

RECENT ADVANCES IN KNOEVENAGEL CONDENSATION

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ABSTRACT

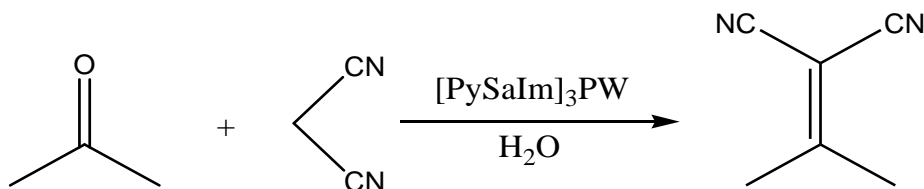
Chemistry of several named reactions have been modified day by day. Because it needs to modify named reactions regarding their procedure modification, catalysis and use of solvents. Literature survey reveals that over last five years the Knoevenagel condensation is one of the prime condensation reaction in pharmaceutical chemistry and other transformations which is used by several chemists and Researchers. Basically it is a Carbon-Carbon bond forming reaction which needs carbonyl compounds containing active methylene group. Here we have described recent developments of Knoevenagel condensations.

KEYWORDS: Because it needs to modify named reactions regarding their procedure modification, catalysis and use of solvents.

INTRODUCTION

The Knoevenagel reaction was most commonly used in synthetic procedures for new sigma bond between two carbon atoms.^[1-5] The reaction is catalyzed by various amines, their corresponding ammonium salts^[9] or Lewis acids (like TiCl₄/base, ZnCl₂, BiCl₃, and CdI₂.bases or acids.). A number of researchers have revealed the effectiveness of acid–base bifunctional catalysts on account of the synchronic activation of carbonyl on acid sites and the capture of the proton from methylene on basic sites. On the other hand, ionic liquids (ILs) are well-known reaction media with the advantages of low volatility, high thermal stability, adjustable solubility, and versatile structures. In particular, “task-specific” ionic liquid catalysts with basic and acidic functional groups have been reported for Knoevenagel reactions.^[6-7]

Boronat and its coworkers reported an acid–base [diamine-A]BF₄ catalyst^[8] used for condensation of benzaldehyde with methylene compounds which needs of bifunctional catalysts or supporting organic bases on acidic porous carriers^[9-10], These efforts could not control the distance between acid and base terminals, which is a key influential factor for Knoevenagel condensation^[11], Thus it is of interest to design an efficient acid–base bifunctional catalyst with a controllable acid–base distance for heterogeneous Knoevenagel condensations.^[12] In year 2012 Mingjue Zhang and others were developed a new acid–base bifunctional catalyst, that abbreviated as [PySaIm]₃PW for Knoevenagel condensations. Scheme-1.



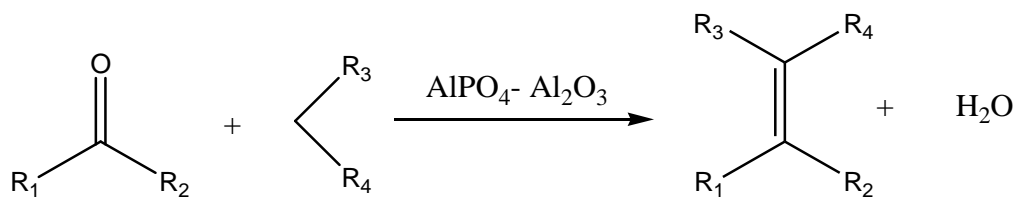
Scheme-1: Solvent Free Knoevenagel condensation.

Thus they believe that catalyst should possess involvement of active sites of acid (the proton of salicyl hydroxyl) and base (the nitrogen of imine) [PySaIm]₃PW within a Schiff base composition.

Jose A. Cabello gave the description of AlPO₄- Al₂O₃ in solid system as the basic catalyst (Heterogeneous phase) for Knoevenagel condensation at r.t. and without solvents. Since discovery of Knoevenagel condensation

has been wide synthetic applications^[13] and is catalyzed by very weak bases or weak base-acid mixture, although their presence is not always indispensable. When aldehydes are used in the reaction as stereoselective, yielding the E isomer Prepared catalyst AlPO₄-Al₂O₃ was used for condensation of O-Hydroxybenzaldehyde 2-Imino-2H-1-benzopyran-3-carbonitrilhaed after 2-0~0-2H-1-benzopyran-3-carbonitrilhaed 2-Imino-2H-1-

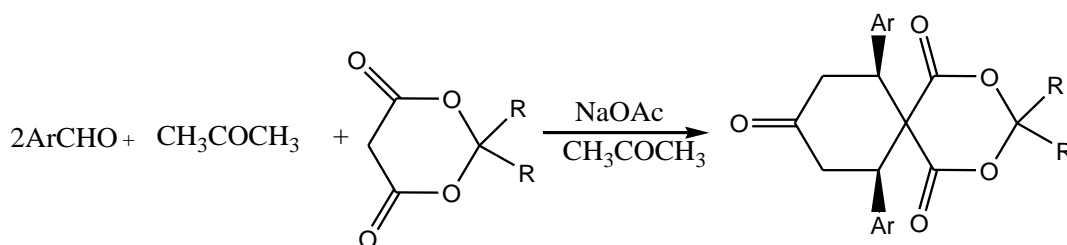
benzopyran-3-carboxylic acid ethyl ester had 2-Oxo-2H-1-benzopyran-3-carboxylic acid ethyl esters.^[14]



Scheme-2: AlPO₄- Al₂O₃ in solid basic catalyst (Heterogeneous phase)

Multicomponent reactions (MCRs) with at least three different substrates reacting in a well-defined manner to form a single compound have emerged as an effective tool for atom economic and benign organic synthesis. Because of their convergence, productivity, facile execution and generation of highly diverse products from easily available starting materials. The design of multicomponent reactions is an important field of research from the point of view of organic synthesis and combinatorial chemistry. In recent years, the hetero-Diels-Alder reactions have been used widely in numerous reactions of prominence in organic synthesis because of their economical and stereo-controlled nature importance.

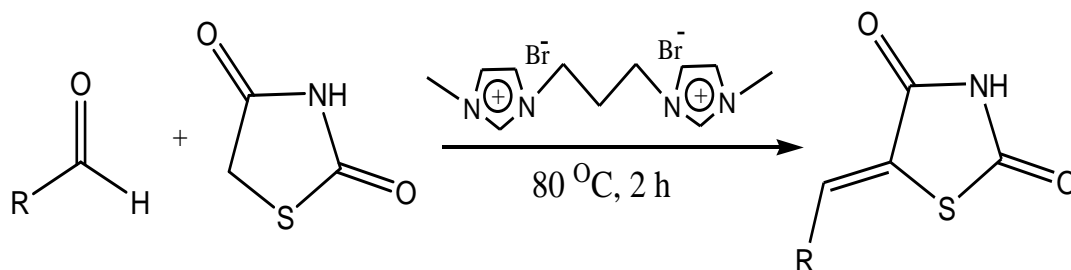
An, Lin *et al* gave method in which sodium acetate catalyst used in three-component reaction of aromatic aldehyde, acetone and Meldrum acid or spiro lactone at room temperature gave stereospecific 7,11-cis-diaryl-2,4-dioxaspiro[5,5]undecane-1,5,9-triones in a very efficient manner. They have developed a three component reaction involving aromatic aldehydes, acetone with Meldrum acid or 1,5-dioxaspiro[5,5]undecane-2,4-dione catalyzed by sodium acetate. This simple and practical approach can be used to prepare efficiently spiranes and dispiranes in a diastereospecific fashion shown in scheme-3.



Scheme 3: Synthesis of 7,11-cis-diaryl-2,4-dioxaspiro[5,5]undecane-1,5,9-triones

It is interesting to find that the prepared spirocyclic compounds in this work were in very pure form because they gave high quality of analytical data only after crystallization in acetone. The formation of the spirocyclic compounds could be rationalized by domino Knoevenagel condensation, aldol condensation and Michael addition.^[15]

Jawale *et al* has worked on environmental benign synthetic route for the synthesis of 5-arylidene-2,4-thiazolidinediones by allowing the condensation of aryl/heteryl aldehydes, with 2,4-thiazolidinedione in 3-methyl-1-[3-(methyl-1H-imidazolium-1-yl)propyl]-1H imidazolium, dicationic ionic liquid at 80°C for 2 h (Scheme-4).

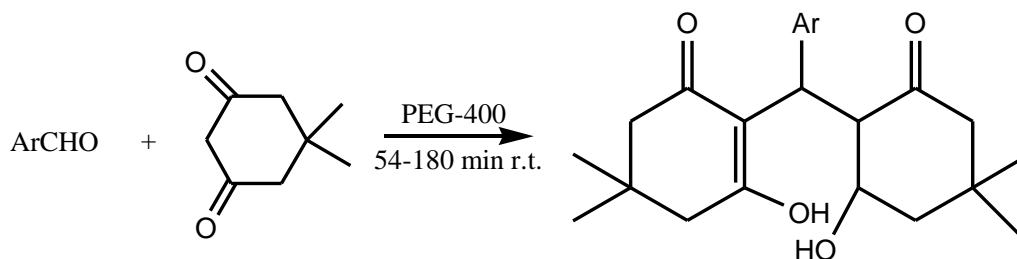


Scheme 4: Synthesis of 5-arylidene-2,4-thiazolidinediones.

Jawale and co-workers gave a safer, economic, one pot synthetic path for the synthesis of 5-arylidene-2,4-thiazolidinediones. The fascinating scope of this synthetic strategy is that products are rapidly obtained with non tedious isolation work up.^[16]

Polyethylene glycol promoted reactions have attracted organic chemists. This solvent possesses unique properties such as recyclability, ease of work up, the thermal stability, no flammability and economical cost. In addition, numerous solvating ability of PEG-400, makes

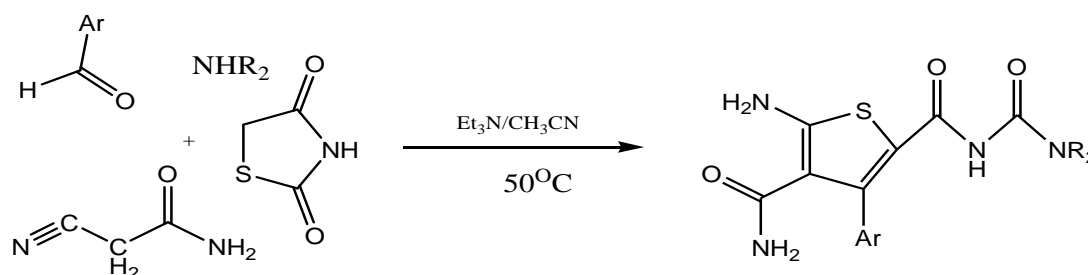
the system homogeneous so allowing molecular interactions to be more efficient.^[17]



Scheme-5: Knoevenagel condensation catalyzed by PEG-400.

Firouzeh and Hossein have established a green and simple method for the preparation of tetraketones. Yao and its coworkers studied Knoevenagel condensation of cyanoacetamide with aromatic aldehyde were found interesting molecular diversity for the Knoevenagel reaction. The domino reactions of cyanoacetamide,

aromatic aldehydes, 1,3-thiazolidinedione and cyclic secondary amines yielded the poly substituted thiophenes it is the basic catalytic Knoevenagel condensation of cyanoacetamide with aromatic aldehyde gives arylidencyanoacetamide^[18] shown in scheme 6.

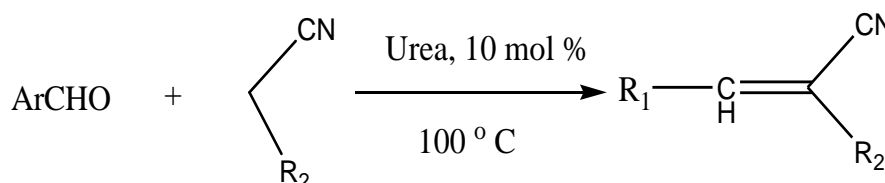


Scheme 6: The synthesis of thiophenes four components reaction.

The Knoevenagel-Doebner reaction is widely recognized as the main method to construct the carbon-carbon double bond, which is necessary to provide the α,β -unsaturated carboxylic acids.^[19-21]

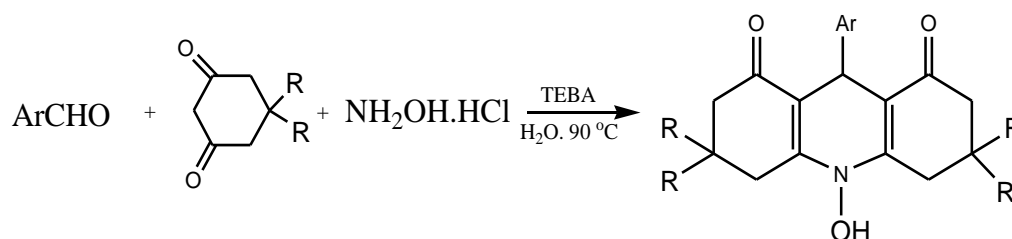
Recent days are awareness of environmental issues in chemical research and industry. Efficient, economic and clean procedure has received increased attention in recent years. According to this, Sun *et al* gave the reaction of cinnamaldehyde with ethyl cyanoacetate was

then probed and quantitative yield was also achieved.^[22] The nitro, hydroxyl, heterocycle and carbon-carbon double bond are well tolerable to the reaction conditions. It could be due to the short reaction time and relatively mild reaction conditions. It is an efficient and green procedure for the Knoevenagel condensation has been reported. Its advantages are inexpensive and easily available catalyst, short reaction time, excellent yields, and environmentally friendly reaction conditions shown in scheme 7.



Scheme-07: Knoevenagel Condensation using Urea.

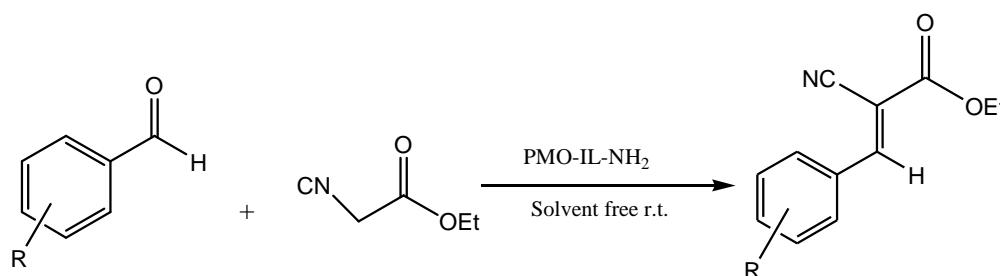
Shi *et al*^[22a] reported one-pot synthesis of *N*-hydroxylacridine derivatives in aqueous media. The given method is also a convenient and attractive alternative to the existed methods for synthesis of acridines as shown in scheme 08.



Scheme-08: Synthesis of acridines.

Dawood Elhamifar et al gave a novel amine-functionalized ionic liquid-based periodic mesoporous organosilica (PMO-IL-NH₂)^[23] was prepared and characterized. It's catalytic performance was investigated in the Knoevenagel reaction. PMOIL- NH₂ was prepared

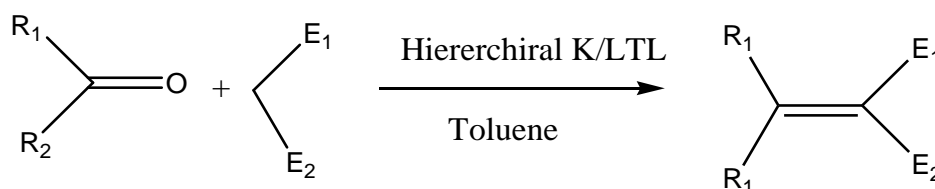
by simultaneous co-condensation of 3-aminopropyltrimethoxysilane, an ionic liquid and tetramethoxysilane in the presence of a surfactant template under acidic conditions shown in scheme 9..



Scheme-9: The Knoevenagel condensation of aldehyde with ethyl cyanoacetate in the presence of PMO-IL-NH₂ nanocatalyst.

A new protocol of cascade synthesis for biologically active 2-cyanoacrylamides was developed. The reaction proceeds over a novel magnetically retrievable solid-acid composite of iron oxide, poly(vinylpyrrolidone) and phosphor tungstic acid (Fe₃O₄/PVP-PWA) in AcOH-H₂O medium under reflux conditions. This transformation is facilitated through single-site Brønsted acid catalyzed cascade reactions involving deacetalization and/or Knoevenagel condensation followed by selective monohydration of nitriles starting from acetals and aldehydes with malononitrile as shown in scheme 10.

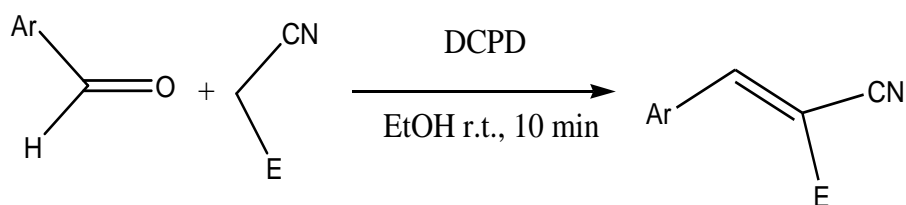
Zakaria Benzekri describes the catalytic activities of dicalcium phosphate dihydrate (DCPD) in the condensation reaction of various substituted benzaldehydes with active methylene compound malononitrile.^[24] The influences of reaction conditions on the corresponding catalytic behavior have been investigated. The results showed that the DCPD exhibited high catalytic activity, versatility and it can be recycled without significant loss of its activity for the condensation reactions as shown in scheme 11.



Scheme-11: Knoevenagel Condensation reaction using hiererchiral K/LTL catalyst.

The phosphate compound is an environmentally useful substance with good mechanical power and stability. Most of heterogeneous catalysts have been reported for the Knoevenagel condensation reaction, some of them are lies on phosphate calcium catalyst. Chemist reports dicalciumphosphatedihydrate (DCPD) used as catalyst

for the Knoevenagel condensation reaction. The catalyst has retains and recovered property. The optimization were done screening of the catalyst quantity, progress of reaction(time), solvent and temperature for the Knoevenagel condensation reaction between benzaldehyde and malononitrile.



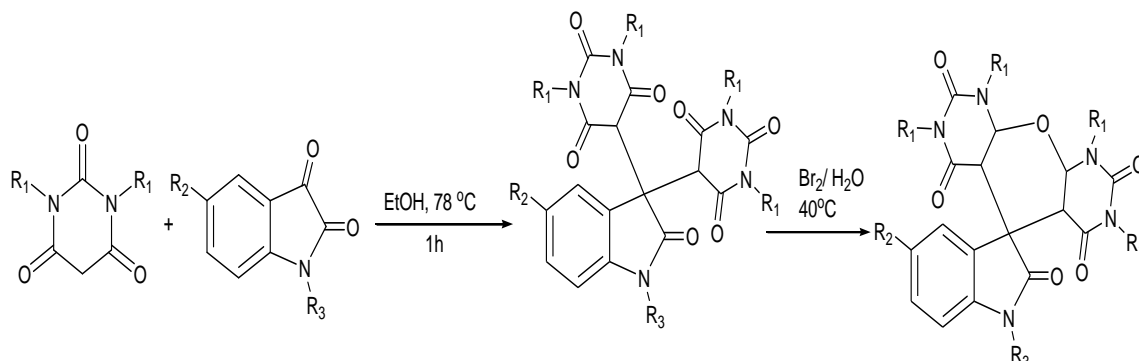
Scheme: 12: DCPD as catalyst for the Knoevenagel condensation.

Zakaria Benzekri and its coworkers employed DCPD as a new and efficient catalyst for the Knoevenagel condensation of aromatic aldehydes with active methylene compounds in ethanol. Furthermore, the attractive features of this method are the green and mild Barbituric acid was first discovered by a German chemist, Adolf von Baeyer in 1864.^[25] It was synthesized through a condensation reaction of urea with malonic acid. The derivatives of barbituric acid commonly known as barbiturates have a special place in pharmaceutical chemistry because of their biological activities such as hypnotic^[26-27], sedative^[28], anticonvulsant^[29-30], antimicrobial^[31], anaesthetic^[32], anticancer and antitumor properties.^[33-34] Multicomponent reactions are generally

reaction conditions, short reaction times, excellent yields and operational simplicity. The catalyst can be recycled more than seven times without obvious loss of catalytic activity.^[24]

defined as reactions where more than two starting materials react to form a product, incorporating essentially all of the atoms of the adducts.

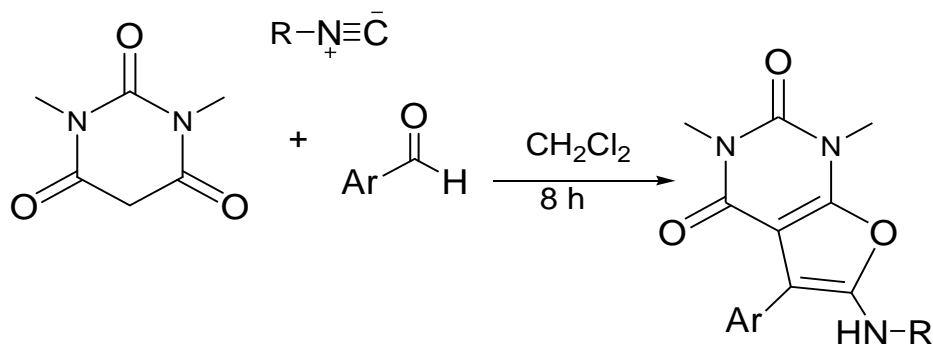
M. N. Elinson gave cascade process for one-pot transformation of barbituric acids and is at ins by the direct action of the only bromine in ethanol resulted in the formation of substituted 2''H-dispiro[indole-3,5'-furo[2,3- d]pyrimidine^[35] as shown in Scheme 13.



Scheme-13: Formation of substituted 2''H-dispiro[indole-3,5'-furo[2,3- d]pyrimidine.

M. T. Maghsoodlou explains a new furo[2,3-d]pyrimidine derivatives were obtained by three-component condensation reaction of isocyanides,

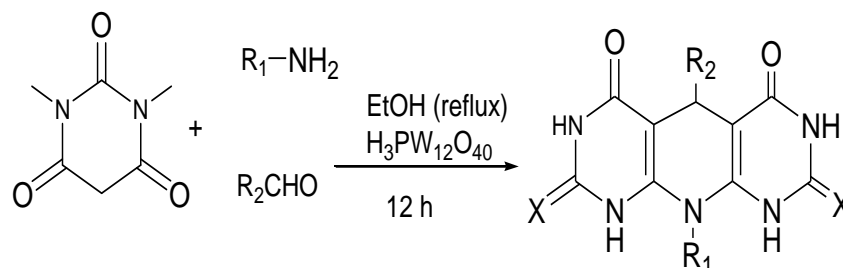
aldehydes and 1,3-dimethylbarbituric acid at room temperature without any prior activation or modifications^[36] (Scheme 14).



Scheme-14: Synthesis' of Furo[2,3-d]pyrimidine.

F. Panahi was done synthesis of a set of pyrimidine-fused heterocycles via the treatment of barbituric acid with amines and aldehydes allowed the discovery of new

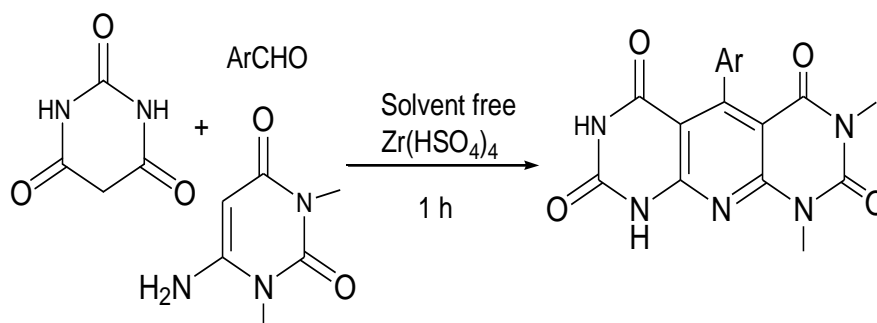
ligands with modest and selective inhibitory activity^[37] as shown in scheme 15.



Scheme-15: Synthesis of a set of pyrimidine-fused heterocycles.

The studies done by A. R. Bhat (2015) and G. Mohammadi Ziarani (2015) of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)^[38] and SBA-Pr-

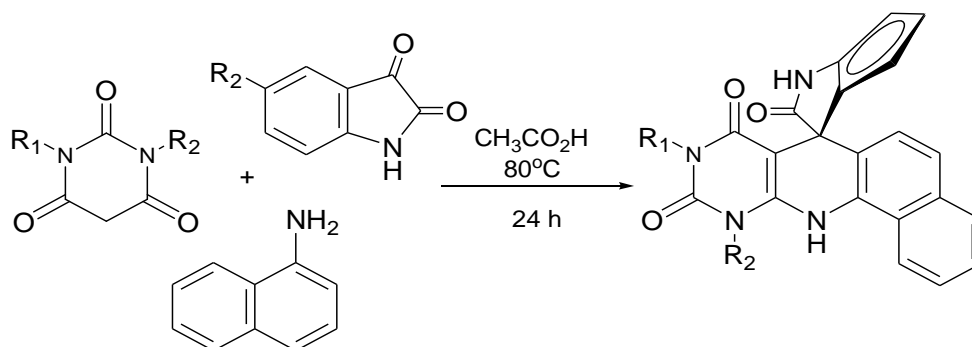
SO₃H^[39] have been reported as efficient catalysts in this reaction.



Scheme-16: Synthesis of 1,8-diazabicyclo[5.4.0]undec-7-ene.

Rahmati and Eskandari-Vashareh have reported an efficient one-pot synthesis of a new series of spiro[benzo[h]quinoline-7,3'-indolines] by the reaction

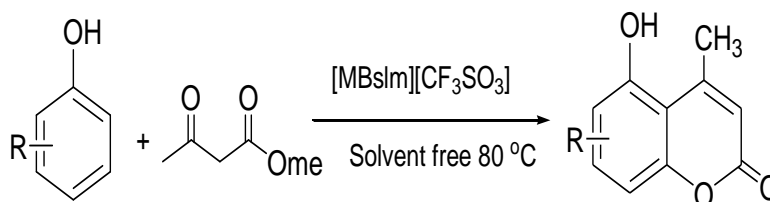
of isatins, 1-naphthylamine and barbituric acid in acetic acid^[40] as shown in scheme 17.



Scheme-17: Synthesis of spiro[benzo[h]quinoline-7,3'-indolines]

Ionic liquids (ILs) have recently emerged as a potential replacement for toxic, hazardous, flammable, and highly volatile organic solvents (VOCs) and as a catalyst under solvent-free conditions.

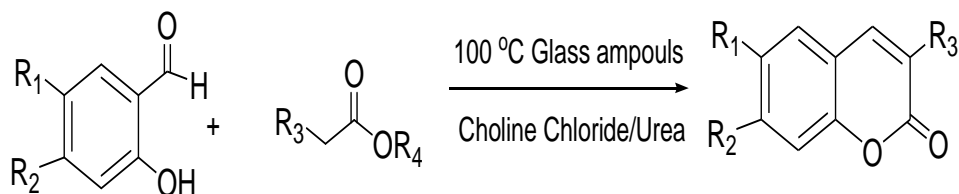
In 2005 Gu *et al.* disclosed the non-chloroaluminate acidic ionic liquid [MBSIm][CF₃SO₃]^[41] as the best catalyst among the four tested ionic liquids for the synthesis of eight coumarin derivatives via Pechmann reactions between phenols and methyl acetoacetate under solvent-free conditions (scheme 18).



Scheme-18: Pechmann reaction performed in ionic liquid [MBSIm][CF₃SO₃]

Choline chloride/urea is the first ionic liquid that belongs to the family of deep eutectic solvents (DES). Hosanagara et al. showed that choline chloride/urea can be effectively used as a solvent and catalyst for the synthesis of 3-substituted coumarins via Knoevenagel

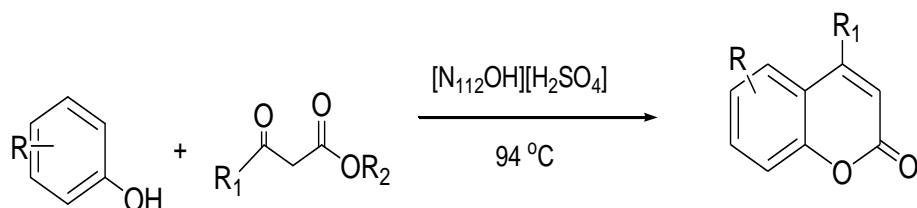
condensation between substituted salicylaldehydes and active methylene compounds (scheme 19). Coumarin analogues were obtained in very high yield over 93% within 1-4 h.



Scheme: 19: Synthesis of various 3-substituted coumarins via Knoevenagel condensation in choline chloride/urea.

The developed synthetic approach produces better results than conventional methods both in regards of reaction times and yields. Moreover, choline chloride/urea is soluble in the water helping the isolation of the products.^[42]

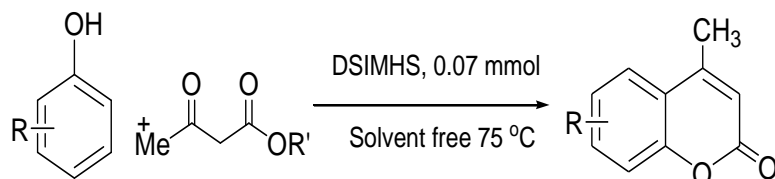
Zhang and coworkers identified the ionic liquid N,N' -dimethylaminoethanol hydrosulfate ($[N_{112}OH][HSO_4]$) as a nontoxic catalyst for the synthesis of coumarin analogs under solvent free conditions^[45] shown in scheme 20.



Scheme-20: Synthesis of coumarin analogs in the presence of $[N_{112}OH][H_2SO_4]$

In 2015 Shirini et al. presented the synthesis of coumarin derivatives via Pechmann condensation in the presence of 1,3-Disulfonic acid imidazolium hydrogen sulfate

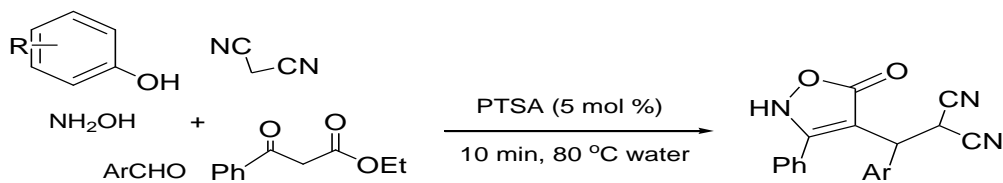
(DSIMHS) as an inexpensive catalyst under solvent-free conditions^[43] shown in scheme 21.



Scheme-21: DSIMHS as a catalyst in the synthesis of coumarin derivatives.

Isoxazole derivatives are classified as one of the privileged useful synthetic building blocks in medicinal chemistry^[44] Isoxazol-5(2H)-ones are classified as an important class of isoxazole derivatives. Therefore

several synthetic strategies have been reported in the literature to produce isoxazol-5(2H)-ones derivatives in the past few years shown in scheme 22.

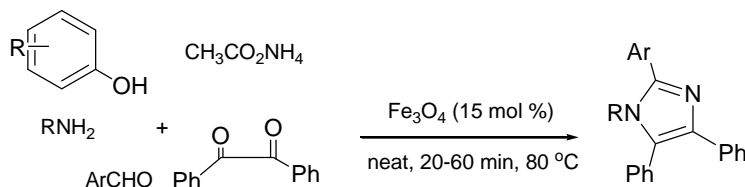


Scheme: 22: Four component synthesis of isoxazol-5(2H)-one.

Sarrafı Yaghoob and Eghtedari Mohammad reported a simple, efficient, and environmentally friendly approach for the synthesis of isoxazol-5(2H)-ones in the presence of PTSA in water. Aqueous media, excellent yields and simple purification step along with utilization of

inexpensive starting materials are considered as the main advantages of this method mixing ethyl benzoylacetate and hydroxylamine in the presence of PTSA (5 mol%). Then, aromatic aldehyde and malononitrile were added. The reaction was completed at 80°C in water within 10

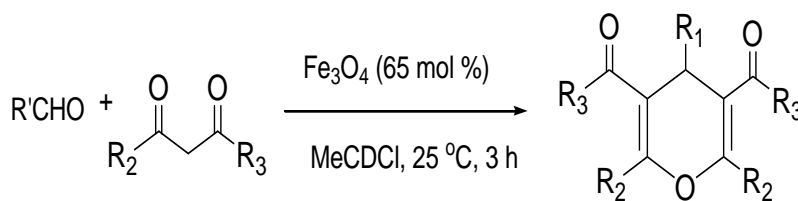
minutes producing isoxazol-5(2H)-one derivatives^[45] as shown in scheme-23.



Scheme: 23: Fe₃O₄ Catalyzed synthesis of imidazoles.

The synthesis of imidazoles^[46], as well as other heterocycles,^[47] has also been described. The synthesis was accomplished in absence of solvent and the magnetite could be recycled ten times without detriment on yields. As in the previous case, the magnetite structure was confirmed by XRD and the same size was maintained after these cycles Shown in scheme 24.

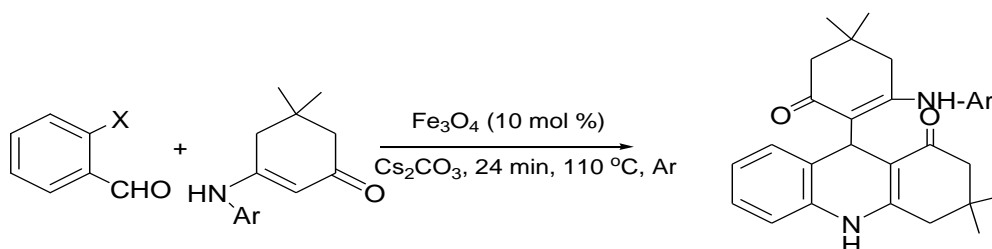
The Knoevenagel condensation, used magnetite as an efficient and recyclable catalyst. Thus, in 2011, this reaction followed by a Michael-type addition and subsequent dehydration lead to the synthesis of 4-substituted-4H-pyrans, in a cascade process^[48-49] as shown in scheme 24.



Scheme-24: Fe₃O₄ catalyzed 4H-pyrans synthesis

Most of heterocyclic was synthesized using Knoevenagel condensation as starting step.^[50-51] The synthesis of 1,4-dihydroquinolines was accomplished.^[48] The synthesis of these substrates was performed by a protocol involving a

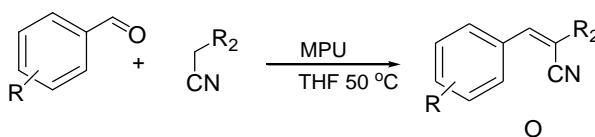
Knoevenagel condensation, an enamine Michael-type addition and an intra molecular CN cross coupling (Buchwald–Hartwig type reaction) shown in scheme 25.



Scheme-25: Fe₃O₄-catalyzed 1,4-dihydroquinolines synthesis.

The development of functional porous organic frameworks (POFs) assembled from simple molecular building blocks have gained considerable attention in recent times,^[52-53] mainly because of their potential applications in gas storage and separation,^[54] catalysis,^[55] optoelectronics^[56] and nanotechnology.^[57] Considering a number of covalent linkages that can be derived by

applying different synthetic reactions of a wide variety of molecular building blocks, it has become increasingly important to develop new functional POFs having high specific surface area, catalytically active pore surface, and remarkable chemical and thermal stability shown in scheme 26.



Scheme: 26Knoevenagel condensation using MPU

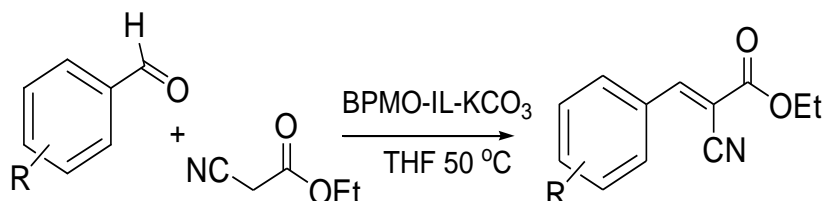
Sandeep Kumar Dey have reported a catalytically active new microporous polyurethane material with sponge like morphology obtained by solvothermal synthesis in

DMSO. Due to its confined microporosity and the presence of mildly basic urethane (carbamate) functional groups along the pore walls, the MPU showed catalytic

efficiency with pronounced size selectivity in the Knoevenagel condensation of aromatic aldehydes with malononitrile or methylcyanoacetate.^[58]

The discovery of periodic mesoporous organosilicas (PMOs) with unique physicochemical properties.^[59-61]

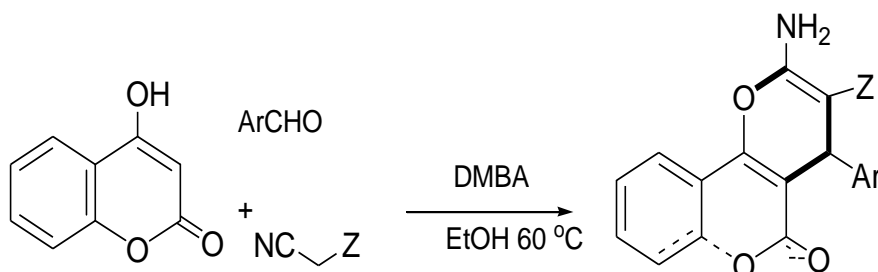
Dawood Elhamifar and Somayeh Kazempoor gave route for Knoevenagel reaction of novel ionic liquid based bifunctional periodic mesoporous organosilica supported potassium carbonate which was prepared, characterized and its catalytic activity was investigated^[62] as shown in scheme 27.



Scheme: 27: The Knoevenagel condensation of aldehyde with ethyl cyanoacetate in the BPMO-IL-KCO₃

The multicomponent reactions (MCRs) play an essential role in modern organic synthesis for the construction of several bonds in a one-step operation. The N,N-dimethylbenzylamine (DMBA), as an efficient and commercially available organocatalyst was employed for the one-pot synthesis of dihydropyrano[3,2-c]chromene derivatives in ethanol medium. In this work the one-pot

Knoevenagel-Michael-Thorpe-Ziegler type cascade heterocyclization has been developed for the synthesis of dihydropyrano[3,2-c]chromene-containing heterocycles from the one-pot multicomponent condensation reaction of 4-hydroxycoumarin, malononitrile/ethyl cyanoacetate, and various aldehydes at 60 °C shown in scheme 28.



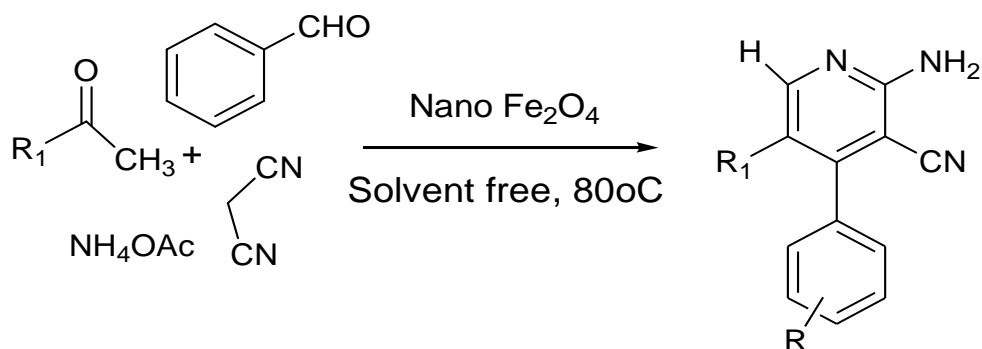
Scheme-28: Synthesis of dihydropyrano[3,2-c]chromene-containing heterocycles.

Hamzeh Kiyani and Mozghan Sada Jalali studied and describes the first report on one-pot, 3CA, DMBA-catalyzed the synthesis of various dihydropyrano[3,2-c]chromene heterocyclic compounds^[63-64] shown in scheme 28.

2-amino-3-cyano derivatives have recently received considerable attention due to their potential biological and pharmaceutical activities.^[66-67]

The development of efficient methods for the construction of poly-functionalized heterocyclic compounds has allocated a broad area of organic and medicinal chemistry.^[65] Among heterocyclic compounds,

Majid M. Heravi *et al* gave synthesis of 2-amino-3-cyanopyridine and 2-amino-3-cyano-4H-pyran derivatives in the presence of high surface area Fe₃O₄ as a highly effective heterogeneous catalyst via one-pot multicomponent cyclocondensation reaction^[68] shown in scheme 29.

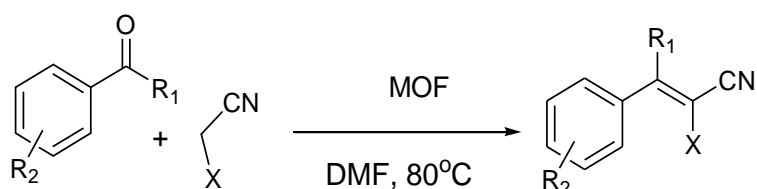


Scheme-29: Synthesis of 2-amino-3-cyanopyridine and 2-amino-3-cyano-4H-pyran derivatives.

An extremely efficient, mild, facile and economical method for the preparation of poly functionalized pyridine and pyran derivatives has been developed, via a one-pot MCR, in the presence of high surface area Fe_3O_4 (MNPs) as a highly effective heterogeneous catalyst. The catalysts show environmental friendly character and recyclability, being re-used at least in four consecutive runs without significant loss of catalytic activity. This development in the synthesis of two important heterocyclic systems, in comparison with previously reported methods, not only affords the desired products in excellent yields but also required shorter reaction times. The most important advantage of our protocol is the convenient separation of the commercially

purchasable or readily available nano- Fe_3O_4 catalyst from reaction mixture and reusing it in several runs without appreciable loss of activity. The Knoevenagel condensation by alkali metal hydroxides^[70] also using catalytic activity of basic catalysts.^[69]

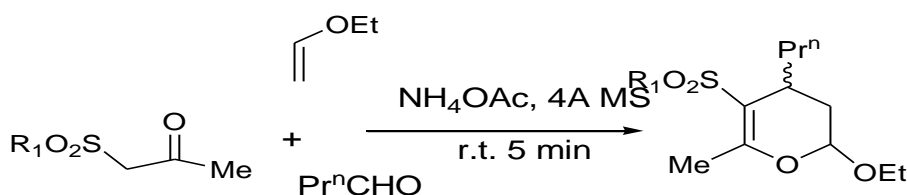
Abu Taher gave a highly efficient and reusable catalyst based on metal-organic frame works (MOF) has been synthesized by post-functionalization and applied in Knoevenagel condensations of various Aldehydes and ketones. The catalyst maintained its unique framework after the reaction and could be recycled and reused several times without significant loss of activity as shown in scheme 30.^[71]



Scheme-30: Knoevenagel condensations via metal-organic frameworks.

Chao Li developed a three-component 'one-pot' sequential reaction of β -keto perfluoroalkane sulfones, aldehydes and electron-rich olefins to synthesis tetra substituted 2, 3-dihydropyran derivatives. The reaction conditions are very mild. The methodology didn't require the isolation of the unsteady α -

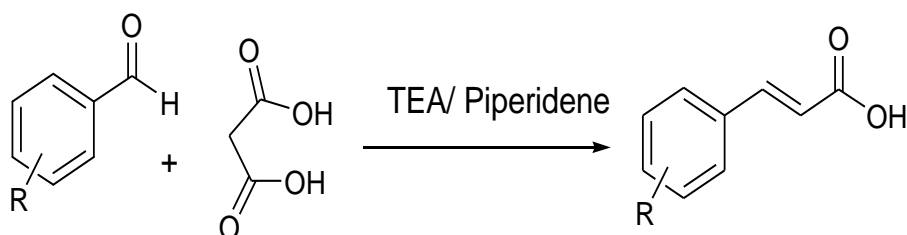
perfluoroalkanesulfonyl- α , β -unsaturated ketones, which diminished the wastes of reactions, simplified the operation procedure and increased the synthetic efficiency. Furthermore, the substrates scope were greatly expanded^[72] shown in scheme 31.



Scheme: 31: Synthesis of tetrasubstituted 2,3-dihydropyran derivatives.

A new strategy for synthesis of cinnamic acids was successfully investigated by Hitesh. S. Pawar et al by using a pyridine free Knoevenagel condensation in the presence of triethylamine, as neat solvent or in combine action with toluene with catalytic amounts of piperidine. To the best of our knowledge this is the first report on exploring triethylamine as a base in place of pyridine for

condensation of aromatic aldehyde and malonic acid. The in situ FTIR analysis was performed to investigate the reaction mechanism. It was found that the triethylamine also plays a dual role of a base as well as a solubilizing agent for promoting the reaction both in toluene and TEA itself shown in scheme 32.



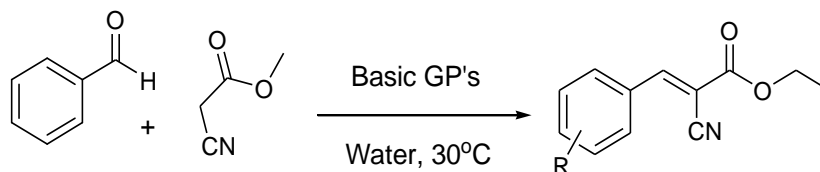
Scheme-32: General reaction for pyridine free synthesis of cinnamic acid.

Li shown important materials for catalysts for chemical transformations in the laboratory and in industrial processes. In particular, polymer catalysts have been extensively studied and rapidly developed.^[73-76] Polymer

catalysts are broadly classified into two categories: molecular catalysts that are prepared by the polymerization of monomers with catalytic groups on their side chains and polymer-supported catalysts that are

loaded with catalysts, such as metals. The catalytic sites are covalently incorporated in the former and non-

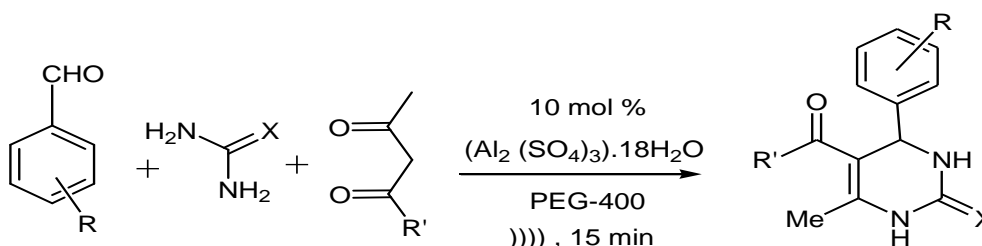
covalently incorporated into the latter shown in scheme 33.



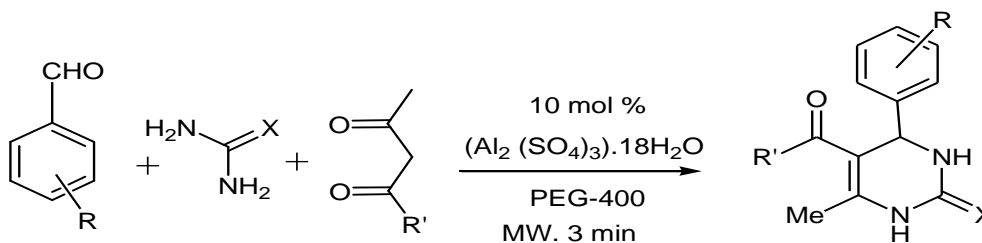
Scheme-33: GP catalysts that catalyze the Knoevenagel condensation.

Hirokazu Seto gave Basic GP catalysts that catalyze the Knoevenagel condensation reaction in water at room temperature were developed. The catalytic activity for the Knoevenagel condensation depends on the base

strength, that is the pKa values of the GPs. The DMAPM GPs had the highest activity out of the prepared basic catalysts, including bulk gel and silica gel.^[77]



Scheme-34: Synthesis of DHPMs by using PEG-400 under Ultrasound



Scheme-35: Synthesis of DHPMs by using PEG-400 under Microwave.

B. R. Chaudhari and its coworkers gave a Ultrasound^[78] (Scheme-34) and Microwave^[79] (Scheme-35) promoted route for synthesis of 3,4-dihydropyrimidin-2(1H)-one/thione (DHPMs) in presence of Aluminium sulphate as a catalyst for aromatic aldehydes, 1,3-dicarbonyl compounds & (thio)urea in PEG as a reaction solvent.

CONCLUSION

In summery, we gave some modern methods which were useful for development of catalysis and synthesis among all the Knoevenagel reaction. In last five year's literature survey and publications showed its fast growing importance towards organic synthesis due to its ability to perform a variety of transformations and novel structures synthesis. It is also complimented by their readily availability, nature friendly, stability, tolerance to moisture and water, easy procedures. Various derivatives of Knoevenagel can also show versatile application in green synthetic process.

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