WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 7.523
Volume 6, Issue 13, 308-331. Review Article ISSN 2277– 7105

RECENT ADVANCES IN THE SYNTHESIS CHROMENES AND ITS DERIVATIVES

Pritesh R. Jain, Samadhan R. Patil and Ashok A. Patil*

P.G. Research Centre, Department of Chemistry, JET's Z.B. Patil College, Dhule 424002 Maharashtra, India.

Article Received on
31 August 2017,

Revised on 21 Sept. 2017,
Accepted on 12 Oct. 2017

DOI: 10.20959/wjpr201713-9914

***Corresponding Author**
Ashok A. Patil
P.G. Research Centre,
Department of Chemistry,
JET's Z.B. Patil College,
Dhule 424002 Maharashtra,
India.

ABSTRACT

The chromenes and its derivative are an important class of organic and heterocyclic compounds. The chemistry of these compounds modified day by day because these are one of the most privileged medicinal pharmacophore which appears as an important structural part in many naturally occurring and synthetically prepared compounds. Literature survey reveals that over a last year many chemists and researchers are engaged in the synthesis of chromenes and its various derivatives as they having great biological and pharmacological activities. Generally synthesis of chromenes involve one pot multicomponent reaction of various aldehydes, active methylene compound and enolisable 1,3-dione or derivatives of phenols.

KEYWORDS: Synthesis of chromenes, ionic liquids, nanocatalyst, Michael addition.

INTRODUCTION

Chromenes and its derivatives are an important class of compounds and widely spread in nature. These are heterocyclic compounds with ring system consisting of benzene ring fused 5,6-positions with pyran oxygen ring heterocycles, therefore also termed as benzopyrans. Chromenes are privileged pharmacophore which appears as an important structural part in so many naturally occurring and synthetically prepared heterocyclic compounds.

Synthesis of chromenes is the subject of widespread research in pharmacological, industrial and synthetic point of views, because of the number of naturally or synthetically available compounds having chromene as their important core structure showing interesting

pharmacological and biological activities including anticancer,[1] antiviral,[2] antimicrobial,[3] anti-inflammatory activities,[4] antitumor,[5] antiproliferative,[6] antioxidant,[7] antifungal,[8] antitubercular,[9] anti-influenza,[10] antispasmolytic,[11] anti HIV,[12] anticoagulant, anti-anaphylactic activity[13] and mutagenicitical.[14] In addition, they can be used as for the treatment of neurodegenerative diseases[15] including Alzheimer's disease, amyotrophic lateral sclerosis, Huntington's disease, Parkinson's disease as well as for the treatment of schizophrenia and myoclonus.[16] 2-Amino-4H-chromene derivatives bearing nitrile functionality showed potential application in the treatment of human inflammatory TNFα-mediated diseases, such as rheumatoid and psoriatic arthritis.[17,18]

Chromene derivatives play also an important role in the production of highly effective fluorescent dyes for daylight fluorescent pigments and synthetic fibers.[19] Chromenes with cyano-functionality has a wide range of applications in chemistry such as lasers, optical brighteners, fluorescence markers and cosmetics.[20]

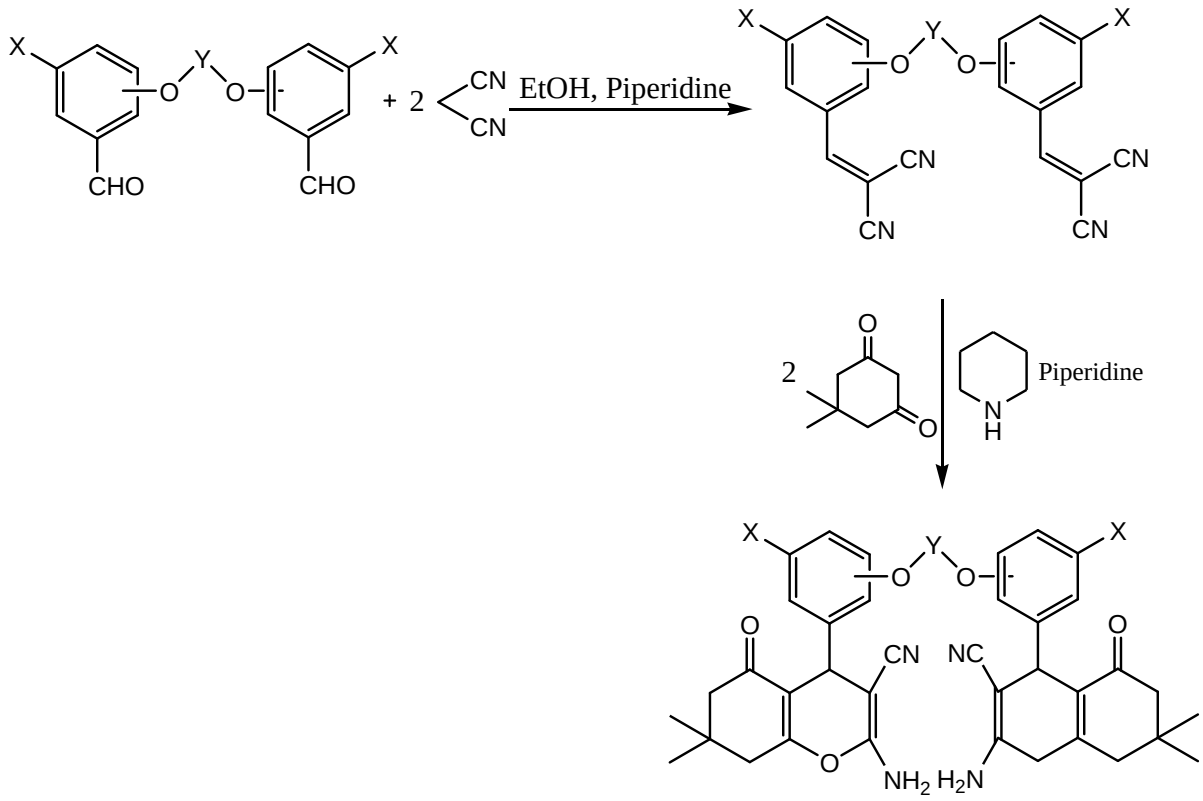
The chromene derivatives have found extensive applications with broad range of remarkable properties. Despite their importance comparatively few methods for the preparation of chromenes derivatives have been reported. Hence, development of synthetic strategies for the building of the chromene ring-system through economical and environment friendly processes is always advantageous in synthetic chemistry. Over the last few years many synthetic methods have been developed for the building of chromenes. Some chromene derivatives prepared by using organic bases like piperidine in an organic solvent.[21] They are also prepared in the presence of diammonium hydrogen phosphate in aqueous ethanol[22] and K_2CO_3 under microwave irradiation.[23] Some efforts based on transition metal[24] and organocatalyst[25] catalyzed reactions. Various catalysts such as sodium acetate,[26] DABCO,[27] K_3PO_4,[28] Na_2CO_3[29] under grinding, PEG-400,[30] $LiOH.H_2O$,[31] basic ionic liquids,[32] $Ca(OH)_2$,[33] zinc chloride,[34] CAN[35] and nano-powder $ZnAl_2O_4$–Bi_2O_3 had also been reported for the synthesis of chromene compounds.

Out of these some of the reported procedures require long reaction times, multi-step reactions and complex synthetic pathways, toxic organic solvents, difficult work-up procedures, harsh reaction conditions, use of not readily available starting materials, non reusability of the catalysts employed. Therefore, the development of more effective methods for their research is still going on using multicomponent reactions and green chemistry approach.

Multicomponent reactions had received much attention from synthetic organic chemists due to their application in the building of highly functionalised chromene derivatives and pharmacologically important heterocyclic compounds. This strategy makes it possible to synthesized complicated compounds using a one pot reaction reaction in a rapid, efficient and time saving process without the need for separation of intermediates. Similarly green chemistry is a rapidly emergent field that provides protective path for the sustainable progress of future. Green chemistry uses economical, highly efficient and environment friendly synthetic protocols for building of chromene derivatives with reduced needless environmental impact.

LITRETURE REVIEW

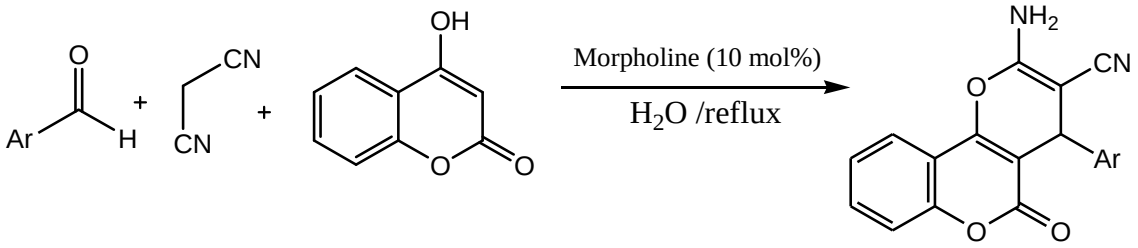
Ahmed H. M. Elwahy and Ismail A. Abdelhamid et al reported an efficient and simple synthesis of novel bis-4H-chromene-3-carbonitrile derivatives having effectiveness in treatment of cancer and inflammation and anti-influenza virus activities and other activities. It was achieved by Michael addition reactions of α,β-unsaturated nitriles with β-diketones an interesting route for the synthesis of chromene and fused chromene derivatives as shown in the scheme 1.



Scheme 1: Synthesis of bis(4H-chromene) derivative.

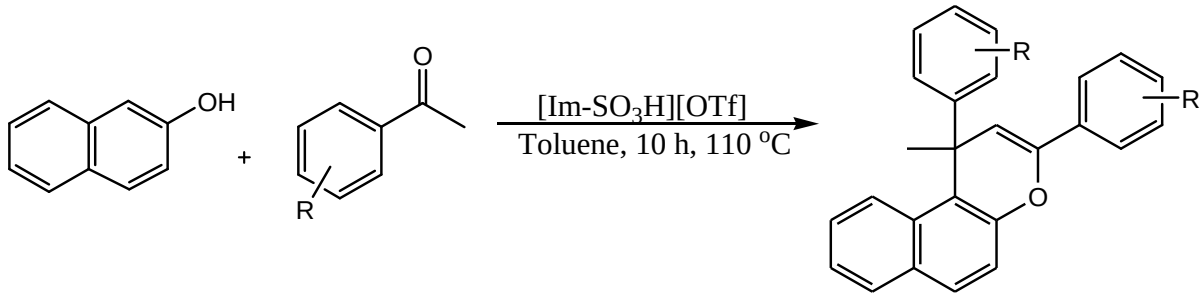
Bis-4H-chromene-3-carbonitrile molecules are obtained from new bisarylidenemalononitrile derivatives which was obtained by Knoevenagel condensation of one mole of bis-aldehyde derivatives with two moles of malononitrile in ethanol and in the presence of piperidine as a basic catalyst. One mole of the bis-arylidenemalononitrile derivatives was reacted with two moles of dimedone, in the presence of piperidine via Michael addition followed by cyclization reaction to yield bis-4H-chromene-3-carbonitrile derivatives in good yields.[36]

Heravi Majid M. et al gave readily commercially available small organic molecules morpholine and its derivatives as valuable, environment friendly organocatalysts and has been used in condensations of various aldehydes, malononitrile and 4-hydroxycoumarine to form dihydropyrano[c]-chromene derivatives in water under reflux in excellent yields[37] as shown in scheme 2.



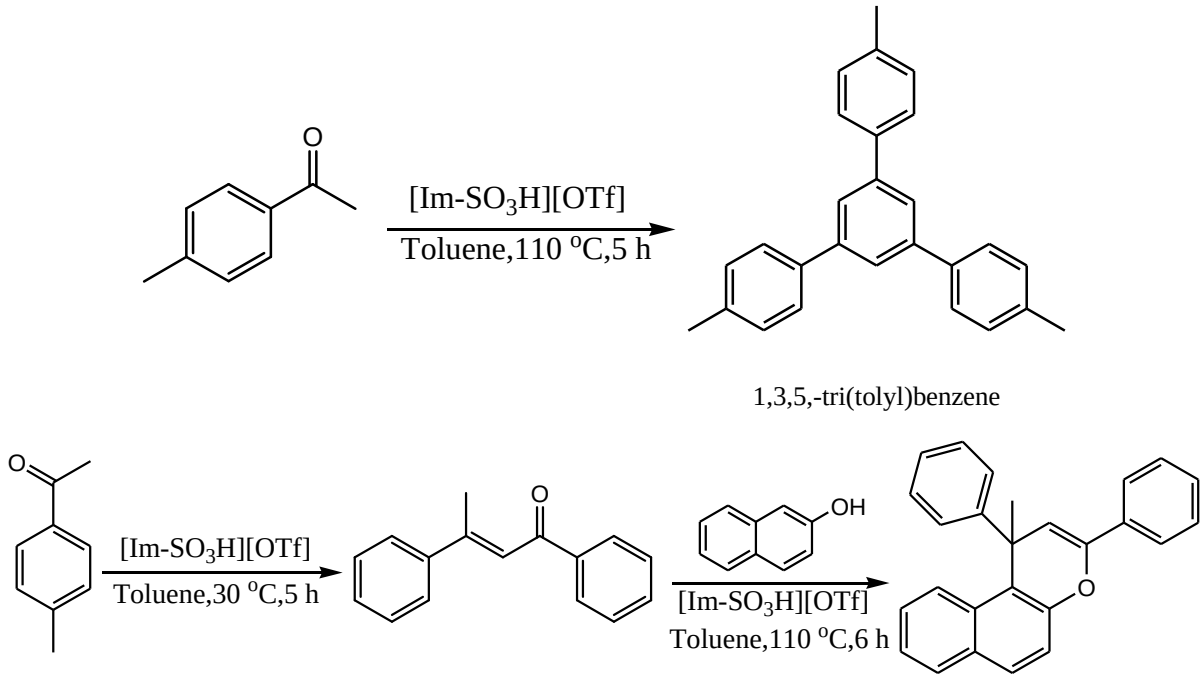
Scheme 2: Morpholine catalyzed synthesis of chromene in water.

Recently, Anil Kumar and co-workers studied Lewis acid catalyzed condensation reaction of readily available starting material like acetophenone and phenols for synthesis chromene. They used environmentally caring onium salts with remarkable reactivity and significant properties in organic transformations which was alternative to the harsh organic solvents, catalysts and reagents typically used for such transformation. The well functionalized onium salts had excellent properties like reaction media, reagents, catalyst and scavengers too. Hence sulfonic acid functionalized imidazolium salts used for estrification reaction has attracted attention of chemists and they had used onium salts such as sulfonic acid functionalized imidazolium triflate [Im-SO_3H][OTf] as mild catalyst in the simple and efficient synthesis of chromene derivatives[38] as shown in scheme 3a.



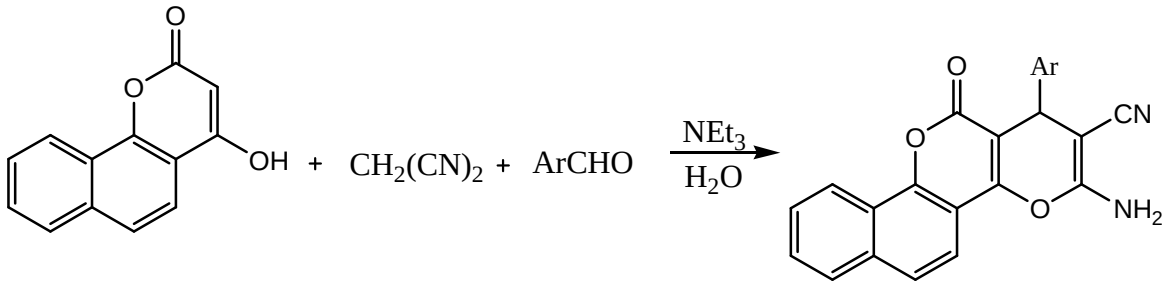
Scheme 3a: Synthesis of chromene derivative.

4-methyl acetophenone was heated in the absence of phenol under controlled and similar reaction conditions then 1,3,5-tri(tolyl)benzene was formed. Similarly, when 4-methyl acetophenone was stirred with [Im-SO_3H][OTf] at 30° C in the absence of phenol then dypnone was formed and when finally it reacted with phenol forms chromene derivative in excellent yield as shown in scheme 3b. Several heterocyclic compounds such as quinolones, 3-vinylindoles and spirooxindole are also synthesized using this type of catalyst.



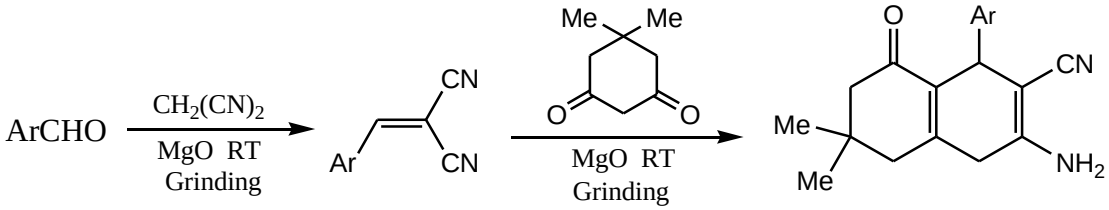
Scheme 3b: Control experiments.

Maryam Abbasi Eshlaghi, Behrooz Mirza and Mohsen Zeeb gave convenient and environment friendly process for the synthesis of 3‑amino-12-oxo-1-phenyl- 1,12-dihydrobenzo[h]pyrano[3,2-c]chromene-2-carbonitrile derivatives by one-pot reaction between 4‑hydroxy-2H-benzo[h]chromen-2-one, aryldehydes and malanonitrile in aqueous medium using NEt_3 as a catalyst[39] as shown in scheme 4.



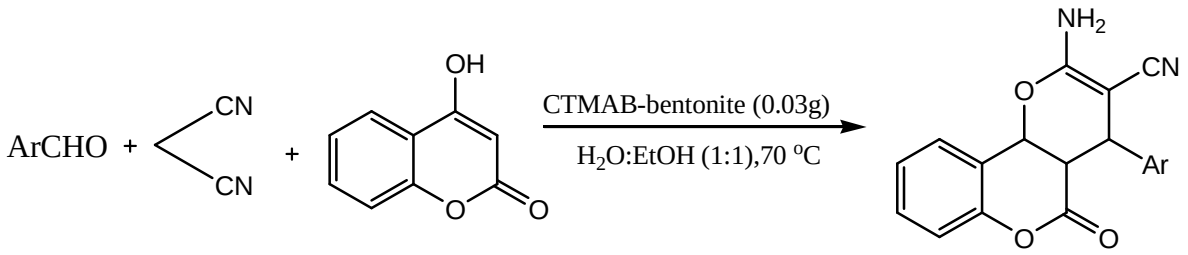
Scheme 4: Synthesis of chromene derivative using NEt_3 in aqueous media.

Dalip Kumar and co-workers developed facile and environmentally benign grinding method for the synthesis of 2-amino-5-oxo-5,6,7,8-tetrahydro-4H-chromenes from grinding the mixture of aromatic aldehyde, malanonitrile and dimedone with MgO as a recyclable catalyst[40] under solvent free condition as shown in scheme 5.



Scheme 5: Synthesis of 2-amino-5-oxo-5,6,7,8-tetrahydro-4H-chromenes.

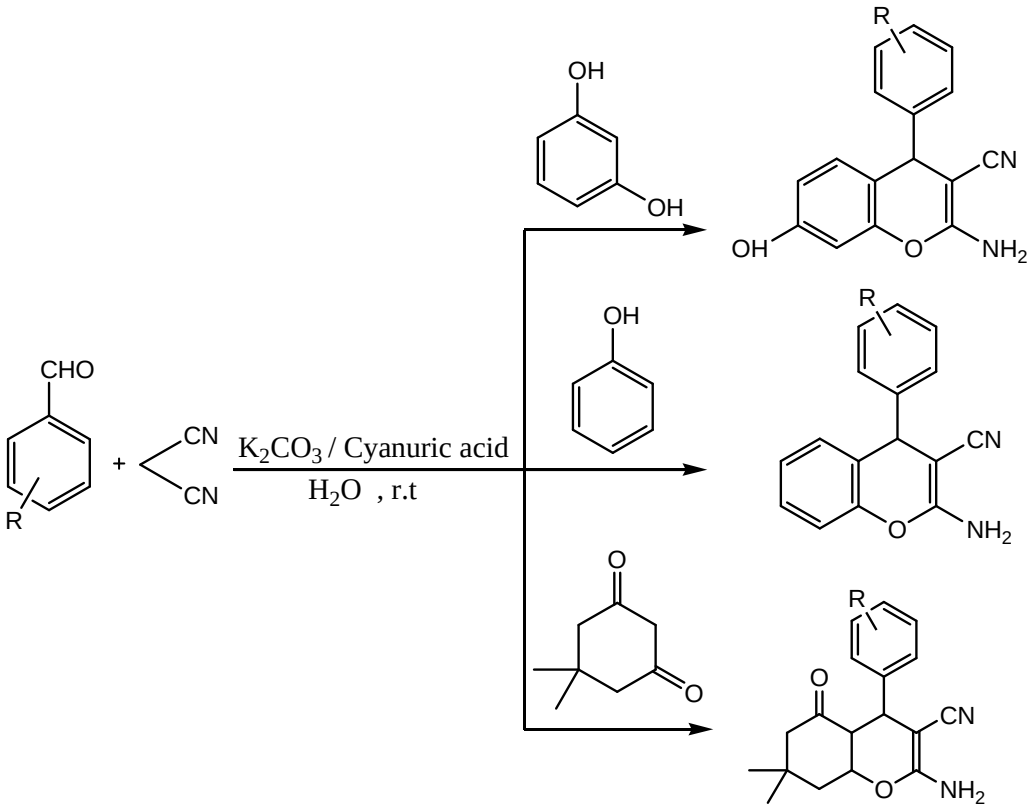
M.E. Sedaghat, M. Rajabpour Booshehri et al are used bentonite very economical, safe, and easily available catalyst to develop modified bentonite as a heterogeneous catalyst. CTMAB-bentonite is one of the most interesting heterogeneous catalysts with surface properties, which suggests that a very rich organic chemistry there. The synthesis of dihydropyrano[3,2-c]chromenes derivatives by one pot three-component condensation reaction of aldehydes, malononitrile and 4-hydroxycoumarin achieved in the presence of modified bentonite (CTMAB-bentonite)[41] as shown in scheme 6.



Scheme 6: Synthesis of 3,4-dihydropyrimidine derivatives.

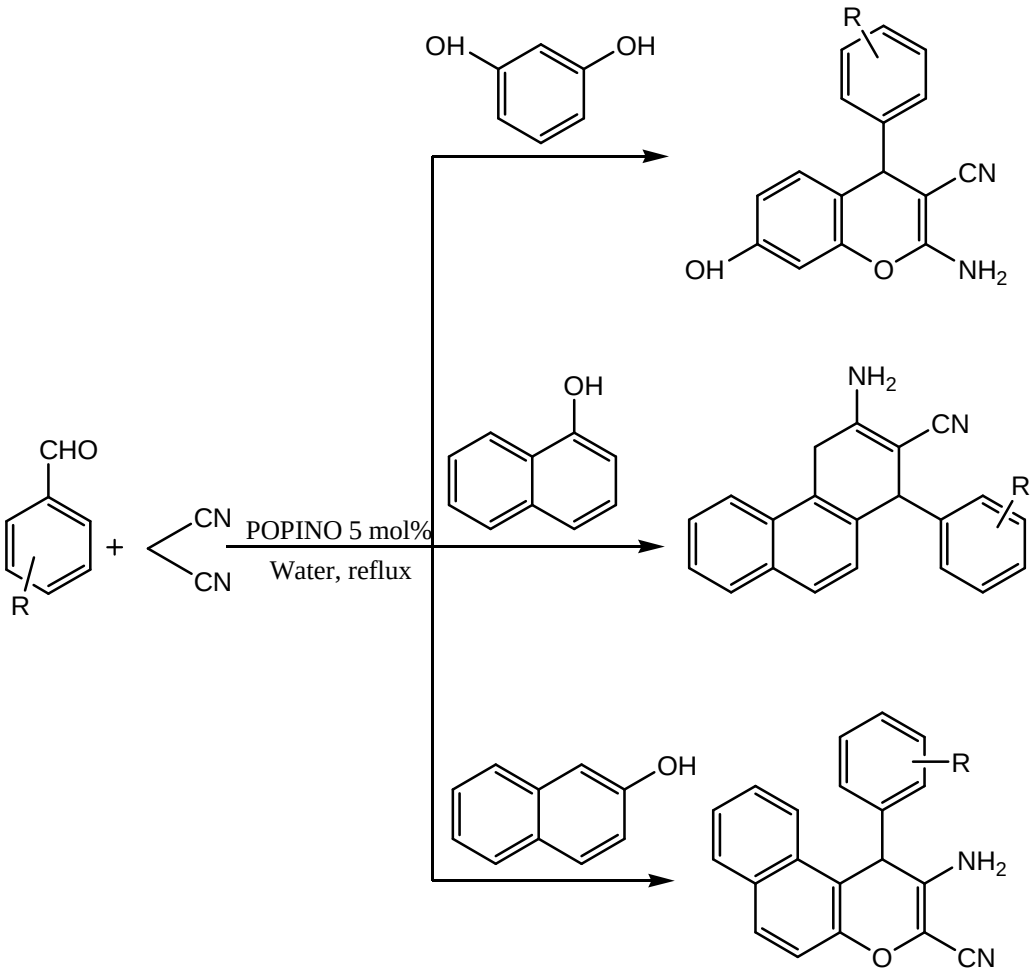
Reza Heydari, Ramin Shahraki, Mahshid Hossaini, Alireza Mansouri had recently reported a rapid, green, and highly efficient method for the synthesis of 2-amino-4H-chromene with

cyano-functionality derivatives. A simple and appropriate method according to the principles of green chemistry for the one-pot reaction between various benzaldehyde, malononitrile and enolizable C–H activated acidic compounds (resorcinol or phenol or dimedone) was performed in the presence of K_2CO_3/cyanuric acid (10 mol% 3:1 (K_2CO_3: cyanuric acid) as a mixture of organic and inorganic available, economic and nontoxic catalysts in aqueous media at room temperature[42] as shown in scheme 7. The main advantages of this method are tiny reaction time, excellent yield, clean reaction medium, easy workup and simple purification.



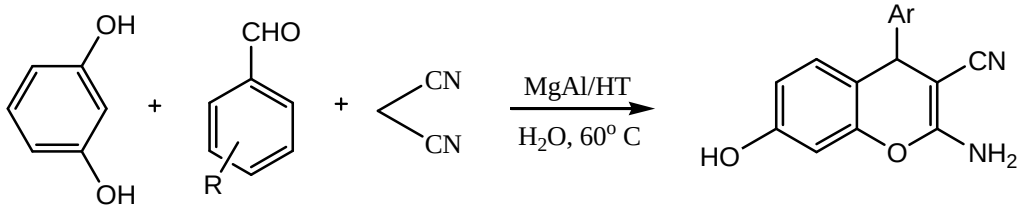
Scheme 7: Synthesis of 2-amino-4H-chromenes.

Mohammad G. Dekamin and co-workers gave a transition metal free route for synthesis of 2-amino-4H-chromene with various substituents in the presence of potassium phthalimide-N-oxyl (POPINO)[43] in water as a green, natural, and high abundance solvent, strongly enhances the rate of reaction due to its strong hydrogen bonding ability, hydrophobic effects and high polarity as shown in scheme 8.



Scheme 8: Synthesis of aminochromenes with POPINO.

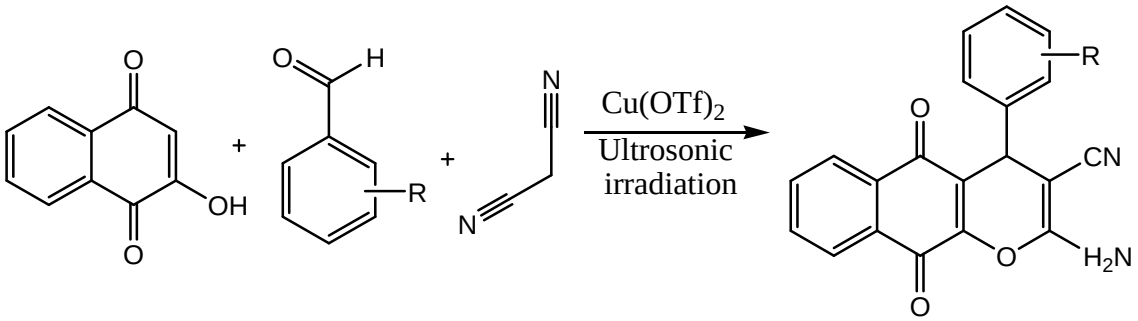
Radha V. Jayaram gave hydrotalcite catalyzed[44] Knoevenagel condensation between aldehyde and malanonitrile followed Michael addition with resorcinol to afford 2-amino-4H-chromene derivatives after rearomatization and cyclization using water as a solvent as shown in scheme 9.



Scheme 9: Synthesis of chromenes using hydrotalcite in aqueous medium.

Manisankar Paramsivam and its co-workers adopted a methodology for the synthesis of novel benzo[g]chromenes by one-pot condensation of 2-hydroxy-1,4- naphthoquinone, substituted aldehyde and malononitrile in the presence of proficient catalyst $Cu(OTf)_2$ under

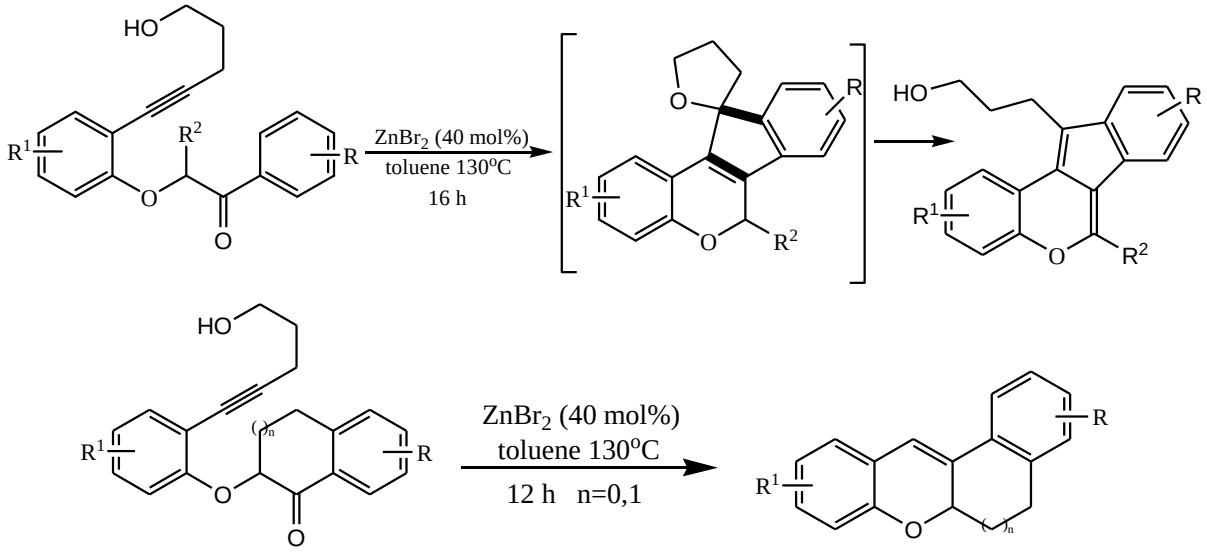
ultrasonication[45] as shown in scheme 10. UV sonicator provides energy to the reaction mixture in the form of high intensity, high frequency sound waves which results in the formation of cavitations which is responsible for good yields of the product.



Scheme 10: $Cu(OTf)_2$ catalyzed Synthesis of benzo(g) chromenes derivatives.

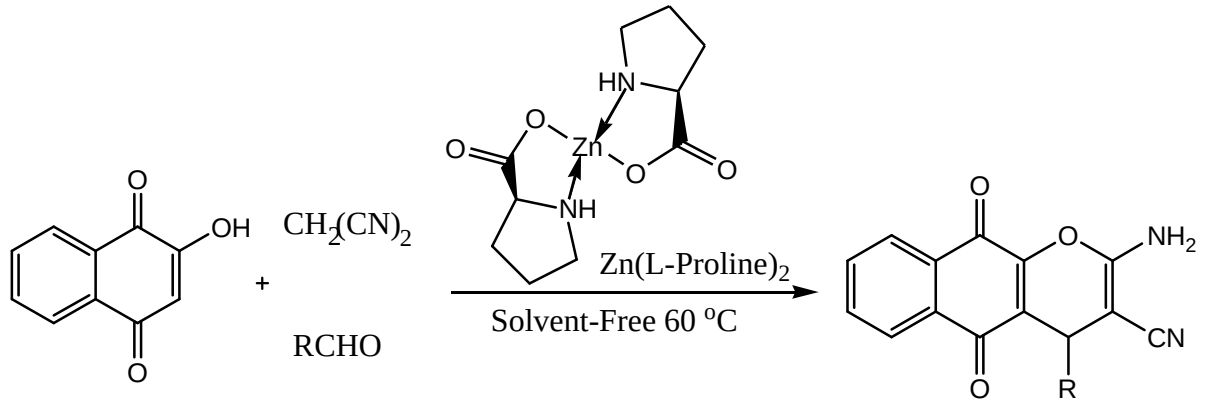
Efficiency of different catalysts such as Scandium triflate, Ytterbium triflate, Indium Chloride and DABCO in PEG under ultrasonication is much less and therefore in multicomponent one-pot synthesis of benzo[g]chromene derivatives was carried out from 2-hydroxy-1,4- naphthoquinone, aromatic aldehyde and malononitrile catalyzed by cupper (II) triflate $Cu(OTf)_2$ in the presence of polyethyleneglycol (PEG) as a solvent under ultrasonication.

Amol Milind Garkhedkar, Gopal Chandru Senadi, and Jeh-Jeng Wang had described a Lewis acid catalyzed cascade annulation of o-alkoxy alkynols for the synthesis of indeno[1,2-c]chromenes. O-alkoxy alkynols are important building blocks for the construction of various heterocycles. Alkynols can undergo cycloisomerization through endo or exo pathways to synthesize different heterocycles. The cascade reactions of alkynols proceed via cyclization with various transformations like Prins-type cyclization, Diels-Alder reaction, Povarov reaction, etc. Lewis acid mediated cascade cyclization of o-alkoxy alkynols in the presence of $ZnBr_2$[46] proceeds through a 5-exo-dig cyclization followed by a Friedel−Crafts reaction and ring opening sequence to afford indeno[1,2-c]chromenes as shown in scheme 11.



Scheme 11: Synthesis of indeno[1,2-c]chromenes from o- alkoxy alkynols.

Behrooz Maleki, Saeed Babaee and Reza Tayebee had discovered an efficient and environmentally friendly method for the synthesis of 2-amino-4H-benzo[g]chromenes. A few methods like triethylbenzylammonium chloride (TEBA)[47] and potassium phthalimide-N-oxyl[43] used as a catalyst are also available for the preparation of 4-aryl-5,10-dihydro-4H-benzo[g]chromene- 5,10-dione derivatives. These methods having some drawbacks, to overcome this problem they developed a more efficient and a general method for the synthesis of 2-amino-4H-benzo[g]chromene derivatives using Zn(L-proline)$_2$ as a catalyst[48] as shown in scheme 12.

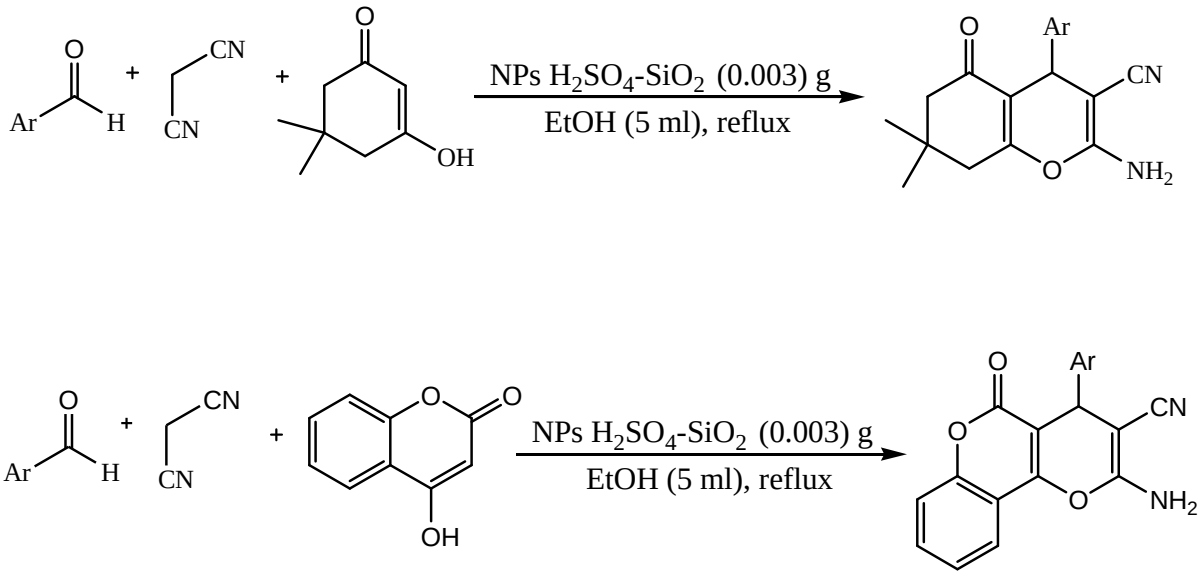


Scheme 12: Synthesis of 2-amino-4H-benzo(g)chromenes catalyzed by Zn(L proline)$_2$.

Zn(L-proline)$_2$ is an efficient, inexpensive, non-toxic, stable and reusable catalyst which is not dissociated under reaction conditions. It has higher solubility in water, insolubility in organic solvents, eco-friendly nature and handy work-up make Zn(L-proline)$_2$ a green catalyst in organic synthesis. A mixture of aromatic aldehydes, malononitrile and 2-hydroxy-

1,4-naphthaquinone with Zn(L-proline)$_2$ (20 mol%) stirred under solvent free condition at 60°C to form 2-amino-4H-benzo[g]chromene derivatives.

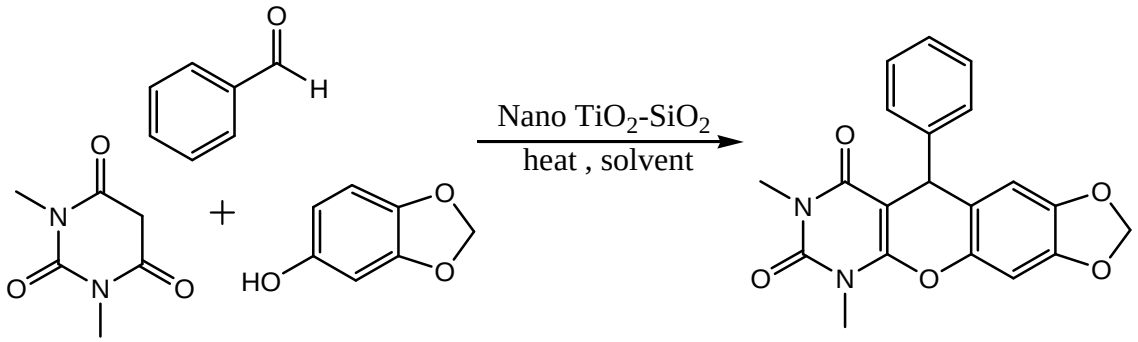
Bahareh Sadeghi, Alireza Hassanabadi and Somayeh Bidaki carried out the synthesis of 4H-chromene derivatives by rapid protocol affording excellent yield using solid phase acidic green catalyst NPs SiO_2–H_2SO_4. The three-component condensation of an aromatic aldehyde, malononitrile, and cyclic 1,3-diketones such as dimedone or 4-hydroxycoumarin in the presence of re-usable 0.003 g NPs SiO_2–H_2SO_4 catalyst[49] to afford 4H- chromene derivatives in shorter reaction times, simple work-up and excellent yield as shown in scheme.13.



Scheme 13: Synthesis of 4H- chromenes using NPs SiO_2–H_2SO_4 as catalyst.

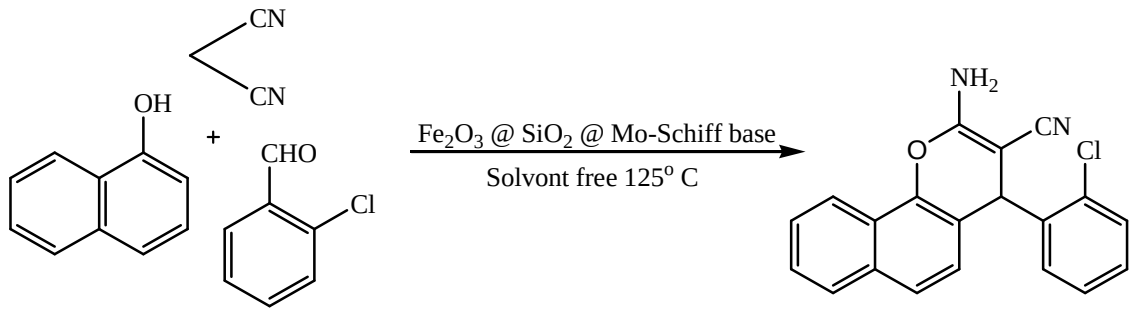
Similarly, nanostructured metal oxides, which possess good physical and chemical abilities, are used to carry out numerous organic transformations. Titanium dioxide nanoparticles (TiO_2 NPs) are considered very close to model nanocatalysts due to their high efficiency, non-toxic, inexpensive, moisture stable and reusable. Shahrzad Abdolmohammadi had already reported the use of TiO_2 NPs as an efficient heterogeneous catalyst in some organic transformations, i.e., solvent-free synthesis of hexahydro-2-quinolinecarboxylic acid derivatives[50] and one-pot four component coupling reactions for the preparation of indeno[1,2-b] quinolinediones [14 of 19] and tetrahydrobenzo[c]acridinones[51] in aqueous media. In addition, Shahrzad Abdolmohammadi et al developed TiO_2 NPs over silica shells (TiO_2–SiO_2 nanocomposite) improved their catalytic efficiency. They report herein a very simple route to synthesise some 6,8-dimethyl-10-aryl-6,10-dihydro-7H-[1,3]-

dioxolo[4′,5′:6,7]chromeno[2,3-d]pyrimidine-7,9(8H)-diones by a condensation reaction of 1,3-dimethylbarbituric acid, various aromatic aldehyde and 3,4-methylenedioxyphenol in aqueous media by using a TiO_2–SiO_2 nanocomposite with a molar ratio of 1:1 as an efficient and green catalyst[52] as shown in scheme 14.



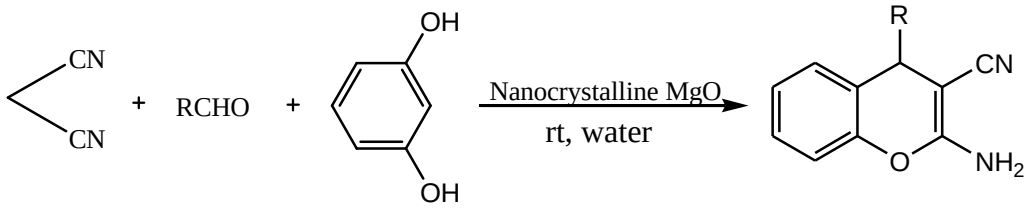
Scheme 14: Synthesis of chromeno[d]pyrimidinone derivatives using a nano TiO_2-SiO_2.

In the recent years, magnetic nanoparticles (MNPs) like Fe_3O_4 have attracted considerable attention by researchers because of particular application and chemical stability, super paramagnetic property, high level contact, environmental sustainability, low price and low toxicity. The efficiency of these Fe_3O_4 nanoparticles improved by the surface coating with SiO_2. Due to the particular properties of magnetic nanoparticles, they can be used as support for homogeneous catalyst. Niaz Monadi and its co-worker developed a new recoverable molybdenum nanocatalyst which was prepared by immobilization of a Schiff base ligand on the surface of silica coated magnetic nanoparticles (Fe_3O_4@SiO_2) through condensation reaction between 3-aminopropyl triethoxysilane and 2-hydroxy1-naphthaldehyde and subsequent reaction with dioxomolybdenum(VI) acetylacetonate ($MoO_2(acac)_2$).[53] This nanocatalyst then used as an efficient catalyst for the synthesis of 2-amino -4H-banzo(h)chromenes under solvent free condition as shown in scheme 15.



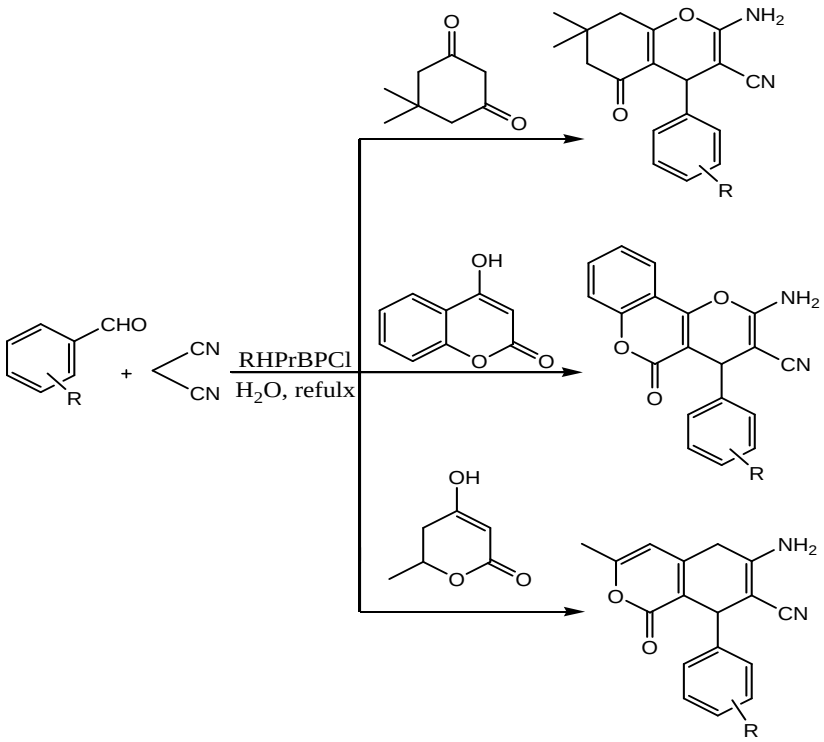
Scheme 15: Synthesis of 2-amino -4H-banzo(h)chromenes in the presence of Fe_2O_3@SiO_2@Mo-Schiff base.

J. Safari et al found excellent selectivity of nanocrystalline magnesium oxide for a MCR leading to 2,4,5-trisubstituted imidazole derivatives in high yields with no formation of other by products. Magnesium oxide has strongly basic properties with large specific surface area are also a potential catalyst support for various reactions**.** J. Safari, Z. Zarnegar, M. Heydarian described convenient and facile multi-component, one pot synthesis of 2-amino-4H-chromene in high yields by using nanocrystalline magnesium oxide[54] with high specific surface area and a crystallite size as a novel and efficient catalyst in water at room temperature as shown in scheme 16.



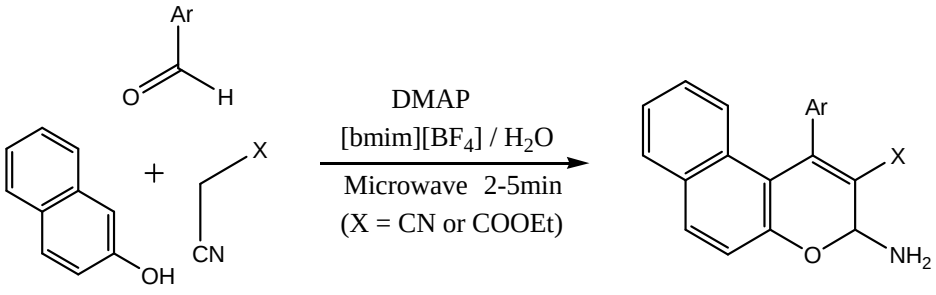
Scheme 16: Nanocrystalline MgO catalyzed synthesis of 2-amino-4H-chromenes.

Ali Reza Kiasat et al gave novel method using nanocomposite, rice-husk-silica supported n-propyl bipyridinium chloride (RHPrBPCl) for the one-pot preparation of chromene derivatives. They had prepared novel rice-husk-silica supported n-propyl bipyridinium chloride (RHPrBPCl) with dual featured being ionic liquid and basic catalyst. One pot synthesis of chormene derivatives in aqueous medium can be achieved from aromatic aldehydes, malononitrile and 1,3-dicarbonyl compounds (dimedone, 4-hydroxy coumarine and 4-hydroxy-6-methyl-2-pyrone) in the presence of RHPrBPCl as a dual ionic liquid-basic catalyst heated in oil bath to form tetrahydrobenzo[b]pyran, dihydropyrano[3,2-c]chromene and dihydropyrano[4,3-b]pyran derivatives[55] was obtained in good yield as shown in scheme.17.



Scheme 17: Synthesis of chromene derivatives in the presence of RHPrBPCl.

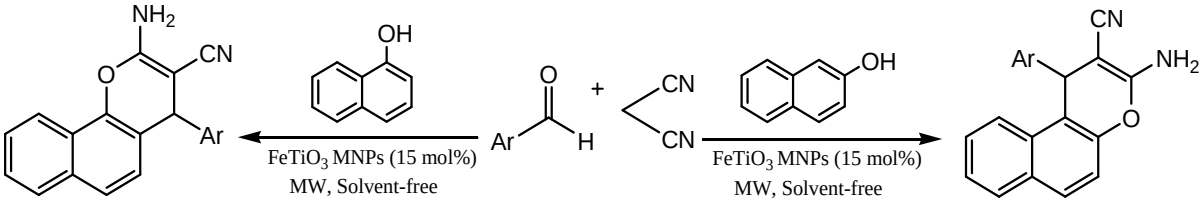
Xin-Min Wen et. al. developed a method for the synthesis of ethyl 3-amino-1-aryl-1H-benzo[f]chromene derivatives using hydrophilic ionic liquid [bmim][BF_4] and water as a solvent and green safe reaction medium using synthetic potentiality of microwave oven induced organic reactions.[56] The microwave assisted three component cyclisation carried out smoothly with good yields. To develop methodology, they carried out the condensation of benzaldehyde with malononitrile and 2-naphthol in the presence of DMAP and H_2O-[bmim][BF_4] (30/70 % wt) micro waved to afford desired products as shown in scheme 18.



Scheme 18: Aqueous [bmim][BF_4] as a green solvent.

Saeid Taghavi Fardood et al developed green and highly efficient method for the synthesis of 2-amino-4H-chromene derivatives in the presence of $FeTiO_3$[57] as magnetic nanoparticles (MNPs) as reusable catalyst via one-pot three-component condensation reaction of α- or β-naphthol, malononitrile, and various aldehydes with no solvent under microwave irradiation

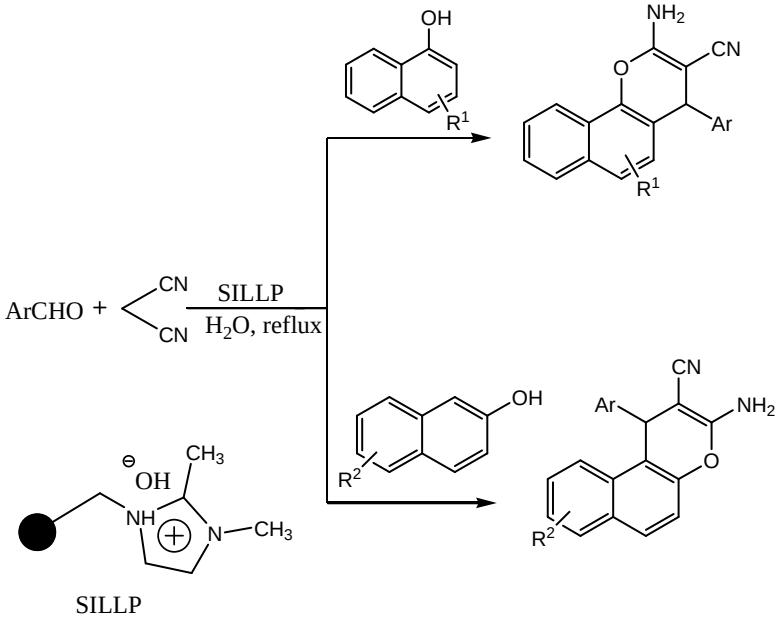
as shown in scheme 19. Its advantages are mild reaction conditions, short reaction times; simple work-up and the catalyst can be easily recovered by a simple magnetic separation and can be recycled several times with no significant loss of catalytic activity.



Scheme 19: Synthesis of 2-amino-4H- chromenes using $FeTiO_3$ MNPs.

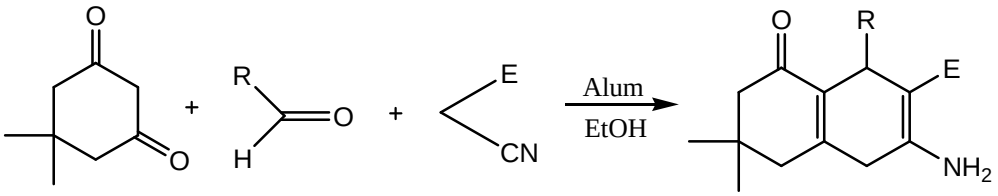
Ionic liquids have attracted increasing attention in the perspective of green chemistry in recent years. They act as solvents for a large group of organic reactions and as a catalyst at the same time. They had unique blend of chemical and physical properties, including nonvolatility, nonflammability, thermal stability and controlled miscibility.

Manouchehr Mamaghani et al described more convenient and benign synthesis of 2-aminobenzo[h]chromene and 3-aminobenzo[f]chromene derivatives using base supported ionic liquid like-phase (SILLP)[58] as efficient and recyclable solid supported heterogeneous catalyst in water. Reactions in aqueous media offered simple operation and high efficiency in many organic reactions and these advantages become even more attractive if such reactions can be performed using ionic liquids as shown in scheme 20.



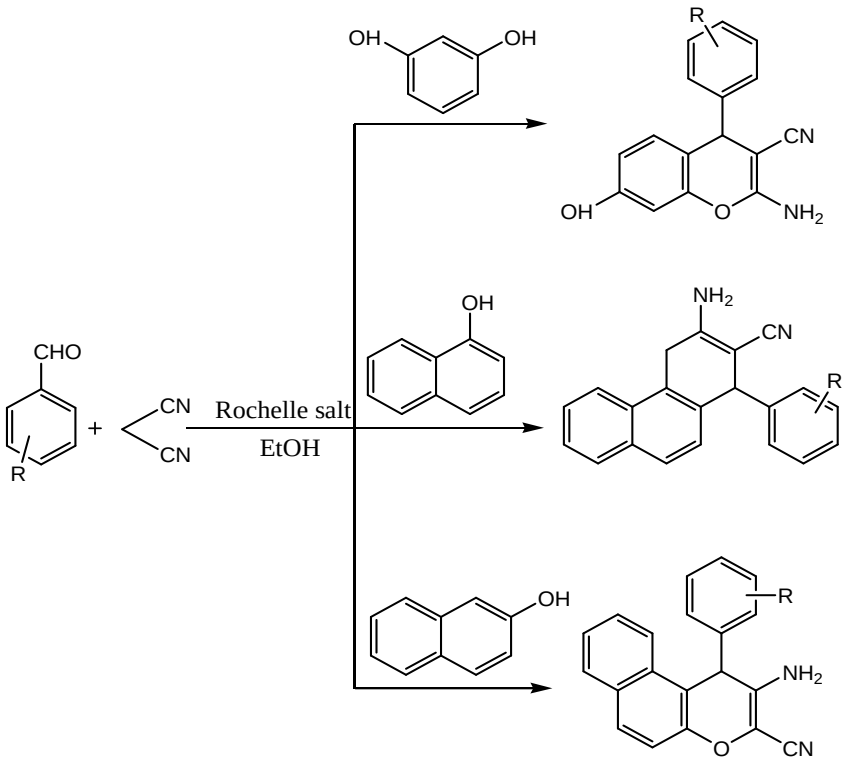
Scheme 20: Synthesis of 2- amino and 3-aminochromene derivatives using SILLP.

Ali A. Mohammadi et al described a heterogeneous, non toxic and inexpensive $NH_4Al(SO_4)_2{\cdot}12H_2O$ (Alum)[59] as an efficient and successful green catalyst in the synthesis of tetrahydrobenzo[b]pyran derivatives by condensation reaction between dimedone, various aldehydes and active methylene compounds as shown in scheme 21.



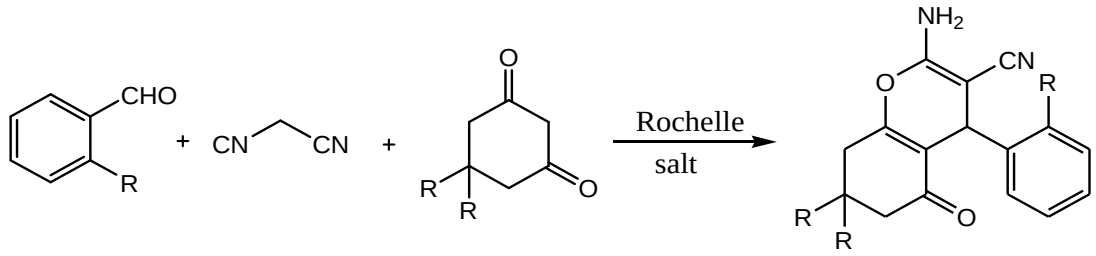
Scheme 21: Synthesis of tetrahydrobenzo[b]pyran using alum

Awatef Mohamed El-Maghraby discovered Rochelle salt catalyzed synthesis of 2-amimo chromenes derivatives.[60] He used novel green heterogeneous and reusable Rochelle salt as a catalyst in the organic synthesis in the one pot three-component condensations reactions between aromatic aldehydes, active methylene reagents, and activated phenols like resorcinol, α-naphthol, or β-naphthol in refluxing ethanol to form 2-amino-4-aryl-7-hydroxy-4H-chromene-3-carbonitriles, 2-amino-4-aryl-4Hbenzo[h]-chromene-3-carbonitriles or 3-amino-1-aryl-1H-benzo[f]-chromenes-2-carbonitriles derivatives respectively as shown in Scheme 22a.



Scheme 22a: Synthesis of aminochromenes using Rochelle Salt.

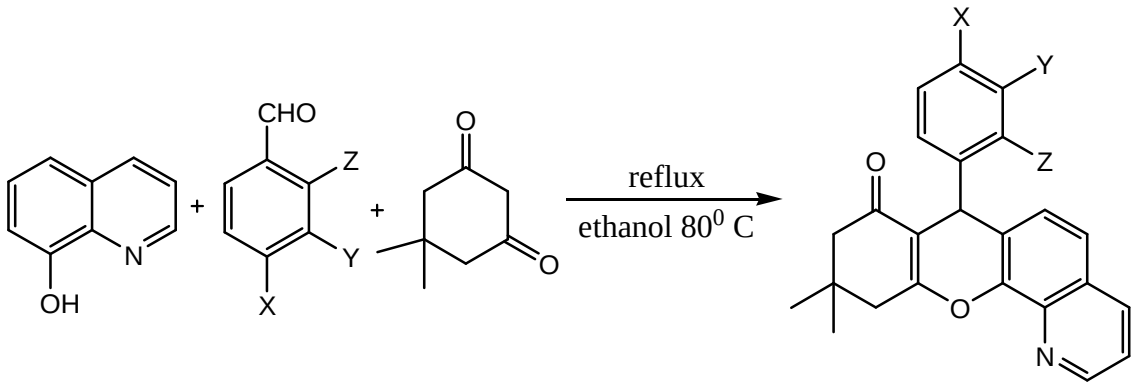
Similarly, Preeti Bansal and Gajanand Sharma also used Rochelle salt mediated green and efficient synthetic route for the synthesis of biologically active chromenes[61] as shown in scheme 22b.



R= H or CH_3

Scheme 22b: Synthesis of biologically active chromenes

Recently, Paul Douglas Sanasi and co-workers reported an efficient greener synthesis of dimethyl-dihydro-7H-chromeno[3,2-h]quinolin-8(9H)-one derivatives has been synthesized through cyclization of aromatic aldehydes, dimedone and 8-hydroxyquinoline in oil bath over hotplate having magnetic stirrer and refluxing at 80^{o} C through one-pot condensation method[62] as shown in scheme 23.



Scheme 23: Synthesis of dimethyl-dihydro-7H-chromeno[3,2-h]quinolin-8(9H)-one derivatives.

CONCLUSION

In summary, we enlist the simple, efficient, one-pot and green methods for the synthesis of chromenes and its derivatives using small organic molecules as a bases, Lewis acids, Lewis bases, ionic liquids and nanoparticles as a catalyst. In last five years literature survey showed that fast growing importance towards its synthesis due to its ability to show important biological and pharmacological activities. These methods offers an advantage of less reaction

time, solvent free, mild reaction conditions, recyclable catalyst, economical, use of inexpensive starting material and simple workup and gives good to excellent yields of product. In all these methods, volatile organic solvents are not used. Thus, these are an environmentally friendly processes.

ACKNOWLEDGEMENT

We great fully acknowledge Chairman, Managing Director of Jai Hind Educational Trust Dhule, Principal JET's Z. B. Patil College, Dhule for providing lab facilities, constant encouragement and useful suggestions.

REFRENCE

1. Patil SA., Wang J., Li XS., Chen J., Jones TS., Hosni-Ahmed A., Patil R., Seibel WL., Li W., Miller DD. "New substituted 4H-chromenes as anticancer agents" Bioorg. Med. Chem. Lett, 2012; 22(13): 4458-4461.
2. Conti C., Desideri N. "Synthesis and antirhinovirus activity of new 3-benzyl chromene and chroman derivatives" Bioorg Med Chem, 2009; 17: 3720.
3. Kidwai M., Saxena S., Rahman Khan MK., Thukral SS. "Aqua mediated synthesis of substituted 2-amino-4H-chromenes and in vitro study as antibacterial agents" Bioorg. Med. Chem. Lett, 2005; 15: 4295-4298.
4. Thomas N., Zachariah S. "Pharmacological activities of chromene derivatives: an overview" Asian J Pharm Clin Res., 2013; 6: 11.
5. Thurston DE., Bose DS., Thompson AS., Howard PW., Leoni A., Croker SJ., Jenkins TC., Neidle S., Hartley JA., Hurley LH. "Synthesis of sequence-selective C8-Linked Pyrrolo[2,1-c][1,4]benzodiazepine DNA interstrand cross-linking agents" J Org Chem, 1996; 61(23): 8141-8147.
6. El Agrody AM., Halawa AH., Fouda AM., M. Al-Dies AA. "Anti-proliferative activity of novel 4H-benzo[h]chromenes, 7H-benzo[h]-chromeno[2,3-d]pyrimidines and the structure-activity relationships of the 2-, 3-positions and fused rings at the2, 3-positions" J. Saudi Chem. Soc, 2016.
7. Symeonidis T., Chamilos M., Hadjipavlou-Litina DJ., Kallitsakis M., Litinas KE. "Synthesis of hydroxycoumarins and hydroxybenzo[f]- or [h]coumarins as lipid peroxidation inhibitors" Bioorg. Med. Chem. Lett, 2009; 19: 1139-1142.

8. Xu ZQ., Pupek K., Suling WJ., Enache L., Flavin MT. "Pyranocoumarin a novel anti-TB pharmacophore: Synthesis and biological evaluation against Mycobacterium tuberculosis" Bioorg. Med. Chem, 2006; 14: 4610-4626.
9. Kamdar NR., Haveliwala DD., Mistry PT., Patel SK. "Synthesis and evaluation of in vitro antitubercular activity and antimicrobial activity of some novel 4H-chromeno[2,3-d]pyrimidine via 2-amino-4-phenyl-4H-chromene-3-carbonitriles" Med. Chem. Res, 2010; 20: 854-864.
10. Patrusheva OS., Zarubaev VV., Shtro AA., Orshanskaya YR., Boldyrev SA., Ilyina IV., Kurbakova SYu., Korchagina DV., Volcho KP., Salakhutdinov NF. "Anti-influenza activity of monoterpene-derived substituted hexahydro-2H-chromenes" Bioorg. Med. Chem, 2016; 24: 5158-5161.
11. Abdelaziz EH., Elnagdi MH., Elagamey AA., El-taweel FM. "Nitriles in Heterocyclic Synthesis: Novel Synthesis of Benzo[c]coumarin and of Benzo[c]pyrano[3,2-c]quinoline Derivatives" A. Heterocycles, 1987; 26: 903-907.
12. Kumar BS., Srinivasulu N., Udupi RH., Rajitha B., Reddy YT., Reddy PN., Kumar PS. "Efficient synthesis of benzo[g]-and benzo[h]chromene derivatives by one-pot three-component condensation of aromatic aldehydes with active methylene compounds and naphthols" Russ J Org Chem, 2006; 42: 1813-1815.
13. (a) Foye WO. Principi Di Chemico Farmaceutica, Piccin, Padova, Italy, 1991; 416.
    (b) Andreani LL., Lapi E. "On some new esters of coumarin-3-carboxylic acid with balsamic and bronchodilator action" Bull. Chim. Farm, 1960; 99: 583-586.
    (c) Bonsignore L., Loy G., Secci D., Calignano A. "Synthesis and pharmacological activity of 2-oxo-(2H) 1-benzopyran-3-carboxamide derivatives" Eur. J. Med. Chem, 1993; 28: 517.
14. Hiramoto K., Nasuhara A., Michiloshi K., Kato T., Kikugawa K. "DNA strand-breaking activity and mutagenicity of 2,3-dihydro-3,5-dihydroxy-6-methyl-4H-pyran-4-one (DDMP), a Maillard reaction product of glucose and glycine" Mutat. Res., 1997; 395: 47-56.
15. Albiston AL., Diwakarla S., Fernando RN., Mountford SJ., Yeatman HR., Morgan B., Pham V., Holien JK., Parker MW., Thompson PE., Chai SY. "Identification and development of specific inhibitors for insulin-regulated aminopeptidase as a new class of cognitive enhancers" Br J Pharmacol, 2011; 164: 37-47.

16. Konkoy CS., Fick DB., Cai SX., Lan NC., Keana JFW. "Silica-Grafted Ionic Liquids as Recyclable Catalysts for the Synthesis of 3,4-Dihydropyrano[c]chromenes and Pyrano[2,3-c]pyrazoles" WO 0075123, 2000 Chem. Abstr, 2001; 134: 29313a.
17. Skommer J., Wlodkowic D., Matto M., Eray M. Pelkonen "HA14-1, a small molecule Bcl-2 antagonist, induces apoptosis and modulates action of selected anticancer drugs in follicular lymphoma B cells" J. Leuk Res, 2006; 30: 322-331.
18. Kemnitzer W., Kasibhatla S., Jiang S., Zhang H., Zhao J., Jia S., Xu L., Crogan-Grundy C., Denis R., Barriault N., Vaillancourt L., Charron S., Dodd J., Attardo G., Labrecque D., Lamothe S., Gourdeau H. Tseng B., Drewe J., Cai S. X. "Discovery of 4-aryl-4H-chromenes as a new series of apoptosis inducers using a cell- and caspase-based high-throughput screening assay. 2. Structure–activity relationships of the 7- and 5-, 6-, 8-positions" Bioorg Med Chem Lett, 2005; 15: 4745-4751.
19. El-Bayouki K., Aly M., Mohamed Y. "Novel 4(3H)-quinazolinone containing biologically active thiazole, pyrazole, 1,3-dithiazole, pyridine, chromene, pyrazolopyrimidine and pyranochromene of expected biological activity" World J Chem, 2009; 4: 161-170.
20. Ghashang M., Sheik Mansoor S., Aswin K. "Synthesis and in vitro microbiological evaluation of novel series of 8-hydroxy-2-(2-oxo-2H-chromen-3-yl)-5-phenyl-3H-chromeno [2,3-d]pyrimidin-4(5H)-one derivatives catalyzed by reusable silica-bonded N-propylpiperazine sulfamic acid" Res. Chem. Intermed, 2015; 41: 3117-3133.
21. Shaker RM. "Synthesis and reactions of some new 4H-pyrano[3,2-c]benzopyran-5-one derivatives and their potential biological activities" Pharmazie, 1996; 51(3): 148-151.
22. Abdolmohammadi SH., Balalaie S. "Novel and efficient catalysts for the one-pot synthesis of 3, 4-dihydropyrano [c] chromene derivatives in aqueous media" Tetrahedron Lett, 2007; 48(18): 3299-3303.
23. Kidwai M., Saxena S. 'Convenient preparation of pyrano benzopyranes in aqueous media" Synth. Commun, 2006; 36: 2737-2742.
24. a) Bera K., Sarkar S., Biswas S., Maiti S., Jana U. "Iron-catalyzed synthesis of functionalized 2H-chromenes via intramolecular alkyne-carbonyl metathesis" J. Org. Chem, 2011; 76: 3539-3544.

    b) Uemura M., Watson IDG., Katsukawa M., Toste FD. "Gold(I)-catalyzed enantioselective synthesis of benzopyrans via rearrangement of allylic oxonium intermediates " J. Am. Chem. Soc, 2009; 131: 3464-3465.

c) Fan J., Wang Z. "Facile construction of functionalized 4H-chromenevia tandem benzylation and cyclization" Chem. Commun, 2008; 5381–5383.

25. a) Rueping M., Uria U., Lin MY., Atodiresei I. "Chiral organic contact ion pairs in metal-free catalytic asymmetric allylic substitutions" J. Am. Chem. Soc, 2011; 133: 3732–3735.
    b) Ye LW., Sun XL., Zhu CY., Tang Y. " Unexpected tandem ylide annulations reaction for controllable synthesis of 2H-chromenes and 4H-chromenes"Org. Lett, 2006; 8: 3853–3856.
    c) Y.-L. Shi, M. Shi, DABCO catalysed reaction of allenic esters and ketoneswith salicyl N- tosylimines: Synthesis of highly functionalized chromenes"Chem. Eur. J., 2006; 12: 3374–3378.
26. Maghsoodlou MT., Safarzaei M., Mousavi MR., Hazeri N., Aboonajmi J., Shirzaei M. A "Green and novel three-component one-pot synthesis of tetrahydrobenzopyran, pyrano[2,3-d]pyrimidine, and 3,4-dihydropyrano[c]chromene derivatives using sodium acetate" Iran. J. Org. Chem, 2014; 6: 1197-1202.
27. Shinde S., Rashinkar G., Salunkhe R. "DABCO entrapped in agar-agar: A heterogeneous gelly catalyst for multi-component synthesis of 2-amino-4H-chromenes" J. Mol. Liq, 2013; 178: 122-126.
28. Zhou Z., Yang F., Wu L., Zhang A. "Potassium Phosphate Tribasic Trihydrate as Catalyst for the Rapid and Clean One-Pot Synthesis of 2-Amino-4H-Chromenes Under Solvent-Free Conditions" Chem. Sci. Trans, 2012; 1: 57-60.
29. Naimi-jamal MR., Mashkouri S., Sharifi A. "An efficient, multicomponent approach for solvent-free synthesis of 2-amino-4H-chromene scaffold" Mol. Divers, 2010; 14: 473-477.
30. Shitole NV., Shelke KF., Sadaphal SA., Shingate BB., Shingare MS. PEG-400 remarkably efficient and recyclable media for one-pot synthesis of various 2-amino-4H-chromenes Green Chem. Lett. Rev, 2010; 3: 83.
31. Gouda MA., Abu-Hashem AA. "An eco-friendly procedure for the efficient synthesis of arylidinemalononitriles and 4,4′-(arylmethylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ols) in aqueous media" Green Chem. Lett. Rev, 2012; 5: 203-209.
32. Gong K., Wang HL., Luo J., Liu ZL. "One-pot synthesis of polyfunctionalized pyrans catalyzed by 1145 basic ionic liquid in aqueous media" Heterocyclic Chem., 2009; 46: 1145-1150.
33. Hyang Park J., Rok Lee Y., Hong Kim S. "A novel synthesis of diverse 2-amino-5-hydroxy-4H-chromene derivatives with a spirooxindole nucleus by Ca(OH)2-mediated

three-component reactions of substituted resorcinols with isatins and malononitrile" Tetrahedron, 2013; 69: 9682-9689.

34. Srinivas V., Rao VR. "One-Pot Synthesis of 2-Amino-5,10-dihydro-5,10-dioxo-4-phenyl-4H-benzo[g]chromene Derivatives Catalyzed by $ZnCl_2$" Synth. Commun, 2011; l41: 806-811.
35. Wang LM., Shao JH., Tian H., Wang YH., Liu B. "Rare earth perfluorooctanoate [$RE(PFO)_3$] catalyzed one-pot synthesis of benzopyran derivatives" J. Fluo. Chem, 2006; 127: 97-100.
36. Amna M. Abdella, Yassmin M., Mohamed A. Ali, Ahmed HM Elwahy., Ismail A. Abdelhamid. "Synthesis and Anti-influenza Virus activity of novel bis(4H-chromene-3-carbonitrile) derivatives" J. of Heterocyclic Chem., 2016; 00,00.
37. Heravi Majid M., Zakeri M., Mohammadi N. "Morpholine catalyzed one-pot multicomponent synthesis of compounds containing chromene core in water" Chin. J. Chem, 2011; 29: 1163-1166.
38. Pandey K., Saroj, Choudhary S., Anil K. "A facile and convenient synthesis of chromenes using reusable sulfonic acid functionalized Imidazolium salt chemistry" Select, 2017; 2: 4452-4455.
39. Maryam AE, Behrooz M., Mohsen Z. "Green synthesis of 1‑aryl-1,12-dihydrobenzo[h]pyrano[c]chromene derivatives" Journal of Chemical Reasearch, June 2014; 38: 341–342.
40. Dalip K., Buchi Reddy V., Shashwat S., Urvashi D., Suman K. "Nanosized magnesium oxide as catalyst for the rapid and green synthesis of substituted 2-amino-2-chromenes" European Journal of Medicinal Chemistry, 2009; 44: 3805-3809.
41. Sedaghat ME., Rajabpour Booshehri M., Nazarifar MR., Farhadi F. "Surfactant modified bentonite (CTMAB-bentonite) as a solid heterogeneous catalyst for the rapid synthesis of 3,4-dihydropyrano[c]chromene derivatives" Applied Clay Science, 2014.
42. Reza H., Ramin S., Mahshid H., Alireza M. "K_2CO_3/cyanuric acid catalyzed synthesis of 2-amino- 4H-chromene derivatives in water" Research On Chemical Intermediates, 2017; 43(8): 4611-4622.
43. Mohammad GD., Mohammad E., Ali Maleki. "Potassium phthalimide-N-oxyl: a novel, efficient, and simple organocatalyst for the one-pot three-component synthesis of various 2-amino-4H-chromene derivatives in water" Tetrahedron, 2013; 69: 1074-1085.

44. Kale SR., Kahandal SS., Burange AS., Gawande MB., Jayaram RV. "A benign synthesis of 2-amino-4H-chromene in aqueous medium using hydrotalcite (HT) as a heterogeneous base catalyst" Catal. Sci. Technol., 2013; 3: 2050-2056.
45. Muthuraja P., Prakash S., Sethuraman V., Radhakrishna S., and Manisankar P., "Environmentally benign Copper triflate-mediated multicomponent one-pot synthesis of novel benzo[g] chromenes possess potent anticancer activity" Chemistry Select, 2017; 2: 5068-5072.
46. Garkhedkar AM., Senadi GC., Wang JJ. "$ZnBr_2$-Mediated cascade reaction of o-alkoxy alkynols: synthesis of indeno[1,2-c]chromenes" Org. Lett., 2017; 19(3): 488-491.
47. Changsheng Y., Chenxia Y., Tuanjie L., Shujiang T. "An efficient synthesis of 4H-benzo[g]chromene-5,10-dione derivatives through triethylbenzylammonium chloride catalyzed multicomponent reaction under solvent-free conditions" Chin. J. Chem, 2009; 27: 1989-1994.
48. Behrooz M., Saeed B. and Reza T. "$Zn(L\text{-proline})_2$ as a powerful and reusable organometallic catalyst for the very fast synthesis of 2-amino-4H-benzo[g]chromene derivatives under solvent-free conditions" Appl. Organometal. Chem, 2015; 29: 408-411.
49. Bahareh S., Alireza H., Somayeh B. "Synthesis of nanoparticles silica supported sulfuric acid (NPs SiO_2–H_2SO_4): a solid phase acidic catalyst for one-pot synthesis of 4H-chromene derivatives" Journal of Chemical Research, 2011; 35(11): 666-668.
50. Abdolmohammadi S. "TiO_2 nanoparticles as an effective catalyst for the synthesis of hexahydro-2-quinolinecarboxylic acids derivatives" Chin. Chem. Lett., 2012; 23: 1003-1006.
51. Abdolmohammadi S., Mohammadnejad M., Shafaei F. "TiO_2 nanoparticles as an efficient catalyst for the one-pot preparation of tetrahydrobenzo[c]acridines in aqueous media" Z. Naturforsch., 2013; 68b: 362-366.
52. Mehrdad K., Abdolmohammadi S., Janitabar-Darzi S. "Fast and efficient synthesis of chromeno[d]pyrimidinediones catalysed by a TiO_2–SiO_2 nanocomposite in aqueous media" Journal of Chemical Research, 2017; 41: 337-340.
53. Naghmeh D., Niaz M., Mahmood T. "Preparation and characterization of a Molybdenum(VI) Schiff base complex as magnetic nanocatalyst for synthesis of 2-amino-4H-benzo[h]chromenes" J Nanostruct, 2016; 6(4): 312-321.

54. Safari J., Zarnegar Z., Heydarian M. "Practical, ecofriendly, and highly efficient synthesis of 2-amino-4H-chromenes using nanocrystalline MgO as a reusable heterogeneous catalyst in aqueous media" J. of Taibah University for Science, 2013; 7: 17-25.
55. Ali Reza K., Sheida H., Seyyed JS. "Synthesis and characterization of a novel nanosilica supported bipyridinium chloride nanocomposite and its application as a basic catalyst in the one-pot preparation of tetrahydrobenzo[b]pyran, dihydropyrano[3,2-c]chromene and dihydropyrano[4,3-b] pyran derivatives" Nanochem Res, 2016; 1(2): 157-165.
56. Wen XM, Wang HY and Li SL. "Aqueous [bmim][BF_4] as green solvent in microwave-assisted organic reactions: clean synthesis of 1H-benzo[f]chromene derivatives" Journal of Chemical Research, 2006; 12: 776-778.
57. Saeid TF, Ali Ramazani, Pegah AA., Yousef BF., Behrooz E. "Microwave-assisted multicomponent reaction for the synthesis of 2-amino-4H-chromene derivatives using ilmenite (FeTiO3) as a magnetic catalyst under solvent-free conditions" Asian Journal of Green Chemistry, 2017; 1: 34-40.
58. Leila K., Manouchehr M., Nosrat Ollah M., Asieh Y., Seyedeh Saeedeh MZ. "Studies on the synthesis of substituted 2-amino-4H-benzo[h]chromene and 3-amino-1H-benzo[f]chromene derivatives using base supported ionic liquid like-phase (SILLP) as an efficient green catalyst" Journal of Chemical Research, 2016; 41: 21-24.
59. Ali A. Mohammadi, Mohammad RA., Armin H. "Synthesis of tetrahydrobenzo[b]pyran under catalysis of $NH_4Al(SO_4).12H_2O$ (Alum)" Arabian journal of Chemistry, 2013.
60. Awatef Mohamed El-Maghraby. "Green chemistry: new synthesis of substituted chromenes and benzochromenes via three-component reaction utilizing Rochelle salt as novel green catalyst" Hindawi Publi. Corp. Org. Chem. Inter. Vol., 2014.
61. Preeti B., Gajanand S. "Green chemical approach for the synthesis of chromenes derivatives in presence of novel green catalyst (Rochelle salt) and their biological activity" Inter. Journal of Recent Research Aspects, 2015; 2(2): 45-50.
62. Sruthi V., Sunitha M., Satheesh A., Ravi K.M., Mastan RK., Chikurumilli CS, Annapurna N., Paul Douglas S. "Catalyst free one-pot synthesis of chromeno quinolines and their antibacterial activity" Green and Sustainable Chemistry, 2017; 7: 141-151.