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Research Article

MULTICOMPONENT REACTIONS (MCRS) AS A GREEN APPROACH TOWARDS THE SYNTHESIS OF VARIOUS HETEROCYCLIC COMPOUNDS

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ABSTRACT
Green Chemistry is a philosophy of chemical research and engineering that encourages the design of products and processes that minimize the use of and generation of hazardous substances. For, example solvent free organic syntheses have offered more advantages as compared to homogenous counter parts as the growing concern for the influence of the organic solvent on the environment as well as on human body. Catalysts are extensively used and have played an important role in making bulk chemical manufacturing. If they are recyclable then more preferred and the process becomes environmentally benign. Similarly reactions promoted by microwave or ultra sound irradiation have already established their importance in synthetic organic chemistry. Shorter reaction time, excellent yields and easy workup are additional convenience offered by these techniques. In recent years, various multi-component reactions supported by these techniques are used to synthesize various heterocycles which is a key nucleus for various drugs.
Heterocycles make up an exceedingly important class of compounds. In fact more than half of all known organic compounds are heterocyclic. The basic skeleton of the genetic material (DNA) is made up of heterocyclic like adenine, guanine, cytosine and thymine. Many natural drugs such as quinine, procaine, codeine, morphine and reserpine are heterocycles. Almost all the compounds we know as synthetic drugs such as diazepam, chlorpromazine, isoniazid, metronidazole and azidothymidine, are also heterocyclic.

***Key Words**: Multicomponent Reactions (MCRS), Green Chemistry, Heterocyclic Compounds*

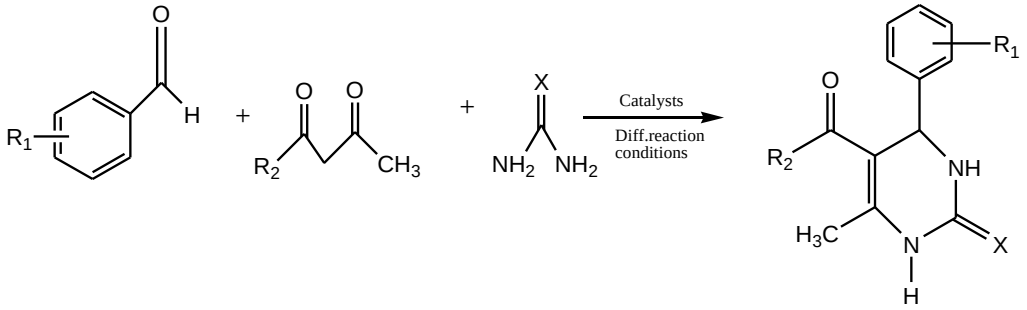
INTRODUCTION
Chemistry has a lot of fascinating fact; one such is hetero cyclic compounds. Every first step of life starts with hetero-cyclic compounds. Every man's potential to think, intelligence, behavior, character depends on his gene. The basic skeleton of the genetic material (DNA) (Russell and Peter, 2001) is made up of hetrocycles like adenine, guanine, cytosine and thymine. Thus knowing about heterocyclic compound and its application is part of venturing human life.
Heterocycles make up an exceedingly important class of compounds (Maes, 2006-2013). In fact more than half of all known organic compounds are heterocycles. Many natural drugs such as quinine, procaine, codeine, morphine and reserpine are heterocycles. Almost all the compounds we know as synthetic drugs such as diazepam, chlorpromazine, isoniazid, metronidazole and azidothymidine, are also heterocycles. Some dyes (e.g. mauveine), luminophores, (e.g. acridine orange), pesticides (e.g. diazinon) and herbicides (e.g. paraquat) are also heterocyclic in nature.
Many natural drugs such as quinine, procaine, codeine, morphine and reserpine are heterocycles. Almost all the compounds we know as synthetic drugs such as diazepam, chlorpromazine, isoniazid, metronidazole and azidothymidine, are also heterocycles. Some dyes (e.g. mauveine), luminophores, (e.g. acridine orange), pesticides (e.g. diazinon) and herbicides (e.g. paraquat) are also heterocyclic in nature.
Many natural drugs such as quinine, procaine, codeine, morphine and reserpine are heterocycles. Almost all the compounds we know as synthetic drugs such as diazepam, chlorpromazine, isoniazid, metronidazole and azidothymidine. By seeing the importance of heterocyclic compounds, it is advisable to synthesize them. Green chemistry emphasizes the development of environmentally benign chemical processes and technologies (Anastas and Warner, 1998). Multi component reactions (MCRs) are

processes in which three or more reactants are combined in a single chemical step to produce products that incorporate substantial portions of all the reactants. MCRs comply with the principles of green chemistry in terms of economy of steps as well as many of the stringent criteria of an ideal organic synthesis. These reactions are effective in building highly functionalized small organic molecules from readily available starting materials in a single step with inherent flexibility for creating molecular complexity and diversity coupled with minimization of time, labor, cost and waste products (Zhuj and Bienayme, 2005). Hence, the development of multi-component reaction protocols for the synthesis of heterocyclic compounds has attracted various medicinal chemists.Some of the Multicomponent Reactions (MCRs) are as under, which can be exploited for constructing various heterocycles, eventually lead to different synthetic drugs.

Synthesis of Dihydropyrimidine-2(1h) One Derivative (Biginelli Reaction)

In recent years, dihydropyrimidine-2(1H)one derivatives have gained much interest for their biological and pharmaceuticals Properties such as HIV gp-120-CD_4 inhibitors calcium channel blockers (Atwal *et al.*,1990) α-adrenergic and neuropeptide Y antagonists (Kappe *et al.*,2000). As well as antihypertensive, antitumar, antibacterial, antiinflamatory agent. The scope of this pharmacophore has been further increased by the identification of the Monostrol as a novel as a cell-permeable lead compound for the development of the new anticancer drugs (Mayer *et al.*, 1991) bearing the dihydropyrimidones core. Thus the development of facile and environmental friendly synthetic method towards dihydropyrimidines constitute active area of investigation of in organic synthesis, the first synthetic method for the preparation of dihydropyrimidine-2(1H) ones (DHPMs) was recorded by Biginelli (Biginelli, 1893), that involves the one pot three component condensation of aldehyde, 1, 3-dicarbonyl compounds and urea or thiourea in ethanol under strongly acidic conditions producing DHPMs, albeit in low yields. In the view of the pharmaceuticals importance of these compounds many improved catalytic methods have been developed (Khodaei *et al.*, 2004).Similarly Improvement in Reaction Condition, is always continuously sought (Barluengo *et al.*, 1979).The reaction is shown in scheme-I and mechanism is depicted in Scheme-II (Nazeruddin *et al.*, 2010).

The Synthesis of Dihydropyrimidine-2(1h) Derivatives Scheme-I



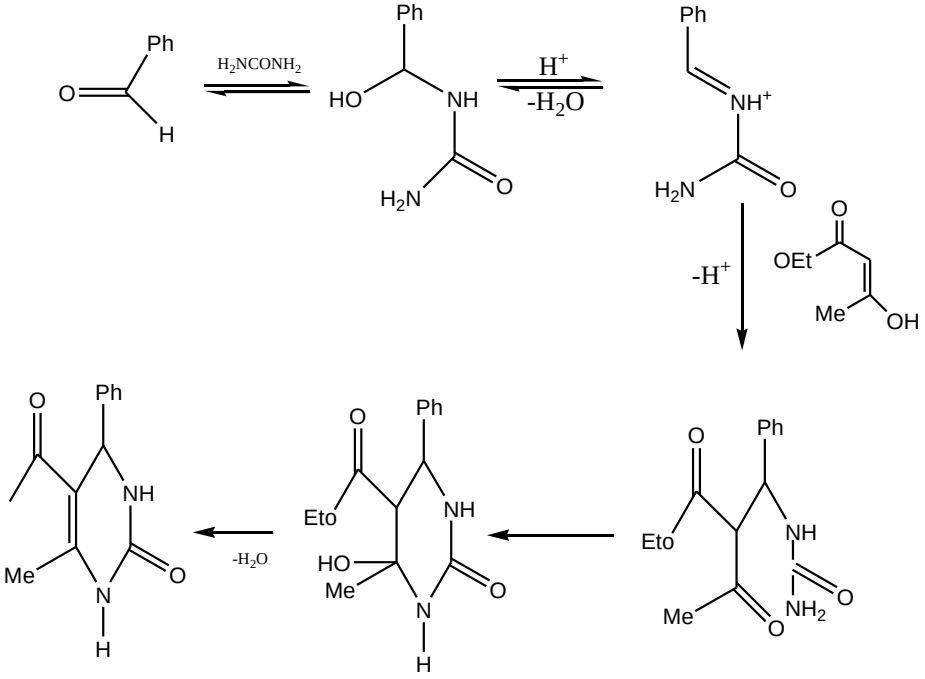
R_1= Diff. Substituent; R_2 = OEt, Me; X= O/S.

Synthesis of Xanthene and Benzoxanthene

Xanthenes and benzoxanthenes have attracted considerable interest because they possess various pharmaceutical activities. In addition, these compounds have been employed as dyes, (Banerjee, 1981) and pH-sensitive fluorescent materials for visualization of biomolecular assemblies (Knight, 1989) and utilized in laser technologies. The well known dyes having xanthene nucleus are Rhodamine B and Rhodamine 6G. Thus a broad utility range has made xanthenes as prime synthetic candidates there by accentuating the need to develop newer synthetic routes for scaffold manipulation of xanthene derivatives. The synthesis of tetrahydrobenzo[a]xanthen-11-ones has been reported in the presence of strontium triflate(Li, 2008) , indium trichloride, phosphorus pentaoxide (Nandi, 2009) $NaHSO_4$-SiO_2 under reflux in halogenated solvents (Das, 2007) for long hours. Thus, there is a need for development of an alternative route to synthesize the xanthene derivatives. In this context, we decided to investigate the possibility of synthesizing tetrahydrobenzo[a]xanthen-11-one derivatives through one-pot three-

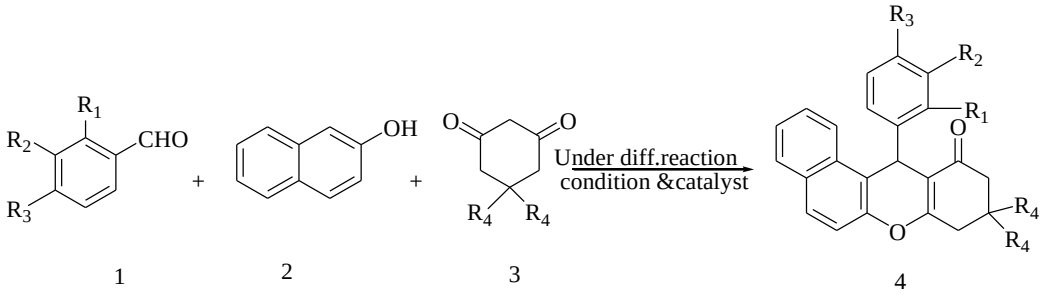
component condensation reaction strategy of β-naphthol with aldehydes and cyclic 1, 3-dicarbonyl compounds using various catalyst such as Silica sulfuric acid (SSA) (Nazeruddin etal,2011)or Amberlyst-15 (Nazeruddin *et al.,* 2011) as an efficient and reusable heterogeneous catalyst has been used for the preparation of 12-aryl-8,9,10,12-tetrahydrobenzo[a]xanthen-11-one derivatives under solvent-free conditions in good to excellent yields and short reaction times.

The Mechanism of the Reaction Dihydropyrimidine-2(1h) Scheme-II



Similarly under microwave irradiation (Nazeruddin *et al.,* 2011) using perchloric acid as catalyst and under ultrasound (Al-Kadasi *et al.,* 2011) irradiation using chlorosulphonic acid ($ClSO_3H$) as a catalyst the desired product was obtain in excellent yield. All these methodologies are efficient and environmentally benign and can be developed further for industrial applications.

Reaction for Synthesis of Xanthene and Benzoxanthene Scheme-III



$R_1,R_2,R_3 = H,Cl,OCH_3,NO_2,OH \quad R_4 = H,CH_3$

Concerning the reaction mechanism, it is proposed that a carbocation is initially formed from aryl aldehydes with β-naphthol; this carbocation is reacted with cyclic 1, 3-dicarbonyl compounds in the second step, which then undergo dehydration to give the final product which is similar to the literature reports (Rashidi-Ranjbar, 2001).

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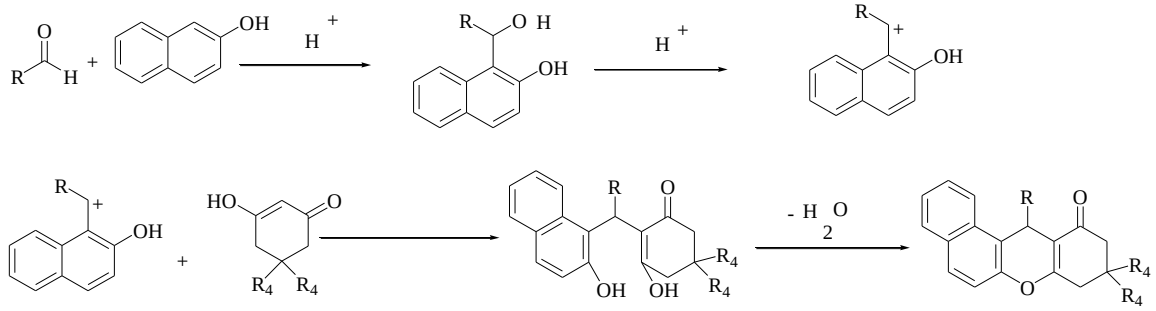
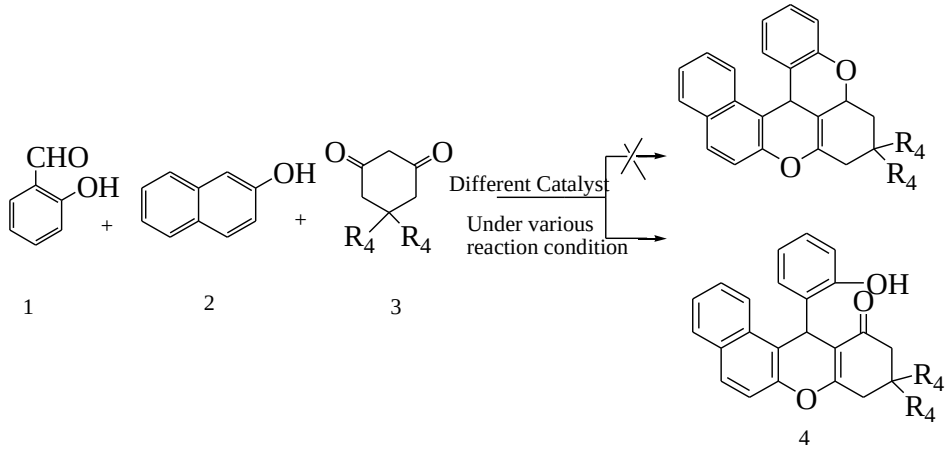
Mechanism of Synthesis of Xanthene and Benzoxanthene Scheme-IV



It is interesting to note that in this multi component reaction there is no formation of epoxide with 2-hydroxy bezaldehyde as depicted in scheme- V. However in literature there are several reports that there is generally epoxide formation in such type of multi component reactions.

Formation of the Desired 12-(2-Hydroxyphenyl)-9, 9-dimethyl-8, 9, 10, 12-tetrahydrobenzo[a]xanthen-11-One without Formation of the Epoxide Scheme-V



One-Pot Synthesis of Highly Functionalized Pyridine Derivatives

Synthesis of pyridine, coupled with high-throughput library screening, this strategy was an important development in the drug discovery in the context of rapid identification and optimization of biologically active lead compounds. Among them, 2-amino-3,5-dicarbonitrile-6-sulfanylpyridines exhibit various pharmacological activities and are useful as anti hepatitis B virus, antiprion (Perrier, 2000) antibacterial (Levy *et al.,* 2005), anti cancer agents (Anderson *et al.,* 2004) and as potassium channel openers for treatment of urinary incontinence (Harada etal, 2002)Moreover, some of these compounds were found to be highly selective ligands for adenosine receptors (Beukers *et al.,* 2004), implicated Parkinson's disease, hypoxia/ischemia, asthma, kidney disease, and epilepsy (Fredholm,2001).

A three-component condensation of aldehyde, malononitrile, and thiol is one of the most prominent existing procedures used for the synthesis of 2-amino-3, 5-dicarbonitrile-6-thio-pyridines. Generally, this condensation has been carried out under basic conditions using various bases such as, Et_3N, DABCO, piperidine (Evdokimov *et al.,* 2006). Morpholine, thiomorpholine, pyrrolidine, N, N-DIPEA, pyridine, 2, 4, 6-collidine, DMAP, aniline, N-methylaniline, N, N-dimethylaniline, and N, N-diethylaniline and DBU (Evdokimov *et al.,* 2007). Moreover, basic ionic liquid 1- methyl-3-butylimidazolium Lewis hydroxide, that is [bmim] OH (Mamgain *et al.,* 2009) and using a variety of Lewis acids such $ZnCl_2$, $AlCl_3$, $FeCl_3$, I_2, Cu $(OTf)_3$, $InCl_3$, and $BF_3.Et_2O$ (Sridhar *et al.,* 2009).

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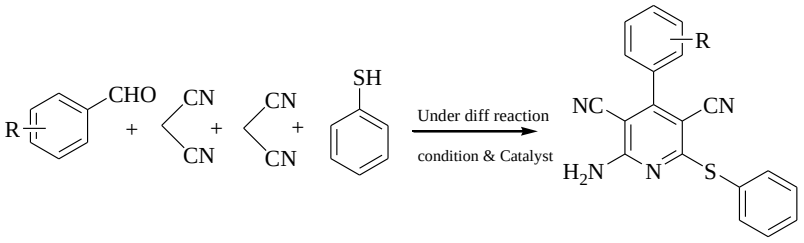
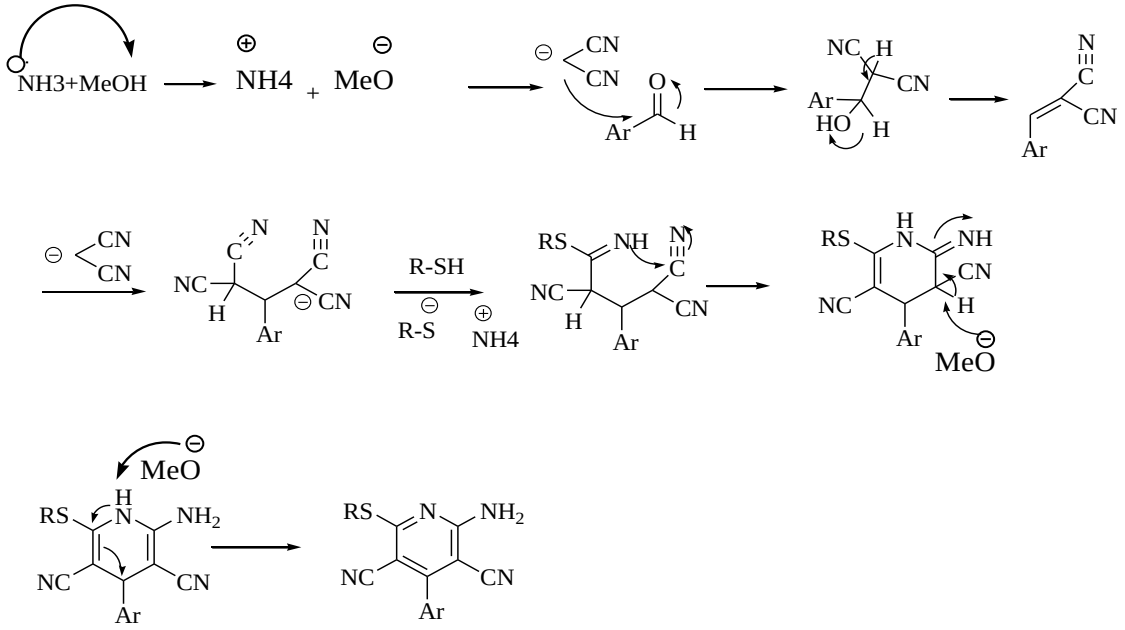
Synthesis of Highly Functionalized Pyridine Derivatives Scheme-VI



1. R=H , 2. R= 4-OCH_3 , 3. R= 4-OH, 4. R= 2-OCH_3, 5.R= 3,4-$(OCH_3)_2$, 6. R= 2-NO_2

Mechanism of Highly Functionalized Pyridine Derivatives Scheme-VII

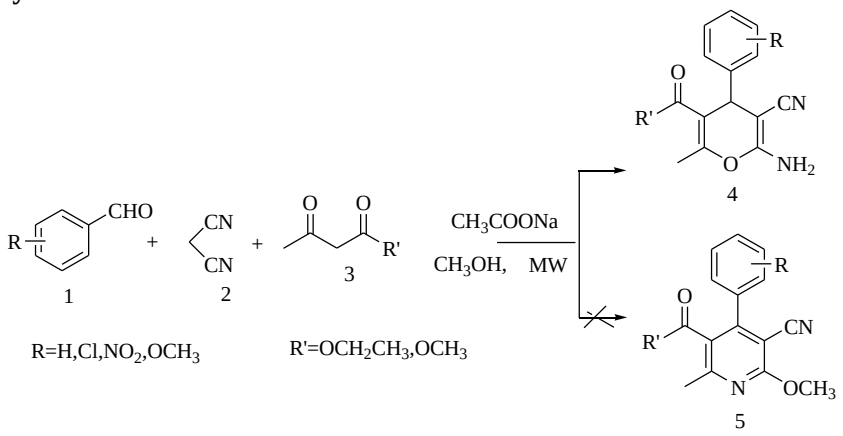


One Pot Synthesis of Poly Functionalized 4h-Pyrans

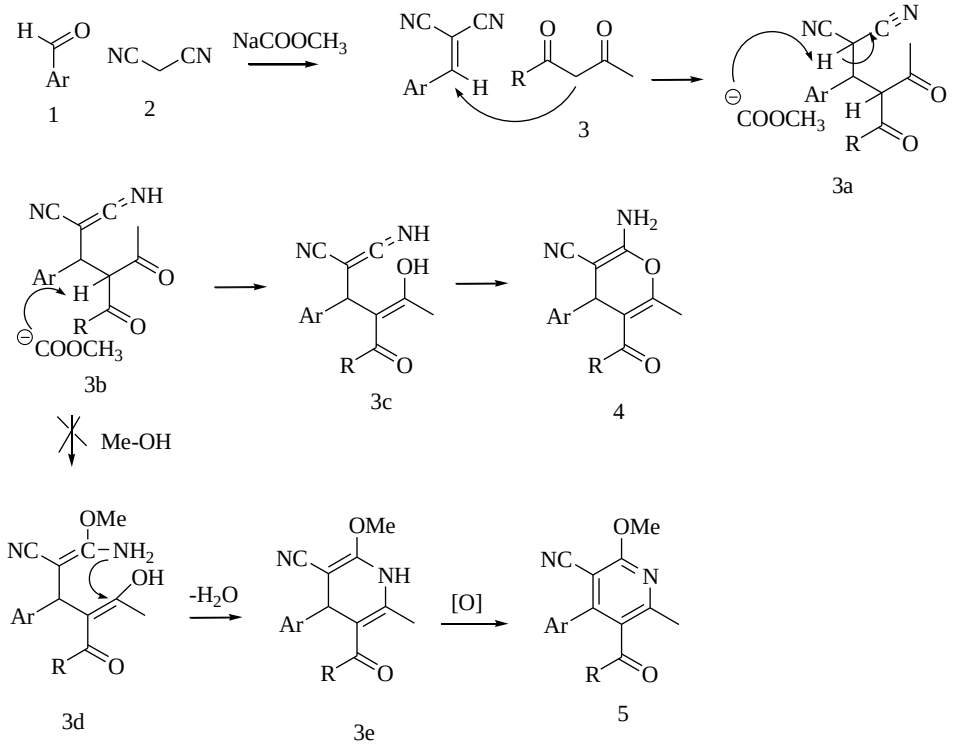
Polyfunctionalized 4H-pyrans constitute a structural unit of a number of natural products (Hatakeyama, etal,1988)and inherent reactivity of the pyran ring is versatile synthons .These 4H-pyrans are isosters of 1, 4-dihydro pyridine (Goldmann *et al.,* 1991) with potential pharmacological interest and active synthons that have been extensively used in heterocyclic synthesis. In addition, polyfunctionalized 4H-pyrans are biologically interesting compounds which possess various pharmacological activities e.g. antiallergic (Witte *et al.,* 1986) and antitumor (Wang *et al.,* 2000) activities. 4H-pyrans are also useful intermediates for the synthesis of various compounds, such as pyranopyridine derivatives polyazanaphthalenes, pyrano[2,3-d]pyrazoles(Quintela *et al.,* 1995),pyrano pyrimidines and pyridin-2-ones (Srivastava,1996), with various other biological activities. The 4H-pyrans are synthesized mainly by a three-components coupling reaction of aromatic aldehydes, malononitrile and β-diketones catalyzed by bases like Triethylamine(Martin *et al.,* 1988), Piperidine (Heber *et al.,* 2003), Rubidium fluoride Recently, Shestopalov and co-workers (Shestopalov *et al.,* 1999) have developed a one-pot electrochemical synthesis of title compounds catalyzed by electro generated base with the yields ranged from 60 to 80%. However, many of these procedures suffer from one or more disadvantages such as harsh reaction conditions, prolonged time period, poor yields and use of hazardous and expensive catalysts. Therefore, the development of a clean, high-yielding and environmentally benign approach is still desirable. We

have reported a clean and efficient method for the synthesis of 4H-pyran derivatives in excellent yields through one-pot condensation of aromatic aldehydes, malononitrile and dicarbonyl compounds using sodium acetate as catalysts in methanol as a solvent under microwave irradiations (Nazeruddin *et al.*, 2012). The reaction is depicted in Scheme-VIII.

Synthesis of 4h-Pyran Derivatives Scheme- VIII



Proposed Mechanism for the Formation of 4h Pyran Derivatives Scheme- IX



CONCLUSION

Thus, a multicomponent reaction (MCR) is a green approach towards the synthesis of various heterocyclic compound and for a researcher there is lot of scope to change the reaction condition, to change the catalyst or to modify the catalyst or even to develop various novel multicomponent reactions.Apart from all these a polyfunctionlised heterocyclic product obtained from a multicomponent reaction can be tailored to novel pharmacophore (Wermuth *et al.*, 1998) as per the need.

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