Heterocyclic Synthesis By Microwave Techniques

The heterocycles are of immense importance not only both biologically and industrially but to the functioning of any developed human society as well. Their participation in a wide range of areas cannot be underestimated. The majority of pharmaceutical products that mimic natural products with biological activity are heterocycles. Most of the significant advances against disease have been made by designing and testing new structures, which are often hetero aromatic derivatives. In addition, a number of pesticides, antibiotics, alkaloids, and cardiac glycosides are heterocyclic natural products of significance for human and animal health. Therefore, researchers are on a continuous pursuit to design and produce better pharmaceuticals, pesticides, insecticides, rodenticides, and weed killers. A significant part of such biologically active compounds is composed of heterocycles. These compounds play a major part in biochemical processes and the side groups of the most typical and essential constituents of living cells. Organic chemists have been engaged in extensive efforts to produce these heterocyclic compounds by developing new and efficient synthetic transformations.

Dr. Kirti S. Niralwad is Assistant Professor and Head Department of Chemistry in the Nutan Mahavidyalaya, Sailu, Maharashtra. She received her Ph.D in Chemistry from Dr. B.A.M. University, Aurangabad. She has published 23 research papers (National & International with Impact Factor). she is Editor Board Member on different International Journals.

978-3-639-76180-1

Scholars' Press

Kirti Sadhurao Niralwad
Ishwar Baburao Ghorade

Heterocyclic Synthesis By Microwave Techniques

Kirti Sadhurao Niralwad
Ishwar Baburao Ghorade

Heterocyclic Synthesis By Microwave Techniques

Kirti Sadhurao Niralwad
Ishwar Baburao Ghorade

Heterocyclic Synthesis By Microwave Techniques

Scholar's Press

Impressum / Imprint
Bibliografische Information der Deutschen Nationalbibliothek: Die Deutsche Nationalbibliothek verzeichnet diese Publikation in der Deutschen Nationalbibliografie; detaillierte bibliografische Daten sind im Internet über http://dnb.d-nb.de abrufbar.

Bibliographic information published by the Deutsche Nationalbibliothek: The Deutsche Nationalbibliothek lists this publication in the Deutsche Nationalbibliografie; detailed bibliographic data are available in the Internet at http://dnb.d-nb.de.

Coverbild / Cover image: www.ingimage.com

Verlag / Publisher:
Scholar's Press
ist ein Imprint der / is a trademark of
OmniScriptum GmbH & Co. KG
Heinrich-Böcking-Str. 6-8, 66121 Saarbrücken, Deutschland / Germany
Email: info@scholars-press.com

Herstellung: siehe letzte Seite /
Printed at: see last page
ISBN: 978-3-639-76180-1

Zugl. / Approved by: Dr. Babasaheb Ambedkar Marathwada University, Aurangabad (M.S) INDIA., 2011.

SYNTHESIS OF SOME HETEROCYCLIC COMPOUNDS USING MICROWAVE-IRRADIATION TECHNIQUES

Dr. Kirti Sadhurao Niralwad (M.Sc., Ph.D)

Assistant Professor and Head

Department of Chemistry,

Nutan Mahavidyalaya,

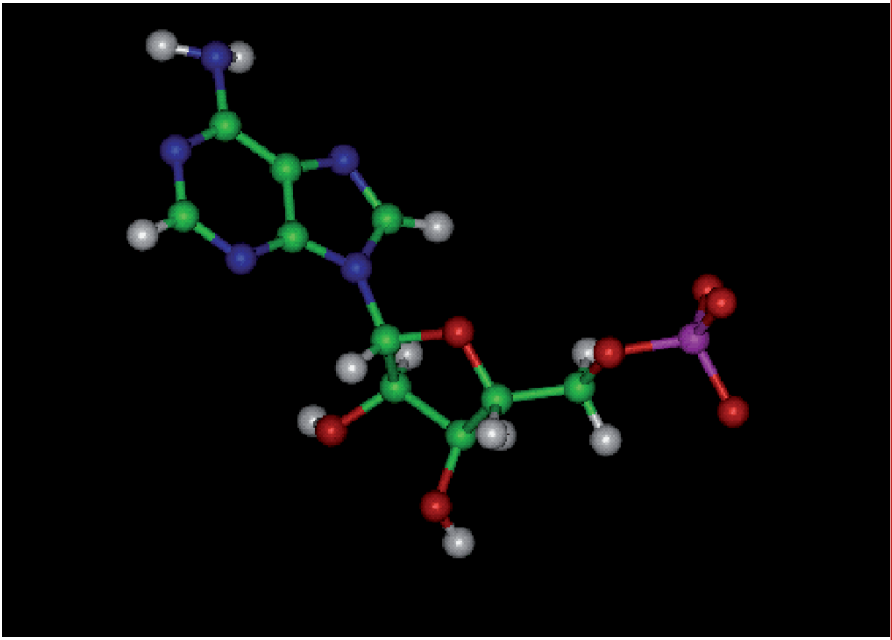
Sailu, India

Dr. Ishwar Baburao Ghorade (M.Sc., Ph.D)

Assistant Professor

Government College of Engineering

Aurangabad, India.



Dedicated to my Parents

CHAPTER-I

GENERAL INTRODUCTION

HETEROCYCLIC COMPOUNDS:-

Compounds classified as heterocyclic probably constitute the largest and most varied family of organic compounds. After all, every carbocyclic compound, regardless of structure and functionality, may in principle be converted into a collection of heterocyclic analogs by replacing one or more of the ring carbon atoms with a different element. Even if we restrict our consideration to oxygen, nitrogen and sulfur (the most common heterocyclic elements), the permutations and combinations of such a replacement are numerous.

Moreover, heterocycles are of immense importance not only both biologically and industrially but to the functioning of any developed human society as well. Their participation in a wide range of areas cannot be underestimated. The majority of pharmaceutical products that mimic natural products with biological activity are heterocycles. Most of the significant advances against disease have been made by designing and testing new structures, which are often hetero aromatic derivatives. In addition, a number of pesticides, antibiotics, alkaloids, and cardiac glycosides are heterocyclic natural products of significance for human and animal health. Therefore, researchers are on a continuous pursuit to design and produce better pharmaceuticals, pesticides, insecticides, rodenticides, and weed killers by following natural models. A significant part of such biologically active compounds is composed of heterocycles. These compounds play a major part in biochemical processes and the side groups of the most typical and essential constituents of living cells. Organic chemists have been engaged in extensive efforts to produce these heterocyclic compounds by developing new and efficient synthetic transformations. Among the new synthetic transformations, cyclocondensation reactions are among the most attractive methodologies for synthesizing heterocyclic compounds.[1,2] In the past, most of the reactions have been heated using traditional heat transfer equipment such as oil baths, sand baths and heating jackets. These heating techniques are however, rather slow and

temperature gradient can develop within the sample. In addition overheating can lead to product, substrate and reagent decomposition.

Microwave Irradiation Technique:-

In the past few years there has been growing attention on the use of microwave heating in organic synthesis since the first contributions by Gedye and Giguere in 1986.[3,4] It has several advantages over conventional technology such as remarkable decrease in the time necessary to carry out reactions, improved isolated yields of products and sometimes remarkable effects on chemo-, regioand stereoselectivity. It also appears that microwaves have a specific 'microwave effect' that lowers the activation energy of a reaction. Thus, microwave mediated organic reactions take place more rapidly, safely, environmentally friendly and with high yields.

The first application of microwave energy in organic synthesis is the aqueous emulsion polymerization of butyl acrylate, acrylic acid and methacrylic acid using pulsed electromagnetic radiation.[3] After that, several groups have demonstrated that chemical synthesis may be dramatically accelerated using MW irradiation. The superheating conditions caused by this kind of heating, lead directly to acceleration in the reaction times compared with conventional reflux conditions.

Microwave irradiation takes a particular place being an emerging technique that provides an alternative to conventional heating for introducing energy into

chemical reactions by using the ability of some liquids and solids to transform electromagnetic energy into heat. With microwaves, the heating is created in the interior of the sample and is then radiated outward. This is contrast with conventional heating, where the heat is generated in the outer region and directed towards the center.

In a MW oven, microwaves are generated by a magnetron[5] was designed by Randall and Booth at the University of Birmingham as part of the development of RADAR during the Second World War.

Microwaves form a part of the electromagnetic spectrum with the wavelength lying between 1 cm and 1 m. In order to avoid interference with radar and telecommunication activities, which also operate in this region, most commercial and domestic microwave ovens operate at 2450 MHz (12.25cm). The difference between microwave energy and other forms of radiation, such as X- and Y-rays, is that microwave energy is non-ionizing and therefore does not alter the molecular structure of the compounds being heated-it provides only thermal activation.

Microwave Synthesis on Solid Supports

Microwave heating for carrying out reactions on solids has also attracted considerable attention in recent years. For such 'dry media' reactions, solid supports such as alumina, silica and bentonite, montmorillonite clays and zeolites have been investigated. Although this technique seems best suited to transformations involving a single organic species, condensation reactions have also been reported.

In many cases microwave mediated reactions can also be done in the complete absence of solvents! Therefore, toxic and expensive organic solvents can be avoided for carrying out many organic reactions. Such reactions not only reduce the amount of waste solvent generated, but the products often need very little purification. These processes will hopefully be adapted by big industries and will therefore reduce the pollution of the environment.

***Advantages of MW Heating*[6].**

- Very fast heating
- *Absence of inertia:* only the reaction contents are heated, not the reaction vessel.
- Easy to use, power regulator is easy with instantaneous on and off.
- Better homogeneity in temperature with quick transfer of energy in the whole mass without superficial heating.
- The selective heating of polar molecules.
- Decrease in reaction time.
- Improved conversions.
- Clean product formation and wide scope for the development of new reaction conditions.
- Microwave chemistry is becoming increasingly popular both in industry and in academia. The future for the application of microwave technology looks bright because of its efficiency and its potential to contribute to clean products.

Multicomponent Reactions:-

In chemistry, a multi-component reaction (or MCR) is a chemical reaction where three or more compounds react to form a single product.[7] By definition, multicomponent reactions are those reactions whereby more than two reactants combine in a sequential manner to give highly selective products that retain majority of the atoms of the starting material.

Multicomponent reactions have been known for over 150 years. The first documented multicomponent reaction was the Strecker synthesis of α-amino cyanides in 1850 from which α-amino acids could be derived.

In MCR, a product is assembled according to a cascade of elementary chemical reactions. Thus, there is a network of reaction equilibria, which all finally flow into an irreversible step yielding the product. The challenge is to conduct an

MCR in such a way that the network of pre-equilibrated reactions channel into the main product and do not yield side products. The result is clearly dependent on the reaction conditions: solvent, temperature, catalyst, concentration, the kind of starting materials and functional groups. Such considerations are of particular importance in connection with the design and discovery of novel MCRs.[8]

New MCR's are found by building a chemical library from combinatorial chemistry or by combining existing MCR's.[9] For example, a seven component MCR results from combining the Ugi reaction with the Asinger reaction.[10] MCR's are an important tool in new drug discovery.

CHAPTER –II

SYNTHESIS OF OCTAHYDROQUINAZOLINONE DERIVATIVES USING AMMONIUM METAVANADATE (NH_4VO_3) AS A CATALYST

INTRODUCTION:-

In recent years, the Biginelli reaction has been employed for the synthesis of octahydroquinazolinones, which used cyclic β-diketones instead of open-chain dicarbonyl compounds. These octahydroquinazolinone derivatives have attracted considerable attention since they exhibit potent antibacterial activity against staphylococcus aureus, escherichia coli, pseudomonas aeruginosa[11] and have calcium antagonist activity.[12,13]

Several methods have been developed for the preparation of quinazolinone derivatives. These routes usually involved reaction of aldehydes with $SOCl_2$ and pyridine, then with 2-aminobenzylamine in a refluxing solvent such as benzene or xylene with azeotropic water removal,[14] refluxing in ethanol/acetic acid mixture[15] and by reaction in alkali media.

There are very few reports for the synthesis of octahydroquinazolinone derivatives using catalysts such as TMSCl,[16] Nafion-H,[17] Conc. H_2SO_4[18] and ionic liquid.[9] Octahydroquinazolinone derivatives are also synthesized in absolute ethanol but with low yields of products (19-69%).[12] However, many of these procedures suffer from one or more disadvantages such as harsh reaction conditions, prolonged time period, poor yields, use of hazardous and expensive catalysts. So the development of a clean, high-yielding and environmentally friendly approach is still desirable. The use of ammonium metavanadate (NH_4VO_3) as an inorganic acid[20] meets the demand for an economic catalyst. It is employed similar to vanadium pentoxide[21] and as a catalyst in oxidation reactions with other cocatalysts.[22] It is a reagent used in analytical chemistry, the photographic industry and the textile industry.[21] Gill and coworkers reported the synthesis of benzimidazole[23] and coumarin[24] in the presence of ammonium metavanadate. Very recently, we have reported the synthesis of α-hydroxyphosphonates[25] and α-aminophosphonates[26] using ammonium metavanadate as a catalyst in good yields.

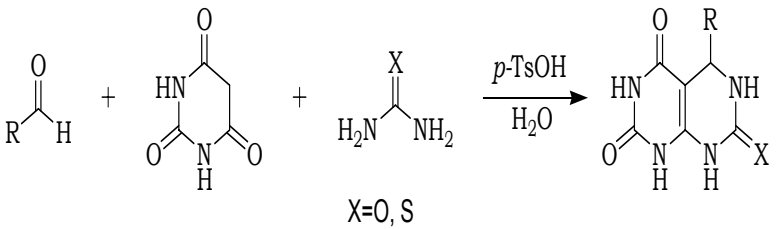
During the last few years, 'non-classical' methods have been developed in organic synthesis in order to improve both yields, selectivity and experimental conditions.[27] Especially the use of microwave technology in conjunction with the use of solvent-free conditions allows expeditious and efficient procedures in organic synthesis.[28-31] However, great interest has been focused recently on "dry media" synthesis using inorganic solid supports under microwave-irradiation. The coupling of a microwave heating mode with the use of solid acid has allowed the synthesis of several organic compounds, with higher purity of products and very simplified ease of manipulation and work-up. They clearly constitute an eco-friendly 'green' approach.[32]

Literature survey reveals that a number of octahydroquinazolinone derivatives have been synthesized by Biginelli reaction conditions using various aldehydes but not a single reference have been found where microwave–irradiation has been used

.

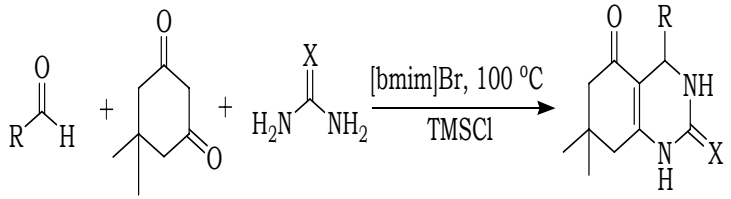
Literature Review of Octahydroquinazolinone Derivatives:-

Bin et *al.* developed[33] a simple, efficient and green procedure for the synthesis of octahydroquinazolinone derivatives by Biginelli-type three-component cyclocondensation reactions of cyclic β-diketones, aldehydes and (thio)urea with *p*-TsOH catalysis in water (**Scheme 1**).



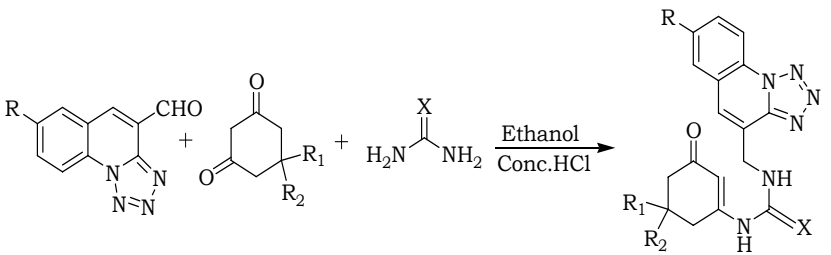
Scheme 1

Kumar et *al.* have reported[34] an easy and efficient protocol for the synthesis of octahydroquinazolinones in the ionic liquids [bmim]Br with 78-94% yield (**Scheme 2**).



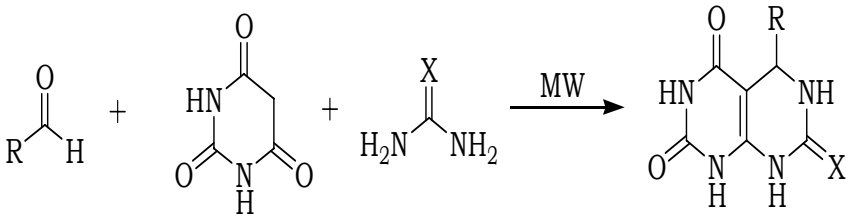
Scheme 2

Patel et *al.* have synthesized[35] some new octahydroquinazolinones by the reaction between corresponding tetrazolo [1,5-a]quinoline-4-carbaldehyde, dimedone or cyclohexane-1, 3-dione and urea in the presence of concentrated HCl in ethanol (**Scheme 3**).



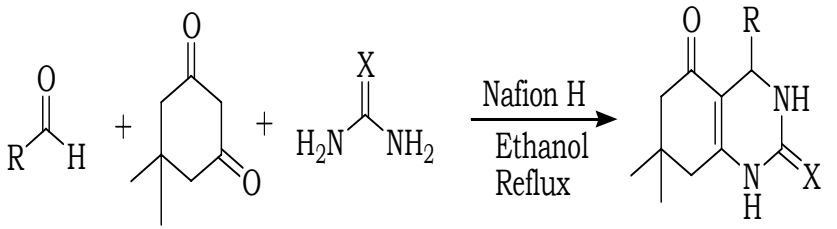
Scheme 3

Shingare et *al.* have synthesized[36] pyrimido [4,5d]pyrimidine derivatives by using an efficient, facile and solvent free procedure. Here, a non conventional synthetic procedure has been developed where solid support of alumina is used as energy transfer medium under microwave irradiation (**Scheme 4**).



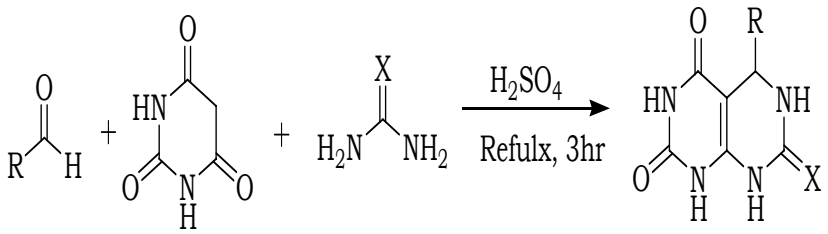
Scheme 4

Lin et *al.* described1[7] Nafion-H catalyzed multicomponent reaction for synthesis of octahydroquinazolinone derivatives with 72-88% yield (**Scheme 5**).



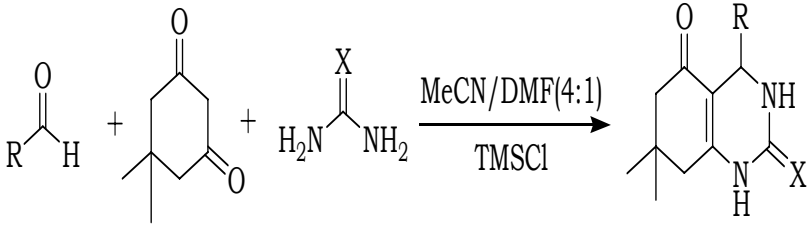
Scheme 5

Islami and co-workers have synthesized[18] octahydroquinazolinone according to the Biginelli reaction using 5,5-dimethyl-1,3 cyclohexanedione, urea or thiourea and appropriate aromatic aldehydes in the presence of two drops of concentrated H_2SO_4 as a catalyst is described in water (**Scheme 6**).



Scheme 6

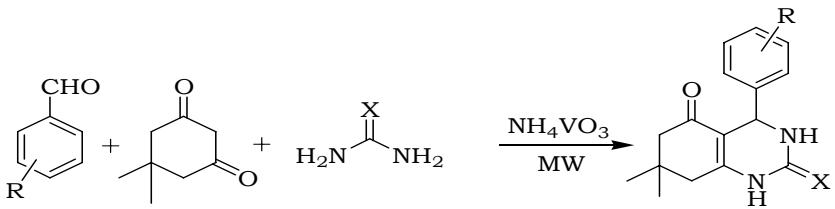
Kantevari et *al.* described[16] a simple, efficient and cost-effective method for the synthesis of octahydroquinazolinone derivatives by a one-pot cyclocondensation of dimedone and aldehydes, with and without urea or thiourea respectively in the presence of trimethylsilyl chloride (TMSCl) in MeCN/DMF which gives 71-95% yield (**Scheme 7**).



Scheme 7

Present Work:-

In present work we described the one-pot three component synthesis of octahydroquinazolinone derivatives from aromatic aldehydes, dimedone and urea/thiourea using ammonium metavanadate as a catalyst under microwave-irradiation gives excellent yield **4**(**a-l**).



1(a-l) **2** **3** **4(a-l)**

X=O, S

Scheme I

Experimental:-

General Procedure

A mixture of aromatic aldehydes **1**(**a-l**) (1 mmol), dimedone **2** (1 mmol) urea/thiourea **3** (1.5 mmol) and ammonium metavanadate (10 mol%) was mixed properly with the help of glass rod and irradiated in a microwave oven at 360 W, as time indicated in Table 4. The progress of the reaction was monitored by TLC (ethyl acetate: hexane, 7:3). After completion of the reaction, the reaction mixture was cooled and dichloromethane (25 mL) was added. Organic solvent was evaporated under reduced pressure and solid compound was crystallized from absolute ethanol to afford the pure corresponding octahydroquinazolinone derivatives **4(a-l)** in excellent yields. All the products were characterized from their spectral data.

Results and Discussion:-

In continuation of our research work of developing methods in various organic transformations, we have developed a methodology for the synthesis of octahydroquinazolinone derivatives using ammonium metavanadate, which makes use of mild catalyst under microwave-irradiation and solvent-free conditions (**Scheme 1**).

The reaction of benzaldehyde (**1a**), dimedone (**2**) and urea (**3**) catalyzed by ammonium metavanadate under solvent-free conditions and microve-irradiation, has been considered as a standard model reaction.

We also screened a number of different catalysts on the model reaction. When the reaction was carried out in the presence of KH_2PO_4, alum, acidic alumina, amberlite-IR 120, sulphamic acid, cellulose sulfuric acid under microwave-irradiation it gave lower yield of product even after prolonged reaction time. However, when the same reactions was conducted under microwave irradiation using ammonium metavanadate as a catalyst it gave excellent yields of product in short reaction time (Table 1, entry 6).

We have studied the catalyst concentration on model reaction. We have varied the concentration of catalyst to 5, 7, 10, and 12 mol%. The results revealed that, when the reaction was carried out in the presence of 5 and 7 mol% of catalyst it gave lower yield of product even after prolonged reaction time. At the same time when the concentration of catalyst was 10 mol% we got excellent yields of product in a short span. Even after increasing the catalyst concentration at 12 mol%, the yields of the products were found to be constant. So, the use of 10 mol% of catalyst appears to be optimal. The results obtained are summarized in (Table 2).

Moreover, we investigated the effect of different microwave power settings such as 180, 360, 540 and 720 W. It was observed that, the irradiation at low power required longer time and at high power suffered from lower yield. This indicates the irradiation at 360 W gives better result (Table 3, entry 2).

After optimizing the conditions, the generality of this method was examined by the reaction of several substituted aldehydes, dimedone and urea/thiourea using ammonium metavanadate as a catalyst under microwave-irradiation, the results are shown in Table 4. We have carried out the similar reaction with various aromatic aldehydes containing electron donating or electron withdrawing functional groups at different positions but it did not show any remarkable differences in the yields of product and reaction time. It was observed

that the reaction of aromatic aldehydes with urea is very fast as compared to thiourea. The results obtained in the current method are illustrated in Table 4.

The role of NH_4VO_3 has been proposed to activate the aldehyde by binding the oxygen atom of aldehyde with vacant'd' orbital of transition metal vanadium to achieve the stable oxidation state, Along with this we recovered the catalyst and reused for further reactions.[37]

Table 1. Screening of Catalysts on the Model Reaction[a]

Entry	Catalysts	Time (min)	Yield[b] (%)
1	KH_2PO_4	15	20
1	Alum	15	65
2	Acidic alumina	15	52
3	Amberlite IR-120	15	68
4	Sulphamic acid	15	54
5	Cellulose sulfuric acid	15	63
6	Ammonium metavanadate	15	94

[a]Reaction of benzaldehyde, dimedone and urea in presence of ammonium metavanadate under microwave-irradiation and solvent-free condition. [b]Isolated yield.

Table 2. Effect of Catalyst Concentration on Model Reaction[a]

Entry	Catalyst (mol%)	Yield[a] (%)
1	5	52
2	7	65
3	10	94
4	12	94

[a]Reaction of benzaldehyde, dimedone and urea in presence of ammonium metavanadate under microwave-irradiation and solvent-free condition. [b]Isolated yield.

Table 3. Effect of Microwave Irradiation Powers for Synthesis of Octahydroquinazolinone Derivaties **4a**[a]

Entry	Power (W)	Time (sec)	Yield (%)[b]
1	180	70	87
2	360	50	94
3	540	40	86
4	720	30	82

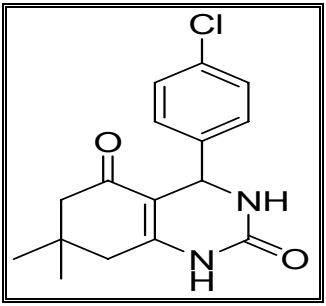
[a] (1 mmol) was treated with dimedone (1 mmol) and urea (1.5 mmol) in presence of ammonium metavanadate (10 mol %) under microwave irradiation. [b]Isolated yield.

Table 4. Synthesis of Octahydroquinazolinone Derivatives Catalyzed by Ammonium Metavanadate Under Microwave-Irradiation[a].

Entry	R-CHO	X	Time (min)	Yield[b] (%)	M.p (°C)
4a	H	O	6	94	290-293
4b	4-Cl	O	5	92	>300
4c	3-OMe, 4-OH	O	8	88	193-195
4d	3-NO_2	O	7	92	298-299
4e	3-OMe	O	8	86	248-249
4f	3-Cl	O	7	85	282-284
4g	4- NO_2	O	5	93	302-304
4h	4-F	O	7	90	134-136
4i	H	S	10	87	283-285
4j	4-OMe	S	12	83	275-276
4k	3-Cl	S	10	85	275-276
4l	4-Br	S	11	86	286-288

[a]Reaction Condition: **1 (a-l)** (1 mmol), **2** (1 mmol), **3** (1.5 mmol) ammonium metavanadate (10 mol%), under microwave-irradiation. [b]Isolated yield. All the products obtained were fully characterized by spectroscopic methods such as, ^{1}H NMR and mass spectroscopy and also comprised with the reference compounds.[16.]

Spectral Data:-



4-(4-chlorophenyl)-3,4,7,8-tetrahydro-7,7-dimethylquinazoline-2,5(1*H*,6*H*)-dione (4b)

^{1}H NMR Spectra:

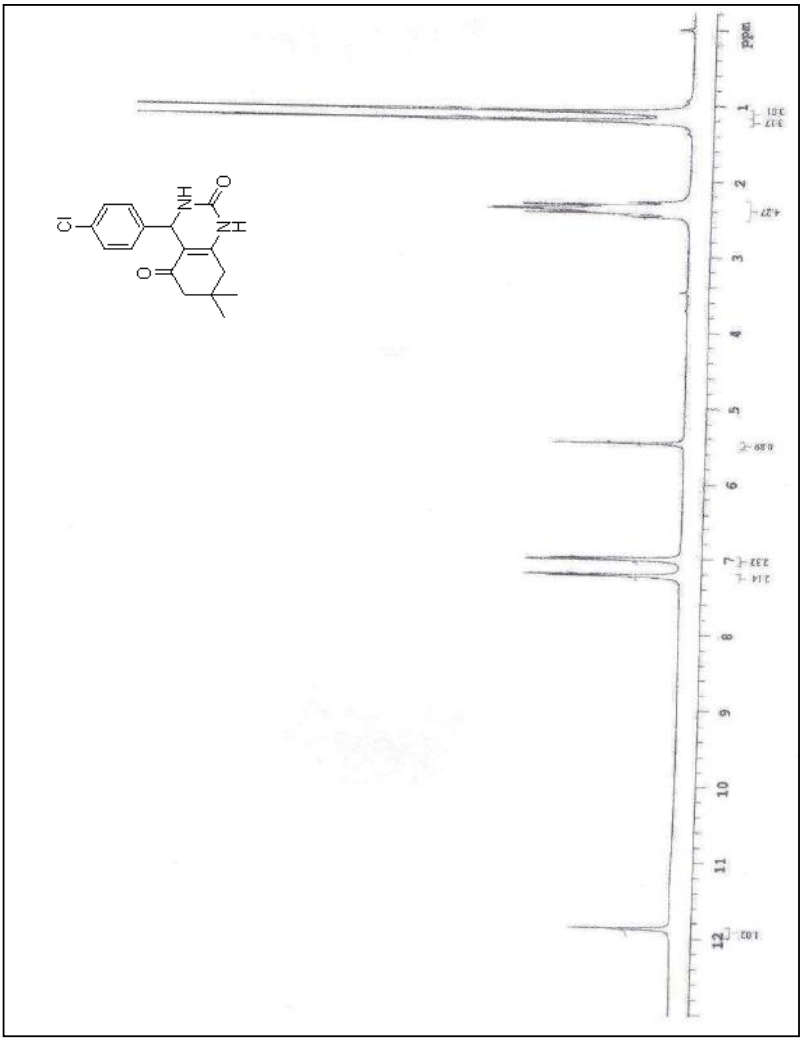
^{1}H NMR spectrum of compound **4b** showed following characteristic signals.

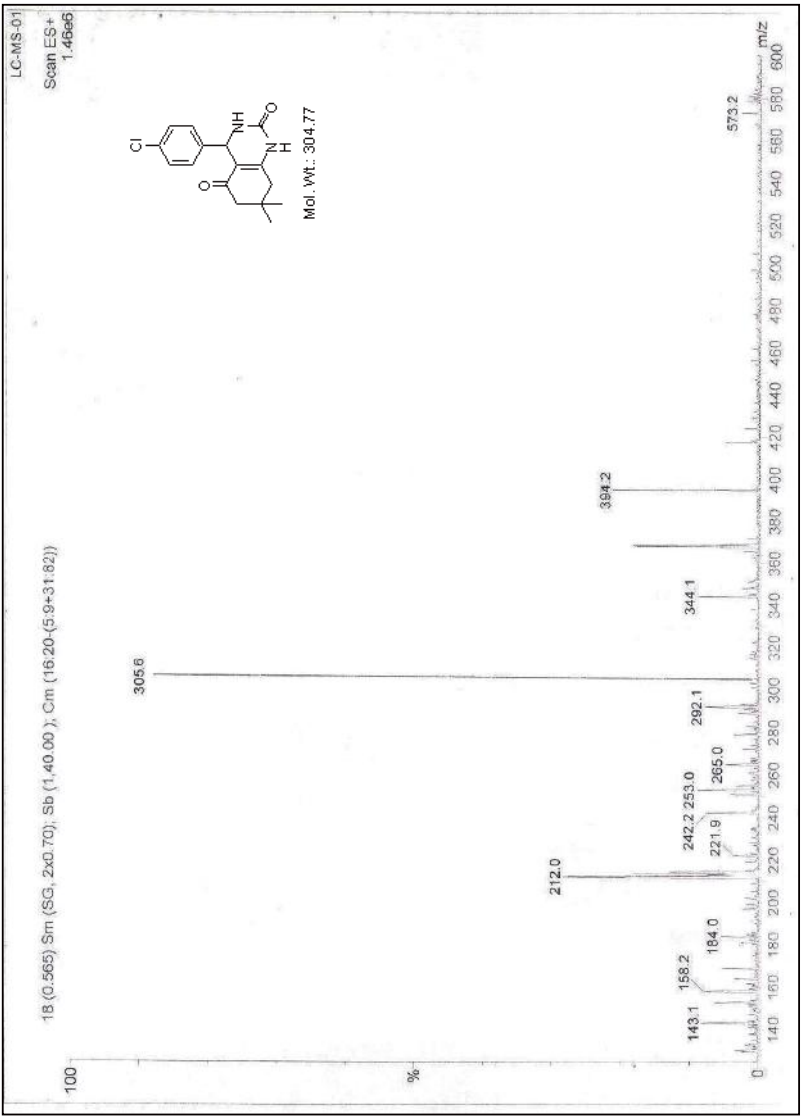
1.2	singlet	6H	due to -CH_3
2.4	singlet	4H	due to CH_2
5.5	singlet	1H	due to –CH
7.0-7.2	doublet	4H	due to Ar-H
11.9	singlet	2H	due to -NH

Mass Spectra:

The mass spectrum of compound **4b** showed following signals.

m/z: 305.6 (M+1).




LC-MS-01
Scan ES+
1.46e6
18 (0.565) Sm (SG, 2x0.70); Sb (1.40.00); Cm (16.20-(5.9+31.82))
100
%
0
Cl
NH
O
N
H
O
Mol. Wt.: 304.77
305.6
212.0
394.2
344.1
573.2
292.1
265.0
253.0
242.2
221.9
184.0
158.2
143.1
140 160 180 200 220 240 260 280 300 320 340 360 380 400 420 440 460 480 500 520 540 560 580 600 m/z

Conclusions:-

In conclusion, ammonium metavanadate (NH_4VO_3) is a readily available, inexpensive and efficient catalyst for the synthesis of octahydroquinazolinone derivatives. The advantages offered by this method are solvent-free reaction conditions, short reaction times, ease of product isolation, and high yields. We believe that this method is a useful addition to the present methodology for the synthesis of octahydroquinazolinone derivatives.

CHAPTER -III

SOLID-PHASE SYNTHESIS OF 2-ARYLBENZOTHIAZOLE USING SILICA SULFURIC ACID UNDER MICROWAVE IRRADIATION

INTRODUCTION:-

Benzothiazole and their derivatives are very important groups of heterocyclic compounds[38] and are well known for their biological and pharmaceutical activities, such as antimicrobial,[39] antiglutamate/antiparkinsonism agents[40] and antitumour,[41] which exhibit nanomolar inhibitory activity against a range of human breast, ovarian, colon and renal cell lines in vitro. In addition, they represent one of the most promising antiamyloid therapies for treatment of a number of a heterogeneous family of diseases referred to generically as amyloidosis, including Alzheimer's disease (AD), type II diabetes, variant Creutzfeldt-Jakob disease, painful joints associated with long term hemodialysis and rare cases of hereditary insomnia.[42,43]

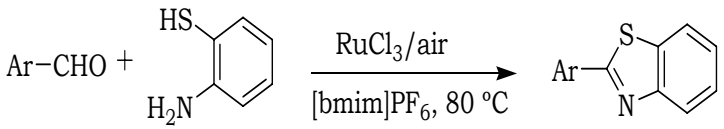
In general, benzothiazoles are synthesized by condensation of 2-aminothiophenol with carboxylic acid derivatives,[44] the base induced cyclization of the corresponding 2 haloanilides,[45] or the radical cyclization of thioacylbenzanilides.[46] On the other hand, the most general synthetic approaches for 2-aryl benzothiazoles involves: (i) arylation of benzothiazole with aryl bromides at 150 °C in a sealed tube catalyzed by $Pd(OAc)_2$, Cs_2CO_3 and CuBr with t-Bu_3P as ligand,[47] or Suzuki biaryl-coupling of 2-bromobenzothiazole with aryl boronic acids,[48] (ii) oxidative cyclisation of phenolic schiff's bases derived from the condensation of 2-aminothiophenols and aldehydes using various oxidants such as $Sc(OTf)_3$ using molecular oxygen,[49] pyridinium chlorochromate[50] and very recently via electrooxidation,[51] a modification of such strategy that involves flash vacuum pyrolysis and photolysis of 2-methylthio-N (arenylidene)anilines has been reported,[52] (iii) condensation of 2-aminothiophenols with carboxylic acids under microwave irradiation[53] or with polymer-bound esters in the presence of a Lewis acid,[54] (iv) direct condensation of 2-aminothiophenol with aromatic aldehydes,[55,56] under microwave-irradiation.[57-59] However, most of these synthetic approaches suffer from drawbacks such as harsh reaction conditions, lengthy procedures, expensive catalysts which may be harmful to the environment. As a consequence, the introductions of new methods to overcome the limitations are still an important challenge.

The science of green chemistry is developed to meet the increasing demand of environmentally benign chemical processes. The application of microwaves (MWs), as an efficient heating source for organic reactions and it has been reported in the literature.[60] The main advantages of MW irradiation usage were: very short reaction time and the solvent less procedures which are eco-friendly.[61,62] To the best of our knowledge MW irradiation has been mostly reported as a heating technique particularly for low molecular weight compound chemical modifications.

Recently, it is shown that the use of solid acidic catalysts has gained importance in organic synthesis due to several advantages such as, operational simplicity, no toxicity, reusability and ease of isolation after completion of the reaction. Silica sulfuric acid has emerged as an efficient heterogeneous catalyst in which sulfuric acid is immobilized on the surface of silica gel *via* covalent bond has the prospect to be used as a substitute for sulfuric acid. The use of silica sulfuric acid as a catalyst that meets the demand for various chemical transformations such as synthesis of thionitrites,[63] synthesis of Beckmann rearrangement,[64] deprotection of acetals[65] and sulfonation of aromatic rings.[66] Owing to the numerous advantages associated with this cheap and non hazardous catalyst, we have considered silica sulfuric acid to be an ideal heterogeneous acid catalyst for the synthesis of 2-arylbenzothiazole. Herein, we would like to report the facile and ecofriendly methodology for the synthesis of 2-arylbenzothiazole.

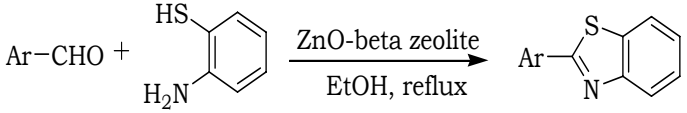
Literature Review of 2-Arylbenzothiazole:-

Fan et *al.* have developed[67]an efficient, practical and environmentally benign method for the synthesis of 2-substituted benzothiazoles through $RuCl_3$-catalyzed oxidative condensation of 2-aminothiophenol with aldehyde in ionic liquid by using air as the oxidant (**Scheme 1**).



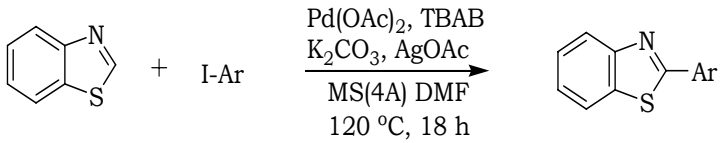
Scheme 1

Lande et *al.* synthesized[68] benzothiazole derivatives with a cheap and recyclable ZnO-beta zeolite as catalyst which gives 86-93% yields (**Scheme 2**).



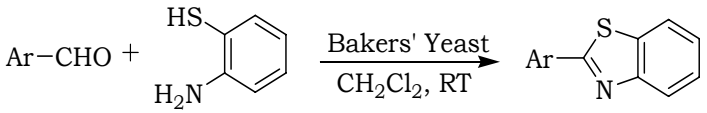
Scheme 2

Ranu et *al.* generated[69] Palladium nanoparticles, as an efficient catalyst for direct 2-C–H arylation of benzothiazole without requirement of any ligand. A wide range of substituted aryl and heteroaryl iodides participate in this reaction producing a series of 2-aryl/heteroaryl-benzothiazoles in high yields (**Scheme 3**).



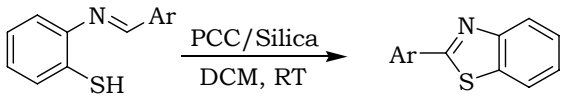
Scheme 3

Mane and coworkers carried out[70] the cyclocondensation of 2-aminothiophenol and aldehydes in dichloromethane using bakers' yeast as a catalyst for obtaining 2-aryl/heteryl benzothiazoles in good yields 51-84% (**Scheme 4**).



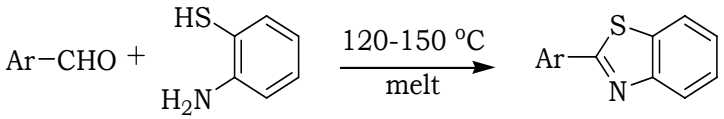
Scheme 4

Perumal et *al.* providing[71] an efficient and convenient method for the synthesis of 2-arylbenzothiazoles using pyridinium chlorochromate (PCC) supported on silica gel effects the oxidative cyclization of structurally diverse thiophenolic Schiff's bases (**Scheme 5**).



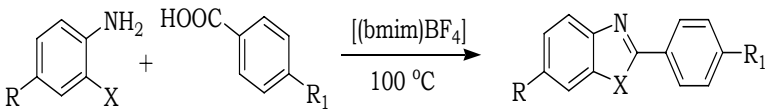
Scheme 5

Naimi-jamal et *al.* have prepared[55b] variety of 2-arylbenzothiazoles by the melt reaction of 2-aminothiophenol and aryl aldehydes under oxygen atmosphere. No further oxidative reagent is needed (**Scheme 6**).



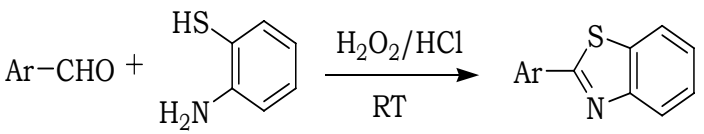
Scheme 6

Chandramouli et *al.* have synthesized[72] benzthiazoles by condensing a variety of carboxylic acids with 2-aminothiophenol under ambient conditions using the ionic liquid 1-butyl 3-methyl imidazolium tetraflouroborate [(bmim)BF_4] at higher temperatures in excellent yields (**Scheme 7**).



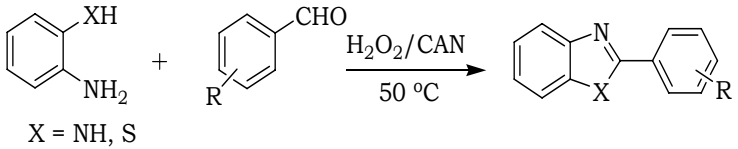
Scheme 7

Guo et *al.* have described[73] a simple and efficient procedure for the synthesis of substituted benzothiazoles through condensation of 2-aminothiophenol with aromatic aldehydes in the presence of H_2O_2/HCl system in ethanol at room temperature (**Scheme 8**).



Scheme 8

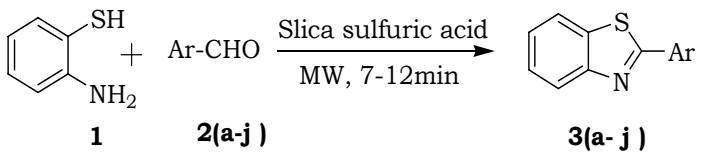
Bahrami and co-workers has described[74] the solvent-free synthesis of 2-arylbenzimidazoles and 2-arylbenzthiazoles from aldehydes and 1,2-phenylendiamine/2-aminothiophenol in the presence of H_2O_2/CAN at 50 °C gives 92-98% yields. (**Scheme 9**).



Scheme 9

Present Work:-

In present work we have synthesize the 2-arylbenzothiazole by the condensation of 2-aminothiophenol with aromatic aldehydes using silica sulfuric acid as a catalyst under microwave-irradiation to gave the product **3(a-j)** in excellent yield.



Scheme I

Experimental:-

General procedure:

A mixture of 2 aminothiophenol (1 mmol), aldehyde (1 mmol) and silica sulfuric acid (100 mg) were taken in a beaker (50 mL). The reaction mixture was mixed properly with the help of glass rod and irradiated in a microwave oven at 45W, for the time indicated in Table 2. The progress of the reaction was monitored by TLC (ethyl acetate: hexane, 7:3). After completion of the reaction, the reaction mixture was cooled and dichloromethane (25 mL) was added. The catalyst was filtered from the reaction mixture; it was then washed with water (10 cm^3) and dried over anhydrous $CaCl_2$. The filtrate was concentrated under vacuum to obtain the product **3(a-j)**. All the products were characterized from their spectral data.

Results and Discussion:-

In continuation of our research work on the development of novel synthetic methodologies, using solid acid catalyst and microwave irradiation techniques, herein, we have developed methodology for the synthesis of 2-arylbenzothiazole using silica sulphuric acid which makes use of mild catalyst under solvent-free condition over the reported procedure as depicted in (**Scheme I**). Here we have carried out the reaction of 2-aminothiophenol (**1**) and 4-methoxy benzaldehyde (**2a**) catalyzed by silica sulfuric acid under microwave irradiation, it has been considered as a standard model reaction.

We have screened a number of different catalysts on model reaction, herein, the result revealed that, when the reaction was carried out in the presence of KH_2PO_4, NH_4VO_3, acidic alumina, amberlite-IR 120, sulphamic acid under microwave-irradiation it gave lower yield of product even after prolonged reaction time. While at the same time, when the model reaction was carried out under reflux condition it gave comparatively low yields of products. However when the same reactions was conducted under microwave irradiation using silica sulfuric acid as a catalyst it gave excellent yields of product in short reaction time (Table 1, entry 6).

After optimizing the catalyst, the generality of this method was examined by the reaction of 2-aminothiophenol and several substituted aryl/heteroaryl aldehydes using silica sulfuric acid as a catalyst under microwave-irradiation, the results are shown in Table 2. Here, we have found that both aldehydes bearing electron-donating substituents (Table 2, entries 1, 5) and electron-withdrawing (Table 2, entries 3, 4) substituents gave desired benzothiazoles in excellent yields. With both electron withdrawing and electron donating groups the reaction proceeds smoothly, with a slight increase in the yield when the aryl substituents was an electron withdrawing group. It can be seen further that 2-arylbenzothiazole bearing nitro functionality on the aryl ring was obtained in good yields (Table 2, entries 3, 4). This method is also applicable for the reaction of heteroaromatic aldehyde with 2-aminothiophenol affording the corresponding 2-heteroaryl benzothiazoles in better yields (Table 2, entries 9, 10). The synthesized compounds were compared (MS and ^{1}H NMR) with compounds that were prepared by using the literature method.[18] This comparison revealed that the compounds synthesized by this newly developed method were exactly similar in all aspects to the reference compounds. The developed methodology is simple with good to excellent yields.

Our attention was then directed towards the possibility of reusability of catalyst is highly preferable for greener process. The reusability of the catalyst in

the model reaction was checked as shown in (Table 3). The separated catalyst can be reused after washing with $CHCl_3$ and dried over anhydrous $CaCl_2$. The catalyst was removed in excellent yields and was used in mentioned reaction for five times, the observation revealed that as the number of the recycle of catalyst increases the activity decreases.

Table 1. Screening of Catalyst[a]

Entry	**Catalyst**	**Under MW**		**Under reflux**	
		Time(mi)	**Yield[b] (%)**	**Time(h)**	**Yield[b] (%)**
1	KH_2PO_4	10	32	5	26
2	NH_4VO_3	10	53	5	46
3	Acidic Al_2O_3	10	57	5	45
4	Amberlite-IR 120	10	64	5	51
5	Sulphamic acid	10	70	5	58
6	Silica sulfuric acid	10	91	5	76

[a]Reaction conditions:- **1** (1 mmol), **2a**(1 mmol), Catalyst (100 mg), [b]Isolated yield

Table 2. Synthesis of 2-Arylbenzothiazole[a]

Entry	Product	Ar	Time (min)	Yield (%)[b]	M.P (ºC)[18]
1	**3a**	4-OCH_3-C_6H_4	9	91	120-122
2	**3b**	C_6H_5	12	90	113-114
3	**3c**	3-NO_2-C_6H_4	8	92	181-182
4	**3d**	4-NO_2-C_6H_4	7	94	226-228
5	**3e**	2-OCH_3-C_6H_4	12	89	103-105
6	**3f**	2-Cl-C_6H_4	9	87	72-74
7	**3g**	4-Br-C_6H_4	8	91	133-134
8	**3h**	4-Cl-C_6H_4	10	90	116-118
9	**3i**	2-Thienyl	9	91	100-102
10	**3j**	2-Pyridyl	10	92	135-136

[a]Reaction conditions:- **1** (1 mmol), **2 (a-j)** (1 mmol), catalyst (100 mg).

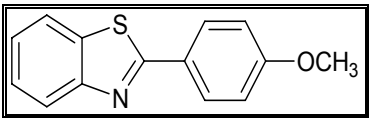
[b]Isolated yield. All the compounds characterized by their spectroscopy method ^{1}H NMR, Mass and melting point and compare to their authentic sample [18]

Table 3. Synthesis of 2-Arylbenzothiazoles **2a** with Recovery of Catalyst[a].

Cycle	Fresh	First	Second	Third	Fourth
Yield (%)[b]	91	88	85	79	76

[a]Reaction conditions:- **1** (1 mmol), **2a**(1 mmol), Catalyst (100 mg), [b]Isolated yield

Spectral Data:-



2-(4-methoxyphenyl)benzo[*d*]thiazole (3a)

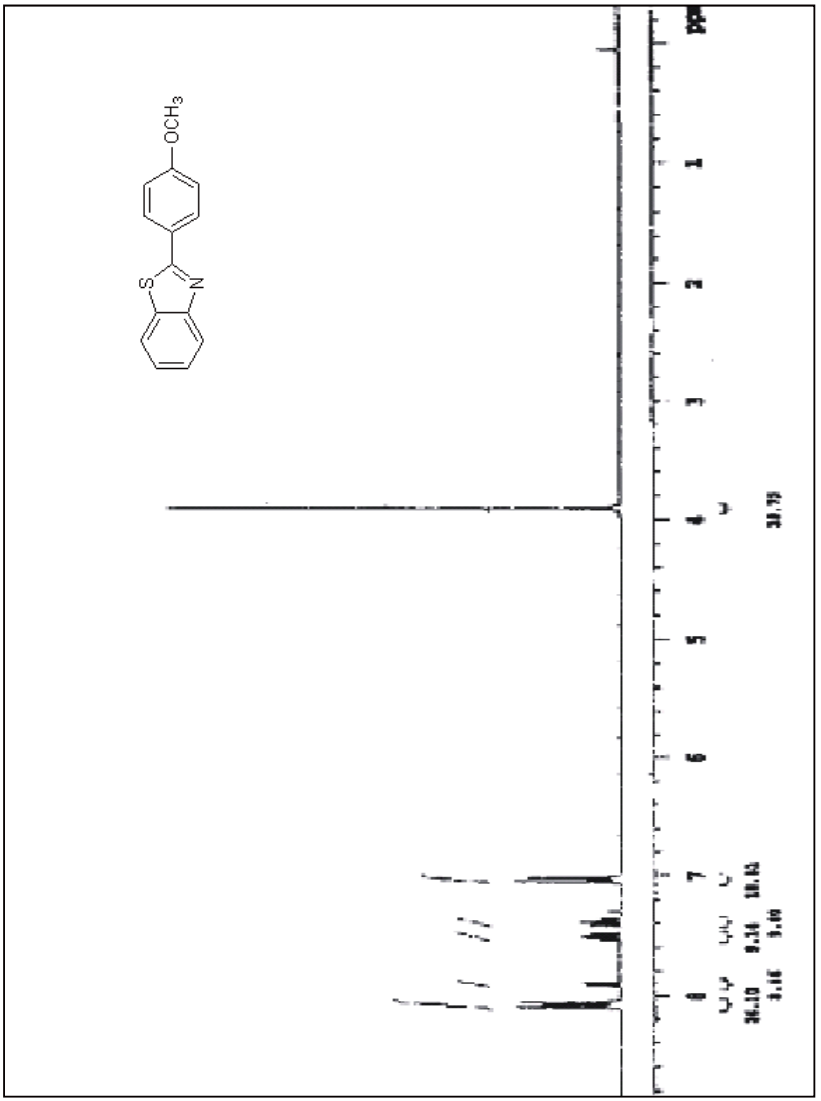
^{1}H NMR Spectra:

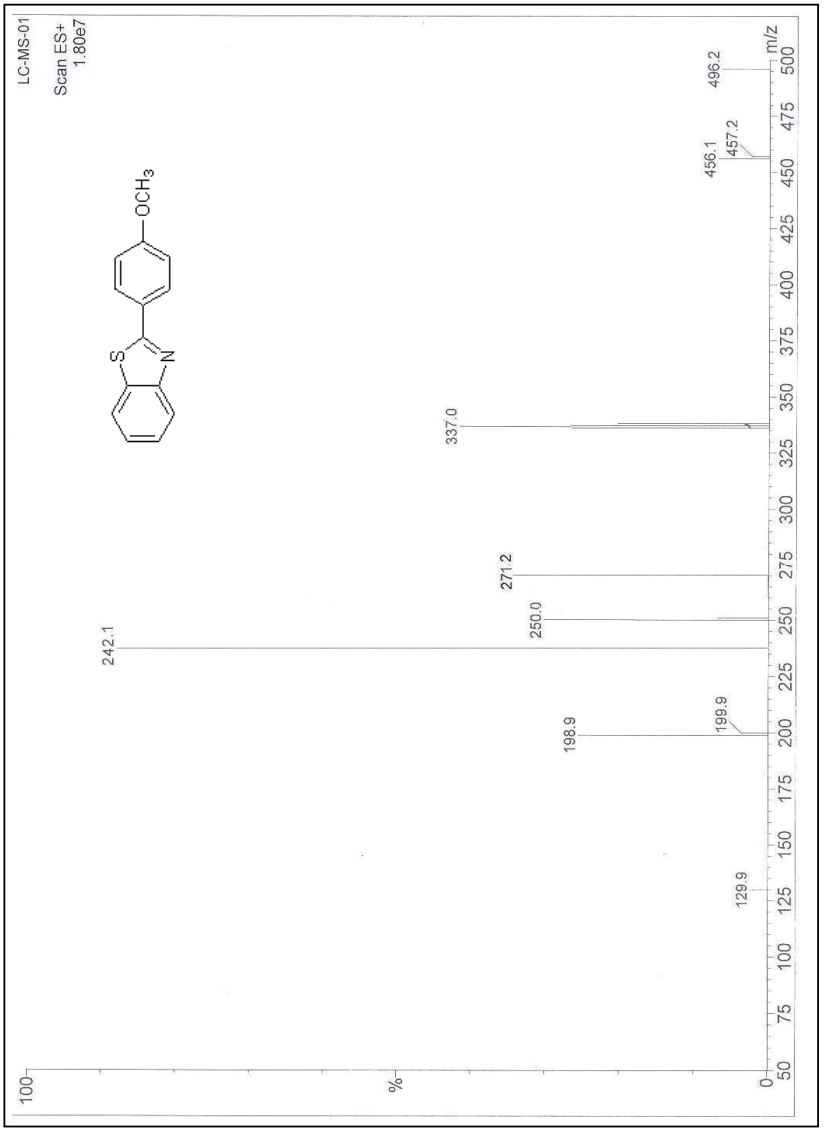
^{1}H NMR spectrum of compound **3a** showed following characteristic signals.

3.87	singlet	3H	due to $-OCH_3$
7.12	doublet	2H	due to -Ar-H
7.43	triplet	1H	due to –Ar-H
7.53	triplet	1H	due to -Ar-H
8.11	doublet	2H	due to –Ar-H
8.01-8.10	multiplet	2H	due to –Ar-H

Mass Spectra:

The mass spectrum of compound **3a** showed following signals m/z: 242.1 (M+1).




LC-MS-01
Scan ES+
1.80e7
100
%
0
50
75
100
125
150
175
200
225
250
275
300
325
350
375
400
425
450
475
500
m/z
242.1
271.2
250.0
337.0
198.9
199.9
129.9
456.1
457.2
496.2
OCH3
S
N

Conclusions:-

In conclusion, silica sulfuric acid was found to be an efficient catalyst for the reaction of 2-aminothiophenol and several substituted aryl/heteroaryl aldehydes to afford the corresponding 2-arylbenzothiazole in good to excellent yields. The main advantages of the present synthetic protocol are mild, solvent-free conditions, ecofriendly catalyst and easy reaction work-up procedure. It is expected that the present methodology will find application in organic synthesis.

CHAPTER VI

SYNTHESIS OF AMIDOALKYL NAPHTHOLS USING 1-HEXANESULPHONIC ACID SODIUM SALT

INTRODUCTION:-

During last 10 years our interest in an efficient and economical techniques for the preparation of some organic synthones has promoted the research in the field of microwave irradiation.[75-77] The use of such non-conventional reaction conditions reveals several features like: a short reaction time compared to conventional heating, ease of work-up after a reaction and reduction in the usual thermal degradation and better selectivity.[78-79] In recent years some important reviews, concerning study of microwave assisted organic reactions, have been published.[80-81] Solvent-free methods are specially adapted to green chemistry principles.[82] When coupled to microwave irradiation, they result in very efficient and clean procedures with noticeable improvements over classical methods.

Multi-component reactions (MCRs) play an important role in combinatorial chemistry because of its ability to synthesize small drug-like molecules with several degrees of structural diversity.[83] A MCR is defined as three or more different starting materials that react to form a product, where most, if not all of the atoms are incorporated in the final product. This reaction tool allows compounds to be synthesized in a few steps and usually in a one-pot operation.[84] Another typical benefit from these reactions is simplified purification, because all of the reagents are incorporated into the final product.

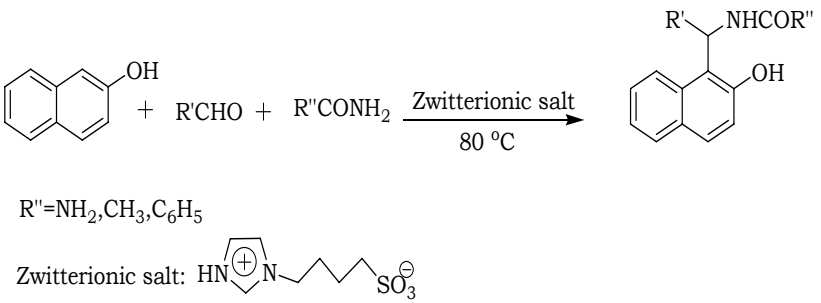
Compounds bearing 1,3-amino oxygenated functional groups are ubiquitous to a variety of biologically important natural products and potent drugs including a number of nucleoside antibiotics and HIV protease inhibitors, such as ritonavir and lipinavir.[85] The preparation of 1-amidoalkyl-2-naphthols can be carried out by condensation of aryl aldehydes, 2-naphthol and acetonitrile or ethaneamide in the presence of Lewis or Bronsted acid catalysts such as montmorillonite K10 clay,[86] $Ce(SO_4)_2$,[87] iodine,[88] $K_5COW_{12}O_{40}.3H_2O$,[89] *p*-toluene sulfonic acid (*p*-TSA),[90] sulfamic acid,[91] cation-exchanged resins,[92] silica-sulfuric acid,[93] SiO_2-$HClO_4$[94] and $NaHSO_4.H_2O$.[95]

Some of these methods, however, suffer from drawbacks, which include the use of hazardous materials, commercially non-available or highly corrosive and difficult-to-handle reagents, long reaction times, low yields, drastic reaction conditions and tedious workup procedures.

A search of the literature revealed that the 1-hexanesulphonic acid sodium salt[96] liberates corresponding acid with extreme wide applications such as sulphonation of alkanes[97] etc. However, there are very few reports using hexane sulphonic acid sodium salt as a catalyst in the organic transformation.[98] For the first time we herein report the use of 1-hexane sulphonic acid sodium salt for the synthesis of α amidoalkyl naphthols under microwave-irradiation and solvent-free condition.

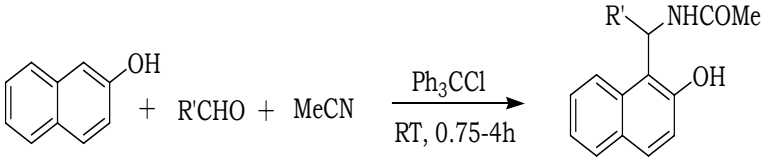
Literature Review of Amidoalkyl Naphthols:-

Hajra et *al.* have synthesized[99] 2-amidoalkyl and 2-carbamatoalkyl naphthol derivatives through a one-pot three-component condensation of 2-naphthol, aldehydes and amide or carbamates in the presence of zwitterionic-type molten salt as mild organocatalyst under solvent-free conditions which gives 74-90% yield (**Scheme 1**).



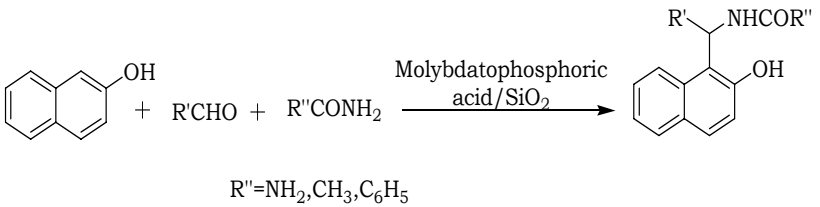
Scheme 1

Khazaei et *al.* have prepared[100] 1-amidoalkyl-2-naphthols via one-pot three-component condensation reaction of 2-naphthol, arylaldehydes and acetonitrile (Ritter type reaction) in the presence of catalytic amount of trityl chloride at room temperature (**Scheme 2**).



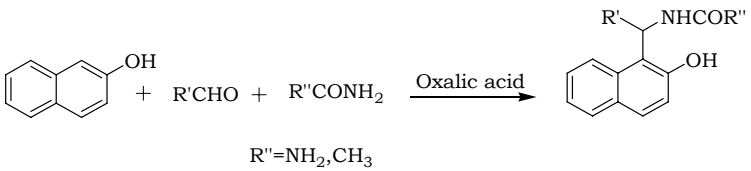
Scheme 2

Khedri et *al.* have described[101] an efficient, green and simple solvent-free method for the synthesis of 1-amidoalkyl-2-naphthols *via* one-pot multi-components condensation of 2-naphthol, aromatic aldehydes and amides in the presence of catalytic amount of silica-supported molybdatophosphoric acid ($H_3PMo_{12}O_{40}.xH_2O/SiO_2$, 3.17 mol%) (**Scheme 3**).



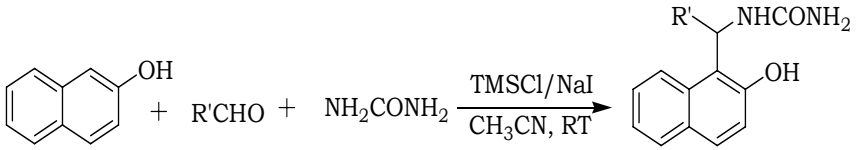
Scheme 3

Shinde and coworkers synthesized[102] α-amidoalkyl-β-naphthols by the three-component reaction of β-naphthol, aromatic aldehydes and amide or urea in the presence of a catalytic amount of oxalic acid under solvent-free conditions (**Scheme 4**).



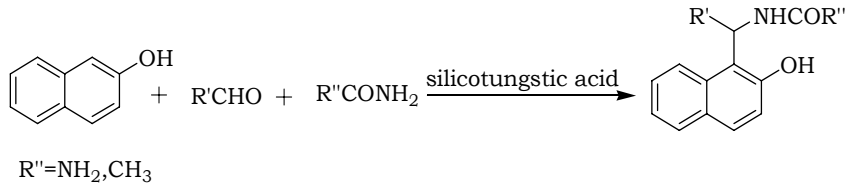
Scheme 4

Sabitha et *al.* have synthesized[103] amidoalkyl naphthol derivatives in a one-pot condensation of β-naphthol, aromatic aldehydes and urea in presence of TMSCl/NaI at room temperature (**Scheme 5**).



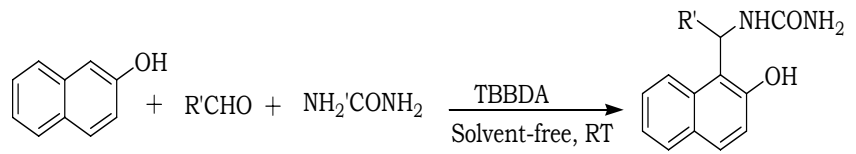
Scheme 5

Gokavi et *al.* reported[104] one pot synthesis of amidoalkyl naphthol by condensation of aromatic aldehydes, 2-naphthol and amide/urea using silicotungstic acid under solvent-free reaction conditions (**Scheme 6**).



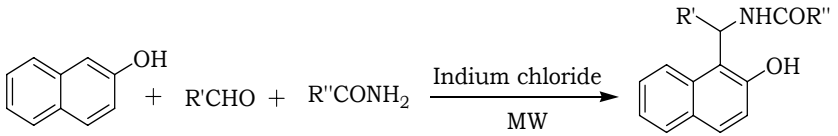
Scheme 6

Ghorbani and coworkers have synthesized[105] amidoalkyl naphthols from β-naphthol, aromatic aldehydes and urea using N,N,N,'N'-Tetrabromobenzene-1,3-disulfonamide [TBBDA] as a reusable catalyst under solvent-free conditions (**Scheme 7**).



Scheme 7

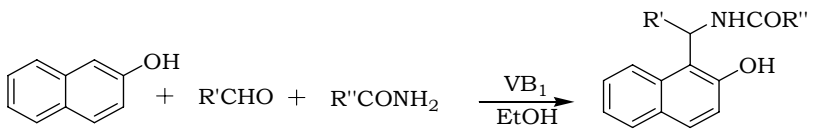
Kusurkar et *al.* have used[106] Indium chloride as an efficient catalyst for the synthesis of amidoalkyl naphthols from β-naphthol, aromatic aldehydes, and acetamide/urea under solvent-free conditions using microwave irradiation (**Scheme 8**).



R''=NH_2,CH_3

Scheme 8

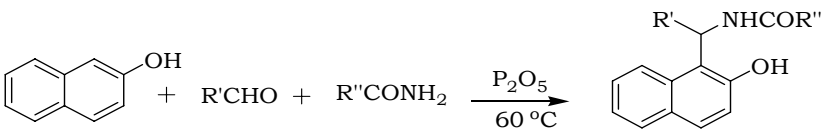
Maa et *al.* have describe[107] a simple, efficient and practical procedure for the synthesis of amidoalkyl naphthols using thiamine hydrochloride (VB1) as a novel catalyst (**Scheme 9**).



R''=NH_2,CH_3

Scheme 9

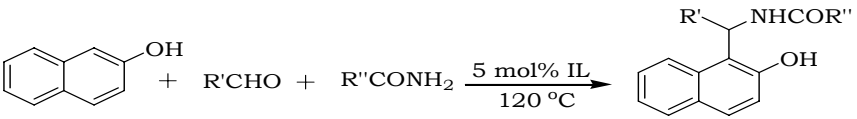
Singh et *al.* developed[108] an atom-efficient and environment-friendly approach for the synthesis of amidoalkyl naphthols *via* multicomponent one-pot reaction of 2-naphthol, aromatic aldehyde and amide catalyzed by P_2O_5 (**Scheme 10**).



R''=CH_3, C_6H_5, CH_2Cl

Scheme 10

Hajipour et *al.* developed[109] a mild and efficient method for the preparation of amidoalkyl naphthols from condensation of aldehydes with amides or urea and 2-naphthol in the presence of a catalytic amount of Brønsted acidic ionic liquid ([TEBSA][HSO_4]) under thermal solvent-free conditions (**Scheme 11**).



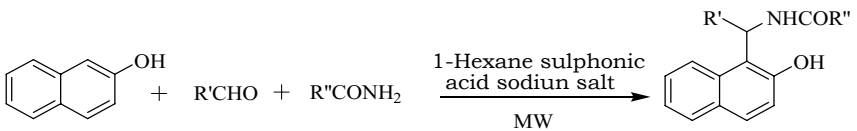
R''=CH_3, C_6H_5, NH_2

IL = $(CH_3CH_2)_3\overset{+}{N}CH_2(CH_2)_2CH_2SO_3H\ HSO_4^-$

Scheme 11

Present Work:-

This section describes the one-pot synthesis of amidoalkyl naphthols using 1-hexane sulphonic acid sodium salt as a catalyst under microwave-irradiation and solvent-free condition.



1 **2(a-j)** **3** **4(a-j)**

R"=NH_2,CH_3,C_6H_5

Scheme I

Experimental:-

General procedure:

The appropriate β-naphthol **1** (1 mmol), aldehydes **2**(**a-j**) (1 mmol), urea **3** (1.5 mmol) and the appropriate catalyst (10 mol %) were introduced into a beaker and mixed. The mixture was irradiated under microwave-irradiation for an appropriate time, the progress of reaction was monitored by TLC. After completion of reaction the mixture was cooled to room temperature and was washed with cold water and then the crude product was recrystallized from 96% ethanol to obtain the pure product. All the products were characterized from their spectral data.

Results and Discussion:-

As a part of our ongoing research devoted to the development of useful synthetic methodologies, herein we report an efficient and practical method for the synthesis of coumarins using 1-hexanesulphonic acid sodium salt which makes use of mild catalyst under solvent-free condition and microwave-irradiation (Scheme I).

Here we have carried out the reaction of β-naphthol (**1**), benzaldehyde (**2a**) and urea (**3**) catalyzed by 1-hexanesulphonic acid sodium salt under solvent-free condition and microwave-irradiation, it has been considered as a standard model reaction.

We also have studied the catalyst concentration on model reaction. We have varied the concentration of catalyst to 0, 2.5, 5, 7.5 and 10 mol%. The result revealed that, when the reaction was carried out in the presence of 0, 2 mol% of catalyst it gave lower yield of product even after prolonged reaction time. At the same time when the concentration of catalyst was 5, 7.5 and 10 mol% we got the excellent yields of product in short span. Even after increasing the catalyst concentration the yields of the products were found to be constant. So, the use of 5 mol% of catalyst is sufficient to push the reaction forward. The obtained results summarized in Table 1.

Further, we have also carried out the reaction by adding the three components, α-naphthol, benzaldehyde and urea to 1-hexanesulphonic acid sodium salt affords the mixture of regioisomers, while same the reaction was carried out using β-naphthol it gave the corresponding product in excellent yield. We have also examined the reaction with aliphatic aldehydes but the yield was low as compared to aromatic aldehydes.

After optimizing the conditions, the generality of this method was examined by the reaction of β-naphthol with several substituted aldehydes and urea/amides using 1-hexanesulphonic acid as a catalyst under microwave-irradiation, the results are shown in Table 2.

Here we extended this reaction on several substituted aromatic aldehydes, β-naphthol and urea/amide under similar conditions, furnishing the respective amidoalkyl naphthols in excellent yields (80-95%). In all cases, aromatic aldehydes with substituent carrying either electron-donating or electron withdrawing groups reacted successfully and gave the products in excellent yields. Also we have found that the reaction with liquid aldehydes required less time than that required for solid aldehydes. All the synthesized compounds were characterized by spectral data and compared (MS and ^{1}H NMR) with authentic sample. This comparison revealed that the compounds synthesized by this newly developed method were exactly similar in all aspects to the reference compounds.[100] The developed methodology is simple and a good contribution in the field of methodology.

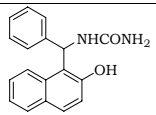
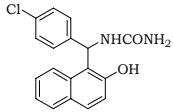
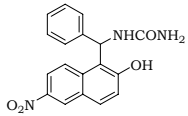
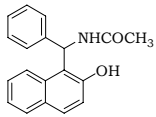
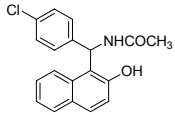
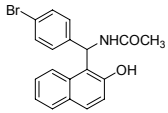
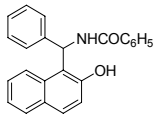
Table 1. Optimization of Mol % for Model Reaction (**4a**)[a]

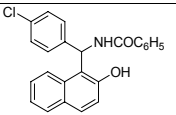
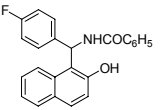
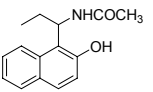
Entry	Catalyst (mol %)	Yield (%)[b]
1	0	35
2	2.5	53
3	5	90
4	7.5	90
5	10	90

[a]Reaction conditions:- **1a** (1 mmol), **2** (1 mmol), **3** urea (1.5 mmol) catalyst (10 mol%)

[b]Isolated Yield.

Table 2. Synthesis of Amidoalkyl Naphthols Catalysed by 1-Hexanesulphonic Acid Sodium Salt Under Microwave-Irradiation[a]

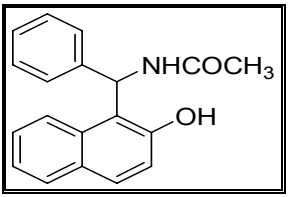
Entry	R'	R"	Product	Time (min)	Yield (%)[b]	M.P. (°C)
4a	C_6H_5	H_2N		4	90	170-172
4b	4-Cl-C_6H_4	H_2N		7	88	167-169
4c	3-NO_2-C_6H_4	H_2N		6	90	192-194
4d	C_6H_5	CH_3		3	95	229-231
4e	4-Cl-C_6H_4	CH_3		4	94	229-230
4f	4-Br-C_6H_4	CH_3		5	90	205-207
4g	C_6H_5	C_6H_5		8	92	235-237

4h	4-Cl-C_6H_4	C_6H_5		10	87	177-179
4i	4-F-C_6H_4	C_6H_5		7	80	192-194
4j	CH_3-CH_2-	CH_3		20	35	173-175

[a]Reaction conditions:- **1** (1 mmol), **2** (1 mmol), **3** urea (1.5 mmol) catalyst (10 mol%)

[b]Isolated Yield. All the compounds characterized by their spectroscopy method ^{1}H NMR, Mass and melting point and compare to their authentic sample.[100]

Spectral Data:-



N-((2-hydroxynaphthalen-1-yl)(phenyl)methyl)acetamide (4a):

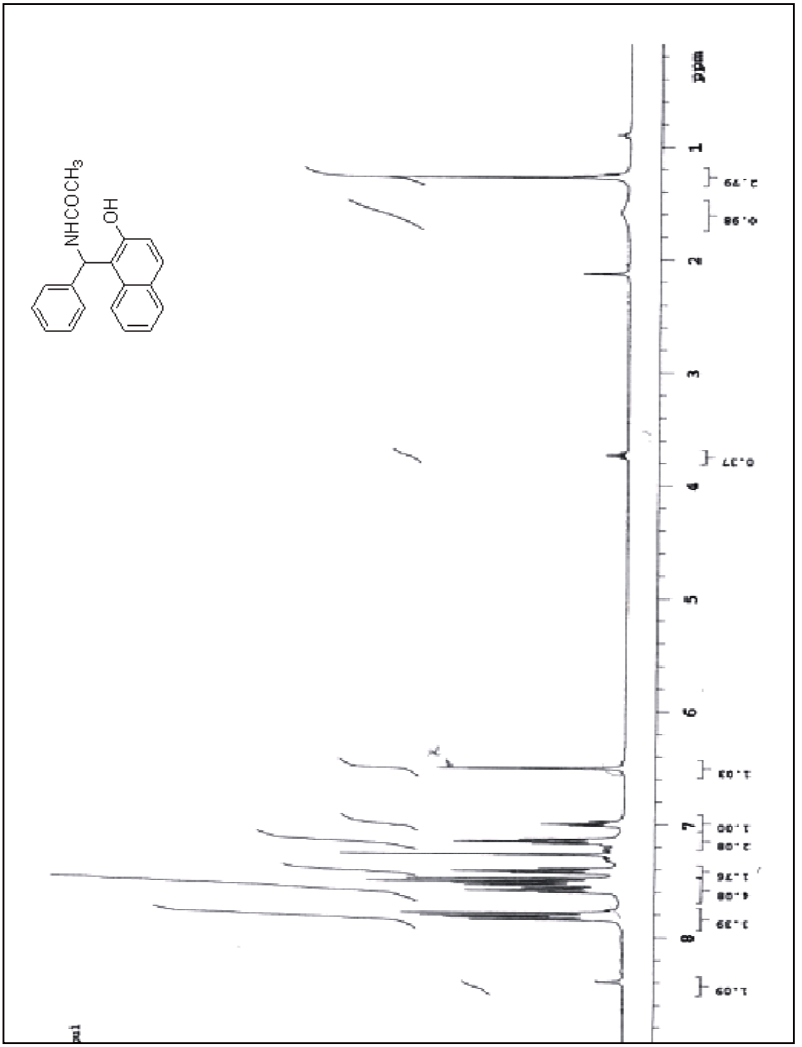
^{1}H NMR Spectra:

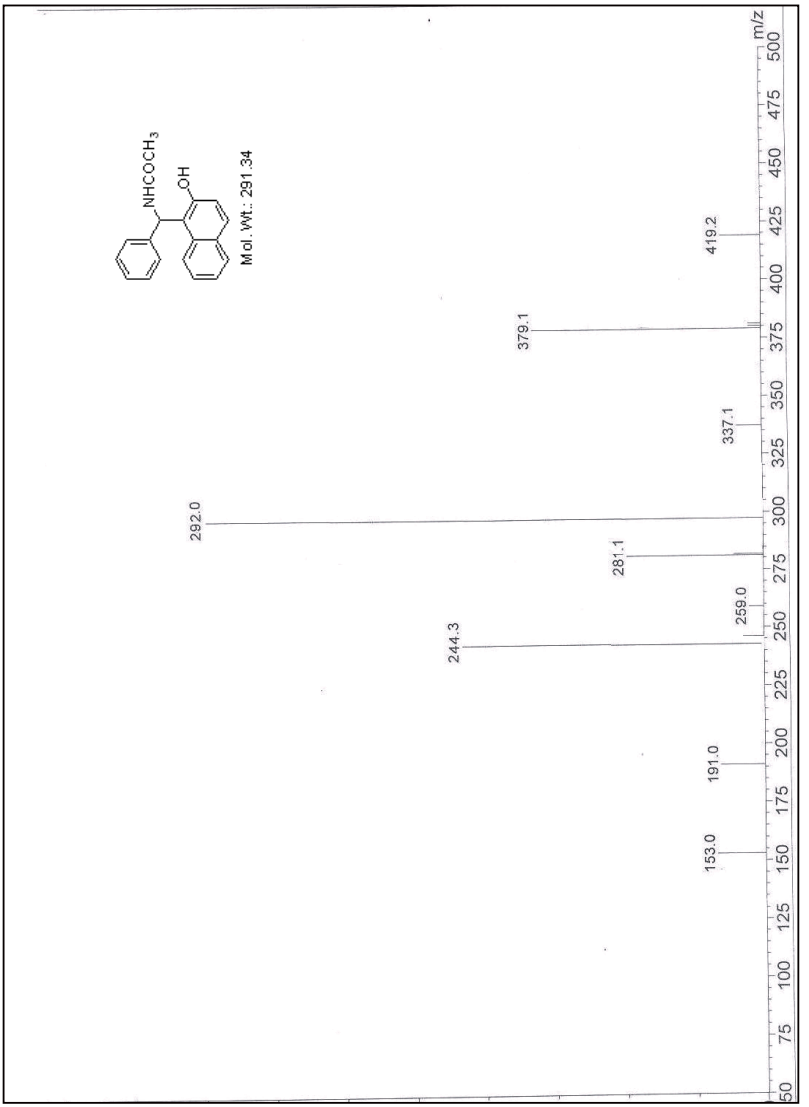
^{1}H NMR spectrum of compound **4a** showed following characteristic signals.

1.23	singlet	3H	due to $–CH_3$
1.59	br.singlet	1H	due to –OH
6.5	singlet	1H	due to –CH
7.0-7.8	multiplet	11H	due to Ar-H
8.4	singlet	1H	due to -NH

Mass Spectra:

The mass spectrum of compound **4a** showed following signals m/z: 292.0 (M+1).




NHCOCH3
OH
Mol. Wt.: 291.34
m/z
50
75
100
125
150
175
200
225
250
275
300
325
350
375
400
425
450
475
500
153.0
191.0
244.3
259.0
281.1
292.0
337.1
379.1
419.2

Conclusions:-

In conclusion, 1-hexanesulphonic acid sodium salt was found to be an efficient catalyst for the reaction of substituted aldehydes, phenol and urea/amide to afford the corresponding product in excellent yields. The notable advantages of the present protocol are mild, solvent-free conditions, ecofriendly catalyst and easy reaction work-up procedure. We believe this will provide a better and more practical alternative to be existing methodologies for the synthesis of amidoalkyl naphthols.

CHAPTER-V

MICROWAVE-ASSISTED SYNTHESIS OF COUMARINS USING POTASSIUM DIHYDROGEN PHOSPHATE

INTRODUCTION:-

Coumarins, the most important classes of fluorescent molecules, constitute important structural features present in a number of bioactive natural products. The heterocycles derived from these intermediates have also been tested for their potential as anti-HIV,[110] anti-inflammatory,[111] anticonvulsant,[112] anti-viral,[113] anti-coagulant,[114] antioxidant,[115] antibacterial,[116] antifungal,[117] anti-carcinogenic material[118] and antihistamine.[119]

Coumarins are an important group of organic compounds and can be used for the preparation of coumarino-α-pyrones, coumarino-g-pyrones, furocoumarins, chromenes, coumarones and 2-acylresorcinols. 7-Hydroxy-4-methylcoumarin acts as a starting material for the preparation of the insecticide Hymecromone. 6-Bromocoumarins are useful synthetic intermediates for various pharmaceuticals and active compounds.[120-122]

Coumarins have been synthesized by several routes including Pechmann,[123] Perkin,[124] Knoevenagel,[125] Reformatsky[126] and Wittig[127] reactions.

The Pechmann reaction is simple and straight forward employing β-keto esters and substituted phenols together with an acid catalyst. In the past, strong acids like H_2SO_4,[123] P_2O_5,[127] $AlCl_3$, $ZnCl_2$,[129] TFA,[130] ionic liquids,[131] sulfated zircon,[132] indium halides,[133] $CuPy_2Cl_2$,[134] palladium[135]and ammonium metavanadate[136] have been used. However, many of these methodologies suffer from the drawback of green chemistry and have been associated with several short comings such as long reaction times, expensive reagents, low product yields and difficulty in recovery and reusability of the catalysts. These shortcomings certainly demand the search for a safe, more convenient and efficient method.

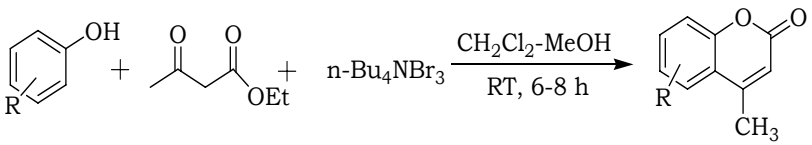
Now a day, it is shown that the use of solid acidic catalysts has gained importance in organic synthesis due to several advantages such as, operational simplicity, no toxicity and ease of isolation after completion of the reaction. In the

current study, the commercially available catalyst potassium dihydrogen phosphate having pH 4.2–4.7 is used as a catalyst but its scope has not been fully explored. Potassium dihydrogen phosphate can be used as buffer, neutralizing agent, sequestrate, yeast food and also as an efficient heterogeneous acid catalyst.[137] Recently, Gill & his co-workers have reported the synthesis of α-hydroxyphosphonates using potassium dihydrogen phosphate[138] under solvent-free condition. Owing to the numerous advantages associated with this cheap and non hazardous catalyst, we have considered Potassium dihydrogen phosphate to be an ideal heterogeneous acid catalyst for the synthesis of coumarins. Herein, we would like to report the facile and eco-friendly methodology for the synthesis of coumarins under solvent-free condition and microwave-irradiation.

Organic synthesis in dry media, eventually under microwave (MW) irradiation is presently under extensive examination. The relatively low cost of modern domestic microwave ovens makes them readily available to academic and industrial chemists and the use of such non-conventional reaction conditions reveals several features such as: a short reaction time compared to conventional heating, reduction of the usual thermal degradation and better selectivity[139] Furthermore, microwave-assisted reactions under solvent-free conditions provide access to work with open vessels and to scale up reactions.[140]

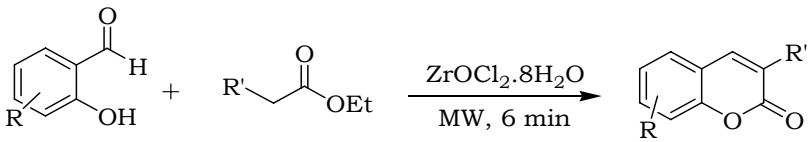
Literature Review of Coumarins:-

Qiang et *al.* have developed[141] a simple and efficient one-pot synthesis of 6-bromocoumarins in good yields *via* the three-component reaction of phenols, 4-substituted acetoacetate and tetra-n-butylammonium tribromide (TBATB) in CH_2Cl_2-MeOH (**Scheme 1**).



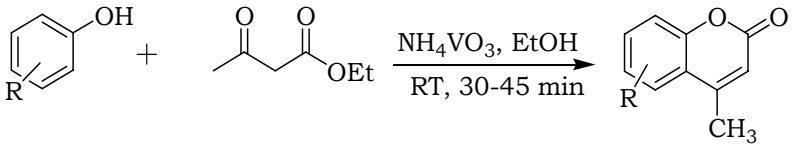
Scheme 1

Moghaddam et *al.* have described[142] an efficient route for the synthesis of 3-substituted coumarins *via* Knoevenagel condensation, using $ZrOCl_2.8H_2O$ (10 mol%) as the catalyst under microwave heating and solvent-free conditions (**Scheme 2**).



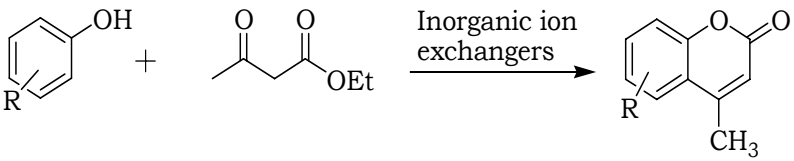
Scheme 2

Gill et *al.* have developed[136] a mild and efficient method for condensation of substituted phenol with β-ketoester in the presence of catalytic amount of ammonium metavanadate at ambient temperature to afford the corresponding substituted 4-methyl-2*H*-chromen-2-one in high yields under mild conditions (**Scheme 3**).



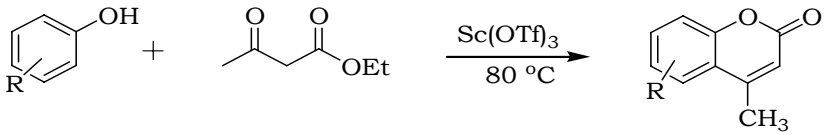
Scheme 3

Chudasama et *al.* have synthesized[143] the coumarins via Pechmann condensation using inorganic ion exchangers as solid acid catalyst under solvent-free condition (**Scheme 4**).



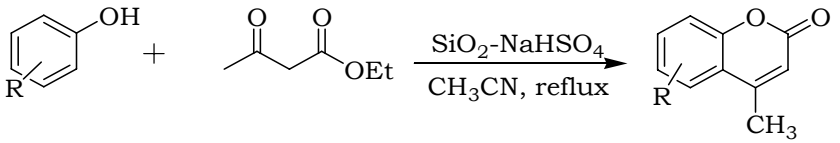
Scheme 4

Ryu and coworkers have developed[144] a simple and efficient one-pot synthesis of coumarins in good yields *via* Pechmann condensation of phenols, substituted acetoacetate in the presence of scandium (III) triflate at 80 °C (**Scheme 5**).



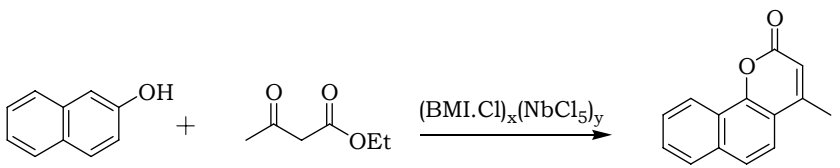
Scheme 5

Shinde and coworkers have used[145] silica gel supported $NaHSO_4$ as an efficient catalyst in the Pechmann condensation of phenols with ethyl acetoacetate, leading to the formation of coumarin derivatives. The reaction proceeded in acetonitrile at reflux temperature with good to excellent yields (**Scheme 6**).



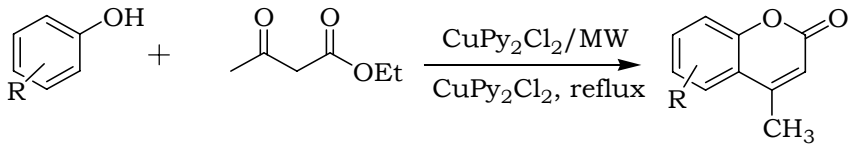
Scheme 6

Suarez et *al.* have described[146] the Pechmann`s reaction of α-naphthol with ethyl acetoacetate in organo-niobate ionic mixture (**Scheme 7**).



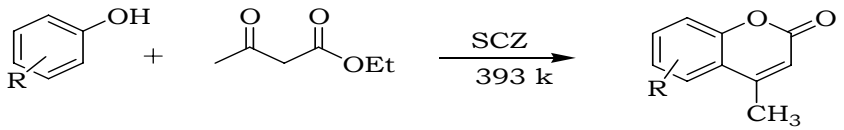
Scheme 7

Rajitha et *al.* have used[134] dipyridine copper chloride as an efficient catalyst in the Pechmann condensation reaction of phenols with ethyl acetoacetate, under solvent-free condition using both conventional heating and microwave irradiation. (**Scheme 8**).



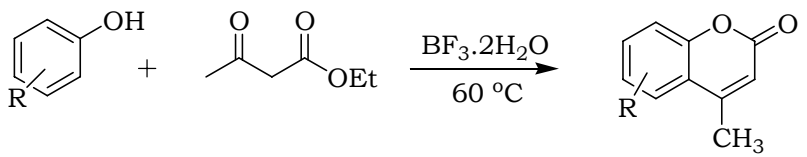
Scheme 8

Reddy et *al.* have employed[147] a novel $SO_4^{2-}/CexZr_{1-x}O_2$ catalyst for Pechmann condensation of phenols under solvent-free conditions (**Scheme 9**).



Scheme 9

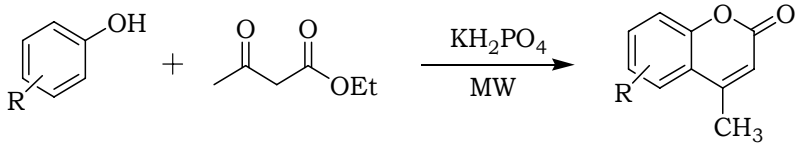
Stoyanov and coworkers have carried out[148] the Pechmann reaction of substituted phenols with methyl acetoacetate by using boron trifluoride dihydrate to give the corresponding coumarin derivatives at room temperature and at 60 °C (**Scheme 10**).



Scheme 10

Present Work:-

In this communication, we report for the first time a facile and efficient synthetic strategy for preparing coumarins in very short reaction time with excellent yield using potassium dihydrogen phosphate as a catalyst under solvent-free condition and microwave-irradiation.



Scheme I

Experimental:-

General procedure:

A mixture of substituted phenol (1 mmol), ethyl acetoacetate (1 mmol) and potassium dihydrogen phosphate (KH_2PO_4) (10 mol%) were placed in a beaker. The mixture was irradiated under microwave-irradiation; the progress of the reaction was monitored by TLC. After completion, the reaction mixture was poured into ice cold water (50 mL) and extracted with ethyl acetate (25 x 2 mL), which was then dried over Na_2SO_4 and the solvent was evaporated under reduced pressure to obtain the pure coumarins. The products **3(a-j)** were confirmed by comparisons with authentic samples, ^{1}H NMR, mass spectra and melting point.[136]

Results and Discussion:-

As a part of our ongoing research devoted to the development of useful synthetic methodologies, using solid acid catalyst and microwave irradiation techniques, herein we report an efficient and practical method for the synthesis of coumarins using potassium dihydrogen phosphate which makes use of mild catalyst under solvent-free condition and microwave-irradiation (Scheme I).

In the first examination, we have performed the different reaction conditions on model reaction. The result revealed that, when the reaction was carried out at stirring and heating condition it gave lower yield of product even after prolonged reaction time. But at the same time when the reaction was carried out under microwave-irradiation we got the excellent yields of product in short span (Table 1).

We have studied the model reaction with various powers of microwave and we found that 400W is good enough to carry out reaction over other powers. The optimization of reaction results with various power of microwave irradiation summarized in Table 2, which have found that, if reaction carried out without microwave irradiation it takes more reaction time (30 min) with negligible yield (20%). As we increase the power of microwave there is increase in yield with decrease in reaction time still at 400 W, but future that there is no significant change observed at 600 W. Hence, we satisfied over 400 W and done all derivatization at 400 W.

After optimizing the various powers of microwave, the generality of this method was examined by the reaction of substituted phenols and ethyl acetoacetate using potassium dihydrogen phosphate as a catalyst under microwave-irradiation, the results are shown in Table 3. Here, we have found that many phenols, such as resorcinol, 4-hydrxy phenol, 3-methoxy phenol, 3-aminophenol could be converted to corresponding coumarins in good yields (entries **3a**-**3c** & **3f**-**3j**). The reactivities of 3-methylphenol and 1-naphthol seem to be inferior as compared with that of the former (entries **3d**, **3e**), only 70% and 75% of the yields were obtained, respectively.

The synthesized compounds were compared (MS and ^{1}H NMR) with compounds that were prepared by using the literature method.[27] This comparison revealed that the compounds synthesized by this newly developed method were exactly similar in all aspects to the reference compounds. The developed methodology is simple with good to excellent yields.

Table 1. Optimization of Model Reaction **3a** at Different Reaction Condition[a]

Entry	Reaction condition	Time	Yield(%)[b]
1	Stirring	12 (h)	40
2	Heating	8 (h)	65
3	Microwave	3 (min)	95

[a]Reaction condition: **1a** (1 mmol), **2** (1 mmol) and KH_2PO_4 (10 mol%).
[b]Isolated yields.

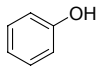
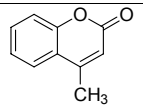
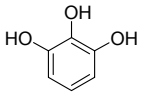
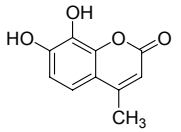
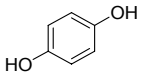
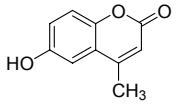
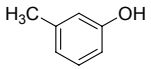
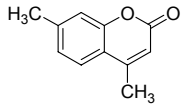
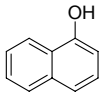
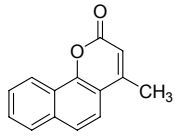
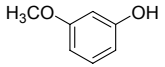
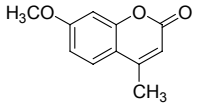
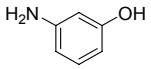
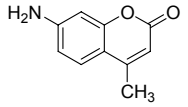
Table 2. Effect of Microwave-Irradiation Powers for the Synthesis of Coumarins[a]

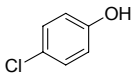
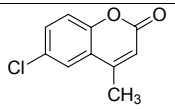
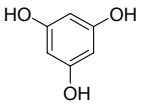
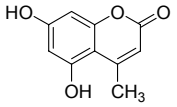
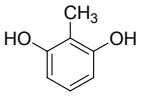
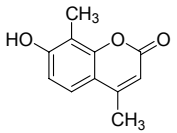
Entry	MW (Watts)	Time(min.)	Yield(%)[b]
1	-	30	20
2	100	30	42
3	200	30	55
4	300	30	60
5	400	3	95
6	600	3	95

[a]Reaction conditions:- **1a** (1 mmol), **2** (1 mmol) and KH_2PO_4 (10 mol%).

[b]Isolated yields.

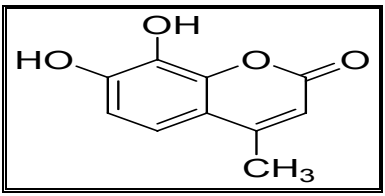
Table 3. Synthesis of Coumarins Catalyzed by Potassium Dihydrogen Phosphate Under Microwave-Irradiation[a]

Entry	Reactant	Product	Time (min)	Yield (%)	M.P (°C)
3a			3	90	78-80
3b			3	91	237-239
3c			5	90	241-243
3d			10	70	129-131
3e			12	75	153-155
3f			7	89	160-162
3g			5	90	220-222

3h			5	89	180-183
3i			7	88	281-283
3j			8	88	137-138

[a]Reaction conditions:- **1** (1 mmol), **2 (a-j)**(1 mmol), catalyst (10 mol%). [b]Isolated yield. All the compounds characterised by their spectroscopy method ^{1}H NMR and Mass melting point and compare to their authentic sample.

Spectral Data:-



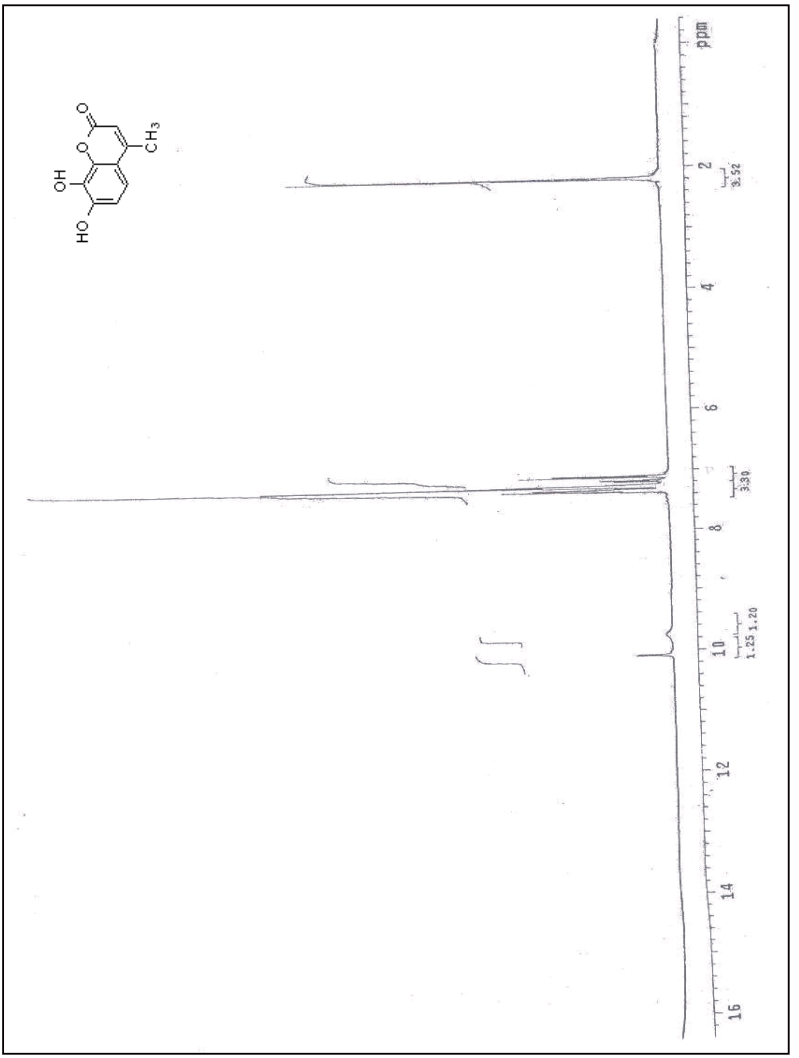
^{1}H NMR Spectra:

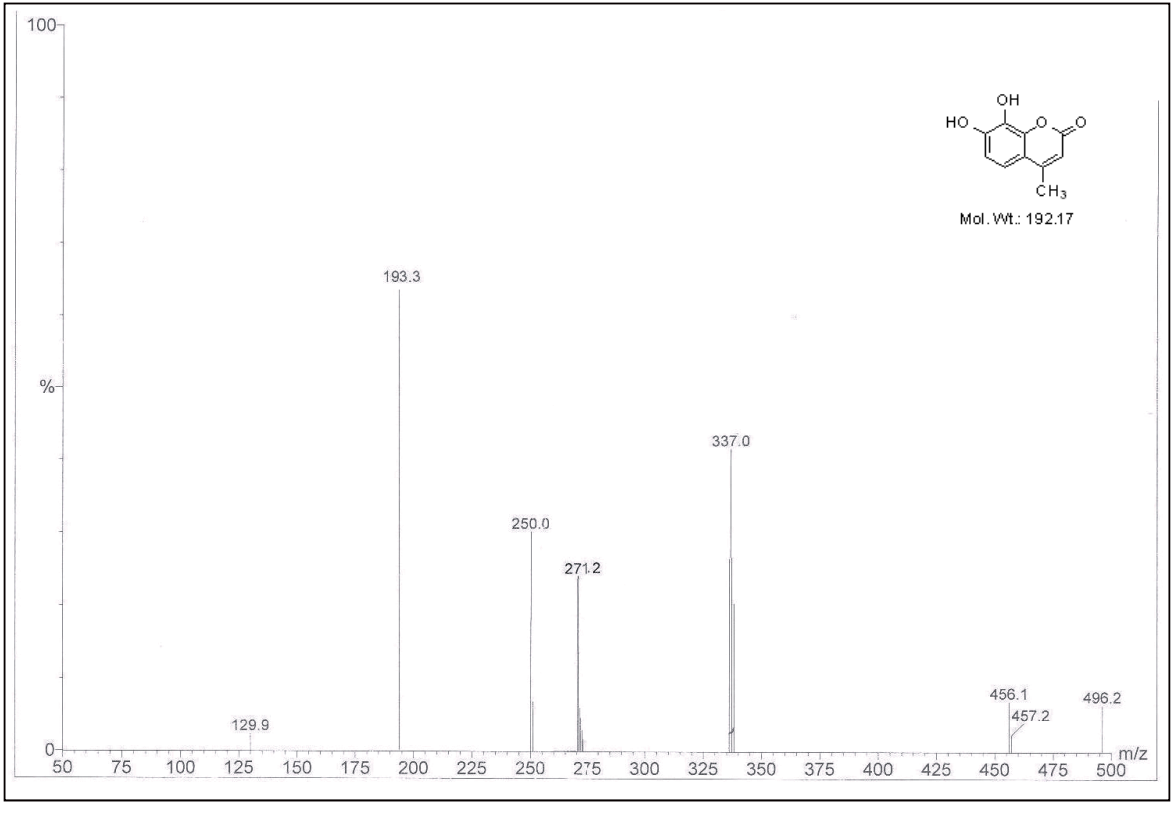
^{1}H NMR spectrum of compound **3b** showed following characteristic signals.

2.2	singlet	3H	due to $-CH_3$
7.1-7.4	multiplet	3H	due to Ar-H
9.7	br.singlet	1H	due to -OH
10.1	singlet	1H	due to –OH

Mass Spectra:

The mass spectrum of compound **3b** showed following signals m/z: 193.3 (M+1).




100
%
0
193.3
337.0
250.0
271.2
129.9
456.1
457.2
496.2
50 75 100 125 150 175 200 225 250 275 300 325 350 375 400 425 450 475 500
m/z
OH
HO
O
O
CH3
Mol. Wt.: 192.17

Conclusions:-

In conclusion we have developed very simple and efficient methodology for the high yielding synthesis of coumarins using potassium dihydrogen phosphate as a catalyst under solvent-free condition and microwave-irradiation. The operational simplicity of the procedure, shorter reaction time, and simple workup procedure makes this method attractive.

REFERENCES:-

1. (a) *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W.; Eds.; Pergamon Press: New York, **1984**, 1; (b) *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R.; Ress, C. W.; Scriven, E. F. V.; Eds.; Pergamon: New York, **1996**, 1.; (c) Balaban, A. T.; Oniciu, D. C.; Katritzky, A. R. *Chem. Rev.* **2004**, *104*, 2777.
2. (a) Martins, M. A. P.; Cunico, W.; Pereira, C. M. P.; Flores, A. F. C.; Bonacorso, H. G.; Zanatta, N. *Curr. Org. Synth.* **2004**, *1*, 391; (b) Druzhinin, S. V.; Balenkova, E. S.; Nenajdenko, V. G. *Tetrahedron* **2007**, *63*, 7753; (c) Ghose, A. K.; Viswanadhan, V. N.; Wendoloski, J. J. *J. Comb. Chem.* **1999**, *1*, 55; (d) Xu, J.; Stevenson, J. *J. Chem. Inf. Comput. Sci.* **2000**, *40*, 1177.
3. Gedey, R.; Smith, F.; Westway, K.; Ali, H.; Baldisera, L.; Laberage, L.; Roussel, J. *Tetrahedron Lett*. **1986**, *27*, 279.
4. Giguere, R. J. *Organic Synthesis: Theory Application* **1989**, *1,* 103.
5. Vanderhoff, J. W. *US*, *3*, **1969**, 432, 413; *Chem. Abstr.* **1969**, 97422v.
6. (a) Loupy, A.; Petit, A.; Pelin-Sud, Special Recherches Universite Paris-Sud, 84, **1997**; (b) Harvey, A. F. *"Microwave Engineering," Academic Press, New York* **1963**.
7. Armstrong, R. W.; Combs, A. P.; Tempest, P. A.; Brown, S. D.; Keating, T. A. *Acc. Chem. Res.* **1996**, *29*, 123.
8. Domling, A. *Org. Chem. Highlights* **2004**, April 5.
9. Recent progress in the chemistry of multicomponent reactions Ivar Ugi *Pure Appl. Chem*. **2001**, *73*, 187.
10. The discovery of new isocyanide-based multi-component reactions Alexander Domling *Current Opinion in Chemical Biology* **2000**, *4*, 318.
11. Kidwai, M.; Saxena, S.; Khalilur, R.; Khan, M.; Thukral, S. S. *Eur. J. Med. Chem*. **2005**, *40*, 816.
12. Yarim, M.; Sarac, S.; Kilic, F. S.; Erol, K. *Il Farmaco* **2003**, *58*, 17.
13. Yarim, M.; Sarac, S.; Ertan, M.; Kilic, F. S.; Erol, K. *Arzneim. Forsch*. **2002**, *52*, 27.
14. Eynde, J. J. V.; Godin, J.; Mayence, A.; Ma-questiau, A.; Anders, E. *Synthesis* **1993**, 867.
15. Kempter, G.; Ehrlichmann, W.; Plesse, M.; Lehm, H. U. J. *Prakt. Chem.* **1982**, *324*, 832.
16. Kantevari, S.; Bantu, R.; Nagarapu, L. *Arkivoc* **2006**, *xvi*, 136.
17. Lin, H.; Zhao, Q.; Xu, B.; Wang, X. *J. Mol. Catal. A: Chem.* **2007**, *268*, 221.
18. Hassani, Z.; Islami, M. R.; Kalantari, M. *Bioorg. Med. Chem. Letts*. **2006**, *16*, 4479.

19. Niralwad, K. S.; Shingate, B. B.; Shingare, M. S. *J. Chin. Chem. Soc.* **2010**, *57*, 89.
20. Synecek, V.; Hanic, F. *Czechoslovak J. Phys.* **1954**, *4*, 120.
21. Stellman, J. M.; *In Encyclopaedia of Occupa-tional Health and Safety, Fourth Edition*, **1998**, III, 63, 43, Geneva.
22. (a) Garcia, T.; Solsona, B.; Murphy, D. M.; Antcliff, K. L.; Taylor, S. H. *J. Catalysis.* **2005**, *229*, 1; (b) Reddy, B. M.; Ratnam, K. J.; Saikia, P. *J. Mol. Catal. A: Chem.* **2006**, *252*, 238; (c) Reddy, B. M.; Rao, K. N.; Reddy, G. K.; Bharali, P. *J. Mol. Catal. A: Chem.* **2006**, *253*, 44; (d) Radhika, T.; Sugunan, S. *Catal. Commun.* **2007**, *8*, 150; (e) Gomez-Bernal, H.; Cedeno-Caero, L.; Gutierrez-Alejandre, A. *Catal. Today* **2009**, *142*, 227.
23. Jadhav, G. R.; Shaikh, M. U.; Kale, R. P.; Gill, C. H. *Chin. Chem. Lett*. **2009**, *20*, 292.
24. Mandhane, P. G.; Joshi, R. S.; Ghawalkar, A. R.; Jadhav, G. R.; Gill, C. H. *Bull. Korean Chem. Soc.* **2009**, *30*, 2969.
25. Sonar, S. S.; Kategaonkar, A. H.; Ware, M. N.; Gill, C. H.; Shingate, B. B.; Shingare, M. S. *Arkivoc* **2009**, *ii*, 138.
26. Sadaphal, S. A.; Kategaonkar, A. H.; Sapkal, S. B.; Shingate, B. B.; Gill, C. H.; Shingare, M. S. *Bullet. Catal. Soc. India* **2009**, *8*, 131.
27. Van Eldik, R.; Hubbard, C. D. *Chemistry under extreme or non-classical conditions*, J. Wiley & Sons: New York, **1996**.
28. Bram, G.; Loupy, A.; Villemin, D. In *Solid Supports and Catalysts in Organic Synthesis*; Smith, K., Ed.; Ellis Horwood, PTR Prentice Hall: Chichester, **1992**, 302.
29. Perez, E. R.; Marrero, A. L.; Perez, R.; Autie, M. A. *Tetrahedron Lett.* **1995**, *36*, 1779.
30. Loupy, A.; Petit, A.; Hamelin, J.; Texier-Boullet, F.; Jacquault, P.; Mathe, D. *Synthesis* **1998**, 1213.
31. Deshayes, S.; Liagre, M.; Loupy, A.; Luche, J. L.; Petit, A. *Tetrahedron* **1999**, *55*, 10851.
32. Varma, R. S. *Green Chem.* **1999**, *1*, 43.
33. Lin, H.-X.; Xie, X.-Z.; Wang, X.-H.; Bin, H. *Lett. Org. Chem*. **2009**, *6*, 557.
34. Khurana, J. M.; Kumar, S. *Monatsh. Chem.* **2010**, *141,* 561.
35. Ladani, N. K.; Patel, M. P.; Patel, R. G. *Arkivoc* **2009**, *vii*, 292.
36. Kategaonkar, A. H.; Sadaphal, S. A.; Shelke, K. F.; Shingate, B. B.; Shingare, M. S. *Ukra. Bioorg. Acta.* **2009**, *1*, 3.
37. (a) Sing, S.; Shukla, I. C.; Shukla, S. *Indian J. Pharm. Sci.* **1988**, *50*, 278; (b) Basavaiah, K.; Krishnamurthy, G. *Mikrochim. Acta.* **1999**, *130*, 197; (c) Kanakpura, B.; Javarappa, M. *Tur. J. Chem.* **2002**, *26*, 551.
38. Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893.

39. Palmer, P. J.; Trigg, R. B; Warrington, J. V. *J. Med. Chem*. **1971**, *14*, 248.
40. Benazzouz, A.; Boraud, T.; Dubedat, P.; Boireau, A.; Stutzmann, J. M.; Gross, C. *Eur. J. Pharmacol* **1995**, *284*, 299.
41. Beneteau, V.; Besson, T.; Guillard, J.; Leonce, S.; Pfeiffer, B. *Eur. J. Med. Chem.* **1999**, *34*, 1053.
42. Mathis, C. A.; Bacski, B. J.; Kajdasz, S. T.; McLellan, M. E.; Frosch, M. P.; Hyman, B. T.; Holt, D. P.; Wany, Y.; Huany, G. F.; Debnath, M. L.; Klunk, W. E. *Bioorg. Med. Chem. Lett*. **2002**, *12*, 295.
43. Mathis, C. A.; Wany, Y.; Holt, D. P.; Huany, G. F.; Debnath, M. L.; Klunk, W. E. *J. Med. Chem.* **2003**, *46*, 2740.
44. Ben-Alloum, A.; Bakkas, S.; Soufiaoui, M. *Tetrahedron Lett.* **1997**, *38*, 6395.
45. Roe, A.; Tuker, W. P. *J. Heterocycl. Chem.* **1965**, *2*, 148.
46. Hutchinson, I.; Stevens, M. F. G.; Westwell, A. D. *Tetrahedron Lett.* **2000**, *41*, 425.
47. Alagille, D.; Baldwin, R. M.; Tamagnan, G. D. *Tetrahedron Lett.* **2005**, *46*, 1349.
48. Majo, V. J.; Prabhakaran, J.; Mann, J. J.; Kumar, J. S. D. *Tetrahedron Lett.* **2003**, *44*, 8535.
49. Toh, T.; Nagata, K.; Ishikawa, H.; Ohsawa, A. *Heterocycles* **2004**, *63*, 2769.
50. Praveen, C.; Kumar, K. H.; Muralidharan, D.; Perumal, P. T. *Tetrahedron* **2008**, *64*, 2369.
51. Okimoto, M.; Yoshida, T.; Hoshi, M.; Hattori, K.; Komata, M.; Tomozawa, K.; Chiba, T. *Heterocycles* **2008**, *75*, 35.
52. Chou, C. H.; Yu, P. C.; Wang, B. C. *Tetrahedron Lett.* **2008**, *49*, 4145.
53. Chakraborti, A. K.; Selvam, C.; Kaur, G.; Bahagat, S. *Synlett* **2004**, 851.
54. Mutsushita, H.; Lee, S. H.; Joung, M.; Clapham, B.; Janda, K. D. *Tetrahedron Lett.* **2004**, *45*, 313.
55. (a) Fawzia, A. Q.; Mekheimer, R. A.; Sadek, K. U. *Molecules* **2008**, *13*, 2908; (b) Sedaghat N.; Naimi-jamal M. R *12th international Electronic Conference on Synthetic Organic Chemistry* 1-30 Nov. **2008**; (c) Chanada; M.; Arup, D. *Heterocycles* **2007**, *71*, 1837.
56. Fazaeli, R.; Aliyan, H. *Appl. Catal.: A* **2009**, *353*, 74.
57. Algul, O.; Kaessler, A.; Apcin, Y.; Yilmaz, A.; Jose, J. *Molecules* **2008**, *13*, 736.
58. Rostamizadeh, S.; Housaini, S. A. *Phosphorus, Sulfur and Silicon Relat. Elem.* **2005**, *180*, 1321.
59. (a) Pratap, U. R.; Mali, J. R.; Jawale, D. V.; Mane, R. A. *Tetrahedron Lett.* **2009**, *50*, 1352; (b) Guo, H. Y.; Li, J. C.; Shang, Y. L. *Chin. Chem. Lett.* **2009**, *20*, 1408.
60. Kahveci, B.; Ozil, M.; Serdar, M. *Heteroatom Chem.* **2008**, *19*, 38.

61. Lange, J. H. M.; Verveer, P. C.; Osnabrug, S. J. M.; Visser, G. M. *Tetrahedron Lett.* **2001**, *42*, 1367.
62. Cakmaka, O.; Başturkmenb, M.; Kisakurek, D. *Polymer* **2004**, *45*, 5421.
63. Zolfigol, M. A. *Tetrahedron* **2001**, *57*, 9509.
64. (a) Xian, L. F.; Peng, J. J.; Xia, C. G. *Chin. Chem. Lett.* **2006**, *17*, 617; (b) Eshghi, H.; Hassankhani, A. *J. Korean Chem. Soc.* **2007**, *51*, 361.
65. Mirijalili, B. F.; Zolfigol, M. A.; Bamoniri, A. *Molecules* **2002**, 751.
66. Hajipour, A. R.; Mirijalili, B. F.; Zarie, A. *Tetrahedron Lett.* **2004**, *45*, 6607.
67. Fan, X.; Wang, Y.; He, Y.; Zhang, X.; Wang, J. *Tetrahedron Lett.* **2010**, *51*, 3493.
68. Katkar, S. S.; Mohite, P. H.; Gadekar, L. S.; Vidhate, K. N.; Lande, M. K. *Chin. Chem. Lett.* **2010**, *21*, 421.
69. Saha, D.; Adak, L.; Ranu, B. C. *Tetrahedron Lett.* **2010**, *51*, 5624.
70. Pratap, U. R.; Mali, J. R.; Jawale, D. V.; Mane, R. A. *Tetrahedron Lett.* **2009**, *50*, 1352.
71. Praveen, C.; Hemanth K.; Muralidharan, Kumar, D.; Perumal, P. T. *Tetrahedron* **2008**, *64*, 2369.
72. Maradolla, M. B.; Allam, S. K.; Mandha, A.; Chandramouli, G. V. P. *Arkivoc* **2008**, *xv*, 42.
73. Guo, H. Y.; Li, J. C.; Shang, Y. L. *Chin. Chem. Lett.* **2009**, *20*, 1408.
74. Bahrami, K.; Khodaei, M. M.; Naali, F. *J. Org. Chem*. **2008**, *73*, 6835.
75. (a) Gedye, R.; Smith, F.; Westaway, K.; Ali, H.; Baldisera, L.; Laberge, L.; Roussel, J. *Tetrahedron Lett*. **1986**, *27,* 279; (b) Loupy, A. *Microwave in Organic Synthesis; Wiley-VC*H: *Weinheim,* **2006**.
76. Giguere, R. J.; Bray, T. L.; Duncan, S. M.; Majetich, G. *Tetrahedron Lett.* **1986**, *27*, 4945.
77. (a) Hwang, D. R.; Moerlein, S. M.; Welch, M. J. *J. Chem. Soc. Chem. Commun.* **1987**, 1799; (b) Vanderhoff, J. W.; U.S. Patent 3, 432, 413; *Chem. Abstr.* **1969**, *70,* 22; (c) Gourdenne, A.; Maassaran, A. H.; Monchaux, P.; Aussudre, S.; Thourel, L. *Polym. Prepr.* **1979**, *20*, 471; (d) Gourdenne, A.; Le Van, Q. *Polym. Prepr.* **1981**, *22*, 125; (e) Jullien, H.; Valot, H. *Polymer* **1983**, *24*, 810; (f) Loupy, A.; Song, S. J.; Cho, S. J.; Park, D. K.; Kwon, T. W. *Synth. Commun.* **2005**, *35*, 79.
78. Loupy, A.; Haudrechy, A. *Masson: Paris* **1996.**
79. (a) Lewis, D. A.; Summers, J. D.; Ward, T.C.; McGrath, J. E. *J. Polym. Sci. Part A* **1992**, *30*, 1647; (b) Berlan, J.; Giboreau, P.; Lefeuvre, S.; Marchand, C. *Tetrahedron Lett*. **1991**, *32*, 2363.
80. Loupy, A.; Petit, A.; Hamelin, J.; Texier-Boullet, F.; Jacquault, P. Matht, D. *Synthesis* **1998**, 1213.

81. (a) Perreux, L.; Loupy, A. *Tetrahedron* **2001**, *57*, 9199; (b) Loupy, A.; Perreux, L.; Liagre, M.; Burle, K.; Moneuse, M. *Pure Appl. Chem.* **2001**, *73*, 161.
82. Strauss, C. R.; Varma, R. S. *Top. Curr. Chem*. **2006**, *266*, 199.
83. (a) Ugi, I.; Domling, A.; Horl, W. *Endeavour.* **1994**, *18*, 115; (b) Tietze, L. F.; Modi, A. *Med. Res. Rev.* **2000**, *20*, 304; (c) Ugi, I.; Domling, A.; Werner, B. *J. Heterocyclic Chem*. **2000**, *37*, 647; (d) Orru, R. V. A.; de Greef, M. *Synthesis* **2003**, 1471.
84. Xu, L.-W.; Xia, C.-G.; Li, L. *J. Org. Chem*. **2004**, *69*, 8482.
85. (a) Juaristi, E.; *Wiley John & Sons: New York* **1997**; (b) Dingermann, T.; Steinhilber, D.; Folkers, G. *Wiley-VCH, Weinheim* **2004**.
86. Kantevari, S.; Vuppalapati, S. V. N.; Nagarapu, L. *Catal. Commun.* **2007**, *8*, 1857.
87. Selvam, N. P.; Perumal, P. T. *Tetrahedron Lett*. **2006**, *47*, 7481.
88. Das, B.; Laxminarayana, K.; Ravikanth, B.; Rao, B. R. J. *Mol. Catal. A: Chem.* **2007**, *261*, 180.
89. Nagarapu, L.; Baseeruddin, M.; Apuri, S.; Kantevari, S. *Catal. Commun.* **2007**, *8*, 1729.
90. Khodaei, M. M.; Khosropour, A. R.; Moghanian, H. A. *Synlett* **2006**, 916.
91. Patil, S. B.; Singh, P. R.; Surpur, M. P.; Samant, S. D. *Ultrason. Sonochem.* **2007**, *14*, 515.
92. Patil, S. B.; Singh, P. R.; Surpur, M. P.; Samant, S. D. *Synth. Commun*. **2007**, *37*, 1659.
93. Srihari, G.; Nagaraju, M.; Murthy, M. M. *Helv. Chim. Acta.* **2007**, *90*, 1497
94. Shaterian, H. R.; Yarahmadi, H.; Ghashang, M. *Tetrahedron* **2008**, *64*, 1263.
95. Shaterian, H. R.; Yarahmadi, H. *Arkivoc* **2008**, *2*, 105.
96. (a) Weiss, J.; V. C. H Verlags gesellschaft mbH, IInd ed., VCH Publisher, Inc. New York, Weinheim, Germany **1995**; (b) Small, H. Ion Chromatography, Plenum Press, New York and London **1989**.
97. Boyer, J. L.; Gilot, B.; Canselierm, J. P. *Phosphorus, Sulphur and Silicon Relat. Elem.* **1984**, *20*, 259.
98. (a) Joshi, R. S.; Mandhane, P. G.; Diwakar, S. D.; Gill, C. H. *Ultrason. Sonochem.* **2010**, *17*, 298; (b) Niralwad, K. S.; Shingate, B. B.; Shingare, M. S. *Ultrason. Sonochem*. **2010**, *17*, 760.
99. Kundu, D.; Majee, A.; Hajra A. *Catal. Commun.* **2010**, *11*, 1157.
100. Khazaeia, A.; Zolfigol, M. A.; Moosavi-Zare, A. R.; Zare, A.; Parhami, A.; Khalafi,-N. A. *Applied Catalysis A: General* **2010**, *386*, 179.
101. Zare, A.; Hasaninejad, A.; Rostami, E.; Moosavi-Zare, A. R.; Pishahang, N.; Roshankar, M.; Khedri, F.; Khedri, M. *E-Journal of Chem*. **2010**, *7*, 1162.

102. Ansari, S. A. M. K.; Sangshetti, J. N.; Kokare, N. D.; Wakte, P. S.; Shinde, D. B. *Ind. J. Chem. Tech.* **2010**, *17*, 71.
103. Gowravaram, S.; Arundhathi, K.; Sudhakar, K.; Sastry, B. S.; Yadav, J. S. *J. Heterocyclic Chem.* **2010**, *47*, 272.
104. Supale, A. R.; Gokavi, G. S. *J. Chem. Sci.* **2010**, *122*, 189.
105. Ghorbani-V. R.; Malaekehpour, S. M. *Cent. Euro. J. Chem*. **2010**, *8*, 1086.
106. Chavan, N. L.; Naik, P. N.; Nayak, S. K.; Kusurkar, R. S. *Synth. Commun.* **2010**, *40*, 2941.
107. Lei, M.; Maa, L.; Hu, L. *Tetrahedron Lett.* **2009**, *50*, 6393.
108. Nandi, G. C.; Samai, S.; Kumar, R.; Singh, M. S. *Tetrahedron Lett.* **2009**, *50*, 7220.
109. Hajipour, A. R.; Ghayeb, Y.; Sheikhan, N.; Ruoho, A. E. *Tetrahedron Lett.* **2009**, *50*, 5649.
110. Huang, L.; Yuon, X.; Yu, D.; Lee, K. H.; Chin, H. C. *Virology* **2005**, *332*, 623.
111. Lin, C. M.; Huang, S. T.; Lee, F. W.; Sawkuo, H.; Lin, M. H. *Bioorg. Med. Chem.* **2006**, *14*, 4402.
112. Bhat, M. A.; Siddiqu, N.; Khan, S. A. *Indian J. Pharm. Sci.* **2006**, *68*, 120.
113. Massimo, C.; Francesco, E.; Federica, M.; Carla, M. M.; Prieto, G. S.; Carlos, R. J. *Aust. J. Chem*. **2003**, *56*, 59.
114. Ruszat, R.; Wyler, S.; Forster, T.; Reich, O.; Christian, G. S.; Thomas, C. G.; Sulser, T.; Bachmann, A. *Eur. Assoc. Urol*. **2006**.
115. Tyagi, A. K.; Raj, H. G.; Vohra, P.; Gupta, G.; Kumari, R.; Kumar, P.; Gupta R. K. *Eur. J. Med. Chem.* **2003**, *40*, 413.
116. Modrana, J. N.; Nawrot, E.; Graczy, K. *Eur J. Med. Chem.* **2006**, *41*, 1301.
117. Sardari, S.; Mori, Y.; Horita, K.; Micetich, R. G.; Nishibe, S.; Daneshtalab, M. *Bioorg. Med. Chem*. **1999**, *7*, 1933.
118. Elinos-Baez, C.; Leon, M. F.; Santos, E. *Cell. Biol. Int.* **2005**, *29*, 703.
119. Mohanty, N.; Rath, P. C.; Rout, M. K. *Indian Chem. Soc.* **1967**, *44*, 1001.
120. Shivashankar, K.; Kulkarni, M. V.; Shastri, L. A.; Rasal, V. P.; Rajendra, S. V. *Phosphorus Sulfur Silicon Relat. Elem.* **2006**, *181*, 2187.
121. Ghate, M. D.; Jadhav, V. B.; Shastri, A.; Kulkarni, M. V.; Kulkarni, G. M.; Chen, C. H. Sun, C. M. *Tetrahedron Lett.* **2008**, *49*, 4394.
122. (a) Kumar, S.; Joshi, S. S. *Indian J. Appl. Chem.* **1963**, *26*, 149; (b) Furuta, T.; Watanabe, T.; Tanabe, S.; Sakyo, J.; Matsuba, C. *Org. Lett.* **2007**, *9*, 4717.
123. Von Pechmann, H. C.; Duisberg, C. *Ber. Dtsch. Chem. Ges*. **1884**, *17*, 929.
124. Johnson, J. R. *Org. React.* **1942**, *1*, 210.
125. Jones, G. *Org. React.* **1967**, *15*, 204.
126. Brafola, G.; Fringuelli, F.; Piermatti, O.; Pizzo, F. *Heterocycles* **1996**, *43*, 1257.

127. Von Pechmann, H.; Duisberg, C. *Ber. Dtsch. Chem. Ges*. **1883**, *16*, 2119.
128. Robertson, A.; Sandrock, W. F.; Hendry, C. B. *J. Chem. Soc.* **1931**, *24*, 26.
129. Sethna, S. M.; Shah, N. M.; Shah, R. C. *J. Chem. Soc.* **1938**, 228.
130. Woods, L. L.; Sapp, J. *J. Org. Chem.* **1962**, *27*, 3703.
131. Potdar, M. K.; Mohile, S. S.; Salunkhe, M. M. *Tetrahedron Lett.* **2001**, *42*, 9285.
132. Selvakumar, S.; Chidambaram, M.; Singh, A. P. *Catal. Commun*. **2007**, *8*, 777.
133. Bose, D. S.; Rudradas, A. P.; Babu, M. H. *Tetrahedron Lett*. **2002**, *43*, 9195.
134. Rajitha, B.; Naveen, K. V.; Someshwar, P.; Venu Madhav, J.; Narsimha Reddy, P.; Thirupathi Reddy, Y. *Arkivoc* **2006**, *xii*, 23.
135. Kadnikov, D. V.; Larock, R. C. *Org. Lett.* **2000**, *2*, 3643.
136. Mandhane, P. G.; Joshi, R. S.; Ghawalkar, A. R.; Jadhav, G. R.; Gill, C. H. *Bull. Korean Chem. Soc.* **2009**, *30*, 2969.
137. Feng, X.; Hong-Xia, L.; Jin-Ping, W.; You-Ping, T.; Jian-Jun, W. *J. Chem. Res.* **2008**, *12*, 707.
138. Mandhane, P. G.; Joshi, R. S.; Nagargoje, D. R.; Gill, C. H. *Tetrahedron Lett.* **2010**, *51*, 1490.
139. Bogdal, D.; Pielichowski, J.; Jaskot, K. *Heterocycles* **1997**, *45*, 15.
140. Abehaim, D.; Diez-Barra, E.; de la Hoz, A.; Loupy, A.; Sanchez-Migallon, A. *Heterocycles* **1194**, *38*, 793.
141. Qiang, W.-L.; Yang, C.-G.; Wu, Y.-F.; Yang, L.-M. *J. Chin. Chem. Soc.* **2009**, *56*, 606.
142. Moghaddam, F. Matloubi, M. Z.; Saeidian, H. *Transactions C: Chem. Chem. Eng.* **2009**, *16*, 12.
143. Joshi, R.; Chudasama, U. *J. Sci. Indus. Res.* **2008**, *67*, 1092.
144. Jung, K.; Park, Y.-J.; Ryu, J.-S. *Synth. Commun.* **2008**, *38*, 4395.
145. Chavan, F.; Madje, B.; Bharad, J.; Ubale, M.; Ware, M.; Shingare, M.; Shinde, N. *Bull. Catal. Soc. India* **2008**, *7*, 41.
146. Soares, V. C. D.; Alves, M. B.; Souza, E. R.; Pinto, I. O.; Rubim, J. C.; Kleber, C.; Andrade, Z.; Suarez, P. A. Z. *Int. J. Mol. Sci.* **2007**, *8*, 392.
147. Reddy, B. M.; Patil, M. K.; Lakshmanan, P. *J. Mole. Catal. A: Chem.* **2006**, *256*, 290.
148. Stoyanov, E. V.; Mezger, J. *Molecules* **2005**, *10*, 762.