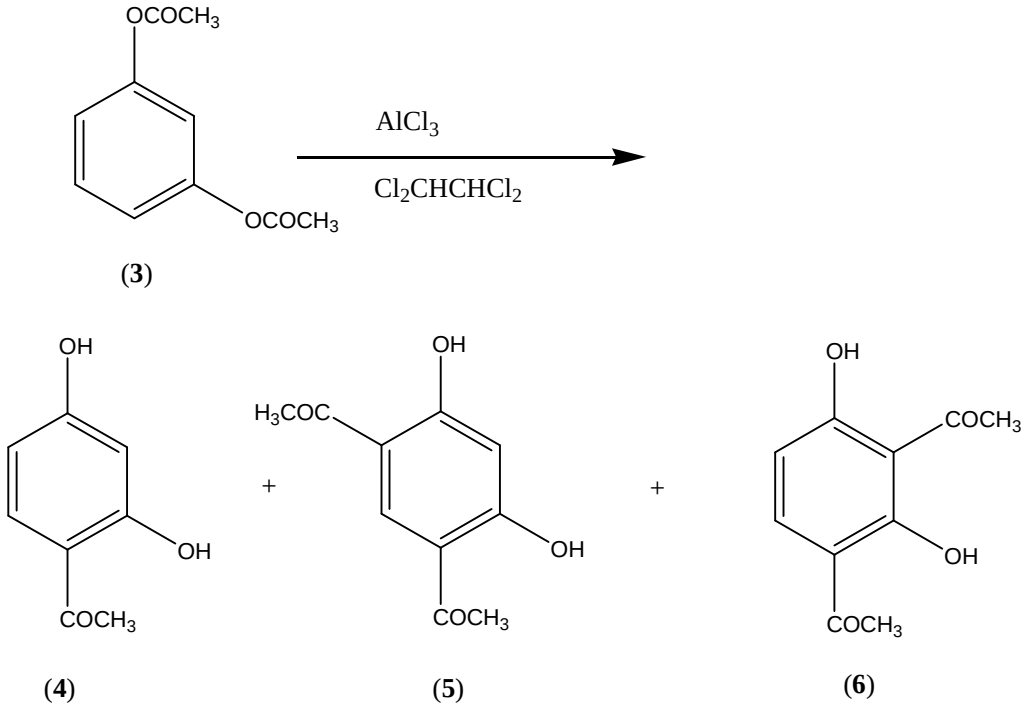
❖ Synthetic methodologies involving lanthanide triflates as catalysts for the Fries rearrangement have been developed[36]. High catalytic activity, low toxicity, moisture and air tolerance make lanthanide triflates attractive catalysts. However the high cost of these catalysts limits their use. Clearly, there was a need for the development of new cheap Lewis acids that can promote these reactions in catalytic amounts. Bismuth compounds have attracted recent attention due to their low toxicity, low cost and good stability[37]. Effective Fries rearrangement using group three and four metal triflates have been carried out[38] and it has been observed that group three metal triflates, especially lanthanide triflates ($Ln(OTf)_3$), are stable lewis acids in water and can be successfully applied as catalysts to several carbon-carbon bond forming reactions[39]. Sreedhar *etal*[40] have evaluated Fries rearrangement with bismuth(III) triflate because it is highly catalytic in nature, relatively stable, insensitive to air and moisture and can be easily prepared from commercially available inexpensive materials such as bismuth(III) oxide and triflic acid[41]. An attractive method using bismuth(III) triflate tetrahydrate as a catalyst for the Fries rearrangement of aryl acetates has also been reported[42]. Hydroxyaryl ketones were obtained efficiently in the presence of 10 mol% of $Bi(OTf)_3$.

- During the course of studies on the Fries rearrangement of phenyl, cresyl and chlorophenyl propionates, use of titanium-tetrachloride as catalyst for their *ortho* rearrangement has been observed[43,44]. Later, a Japanese patent described the preparation of *ortho*-hydroxypropiophenone by this catalyst[45]. Recently titanium-tetrachloride[46] as soft catalyst has been used to carry out the synthesis of six original vicinally polysubstituted *ortho*-hydroxyketones derived from various xylenol and thymol propionates. Preparation of these ketones was made possible, as titanium tetrachloride does not induce migration and/or cleavage of the isopropyl and methyl groups during Fries reaction, contarary to what occurs with aluminium chloride. Martin *etal*[47] have compared the results obtained using titanium tetrachloride for the synthesis of vicinal *ortho*-hydroxyketones with those obtained with aluminium chloride for some aliphatic and aromatic esters of isopropylcresols.
- The structural and mechanistic studies of the lithium diisopropylamide (LDA)-mediated anionic Fries rearrangement of aryl carbamates have been reported[48] (**Scheme-III**). Substituents at the meta position of the arene (-H,-OMe,-F) and the dialkylamino moiety of the carbamate (Me_2N-, Et_2N- and i-Pr_2N-) markedly influence the relative rates of ortholithiation and subsequent Fries rearrangement. Spectroscopic studies have revealed that the reaction proceeds through a number of intermediates. The choice of solvent and substrate dictates which intermediate can be observed as the reaction proceeds.



Scheme-III

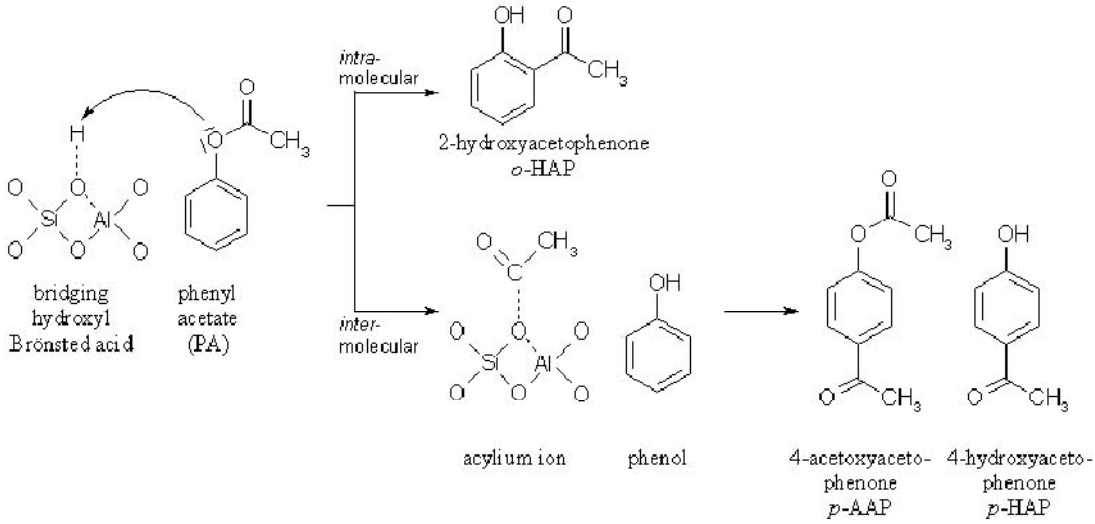
❖ A conventional Fries reaction of resorcinol diacetate (**3**) have been carried out in $AlCl_3$-1,1,2,2-tetrachloroethane complex which results in formation of 2',4'-dihydroxyacetophenone (**4**), 4,6-diacetyl resorcinol (**5**) and 2,4-diacetyl resorcinol (**6**)[49] (**Scheme-IV**).



Scheme-IV

Microwave irradiation of resorcinol diacetate in 1,1,2,2-tetrachloroethane in $AlCl_3$ also produced the substituted resorcinols i.e., 2',4'-dihydroxyacetophenone, 4,6-diacetyl resorcinol and 2,4-diacetyl resorcinol. Microwave irradiation did not show any non-thermal effects on the reaction, however, the reaction time was decreased to 15 minutes to obtain maximum yield of products. Irradiation of diacetate in diethylether solution at 254nm produced 2',4'-dihydroxyacetophenone and 2,4-diacetyl resorcinol. 4,6-Diacetyl resorcinol was not obtained and the product yields were very low. In conclusion, a conventional and microwave irradiated Fries reaction of resorcinol diacetate are good synthetic ways of 2-substituted resorcinol derivatives.

- The conversion of phenyl acetate in the Fries rearrangement over H-ZSM-5 zeolites (an aluminosilicate zeolite mineral) with different Si/Al ratio has been reported by Vogt *etal*[50] (**Scheme-V**). They found a strong dependence of the degree of conversion and selectivity on Si/Al ratio. With decreasing aluminium content in the framework, the conversion was dramatically reduced. On the other hand, Harvey *etal*[51] described only a slight change in the activity of H-beta zeolites with different Si/Al ratio. Roessner and co-workers claimed the presence of Bronsted acidic centres as a prerequisite for the catalytic activity[52], while their investigations on the acylation of anisole over dealuminated beta zeolites confirmed the results of Harvey and co-workers[51]. The heterogeneously catalysed liquid phase Fries rearrangement reaction of phenylacetate carried out on beta zeolites re-exchanged with different amounts of metal cations have been developed[53]. The aim was to determine the influence of the amount of Bronsted acid sites as the catalytic active centers on the conversion and to study differences in their acidic strength. Sodium and potassium ions as well as bivalent calcium and zinc ions were used in the re-exchange procedure. The conversion shows a linear dependency on the degree of ion re-exchange following the theoretically expected values. So the results prove that the bridged hydroxyl groups are indeed the dominating active centers and that their strength seems to be independent on the degree of re-exchange. A special emphasis was placed on the re-exchange with bivalent metal ions. It was shown that one bivalent ion is not able to replace two protons as supposed to be necessary for the charge balance - so a 1:1 stoichiometry needed to be assumed to explain the catalytic results.

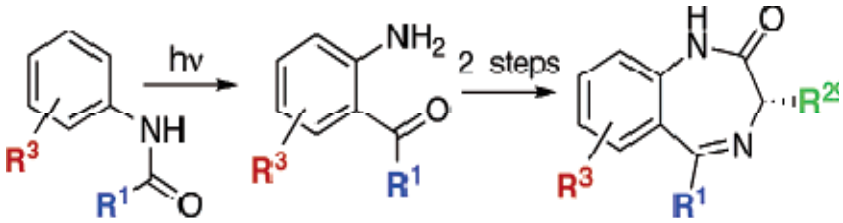


Scheme-V

- The literature pertaining to the Fries rearrangement has been well documented[54,55], but these reviews make no mention of the reaction having been applied to esters of phenols in which acyl group has a branched carbon chain. Since 2-isobutyl phenol and 4-isobutyl phenol were required as a part of programme investigating herbicidal activity of dinitrophenols, their preparation was considered by subjecting isobutyrate to Fries rearrangement and reducing the hydroxyketones thus formed according to the method of Clemmenson[56] as modified by Martin[57]. Phenyl isobutyrate has been reported[58] to undergo a normal Fries rearrangement with anhydrous $AlCl_3$ at 140^oC to give a mixture of 2-hydroxy (40%) and 4-hydroxy-isobutyrophenone (11%). When the reaction was carried out in nitrobenzene at room temperature, the 4-isomer was formed in 86% yield.
- Nafion, a solid perfluorinated resin sulfonic acid, was utilized by Olah *etal*[59] for Fries rearrangement. The catalyst showed general applicability for phenol esters of aromatic carboxylic acids bearing electron donating as well as electron withdrawing groups on both the aromatic rings. In all cases, the *para* isomer was usually predominant. The catalyst could be reused after simple regeneration involving washing with acetone and deionised water and drying. Silica composite materials constituted by Nafion entrapped in a highly porous silica matrix (13 and 40 wt % Nafion) were utilized as catalysts for the Fries rearrangement[60].

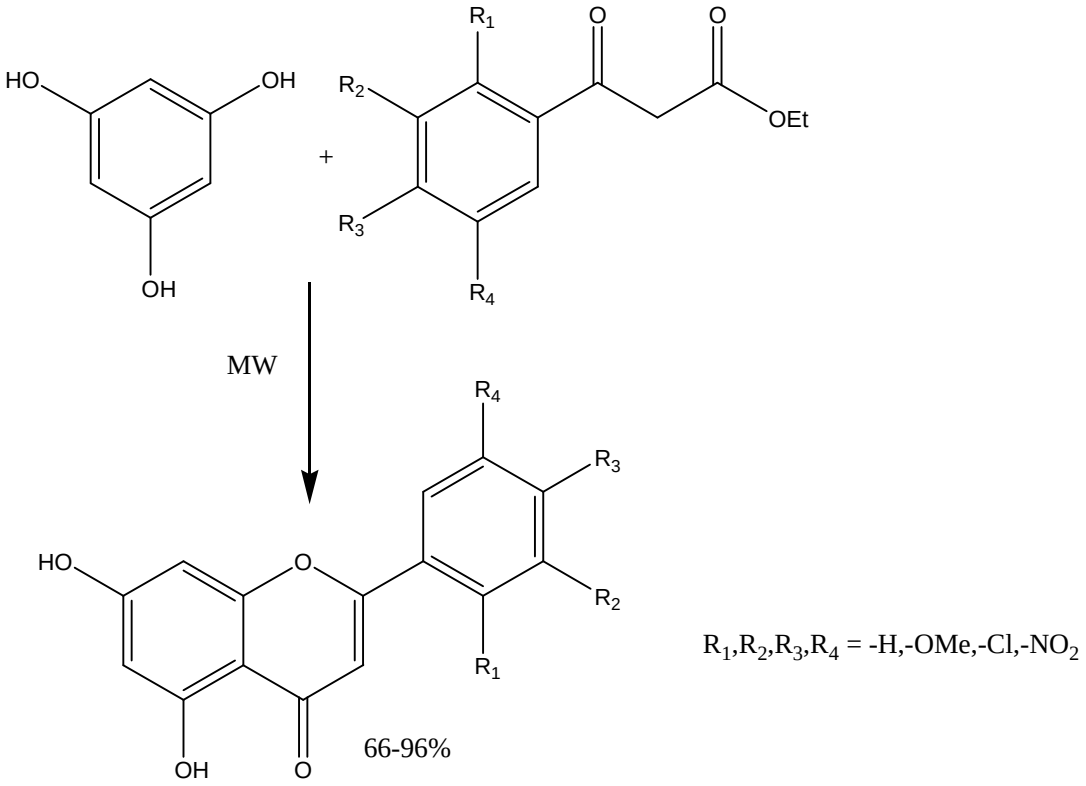
- A much improved and convenient way to carry out Fries rearrangement of phenyl esters to hydroxyphenyl ketones in the presence of Nafion-H, a solid superacidic resin sulphonic acid catalyst, have also been reported[59]. Refluxing a solution of phenol ester in nitrobenzene in the presence of Nafion-H (~5% by wt with respect to esters) effects smooth conversion to the corresponding hydroxyphenyl ketones.
- Even in the most recent literature, the Fries rearrangement of Phenolic esters not substituted in the arene nucleus is held to be an irreversible process yielding *ortho*- and/or *para*-hydroxyaryl ketones[61]. Rosenmund and Schnurr[62] as well as Miguel *etal*[63] have reported a reversal of the Fries rearrangement for 4-acyl-3-alkyl phenols whereas Cullinane and Edwards[64] maintain that the Fries rearrangement is irreversible in this case too. Franz *etal*[65] have reported that there is a qualitative agreement between the isomer distribution for the Fries and the retro Fries rearrangement, this is not sufficient, however, to establish a truly reversible equilibrium, so further investigations are necessary.
- The Fries rearrangement has not been largely explored on amides, as only a few examples of rearrangements starting from simple acetanilides are described. The reaction takes place by heating in the presence of corrosive lewis acids that are not compatible with several functional and protective groups such as Cbz (Carboxybenzyl) and Boc (di-tert-butyl dicarbonate)[33] used for amine group protection. Thus Ferrini *etal*[66] decided to explore the possibility of doing a photochemically induced Fries rearrangement of an amide, finding that the reaction could be effectively carried out using a low pressure Hg lamp at 254nm in cyclohexane as solvent. Better results were obtained with MeCN, although reaction did not go to completion and some starting material was recovered. The best results were obtained using deoxygenated MeCN and irradiation for 24 hrs at room temperature.
- Different anilides derived from carboxylic acids and substituted anilines have been submitted[67] to the photochemically induced Fries rearrangement giving the corresponding *ortho*-aminophenones under the conditions that are not compatible with the presence of acid labile groups (such as Boc or TBDMSo(tert-butyl dimethyl silyl used for protecting primary hydroxyl

group)) on R^1 and R^3. These compounds, not easily obtained in other ways, are useful building blocks for the preparation of benzocondensated heterocycles (**Scheme-VI**).



Scheme-VI

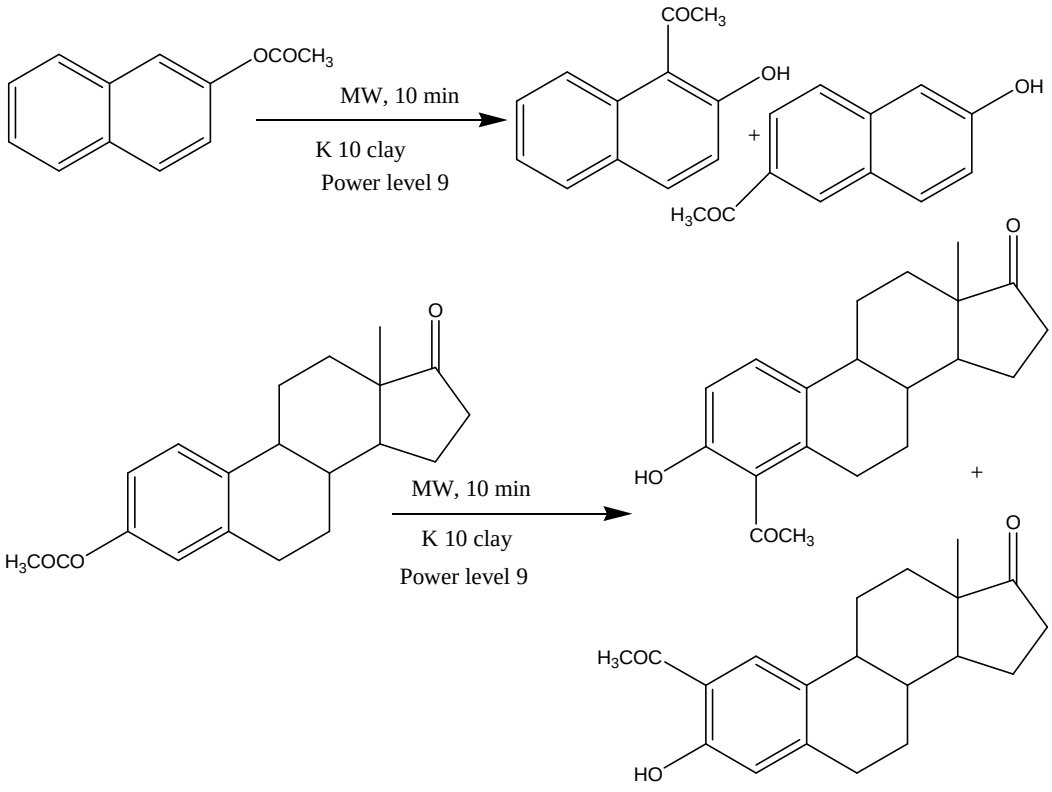
- Earlier reports of Fries rearrangement using microwave heating are those carried out in a sealed tube[68], and dry conditions using K-10 montmorillonite[69,18] as a catalyst. The dramatic rate enhancement which result from microwave irradiation of reactants in a sealed tube are attributed mainly to superheating of solvent due to high pressure[70]. The use of sealed tube or vessels however, can cause hazards due to high pressure build up causing explosions during reactions, and one has to limit oneself to small quantity of reactants. A very safe, simple, fast Fries rearrangement at atmospheric pressure, in the presence of $AlCl_3$ in a modified domestic microwave oven has been reported[71].The method avoids the hazards due to high pressures created in the sealed reaction vessels.
- Ecofriendly direct solvent free synthesis of flavones have been achieved[72] by microwave irradiation of pholoroglucinol and β-ketoesters (**Scheme-VII**). Heating with microwave as compared to classical thermal conditions was shown to be higher yielding, cleaner and faster. The reaction goes through a cycloaddition of an α-oxo ketene intermediate followed by an uncatalysed thermal Fries rearrangement.



Scheme-VII

- Zinc powder in the presence of N,N-dimethylformamide has been reported[73] to efficiently catalyse the selective Fries rearrangement of acetylated phenols under microwave heating or with conventional heating using an oil bath. In some cases different products were obtained using microwave heating and conventional heating. Selective migration of the acyl group have been noted with good yield.
- An efficient one pot synthesis of aromatic hydroxyketones with carboxylic acids as acylating agents without solvent under microwave irradiation have been reported[74]. The reaction time was only 1-5 minutes. Besides, this method has the feature of high yields, low cost, easy manipulation and less pollution. The mixture of phenols, carboxylic acids, phosphoric acid and phosphorus pentoxide (85% H_3PO_4/P_2O_5) were irradiated in a microwave oven, the target products were obtained in one-pot synthesis.
- Trehen *etal*[18] have reported the Fries rearrangement on K-10 montmorillonite in dry open media in 5-10 minutes and represents a step forward from

conventional technique. They used two reactions to illustrate the suitability of microwave acceleration (**Scheme-VIII**). In the first reaction, the acetate of β-napthol was exposed to microwave irradiation at power level 9 in an ordinary household microwave oven for 10 minutes and 70% conversion into *ortho, para* acetylated product in the ratio of 9:1 was observed. The second example used was the steroid estrone . At power level 9 and for 10 minutes, the *ortho*-isomer was formed in 65% yield.



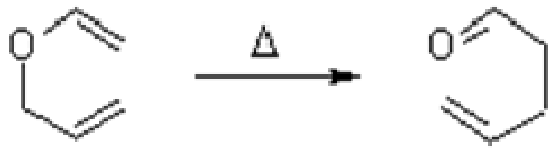
Scheme-VIII

- Thermally conducted Fries reactions give rise to mixtures of *ortho*- and *para*-substituted products, the proportion of each being strongly infuenced by the temperature (high temperature favors *ortho*-shifts) and reaction media. To overcome these problems, new catalysts such as $Hf(OTf)_4$[36(b)], $Sc(OTf)_3$[36(c)] and $ZrCl_4$[75] have been developed recently for this reaction. However, with these catalysts a long reflux time is required and the catalysts are not readily available. Therefore, the development of a new catalyst, which promotes the

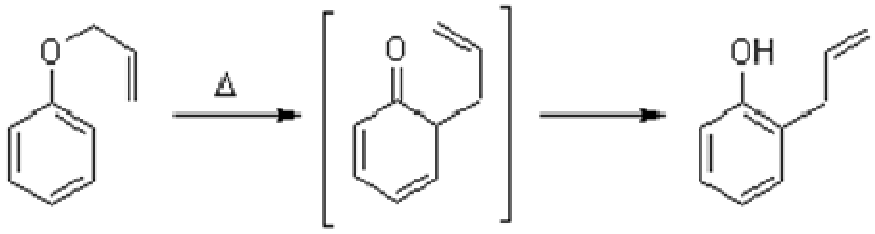
Fries rearrangement cleanly and regioselectively, is required. An $AlCl_3$:$ZnCl_2$ mixture supported on silica gel has been reported as an efficient medium for the promotion of Fries rearrangement without solvent under microwave dielectric heating[76].

Claisen rearrangement

The Claisen rearrangement is a powerful carbon–carbon bond forming chemical reaction discovered by Rainer Ludwig Claisen. It is the first recorded example of [3,3]-sigmatropic rearrangement. The aliphatic Claisen Rearrangement is a [3,3]-sigmatropic rearrangement in which an allyl vinyl ether is converted thermally to an unsaturated carbonyl compound.



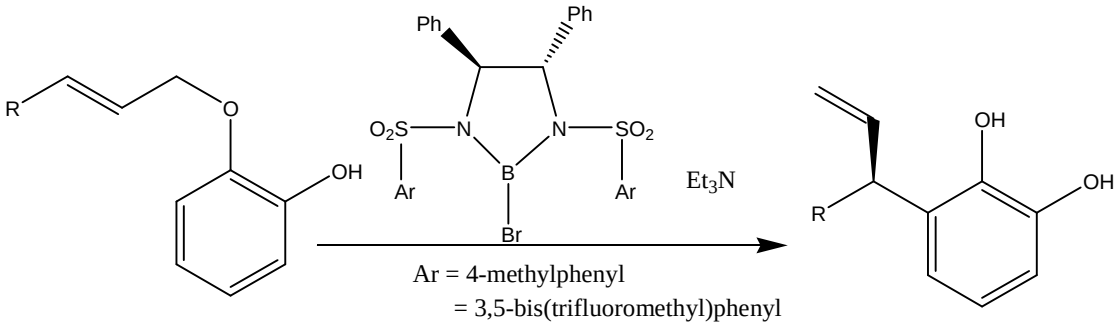
The aromatic Claisen Rearrangement is accompanied by rearomatizatisation.



It involves the conversion of allyl phenyl ethers to the corresponding *ortho*-allyl phenols and is generally performed by heating the ethers at an elevated temperature (>473 K).

This rearrangement[77-79] finds numerous application in the synthesis of natural products[80], such as fatty acids and polyketides. It occupies a unique place in the biomimetic total synthesis of desoxymorrelin[81] and forbesione[82] which proceeds in a regioselective manner and produces desired scaffold exclusively like hanburin[83], morellin[84] and bractatins[85].Since its discovery, this reaction has drawn significant attention for wide application in the synthesis of large variety of important intermediates, fine chemicals and natural products[86].

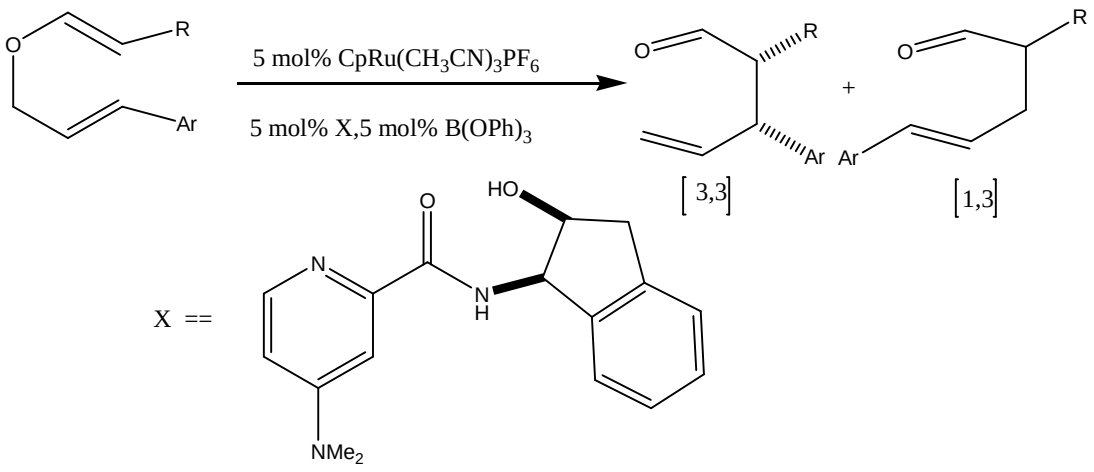
- Keeping in view the importance of Claisen rearrangement of allyl aryl ethers in organic synthesis and in devising environmentally benign methodologies, a simple efficient method has been developed[87] for the Zinc catalysed Claisen rearrangement of allyl aryl ethers to *ortho*-allyl phenols by stirring in an oil bath at 55^{o}C in liquid phase. Moreover, Zinc powder is re-cycable up to six times use without much loss of significant activity. In addition to it, the products are obtained in good to excellent yields and are in a state of high purity.
- Successful enantioselective aliphatic Claisen rearrangements of achiral substrates have been reported by Yamamoto[88], Corey[89] and Kazmaier *etal*[90]. The development of a highly enantioselective aromatic Claisen rearrangement was achieved[91] by the reaction of catechol monoallylic ether with chiral boron reagent. This system was also shown to avoid the formation of *para* rearrangement and abnormal Claisen rearrangement products (**Scheme-IX**).



Scheme-IX

- *Ortho*-Allyl napthols are versatile intermediates in the synthesis of biologically active compounds such as 1,4-napthaquinones[92] and anthracyclinones[93]. The [3,3] sigmatropic shift (Claisen rearrangement) of allyl aryl ethers can provide convenient access to *ortho*-allyl napthols[94]. Bismuth triflate[95] was found to be an efficient catalyst for the Claisen rearrangement of allyl napthyl ethers. The reaction proceeds smoothly with catalytic amount of bismuth triflate (20 mol %) to afford the corresponding *ortho*-allyl napthol in moderate to good yield in most of the cases.

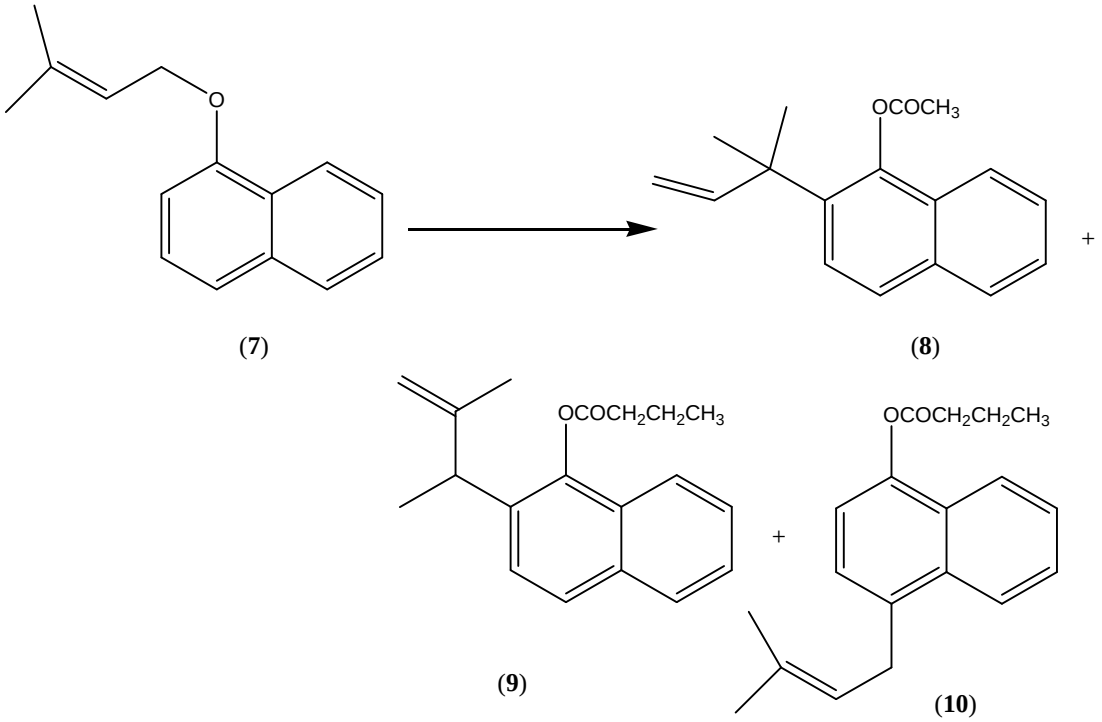
❖ Nearly a century after its original discovery, catalyzed enantioselective varients of Claisen rearrangement remain relatively rare. A cooperative trasition metel–Lewis acid co-catalyst system affects highly enantio- and diastereoselective examples of archetypical Claisen rearrangements. The catalysed Claisen rearrangement proceeds using an easily prepared enantio-enriched transition metal catalyst and a commercially available Lewis acid co-catalyst at ambient temperature in common solvents. As a complementary solution to the development of enantioselective [3,3] sigmatropic rearrangement controlling both absolute and relative stereochemistry, Geharty *etal*[96] have reported Ru(II) catalysed Claisen rearrangement of unactivated allyl vinyl ethers (**Scheme-X**).



Scheme-X

❖ Butyric anhydride in N,N-dimethylaniline have been reported[97,98] to be an effective trap of the normal Claisen product. However this method is not general. When 3-methyl-2-butenyl-napthyl ether (**7**) was subjected to the above conditions, the product mixture showed less than 7% of the normal Claisen product (**8**). The major products were abnormal Claisen product (**9**) and the *para* Claisen product (**10**) in a ratio of 2.7:1, respectively (**Scheme-XI**). Karanewsky *etal*[99] have reported that normal Claisen products can be obtained in good yields as the corresponding acetate by the thermal

rearrangement in the presence of acetic anhydride and either sodium or potassium acetate. Utilisation of these conditions permitted the isolation in 76% yield of the normal Claisen product (**10**), in direct contrast to the results described using butyric anhydride/dimethylaniline conditions.



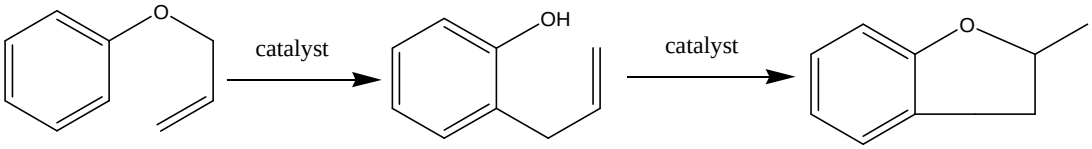
(**7**) (**8**) (**9**) (**10**)

Scheme-XI

- Reports on the use of zeolitic materials as catalysts in Claisen rearrangement are limited. Pichumani and co-workers have observed shape selectivity in ZSM-5 and ZSM-11(silica rich aluminosilicate zeolites) during their study of photo-assisted Claisen rearrangement[100,101]. The use of Faujastic zeolite (H-FAU) and Mordenite (H-MOR) in the rearrangement of allyl phenyl ether in benzene have also been studied[102,103]. Other solid catalysts that have been investigated are mesoporous silica[104] and bentonite[105]. Wagholikar *etal*[106] studied the results of the Claisen rearrangement of allyl phenyl ether over zeolites beta (BEA), Mordenite(MOR) and Faujastic zeolite (Y or FAU). The effect of different zeolites, their aluminium content, acidity, reaction

conditions and solvents on conversion and product selectivity was also studied.

- Claisen rearrangement of allyl phenyl ether to *ortho*-allyl phenol and a dihydrobenzofuran derivative has been reported[107] over MCM-41(Mobil Composition of Matter No.41 is a mesoporous material composed of amorphous silica wall) with different Si/Al ratio. The ether (**11**) first undergoes rearrangement to produce *ortho*-allylphenol (**12**), which cyclises to give 2,3-dihydro-2-methyl benzofuran (**13**) (**Scheme-XII**).

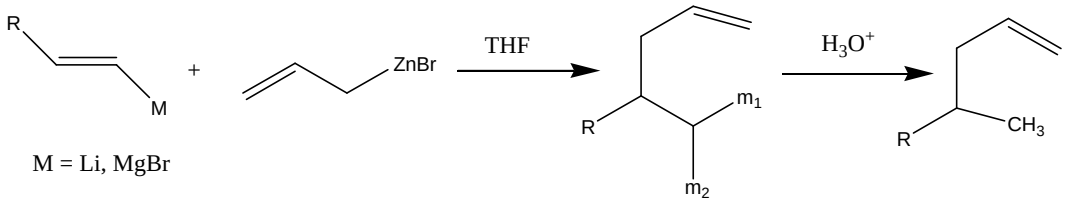


(**11**) (**12**) (**13**)

Scheme-XII

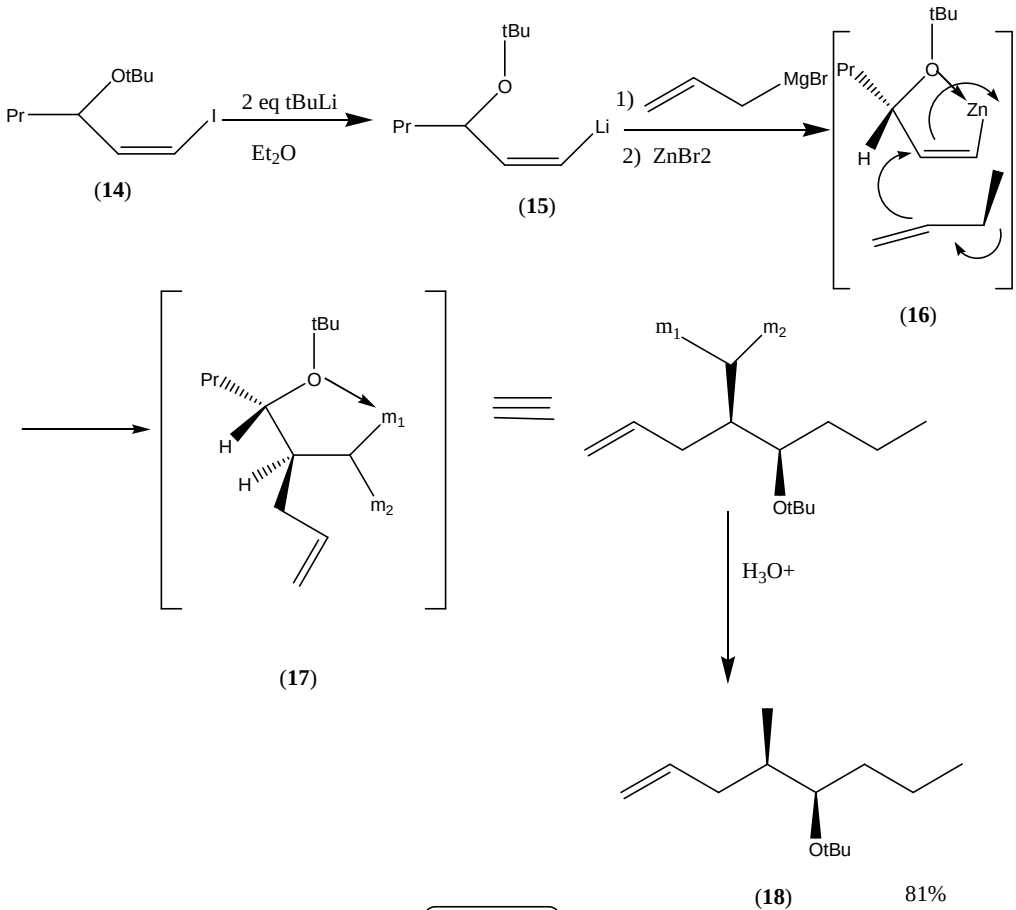
Higher aluminium content, higher reaction temperatures and longer reaction duration favour the formation of the ring compound to benzofuran. There is a close relationship between acidity and conversion, which suggests that the reaction occurs inside the large pores of MCM-41.The influence of temperature and catalyst and Si/Al ratio on the reaction are examined by kinetic analysis, under the assumption of a first order consecutive reaction.

- High-pressure and high temperature water (HPHT-H_2O) micro-reaction system has been reported[108] to be an efficient method to carry out the non-catalytic Claisen rearrangement. Allyl phenyl ether undergoes Claisen rearrangement to give *ortho*-allyl phenol with a very high yield and selectivity of 98% within a short reaction time of 13.4 seconds at 265^{o}C and 5 MPa pressure. Compared to the solvent free micro-reaction, HPHT-H_2O plays an important role to accelerate the reaction as a catalyst by transferring a proton along locally formed hydrogen bond with the substrate.
- Addition of allyl zinc bromide to various alkenyl organometallics[109] could be seen as a metalla-Claisen rearrangement leading to gem dimetallic species (**Scheme-XIII**).



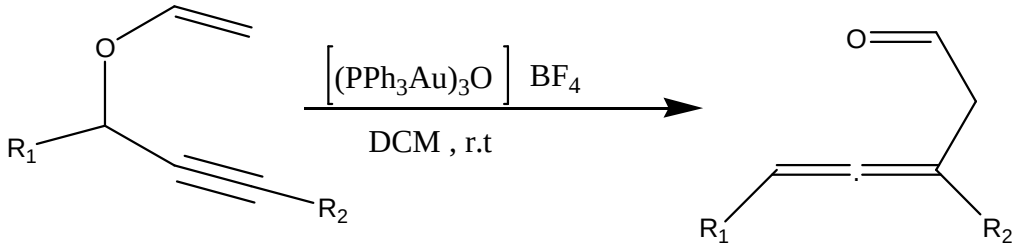
Scheme-XIII

Preliminary results in the area of acyclic stereocontrol by metalla-Claisen rearrangement have been reported[110]. The starting material for this work was, (Z)-γ-Iodo allylic ethers[111] (**14**). Metal halogen exchange with tert-BuLi affords an alkenyllithium reagent (**15**), which reacts with allyl zinc derivatives to give a postulated allyl vinyl zinc compound (**16**) which then undergoes a [3,3] sigmatropic rearrangement leading to the stable 1,1-dimetallic species (**17**) which after acid hydrolysis, gives compound (**18**) with two asymmetric carbon atoms (**Scheme-XIV**).



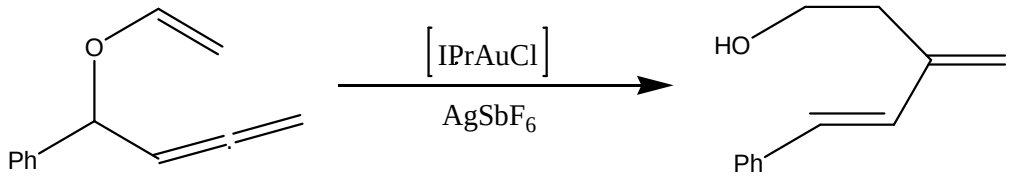
Scheme-XIV

❖ Gold(I) catalysed Claisen type rearrangement of propargylic vinyl ethers to the corresponding homoallenic aldehydes have been reported[112] (**Scheme-XV**).



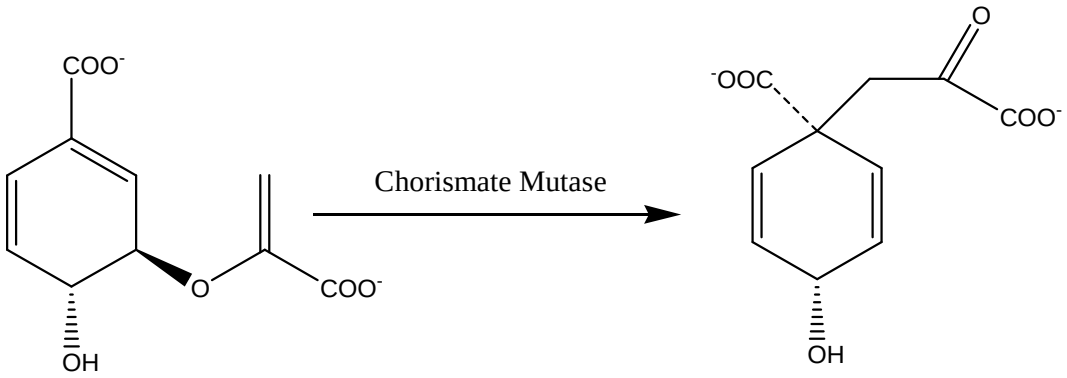
Scheme-XV

Krafft *etal*[113] have reported the synthesis of substituted 1,3-dienes via gold(I) catalysed Claisen rearrangement of allenyl vinyl ethers. The N-heterocyclic carbene gold chloride–catalyst (IPrAuCl) was superior in terms of activity and selectivity and afforded the rearranged product in excellent yields. A proposed cation-pi interaction played a significant role in affecting the reaction rate (**Scheme-XVI**).



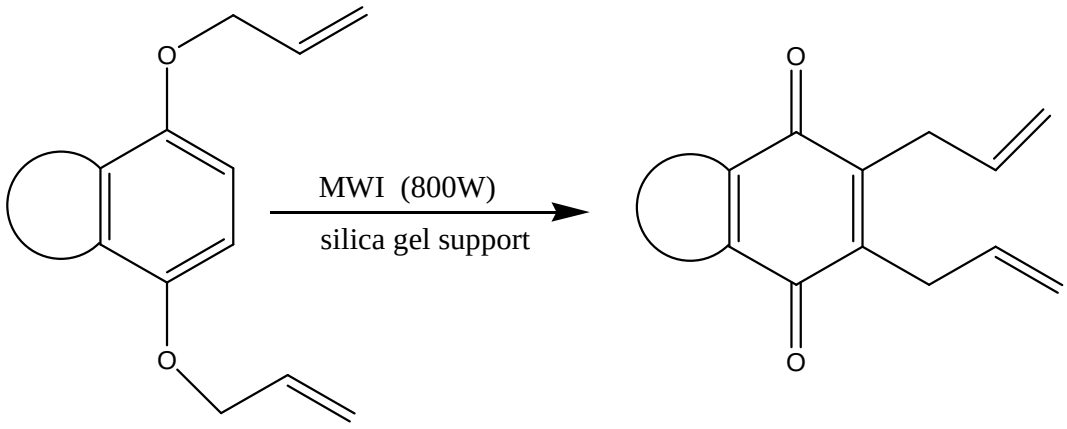
Scheme-XVI

❖ The conversion of chorismate into prephenate[114] is an example of biologically relevant Claisen rearrangement (**Scheme-XVII**). It is a key transformation in the biosynthesis of aromatic amino acids in bacteria, fungi and higher plants[115]. The enzyme chorismate mutase accelerates this reaction 2×10^6 fold over the uncatalysed thermal process[116]. Although the precise mechanism of rearrangement is still contested[117-119], elegant sterochemical studies have implicated a transition state with diaxial chair like geometry[120].



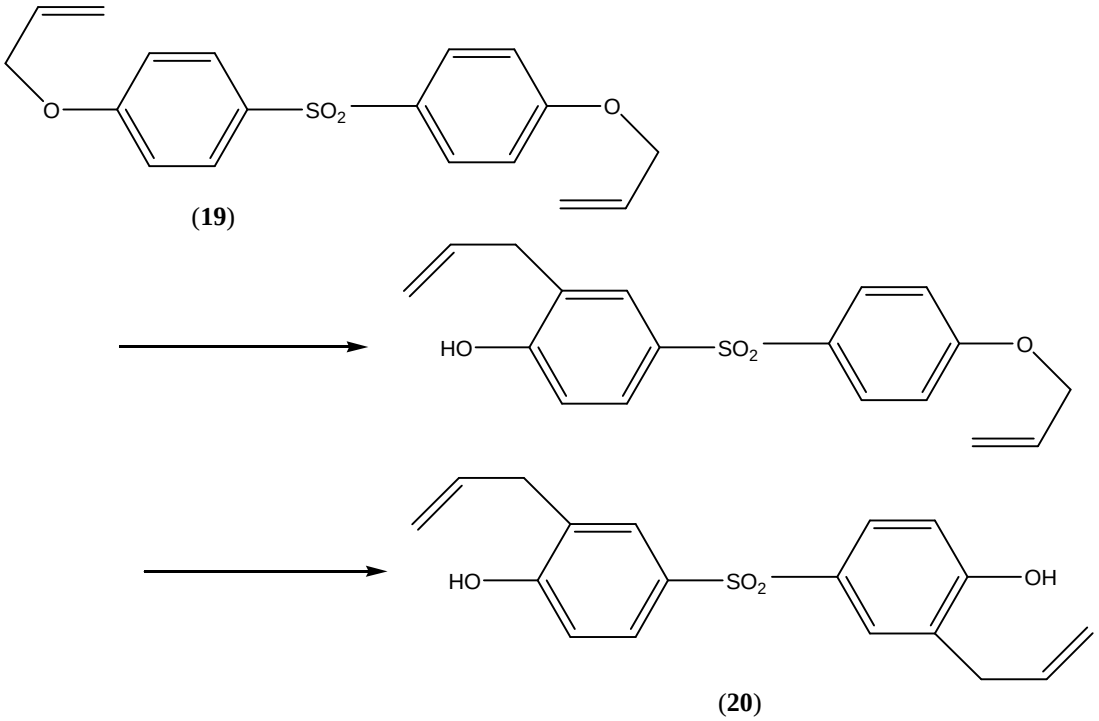
Scheme-XVII

- Under microwaves, a recently developed, chemically stable ionic liquid [b-3c-im][NTf_2], has been used[121] as solvent and successfully applied to accelerate Claisen rearrangement at high temperatures. The reaction times were significantly reduced from hours in conventional heating to ≤ 3 min. This study also demonstrated that [b-3c-im][NTf_2] ionic liquid is a useful solvent substitute and could be recycled multiple times for the rearrangement reaction at elevated temperatures.
- A fast, efficient and environmentally benign solvent-free procedure has been developed for microwave assisted Claisen rearrangement on a silica gel support[122]. Various bis-allyl ketones have been prepared using this protocol (**Scheme-XVIII**).



Scheme-XVIII

- Solvent free Claisen rearrangement of bis(4-allyloxy phenyl) sulphone (**19**) under microwave irradiation for 5 minutes has been reported[123] to give high yields of bis(3-allyl-4-hydroxy phenyl) sulphone (**20**) , which used to be synthesized under conventional heating in 2-30 hours as a color developer for a heat- or pressure-sensitive recording in industry (**Scheme-XIX**).

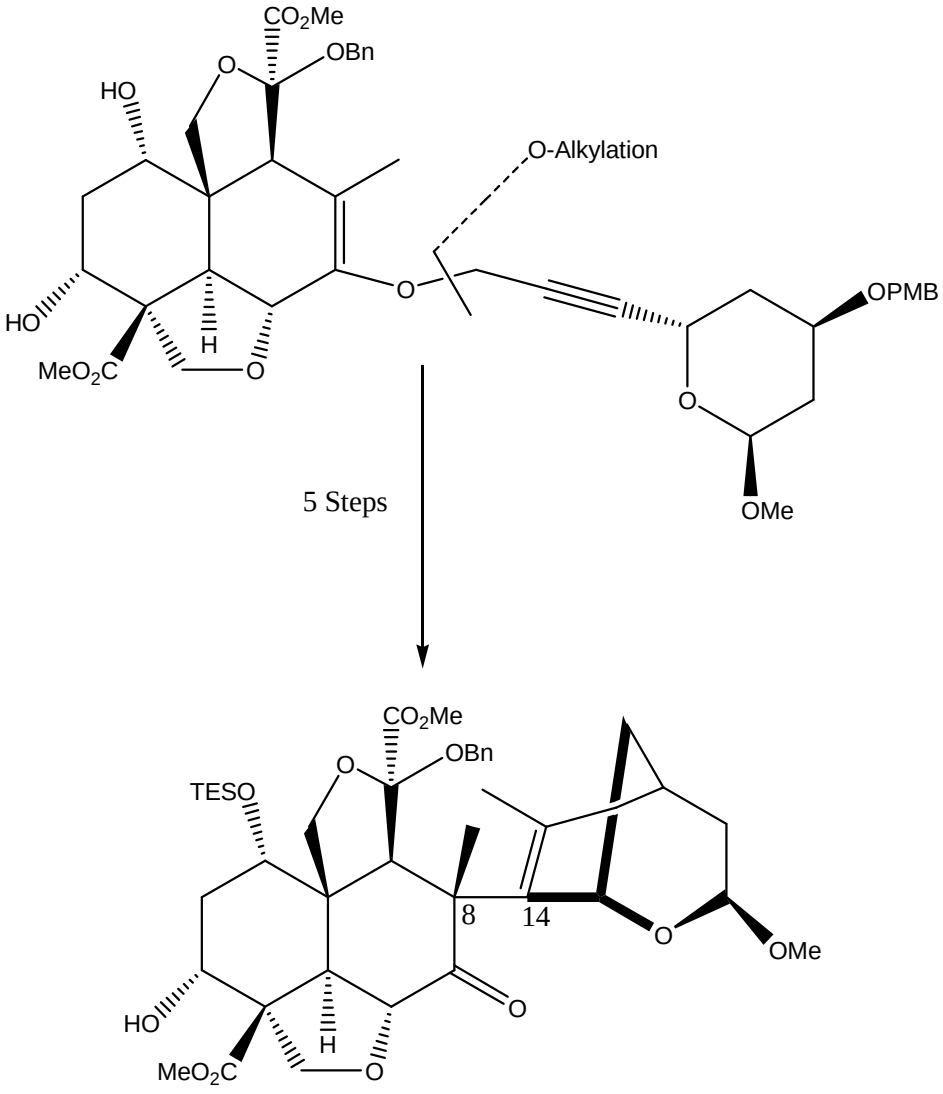


(**19**)

(**20**)

Scheme-XIX

❖ A highly diastereoselective, microwave induced Claisen rearrangement of an appropriately substituted propargylic enol ether have been developed that allows the formation of the sterically congested C_8-C_{14} bond of azadirachtin[124] (**Scheme-XX**). When combined with a radical mediated cyclisation of the corresponding allene, this sequence offers rapid entry to the framework of azadirachtin, which is one of the most structurally complex and highly oxygenated triterpenoid isolated from Indian neem tree Azadirachta indica Meliaceae[125] that has gained considerable attention as a potential nontoxic, biodegradable and natural pesticide[126].



Scheme-XX

- Craig *etal*[127] have reported that microwave assisted double decarboxylative Claisen rearrangement of bis(allyl) 2-tosylmalonates provides substituted 1,6-heptdienes, which may be alkylated, and then converted into pyridines by ozonolysis followed by reaction with ammonia generated in situ under microwave conditions.
- Claisen rearrangement of allyl aryl ethers have been studied extensively over various zeolites under microwave activation and solvent free conditions at 80^{o}C. Deodhar *etal*[128] have found Hβ-zeolite to be an efficient catalyst for the rearrangement. The reaction gives *ortho*-rearranged product selectively instead of expected cyclised dihydrobenzofuran derivative.
- A solvent–free, solid supported and microwave assisted thio-Claisen rearrangement of S-propargylated thioamides having an activated α-methylene group have been developed[129]. The methodology could be used successfully for the synthesis of trisubstituted thiophenes and sulphur containing triarylamines. The reaction takes place in short time and in good yields.

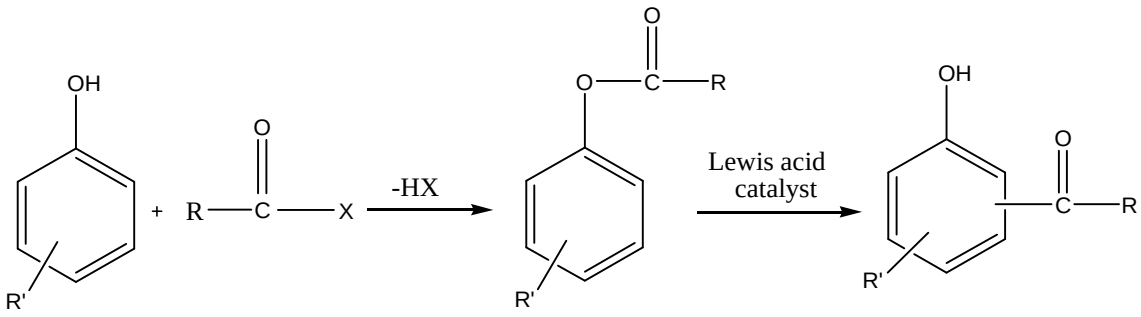
Abstract

"A convenient synthesis of various aromatic hydroxyketones via Fries rearrangement is described by condensing a series of aromatic esters with acidic Al_2O_3-$ZnCl_2$ mixture under microwave conditions. A comparative account of the synthesis of aromatic esters under conventional and microwave conditions is also given. Reactions have been carried out under solvent free conditions with considerable reduction in reaction time and improvement in yield in comparison to classical methods. The adopted procedure provides an energy and time saving protocol."

3.1 Introduction

Aromatic hydroxyketones are useful organic compounds and valuable intermediates in the synthesis of pharmaceuticals[130], perfumery[131], acetophenone resin[132] etc. Products such as 4-hydroxyacetophenone, 4-hydroxybenzophenone, 4-hydroxypropiophenone and others are important drug intermediates[133] that are derived from the Fries rearrangement.

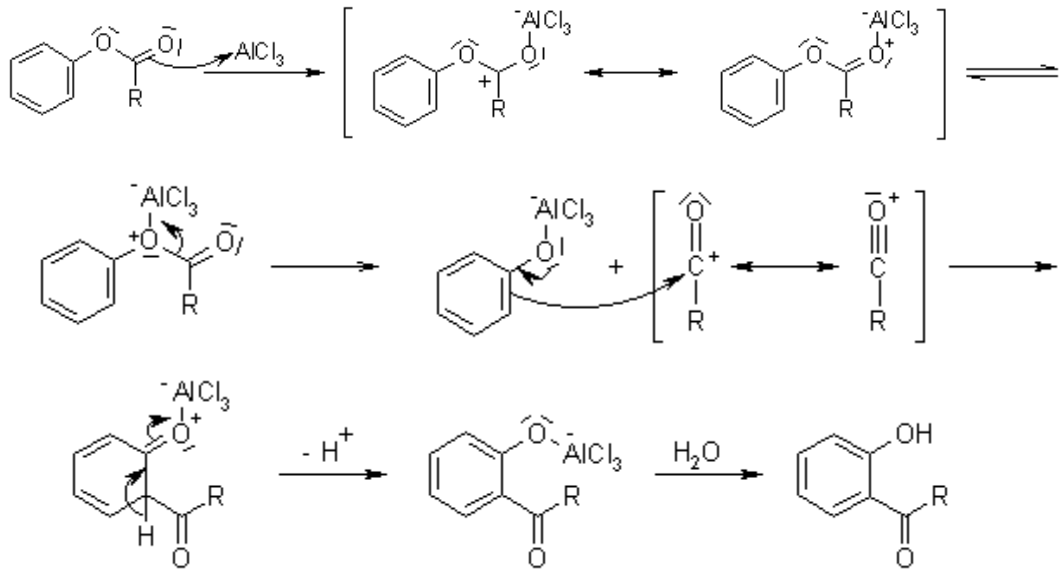
The synthesis of aromatic hydroxyketones commonly involves two steps, esterification of phenols and Fries rearrangement of the ester which is an intermolecular Friedle-Craft acylation (**Scheme-I**). The Fries rearrangement of acyloxy benzenes provides useful routes to acylphenols, a long reflux time with more than a stiochiometric amount of Lewis acids such as $AlCl_3$[134,135], HF[136,135], BF_3[137,135], $TiCl_4$[138] or $SnCl_4$[138] is required. HF which acts both as a catalyst and solvent is very toxic, corrosive, volatile and gives necrosis. $AlCl_3$ is also corrosive and reacts violently with water. BF_3 is very toxic, corrosive and reacts violently with water. Furthermore, the reaction mixture has to undergo a hydrolysis step generating corrosive gases and contaminated salts leading to environmental problems.



R = $-CH_3$ and R' = H or fused aromatic ring

(Scheme-I)

Despite many efforts a definitive reaction mechanism for the Fries rearrangement is not available. Evidence for both inter- and intramolecular mechanisms have been obtained. Reaction progress is not dependent on solvent or substrate. A widely accepted mechanism involves a carbocation intermediate depicted in **Scheme-II**.



(Scheme-II)

Similarly *para*-substitution also occurs to give 4-hydroxyaryl ketones. In the first reaction step a Lewis acid for instance $AlCl_3$ co-ordinates to the carbonyl oxygen atom of the acyl group. This oxygen atom is more electron rich than the phenolic oxygen atom and is the preferred Lewis base. This interaction polarizes the bond between the acyl residue and the phenolic oxygen atom and the aluminium chloride group rearranges to the phenolic oxygen atom. This generates a free acylium carbocation. Depending upon the solvent, an ion pair can form, and the ionic species can react with each other within the solvent cage. However, reaction with a more distant molecule is also possible. After hydrolysis, the product is liberated. The reaction is *ortho*/*para* selective and the site of acylation can be regulated by the choice of temperature. A low reaction temperature favours *para* substitution and at high temperatures the *ortho* product predominates.

However, the requirement for equimolar quantities of the catalyst, the corrosive and toxic conditions and the violent reaction of the catalyst with water has prompted the development of newer protocols. Alternative methods using microwaves have also been developed for the synthesis of aromatic hydroxyketones.

An alternative method that we propose for Fries rearrangement of phenolic compounds is by using acidic Al_2O_3-$ZnCl_2$ mixed reagent. It is an inorganic catalyst

which is adsorbed on silica gel and rearrangement is carried out through microwave irradiation in an eco-friendly way without using solvents and hazardous substances.

3.2 Importance of present work

Since the concept of green chemistry is gaining momentum in the field of organic synthesis[139,140], 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 aromatic hydroxyketones, it is of utmost importance that their synthesis should be achieved by simple, effective and time saving methodologies.

Much work has been done on the synthesis of aromatic hydroxyketones 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, solvent-free conditions and considerable shortening of reaction times.

In this background, we report herein the microwave assisted synthesis of aromatic hydroxyketones with the advantage of minimum solvent usage, improved yields and shortened reaction times. This efficient eco-friendly procedure provides a green chemistry approach for the synthesis of aromatic hydroxyketones.

3.3 Results and Discussion

3.3.1 General study

For the convenient synthesis of aromatic hydroxyketones, phenol and other phenolic esters like 1-napthyl acetate, 2-napthyl acetate and ester of oxygen heterocycles like 4-hydroxycoumarin were treated with acidic Al_2O_3-$ZnCl_2$ mixture. The reactions were carried out under solvent free conditions in a multimode domestic microwave oven at the corresponding times as shown in **Table 3.2**. Optimum reaction times were precisely achieved but the reaction was carried out with intervals of 30 seconds to prevent uncontrolled heat generation. Reactions were monitored periodically with the help of thin layer chromatography. The problems encountered while performing the reactions using solvent were easily overcome by solvent-free technique and the yields obtained were almost quantitative.

The efficiency of microwave irradiation for promoting organic reactions has been demonstrated[141]. Though the use of microwaves for Fries rearrangement is known to be effective but was not ideal, requiring more than one equivalent of $AlCl_3$ in chlorobenzene and use of a sealed tube and was not regioselective for non-substituted phenyl acetate[142]. Also the high pressure developed in the sealed tube may cause hazards, it appeared that the lewis acids supported on silica phase might be good alternative condition for this reaction in dry media[143]. We found that an acidic Al_2O_3-$ZnCl_2$ mixture supported on silica gel is an efficient medium for promotion of Fries rearrangement without solvent under microwave dielectric heating. It is worth noting that the reaction did not proceed on acidic Al_2O_3 or $ZnCl_2$ supported on silica gel alone. The reason as reported in the literature[144] is that, when using acidic Al_2O_3 or $ZnCl_2$, these being strong lewis catalysts, there are circumstances where the substrate is more extensively complexed with the electrophile generating species. This applies even more to electron donating substituents possessing lone pairs available for complexation. To alleviate this problem, we attempted the use of acidic Al_2O_3-$ZnCl_2$ mixed reagent where Al_2O_3 and $ZnCl_2$ are partially complexed and consequently complex to a lesser extend with the aromatic substrate. Under these conditions, there indeed exists a dynamic equilibrium between the complexed entities of the aromatic substrate, the product formed and the electrophile generating species.

The microwaves do not affect the mechanism of the reaction (**Scheme-II**) but the procedure is governed by the same laws as in classical chemistry. However enhanced effects result from the pattern of interaction between the reactants and the energy – a direct insitu generated heat in case of microwave irradiation and indirect conventional heat transfer in case of classical procedures.

Thus the advantage of carrying out Fries rearrangement using the above mentioned reagent under microwaves is that the reaction time has considerably shortened from hours to minutes and the yield has been improved many folds as compared to conventional procedures, reported in the literature[145] (**Table 3.2**).

3.3.2 Comparative Study

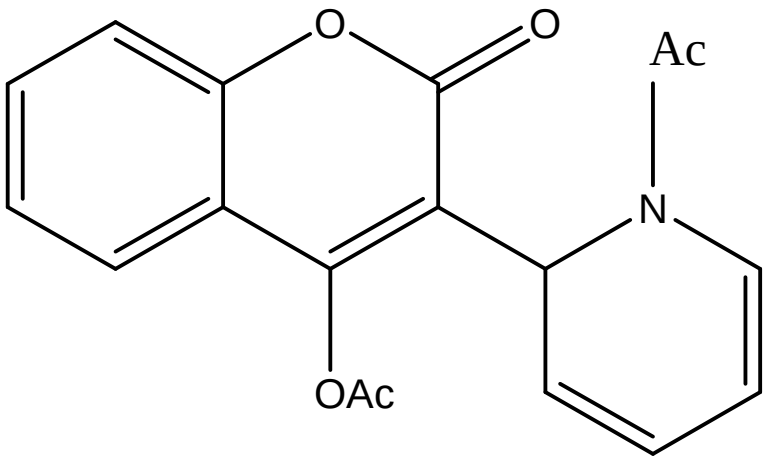
A comparison of microwave assisted synthesis of aromatic esters from phenolic compounds with those carried out under conventional conditions has been drawn in

Table 3.1. 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 time and yield.

For the purpose of converting a phenolic hydroxyl group to acetate derivative, acetic anhydride in presence of pyridine was used as an acetylating agent. Acetic anhydride was chosen due to the fact that unlike higher anhydrides, it is a liquid, thus making a solvent-free system possible.

The comparative study showed the advantage of carrying out the synthesis under microwave conditions by considerably reducing time for completion of reaction from hours to minutes or seconds and also the yield gets improved many folds as compared to conventional procedure. The reason as postulated by various authors[146] is that, energy is readily transferred by the microwave irradiation to the highly polar molecules of acetic anhydride through the characteristic dipolar activation of microwave heating[147].

Acetylation of 4-hydroxycoumarin with Ac_2O/pyridine either fails or gives the acetate in very poor yield, perhaps owing to hydrolysis during workup. Formation of pyridine adduct (**1**) has also been reported[148].



(1)

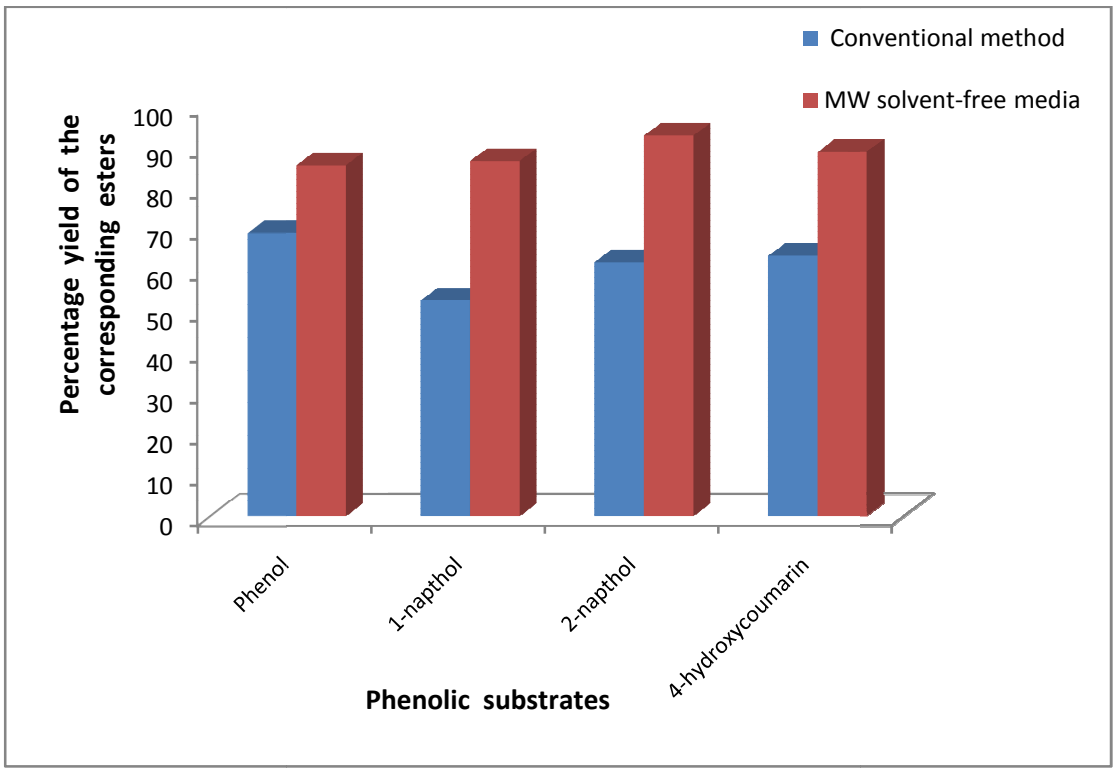


Figure 3.1: Clubbed graph showing the comparative account of % yield of corresponding aromatic esters vs phenolic substrates under two different conditions.

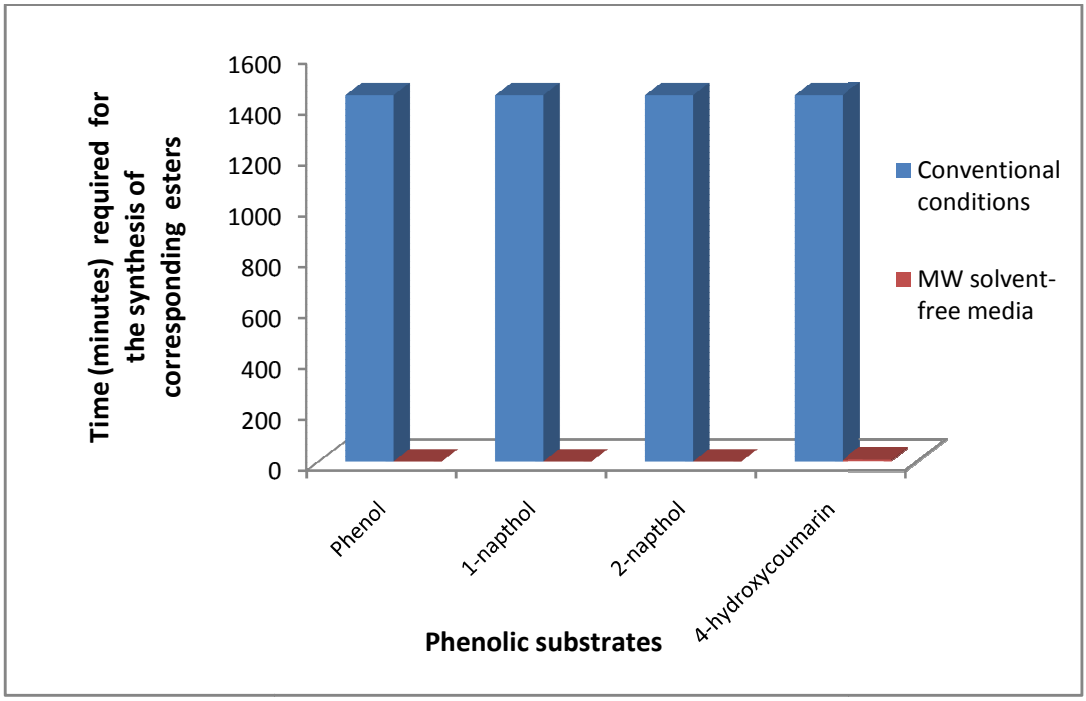


Figure 3.2: Clubbed graph showing the comparative account of time (in minutes) required for the synthesis of corresponding aromatic esters vs phenolic substrates under two different conditions.

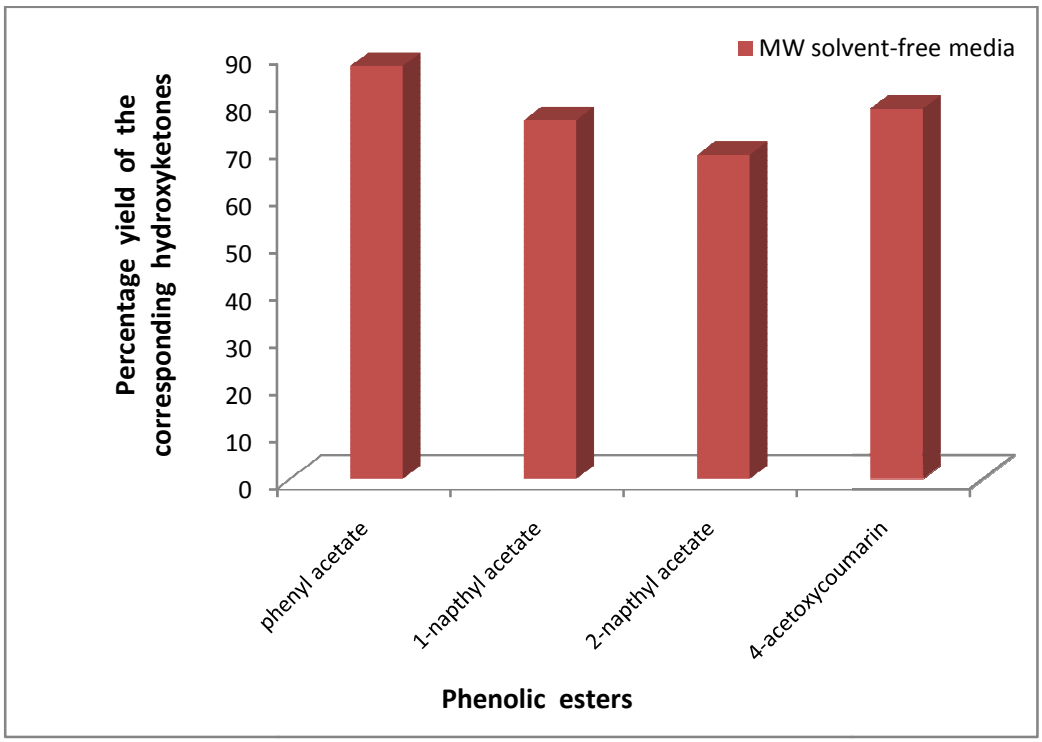


Figure 3.3: Plot of percent yield of the corresponding hydroxyketones vs the phenolic esters under microwave irradiation conditions.

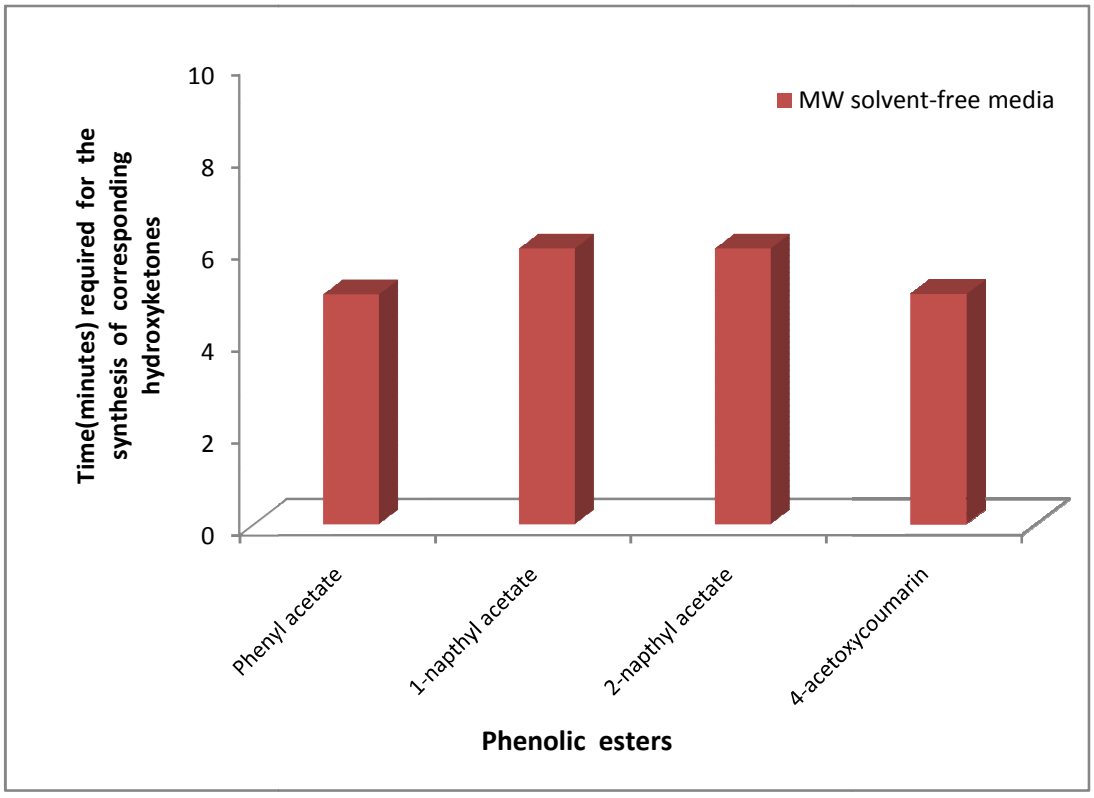


Figure 3.4: Plot of the time (in minutes) required for the synthesis of corresponding hydroxyketones vs phenolic esters under microwave conditions.

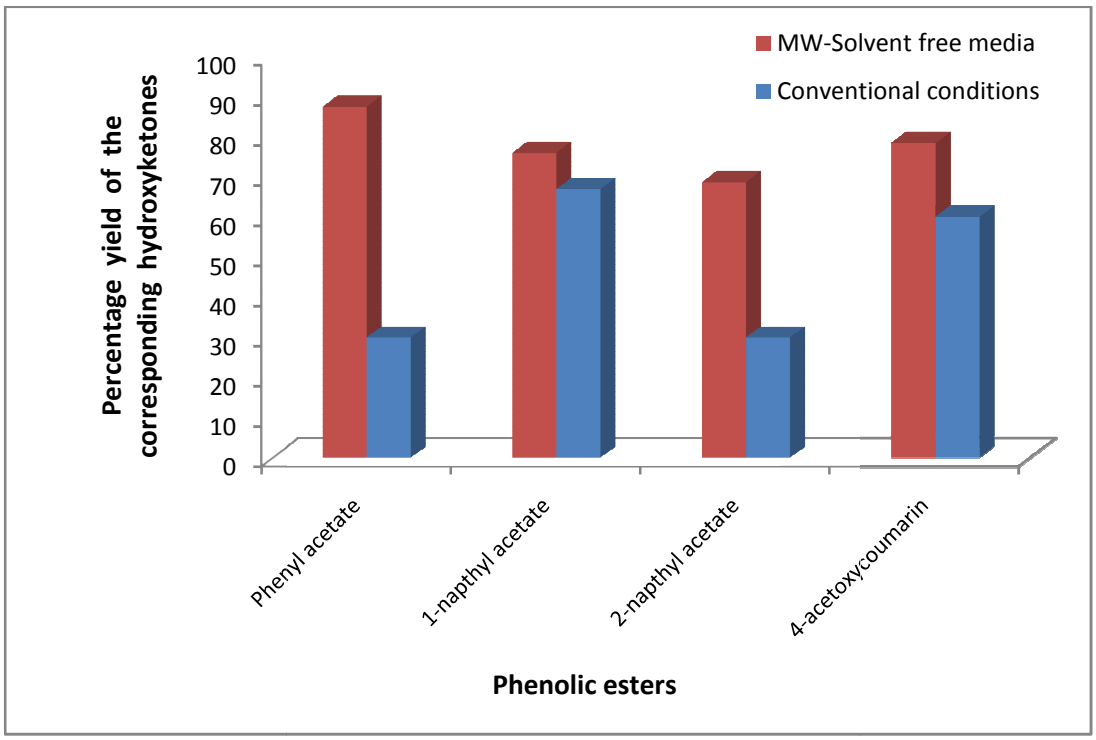


Figure 3.5: Clubbed graph showing the comparative account of % yield of the corresponding hydroxyketones vs phenolic esters under two different conditions.

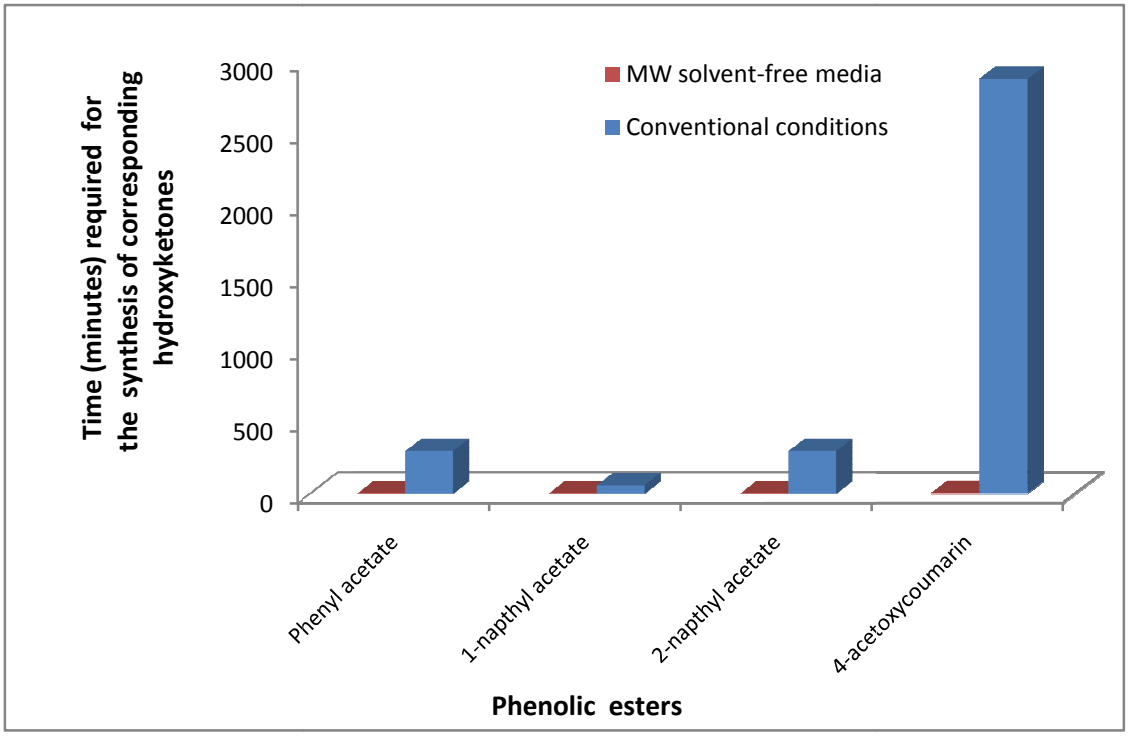


Figure 3.6: Clubbed graph showing the comparative account of time (in minutes) required for the synthesis of corresponding aromatic hydroxyketones vs phenolic esters under two different conditions.

Table 3.1: Comparison of % yield and time (in minutes) for acetylation of phenolic substrates under microwave and conventional conditions.

S. No.	Substrate	Conventional		Microwave	
		Time (minutes)	% Yield	Time (minutes)	% Yield
1	Phenol	1440	69.09	0.5	85.63
2	1 – napthol	1440	52.64	0.25	86.71
3	2 – napthol	1440	61.94	0.25	92.90
4	4-hydroxycoumarin	1440	63.53	5	88.94

Table 3.2: Comparison of % yield and time (in minutes) for Fries rearrangement under microwave conditions with literature data (conventional method).

S.No.	Substrate	Product	Microwave		Literature data (Conventional)	
			Time (minutes)	% Yield	Time (minutes)	% Yield
1	Phenyl acetate	2 –hydroxyacetophenone	5	87.50	300	30
2	1-napthyl acetate	2-Acetyl-1-napthol	6	76.00	60	67
3	2-napthyl acetate	1-Acetyl-2-napthol	6	68.75	300	30
4	4-acetoxycoumarin	3-Acetyl-4-hydroxycoumarin	5	78.33	2880	60

3.4 General procedure for synthesis of aromatic esters

3.4.1 Under Microwave irradiation (solvent free conditions)

A mixture of acetic anhydride and compound to be acetylated dissolved in few drops of pyridine were taken in a glass beaker covered with a glass lid and irradiated under the microwave for corresponding times as shown in **Table 3.1**. Work up of the mixture followed by crystallization using appropriate solvent gives the desired product.

3.4.2 Under Conventional conditions (room temperature)

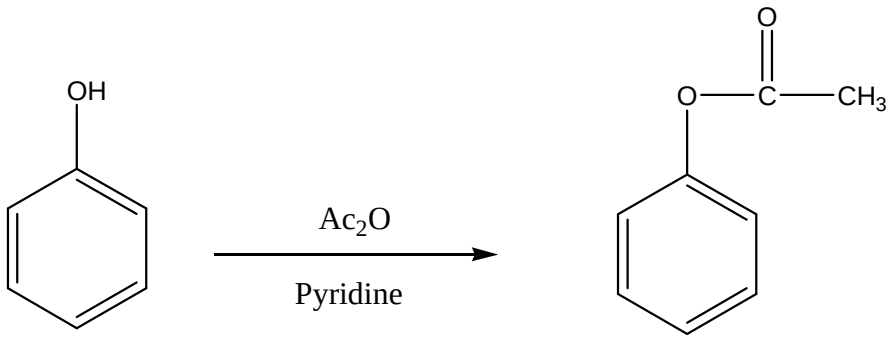
A mixture of acetic anhydride and compound to be acetylated dissolved in few drops of pyridine were taken in a Stoppard glass vial and kept at room temperature. Work up after keeping overnight gives the desired product.

3.4.3 Experimental

Melting points were taken in open capillaries using the electrothermal method on a *Labotech/Perfit* instrument and are uncorrected. All the chemicals and solvents used were of AR grade. All the reactions were irradiated in a multimode *Sharp Carousal*^{TM} microwave oven.

3.4.3.1 Reaction of acetic anhydride with various phenolic substrates

1. **Reaction with phenol**



Phenol Phenyl acetate

A) Under Microwave conditions

A mixture of acetic anhydride (1.5 ml), phenol (0.25gm) and a few drops of pyridine was taken in a 50ml beaker and irradiated in a microwave oven for 15 seconds at

medium power. The reaction mixture was worked up by addition of ice-cold water and extraction with ethyl acetate. Organic layer was washed with water and dried over anhydrous Na_2SO_4 and solvent removed to get a colourless liquid with phenolic odour of phenyl acetate.

Boiling point = 195-196^oC

Yield = 0.31gm

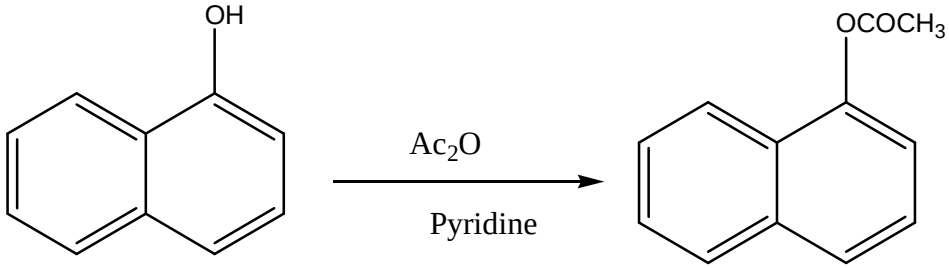
B) Under Conventional conditions

A mixture of acetic anhydride (1.5 ml), phenol (0.25gm) and a few drops of pyridine was taken in a stoppard glass vial and kept at room temperature. Worked up after keeping overnight by addition of ice-cold water and extraction with ethyl acetate. The organic layer after being washed was dried over anhydrous Na_2SO_4 and solvent removed to get a colourless liquid with phenolic odour of phenyl acetate.

Bioling point = 195-196^oC

Yield = 0.25gm

2. Reaction with 1-napthol



1-napthol 1- napthylacetate

A) Under Microwave conditions

A mixture of acetic anhydride (1.5 ml), 1-napthol (0.25gm) and a few drops of pyridine was taken in a 50ml beaker and irradiated in a microwave oven for 15 seconds at medium power. The mixture was poured over crushed ice. The solid residue formed was filtered, washed, dried and crystallised from ethyl acetate as white needles of 1-napthyl acetate.

Melting point = 68^oC

Yield = 0.28gm

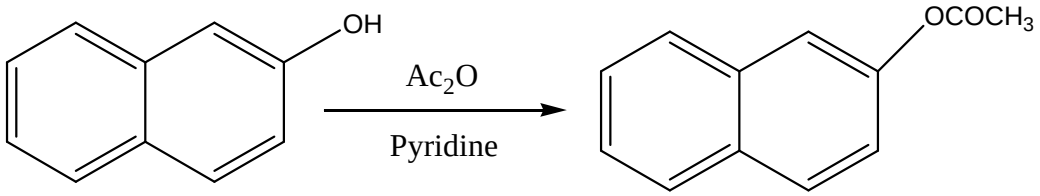
B) Under Conventional conditions

A mixture of acetic anhydride (1.5 ml), 1-napthol (0.25gm) and a few drops of pyridine was taken in a stoppard glass vial and kept at room temperature. Worked up after keeping overnight by addition of ice-cold water. The solid separated was filtered, washed, dried and crystallized from ethyl acetate as white crystals of 1-napthyl acetate.

Melting point = 68^{o}C

Yield = 0.17gm

3. Reaction with 2-napthol



2-napthol 2- napthylacetate

A) Under Microwave conditions

A mixture of acetic anhydride (1.5 ml), 2-napthol (0.25gm) and a few drops of pyridine was taken in a 50ml beaker and irradiated in a microwave oven for 15 seconds at medium power. The mixture was poured over crushed ice. The solid obtained was filtered, washed, dried and crystallized from ethyl acetate as yellow crystals of 2-napthyl acetate.

Melting point = 68.70^{o}C

Yield = 0.30gm

B) Under Conventional conditions

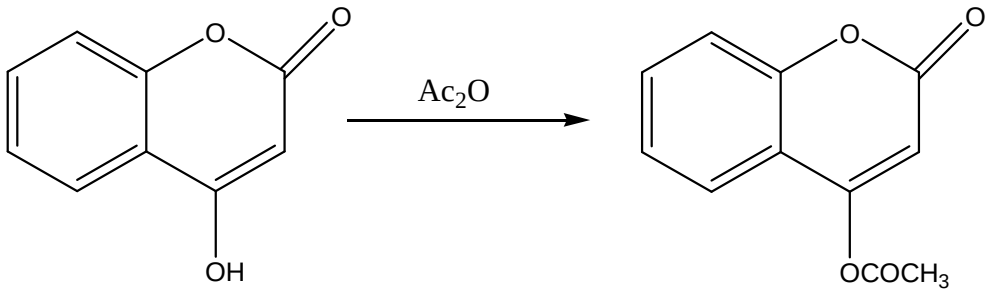
A mixture of acetic anhydride (1.5 ml), 2-napthol (0.25gm) and a few drops of pyridine was taken in a stoppard glass vial and kept at room temperature. Worked up after keeping overnight by addition of ice-cold water. The solid which separated out was filtered, washed, dried and crystallized from ethyl acetate as yellow coloured needles of 2-napthyl acetate.

Melting point = 68.70^{o}C

Yield = 0.20gm

4. Reaction with 4-hydroxycoumarin

A) Under Microwave conditions



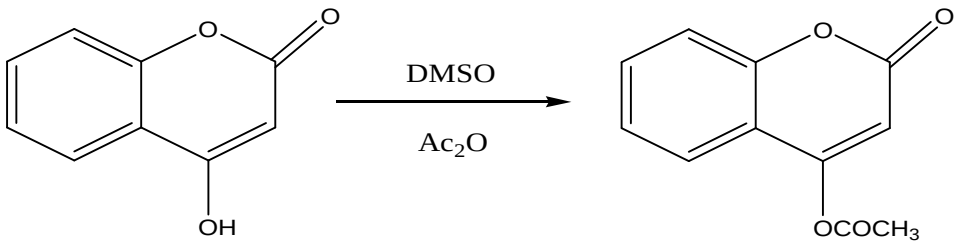
4-hydroxycoumarin 4-acetoxycoumarin

A mixture of 4-hydroxycoumarin (0.25gm) and acetic anhydride (1.5ml) was adsorbed on silica gel by grinding in a motor and pestle and was irradiated in the microwave oven for 5 minutes at high power. The reaction mixture was eluted with acetone and solvent removed. Solid obtained was crystallized from petrol-benzene to yield 4-acetoxycoumarin.

Melting point = 109-110^{o}C

Yield = 0.28gm

B) Under Conventional conditions



4-hydroxycoumarin 4-acetoxycoumarin

4-hydroxycoumarin (0.25gm) was taken in DMSO:Ac_2O (2:1 by volume)(6ml) and was kept at room temperature. Worked up after keeping overnight by addition of

water and extraction with ether. Ethereal solution was washed several times with water in order to remove DMSO and acetic anhydride, dried on anhydrous Na_2SO_4 and solvent removed. Solid obtained was crystallized from petrol-benzene.

Melting point = 109-110^oC

Yield = 0.20gm

3.5 General procedure for the synthesis of aromatic hydroxyketones via Fries rearrangement under microwave conditions

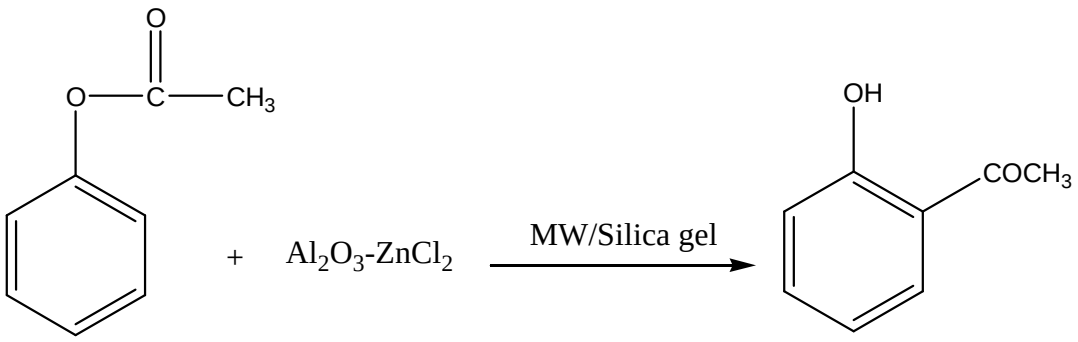
Aromatic esters and acidic Al_2O_3-$ZnCl_2$ mixture in a definite ratio were adsorbed on silica gel (60-120 mesh) by grinding in a mortar and pestle and irradiated under microwave oven for the time indicated in **Table 3.2**.The mixture was then eluted with the appropriate solvent. Removal of solvent afforded the desired product.

3.5.1 Experimental

Melting points were taken in open capillaries using electro thermal method on a *Labotech/Perfit* instrument and are uncorrected. Infrared spectra were recorded on *Interspec-2020-FTIR* spectometer. All the solvents and chemicals used were of AR grade. All the reactions were carried out in a multimode *Sharp Carousel*^{TM} microwave oven. The products formed have been identified by comparison of their spectra with those of authentic samples or reported in the literature. Physical properties were also in accordance with the data reported in the literature.

3.5.1.1 Reaction of acidic Al_2O_3-$ZnCl_2$ mixture with various phenolic esters under microwave conditions

1. **Reaction with phenyl acetate**



Phenyl acetate 2-hydroxyacetophenone

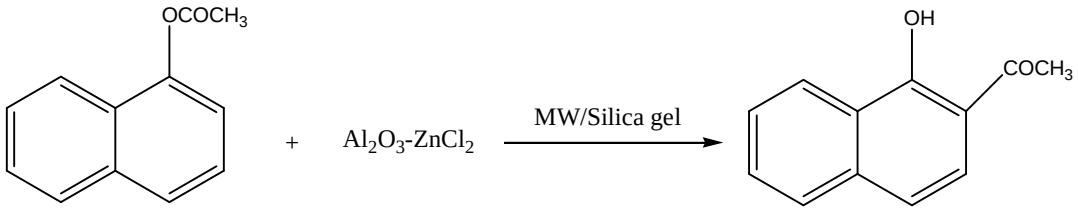
A mixture of phenyl acetate (0.32gm), acidic Al_2O_3 (1 gm) and $ZnCl_2$ (1 gm) were adsorbed on silica gel (60-120) by grinding in a mortar and pestle and irradiated under microwave oven for 5 minutes at medium power level at the intervals of 30 seconds duration to prevent uncontrolled heat generation. Progress of the reaction was monitored by tlc. Deep violet colour upon interaction with alcholic ferric chloride indicated the formation of desired product. Elution with acetone and removal of solvent afforded 2-hydroxyacetophenone.

Yield = 0.28gm

Spectral date: Bioling point = 213^oC

IR (KBr) cm^{-1}: 3436, 2924, 1643, 1458

2. Reaction with 1-napthyl acetate



1- napthylacetate 2-Acetyl-1-napthol

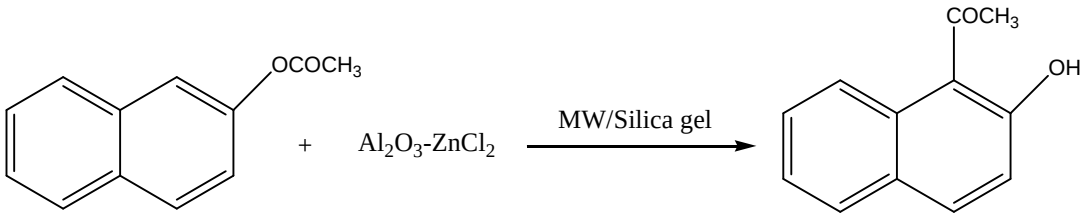
A mixture of 1-napthyl acetate (0.25gm), acidic Al_2O_3 (0.5gm) and $ZnCl_2$ (0.35 gm) was adsorbed on silica gel (60-120) by grinding in a mortar and pestle and irradiated under microwave oven for 6 minutes at medium power level at the intervals of 30 seconds to prevent uncontrolled heat generation. Progress of the reaction was monitored by tlc. Green colouration with alcholic ferric chloride indicated the formation of desired product. Reaction mixture was cooled and eluted with diethyl ether and the ethereal solution was washed several times with water, dried on anhydrous Na_2SO_4 and solvent removed. Solid obtained was crystallized from ethanol to yield 2-Acetyl-1-napthol.

Yield = 0.19gm

Spectral data: Melting point = 97-100^oC

IR (KBr) cm^{-1}: 1633, 3282, 1240, 3052

3. Reaction with 2-napthyl acetate



2- napthylacetate 1-Acetyl-2-napthol

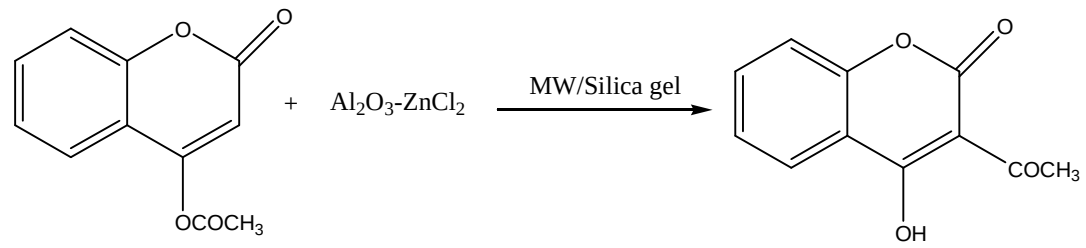
A mixture of 2-napthyl acetate (0.16), acidic Al_2O_3 (0.5gm) and $ZnCl_2$ (0.5gm) were adsorbed on silica gel (60-120) by grinding in a mortar and pestle and irradiated under microwave oven for 6 minutes at medium power level at the intervals of 30 seconds to prevent uncontrolled heat generation. TLC monitoring was employed to keep track of reaction progress. Greenish colour with alcholic ferric chloride indicated the formation of desired product. Reaction mixture was eluted with diethyl ether and the ethereal solution was washed several times with water, dried on anhydrous Na_2SO_4 and solvent removed. Solid obtained was crystallized from ethanol to yield yellow needles of 1-Acetyl-2-napthol.

Yield =0.11 gm

Spectral data: Melting point = 61-63^oC

IR (KBr) cm^{-1}: 1630, 3282, 1240, 3052

4. Reaction with 4-acetoxycoumarin



4-acetoxycoumarin 3-Acetyl-4-hydroxycoumarin

A mixture of 4-acetoxycoumarin (0.12gm), acidic Al_2O_3 (0.3gm) and $ZnCl_2$ (0.3gm) were adsorbed on silica gel (60-120) by grinding in a mortar and pestle and irriadiated under microwave oven for 5 minutes at high power level at the intervals of 30 seconds

to prevent uncontrolled heat generation. Progress of the reaction was monitored with tlc. Yellow colouration with alcholic ferric chloride indicated the formation of desired product. Reaction mixture was eluted with acetone and solvent removed. Solid obtained was crystallized from ethanol to yield 3-Acetyl-4-hydroxycoumarin.

Yield = 0.094gm

Spectral data: Melting point = 134-136^{o}C

IR (KBr) cm^{-1}: 3560, 1699, 1700

3.6 Conclusions

Aromatic hydroxyketones have been prepared with improved yield under solvent free microwave conditions in minimum time as compared to conventional procedures reported so far in literature. This procedure is simple, efficient and the usage of solvent-free conditions makes it an eco-friendly. Although the use of easily accessible domestic microwave oven makes the procedure convenient, consistent reproducibility of the results remain a challenging task.

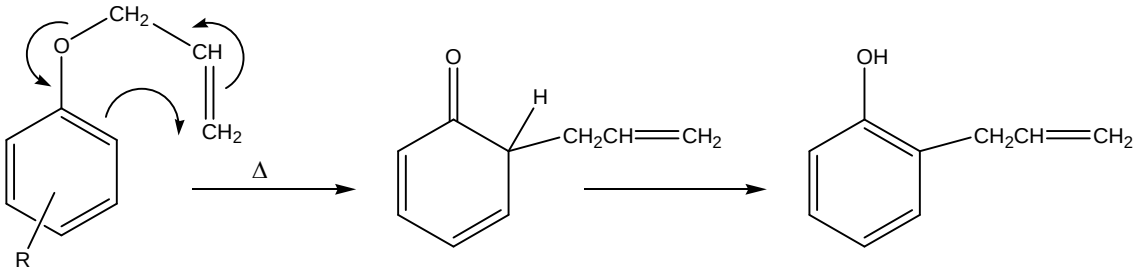
Abstract

"Allyl aryl ethers were treated with $ZnCl_2$ under microwave conditions to yield *ortho*-allylated phenols via Claisen rearrangement. The reactions have been carried out under solvent free conditions in considerably shortened reaction times as compared to the conventional procedure reported in literature."

4.1 Introduction

The Claisen rearrangement, is one of the fundamental reactions of sigmatropic rearrangement and offers a potentially useful method for C-C bond formation[149]. Since after the discovery of this reaction in 1912[150], the rearrangement and its variations[151] have been used extensively in the synthesis of natural products[152] because they are excellent tools for the selective formation of a new carbon-carbon bond[153] and the predictability of stereochemical outcome[154]. The rearrangement has also drawn significant attention for its wide application in the synthesis of large variety of important intermediates, fine chemicals and as a key step in the synthesis of range of naturally occurring 1,4-benzoquinones[155].

Claisen rearrangement involves the conversion of allyl phenyl ethers to the corresponding *ortho*-allyl phenols and is generally performed by heating the ether at an elevated temperature (>473K). The reaction proceeds through a concerted cyclic mechanism as represented below (**Scheme I**):



An allyl phenyl ether

R = H or fused ring

(Scheme-I)

The rearrangement to the *ortho* position is a first order reaction. The breaking of the carbon-oxygen bond and the attachment of the γ-carbon atom to the *ortho*-position must be simultaneous, and this step rather than enolisation of the hydrogen, must be rate determining step.

4.2 Importance of present work

The Claisen rearrangement provides an efficient synthetic route for the preparation of *ortho*-allyl phenols, but it usually requires high temperature to proceed[92,93]. These forcing conditions lead to severe side reactions. Although the reaction is traditionally performed under thermal conditions without any catalyst, there is considerable current interest in the catalysis of the Claisen rearrangement[156] and is reported to be susceptible to catalysis by Bronsted and Lewis acids[157] such as BF_3.HOAc[158], $AlCl_3$[159],$TiCl_4$[160], $Yb(OTf)_3$[161], $Sc(OTf)_3$[162] in ionic liquid, $IrCl_3$[163] and Mo(CO)[164]. However, inspite of having potential utilities, many of these methods involve the use of toxic and expensive reagents[160], longer reaction time[165], high temperatures[166] and tedious work up procedure. However a variety of catalysts were reported such as BCl_3[167], R_2AlCl[168] and $PdCl_2(MeCN)_2$[169], to build up the greener processes by the reduction of energy consumption, reaction time and waste production[170]. In most cases, the Claisen rearrangement requires high boiling solvents such as *ortho*-dichlorobenzene[171], N,N-diethylaniline[172] or quinoline[173] and a long reflux time. These are not eco-friendly reaction conditions and moreover, there are problems in the work up of the reaction mostly pertaining to the removal of solvent. Therefore, there is a demand for carrying out such a rearrangement under solvent less condition and in one step. Alternative methods using microwaves have been developed for the Claisen rearrangement of allyl aryl ethers and reaction times have been shortened dramatically[174-182]. However efforts are still on to find new environmentally benign procedures which are simple, safe, greener and economical for Claisen rearrangement of allyl aryl ethers.

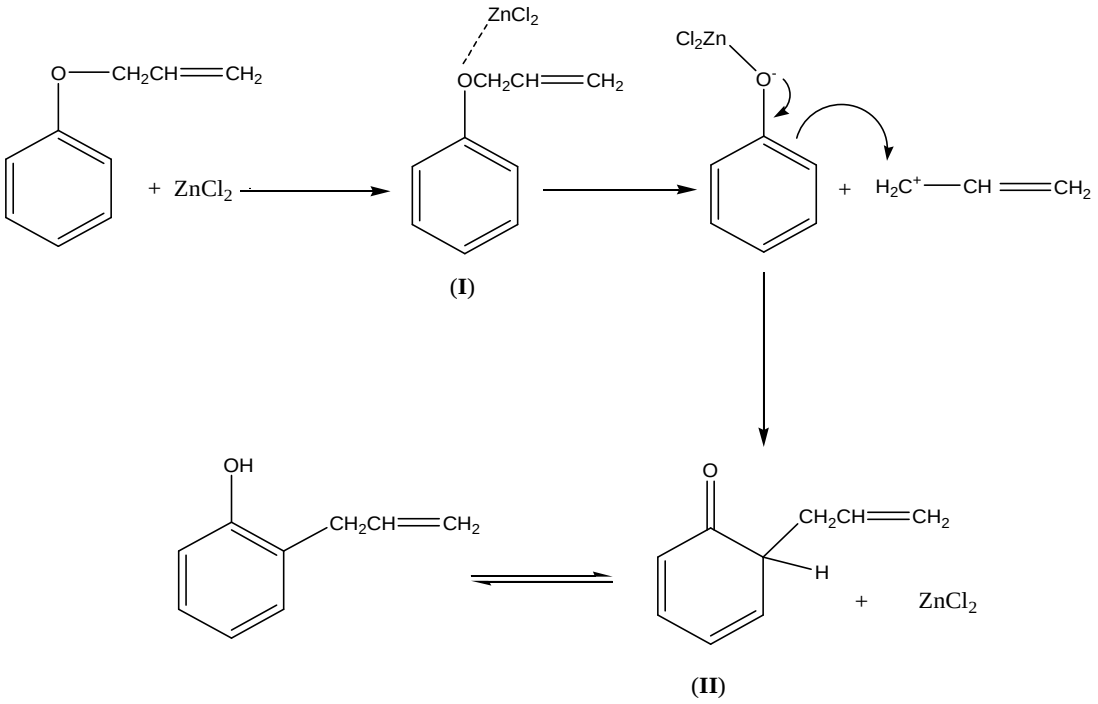
In this background, we report herein the microwave assisted synthesis of *ortho*-allyl phenols with the advantage of minimum solvent usage, improved yields and shortened reaction times. This efficient eco-friendly procedure provides a green chemistry approach for the synthesis of *ortho*-allyl phenols.

4.3 Results and Discussion

For the convenient synthesis of *ortho*-allyl phenols, allyl phenyl ether and ethers of oxygen heterocycles like 4-hydroxycoumarin and 7-hydroxycoumarin were treated with $ZnCl_2$. Reactions were carried out under solvent-free conditions in a multimode

domestic microwave oven for different time durations as shown in the **Table 4.2**. Optimum reaction times were precisely achieved but the reaction was carried out with intervals of 30 seconds to prevent uncontrolled heat generation. Reactions were monitored periodically with the help of thin layer chromatography. The problems encountered while performing the reactions using solvent were easily overcome by solvent-free technique and the yields obtained were almost quantitative.

Heating the mixture of $ZnCl_2$ and allyl aryl ethers under solvent-free conditions revealed that this Lewis acid has the catalytic effect in the Claisen rearrangement. The formation of the products from the zinc chloride catalysed reaction can be explained as follows[183] (**Scheme-II**) :



(Scheme-II)

The Zinc Chloride-allyl phenyl ether complex (**I**) formed through the initial interaction of allyl phenyl ether and Zinc Chloride is cleaved in the usual manner under the influence of the latter resulting in the formation of dienone (**II**) which on aromatization gives the desired product.

Microwaves do not affect the mechanism of the reaction but the procedure is governed by the same laws as in classical chemistry. However enhanced effects

results because there is an insitu generation of heat in case of microwave irradiation and an indirect conventional heat transfer in case of classical procedure.

Thus carrying out Claisen rearrangement using $ZnCl_2$ under microwave not only decreases the time for completion of reaction from hours to minutes but the yield also gets improved many folds as compared to those reported in literature[184] for conventional procedures (**Table 4.2**).

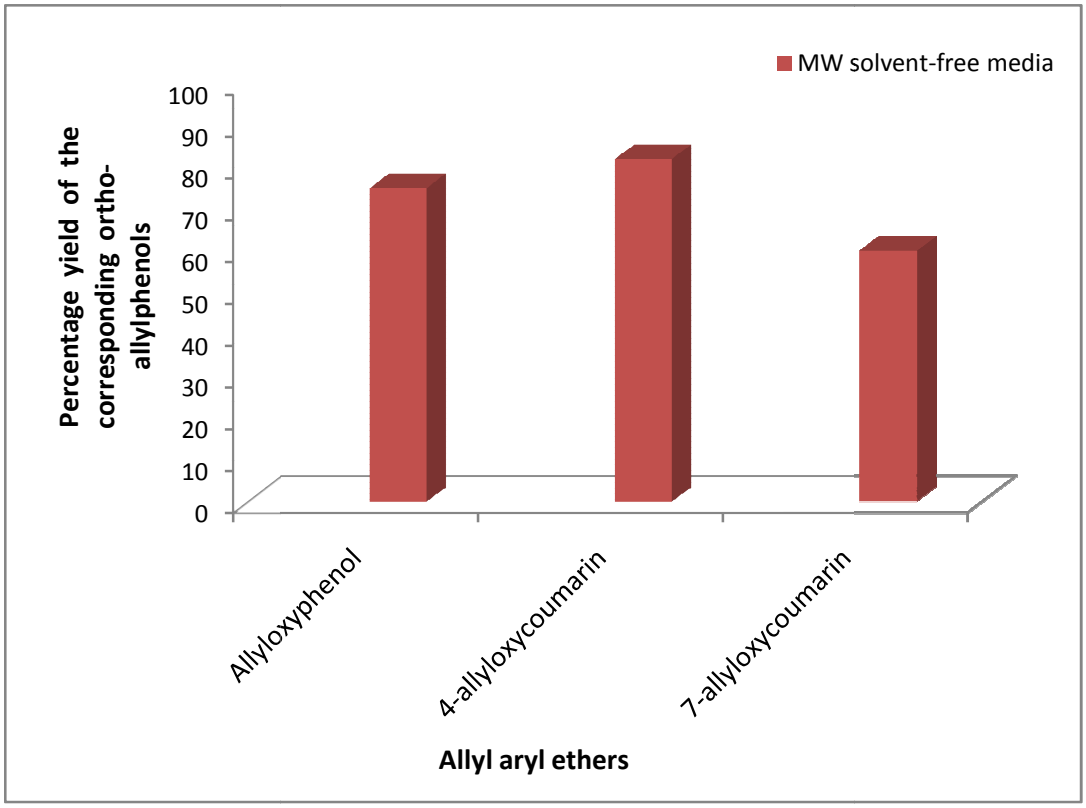


Figure 4.1: Plot of % yield of the corresponding *ortho*-allyl phenols vs allyl aryl ethers under microwave conditions.

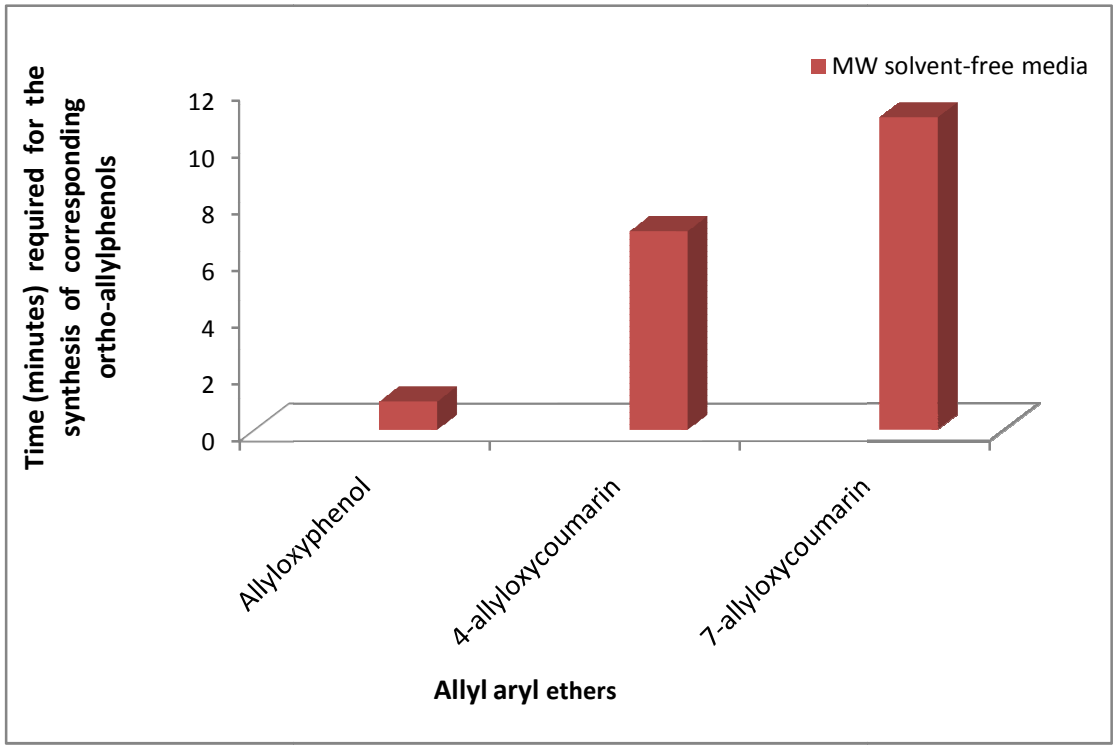


Figure 4.2: Plot of the time (in minutes) required for the synthesis of *ortho*-allyl phenols vs allyl aryl ethers under microwave conditions.

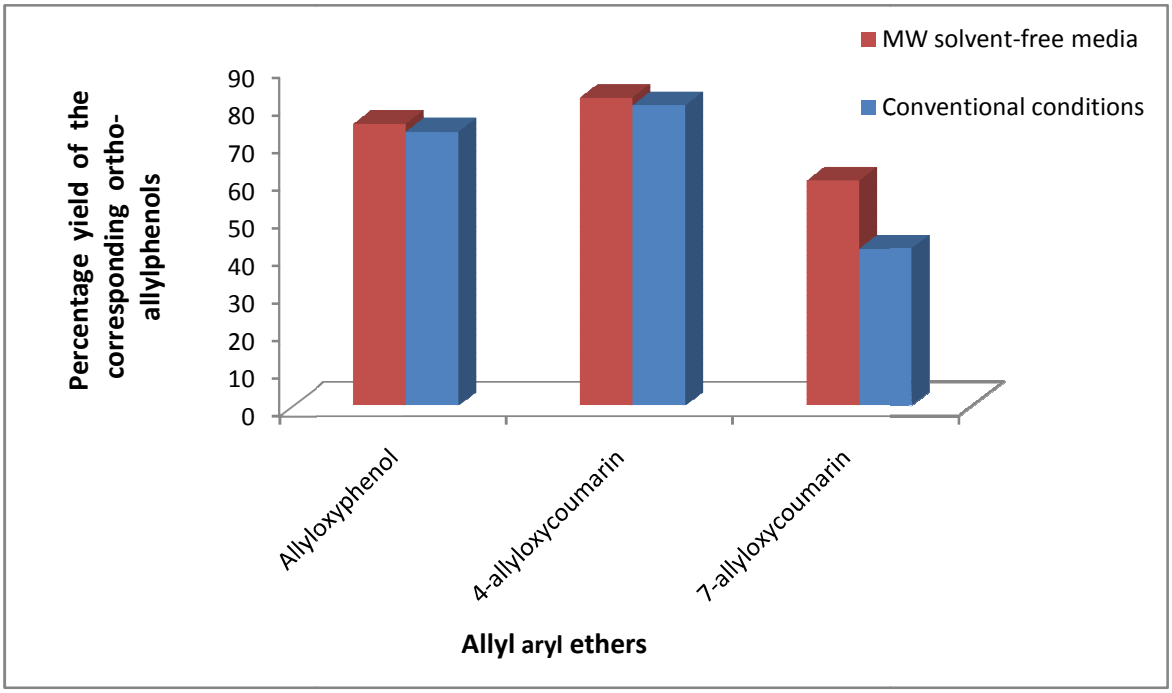


Figure 4.3: Clubbed graph showing the comparative account of % yield of the corresponding *ortho*-allyl phenols vs allyl aryl ethers under two different conditions.

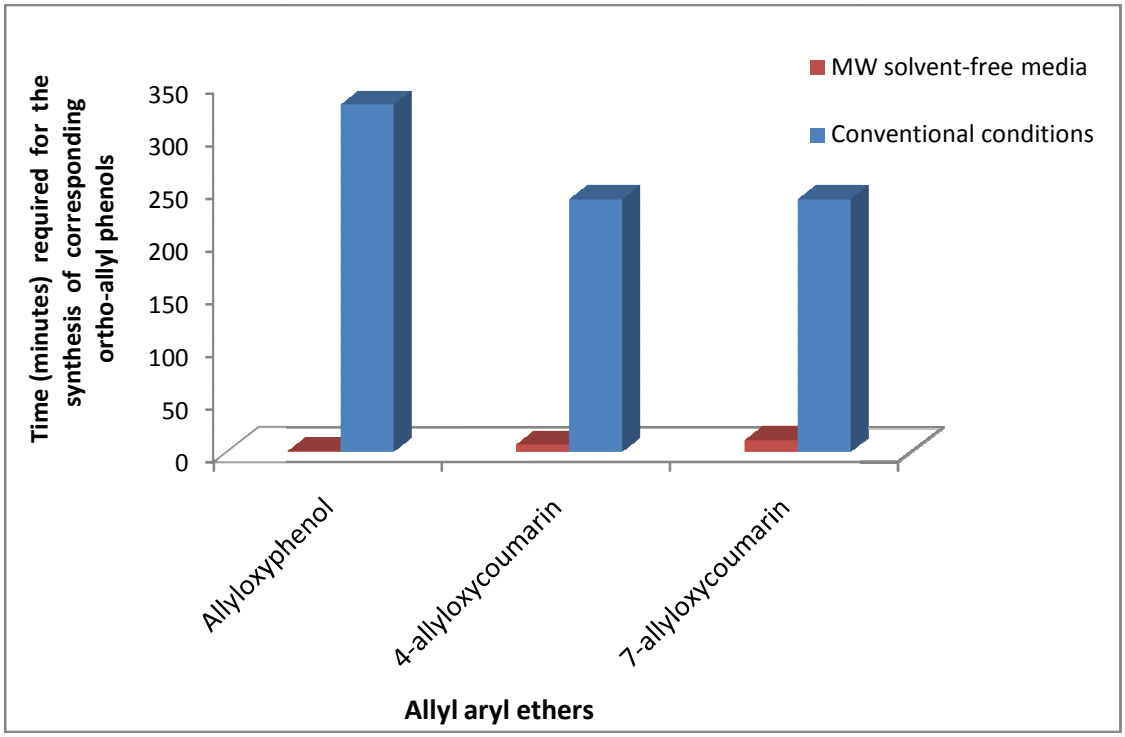


Figure 4.4: Clubbed graph showing the comparative account of time (in minutes) required for the synthesis of corresponding *ortho*-allyl phenols vs allyl aryl ethers under two different conditions.

Table 4.1: Synthesis of various allyl aryl ethers under conventional conditions.

S. No.	Substrate	Product	Room temperature	
			Time (hours)	% Yield
1	Phenol	Allyloxyphenol	8	71.52
2	4-hydroxycoumarin	4-allyloxycoumarin	20	56.45
3	7-hydroxycoumarin	7-allyloxycoumarin	16	76.00

Table 4.2: Comparison of % yield and time (in minutes) for Claisen rearrangement under microwave conditions with those reported in literature and carried out under thermal conditions

S. No.	Substrate	Product	Microwave		Literature data (Conventional)	
			Time (minutes)	% Yield	Time (minutes)	% Yield
1	Allyloxyphenol	2- allylphenol	1	75.00	330	73.00
2	4-allyloxycoumarin	3-allyl-4-hydroxycoumarin	7	82	240	80
3	7-allyloxycoumarin	8-allyl-7-hydroxycoumarin	11	60	240	41.81

4.4 General procedure for the synthesis of aryl allyl ethers

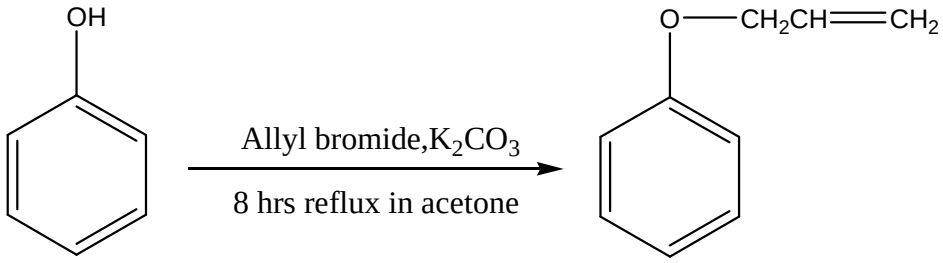
A mixture of phenolic compound, allyl bromide, anhydrous potassium carbonate in acetone were refluxed on the steam bath for the required time (**Table 4.1**). Work up of the mixture followed by crystallization using appropriate solvent gave the desired product.

4.4.1 Experimental

Melting points were taken in open capillaries using electrothermal method on a *Labotech/Perfit* instrument and are uncorrected. All the chemicals and solvents used were of AR grade.

4.4.1.1 Synthesis of allyl aryl ethers

1. Synthesis of Allyloxyphenol



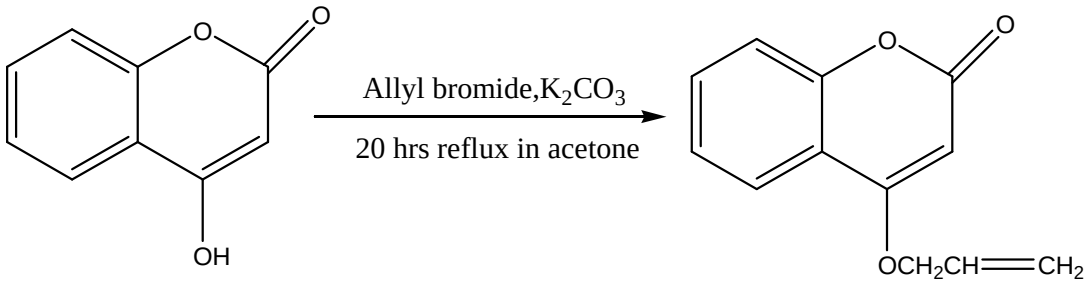
Phenol Allyloxyphenol

A mixture of 5gm of phenol, 4.5 ml of allyl bromide, 7.45gm of potassium carbonate in 10 ml of acetone were refluxed on the steam bath for 8 hours. A heavy precipitate of potassium bromide begins to form soon after the refluxing was started. After cooling, water was added, the product was taken up in ether and washed twice with 10% aqueous sodium hydroxide solution. Ethereal solution was again washed with water several times, dried on anhydrous sodium sulphate and solvent removed to get clear very light yellow coloured liquid having ethereal odour of allyloxyphenol

Boiling point = 192^{o}C

Yield= 5.10 gm

2. Synthesis of 4-allyloxycoumarin



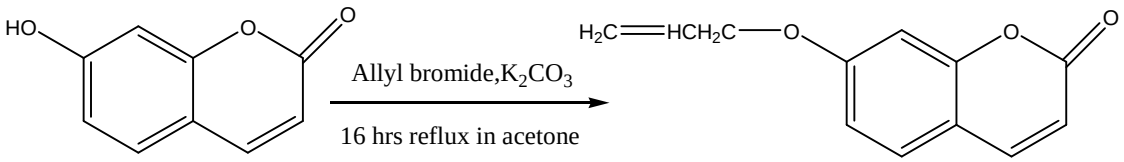
4-hydroxycoumarin 4-allyloxycoumarin

1 gm of 4-hydroxycoumarin was refluxed with 0.6 ml of allyl bromide, ~ 1 gm of anhydrous potassium carbonate in 10ml of dry acetone for 20 hours. Reaction mixture cooled and filtered. The acetone solution evaporated and residue obtained was washed with $NaHCO_3$, and then with water and dried. Crystallisation from petrol-benzene afforded white fluffy crystals of 4-allyloxycoumarin.

Melting point = 114-115.5^oC

Yield=0.70 gm

3. Synthesis of 7-allyloxycoumarin



7-hydroxycoumarin 7-allyloxycoumarin

To slurry of 2.35 gm of anhydrous potassium carbonate in 50 ml of acetone were added 0.6 gm of 7-hydroxycoumarin and 1.7 ml of allyl bromide. The resulting mixture was refluxed for 16 hours, then cooled and filtered. Solvent was evaporated and 50 ml of 5% aqueous ammonium hydroxide was added to precipitate the residue which on crystallization from petrol-benzene yielded light pink crystals of 7-allyloxycoumarin.

Melting point = 83-84^oC

Yield= 0.57 gm

4.5 General procedure for synthesis of *ortho*-allyl phenols via Claisen rearrangement under microwave conditions

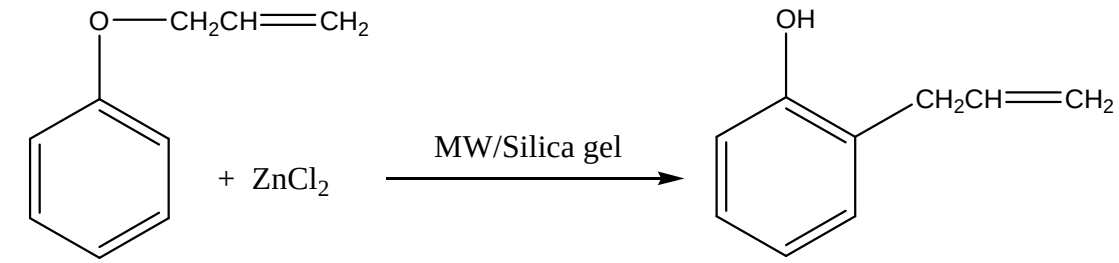
Allyl aryl ethers and $ZnCl_2$ in a definite ratio were adsorbed on silica gel (60-120 mesh) by grinding in a mortar and pestle and irradiated under microwave oven for the time indicated in **Table 4.2**. The mixture was then eluted with appropriate solvent and solvent removed to get the desired product.

4.5.1 Experimental

Melting points were taken in open capillaries using electrothermal method on a *Labotech/Perfit* instrument. Infrared spectra were recorded on a *Interspec-2020-FTIR* spectrometer. All solvents and chemicals used were of AR grade. All the reactions were carried out in a multimode *Sharp Carousel*^{TM} microwave oven. The products formed have been identified by a comparison of their spectra with those reported in the literature. Physical properties also agree in accordance with the data reported in the literature.

4.5.1.1 Reaction of Zinc Chloride with various allyl aryl ethers

1. Reaction with Allyloxyphenol



Allyloxyphenol 2-allyl phenol

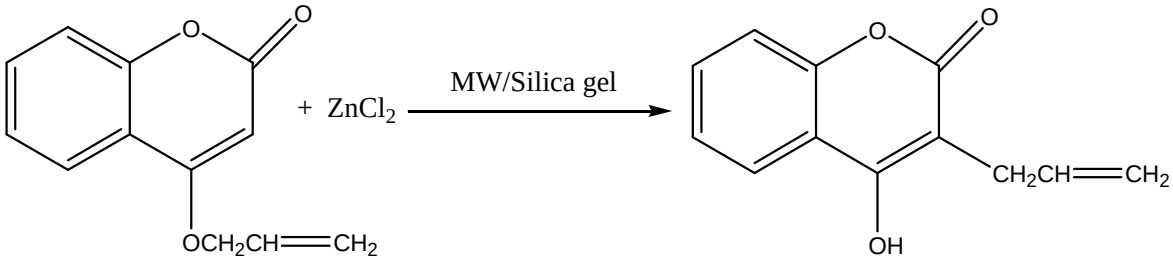
A mixture of 0.20 gm of allyloxyphenol and 0.15 gm of $ZnCl_2$ adsorbed on silica gel (60-120) by grinding in a mortar and pestle were irradiated in a microwave oven for 1 minute at medium power level at intervals of 30 seconds duration. TLC monitoring indicated the progress of reaction. After cooling the reaction mixture was eluted with chloroform and solvent removed to yield 2-allyl phenol.

Yield= 0.15gm

Spectral data: Boiling point = 220^{o}C

IR (KBr) cm^{-1}**:** 3500, 3020, 2925

2. Reaction with 4-allyloxycoumarin



4-allyloxycoumarin 3-allyl-4-hydroxycoumarin

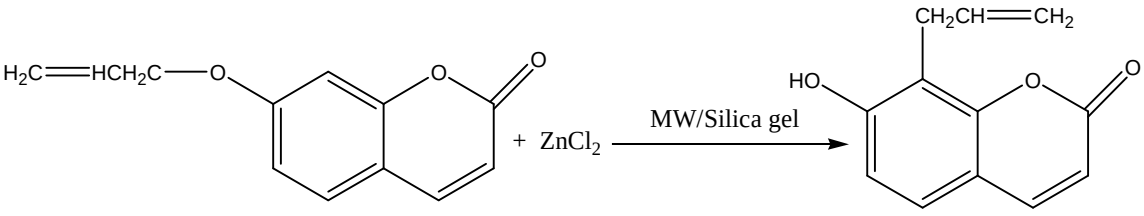
A mixture of 0.10gm of 4-allyloxycoumrin and 0.2 gm of $ZnCl_2$ adsorbed on silica gel (60-120) by grinding in a mortar and pestle were irradiated in a microwave oven for 7 minutes at high power level at intervals of 30 seconds duration. Progress of the reaction was monitored with tlc. After cooling, the reaction mixture was eluted with chloroform and solvent removed to yield 3-allyl-4-hydroxycoumarin. Solid obtained was crystallized from ethanol.

Yield= 0.07gm

Spectral data: Melting point = 132^{o}C

IR (KBr) cm^{-1}: 3373, 1716, 1623, 1248

3. Reaction with 7-allyloxycoumarin



7-allyloxycoumarin 8-allyl-7-hydroxycoumarin

A mixture of 0.10gm of 7-allyloxycoumrin and 0.4 gm of $ZnCl_2$ adsorbed on silica gel (60-120) by grinding in a mortar and pestle were irradiated in a microwave oven

for 11 minutes at high power level at intervals of 30 seconds duration. Progress of the reaction was monitored with tlc. The reaction mixture was cooled and eluted with chloroform and solvent removed to yield 8-allyl-7-hydroxycoumarin. Solid obtained was crystallized from ethanol. **Yield= 0.06gm**

Spectral data: Melting point = 162-163^{o}C

IR (KBr) cm^{-1}: 3332, 1724, 1613, 1125

4.6 Conclusions

A very simple and efficient $ZnCl_2$ catalysed Claisen rearrangement of allyl aryl ethers to *ortho*-allylated phenols have been developed. The products were obtained in minimum time and in good yields as compared to conventional procedures reported in the literature. Moreover, the usage of solvent-free conditions makes it an ecofriendly procedure.

1. Microwave Assisted Organic Synthesis proved to be known for the spectacular accelerations produced in many reactions as a consequence of heating rates that cannot be produced by classical heating.
2. Preparation of aromatic esters under microwave and thermal conditions and a comparative account made in terms of time and yield.
3. Synthesis of aromatic hydroxyketones has been achieved using acidic alumina and anhydrous Zinc Chloride mixed reagent system instead of strong and corrosive lewis acids such as aluminium chloride.
4. Synthesis of *ortho*-allyl phenols has been achieved using anhydrous Zinc Chloride which proved to be an alternative and efficient green tool as compared to the conventional procedures as reported in the literature.

LIST OF TABLES

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