Nano-Ceria (CeO_2): An Efficient Catalyst for the Multi-Component Synthesis of a Variety of Key Medicinal Heterocyclic Compounds

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ABSTRACT: *This review gives an overview of the applications of ceria nanoparticles as inexpensive, efficient, reusable, and environmentally sustainable heterogeneous catalyst for the synthesis of a variety of key medicinal heterocyclic compounds with the emphasis on the mechanistic aspects of the reactions. Literature has been surveyed from 2005 to 2018.*

KEYWORDS: *Ceria nanoparticles; Multicomponent reactions; Heterocycles; Catalyst; Synthesis.*

INTRODUCTION

Organic chemistry covers more than 12.5 million known carbon-containing compounds, about half of them contain heterocyclic systems [1]. In particular, heterocycles are common structural units of the vast majority of marketed drugs [2]. Of the top five small molecule drugs by US retail sales in 2014, four are contained at least one heterocyclic fragment in their structures (Fig. 1) [3]. Due to the diversity of this class of organic compounds in the therapeutic response profile, many researchers have been working to develop novel, practical and convenient protocols for their synthesis to improve energy consumption, atom economy and reaction yields [4].

Multi-Component Reactions (MCRs) represent one of the most efficient one-pot processes for the synthesis 3of heterocyclic compounds, in which more than three reactants are combined sequentially to construct complex organic molecules that contains almost all of the atoms of the starting materials [5]. In addition to avoidance of intermediates separation and purification processes, these reactions are generally environment and user friendly, time and energy saving, cost-efficient, and selective [6].

In the recent past, nanoparticles have gained increasing attention in organic synthesis as reusable and environmentally sustainable catalysts [7]. The high surface to volume ratio and reactive morphology of nanoparticles made them very successful heterogeneous catalysts in multi-component reactions [8]. Among metal nanoparticles, ceria nanoparticles (CeO_2-NPs) have recently received much attention because of their excellent catalytic activities, reusability, cost efficiency, non-toxicity, and

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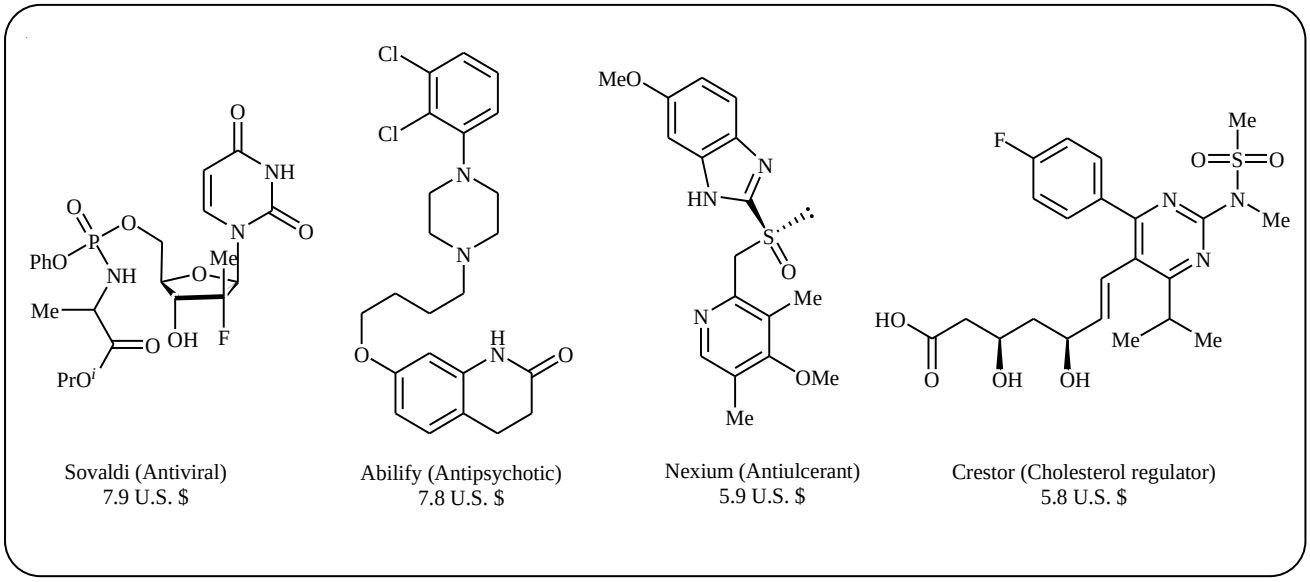


Fig. 1: Heterocycle molecule drugs present in the US top five prescription drugs and respective retail sales in 2014 (in billions of U.S. $) [3].

versatility [9]. To the best of our knowledge, the significance and power of CeO_2-NPs as heterogeneous catalyst in multi-component reactions has not been reviewed thus far. This review includes available information on using CeO_2-NPs as catalyst for the synthesis of a board range of key medicinal heterocyclic compounds through multi-component reactions (Fig. 2). Herein, we have classified these reactions based on the desired products. Literature has been surveyed from 2005 to 2018 and mechanistic aspects of the reactions are considered and discussed in detail.

1,2,3-Triazoles

1,2,3-triazole is a five-membered aromatic heterocycle with molecular formula $C_2H_3N_3$, containing three nitrogen atoms in the 1,2,3-positions. This heterocycle is the base core for a number of drugs, such as voriconazole, fluconazole, isovuconazole, cefatrizine, and tazobactum [10] The synthesis of this framework strongly relies on click chemistry *via* reaction of aryl/alkyl halides, alkynes and NaN_3 [11].

In 2014, *Albadi*, *Shiran*, and *Mansournezhad* reported the preparation of $CuO–CeO_2$ nanocomposite through a co-precipitation of cerium and copper nitrates in water at room temperature [12]. The nanocomposite was used as an efficient heterogeneous catalyst for the click synthesis of biologically important 1,4-disubstituted-1,2,3-triazoles **3** from benzyl and phenacyl bromides **1**, phenyl acetylenes **2**, and amberlite-supported azide in refluxing ethanol (Scheme 1). This $CuO–CeO_2$ NPs-catalyzed azide−alkyne [3 + 2] cycloaddition reaction tolerated a wide range of substituents on the benzyl and phenacyl bromides and was efficient for the use of different phenyl acetylenes with diverse steric and electronic properties. Moreover, the catalyst was reusable and preserved its catalytic activity after recycling for five runs of reaction.

Inspired by this work, Amini and Chae along with their co-workers reported a $CuNPs/CeO_2$ catalyzed preparation of 1,2,3-triazoles **6** starting from different benzyl halides **4**, acetylenes **5**, and sodium azide in water at 70 °C (Scheme 2) [13]. Under optimized conditions, the reaction tolerated both aromatic and aliphatic alkynes and gave corresponding 1,2,3-triazole products in good to excellent yields.

PYRROLES

The pyrrole framework is a privileged structure in chemistry due to its presence in a large number of molecules that exhibit a broad range of biological and pharmaceutical properties, such as anticancer, anxiolytic, antipsychotic, antiprotozoal, antimalarial, antibacterial, antifungal, and many more [14]. Due to these benefits, a number of synthetic methods have been developed

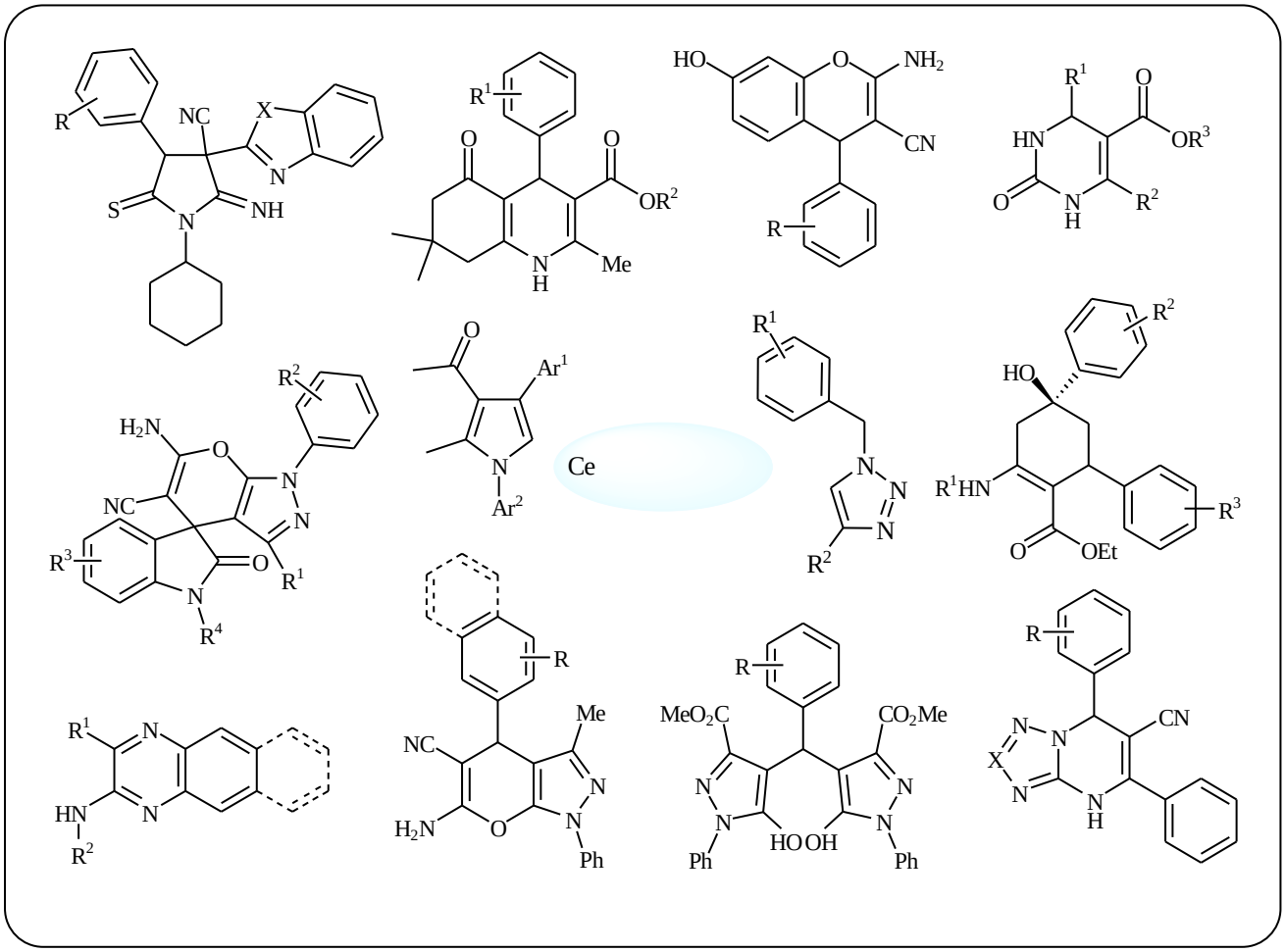
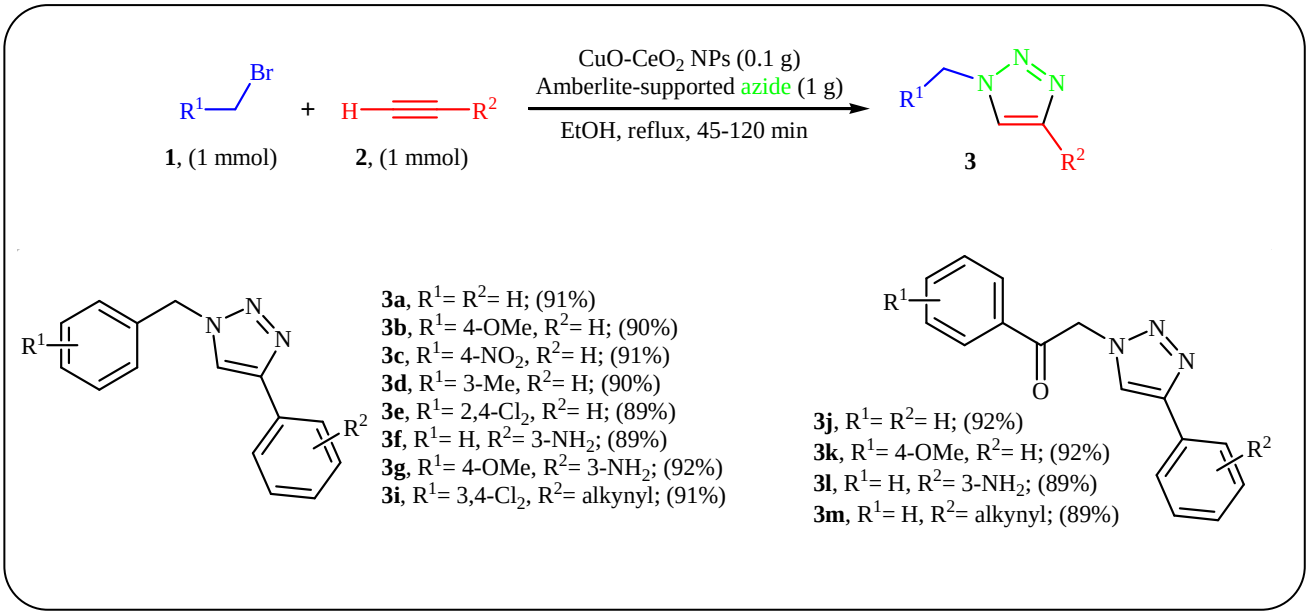
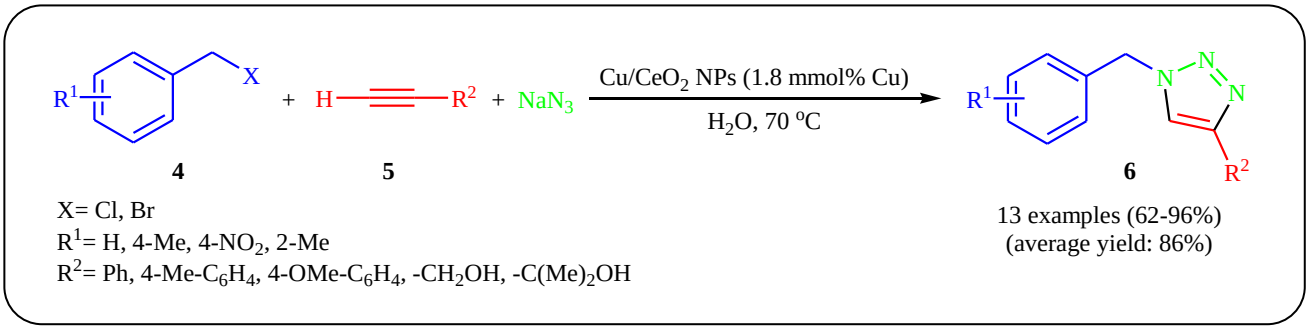


Fig. 2: Some important heterocyclic compounds synthesized by ceria nanoparticles catalyzed multi-component reactions.



Scheme 1: CuO-CeO_2 NPs-catalyzed click synthesis of 1,4-disubstituted-1,2,3-triazoles 3 reported by Albadi.



Scheme 2: Amini's synthesis of 1,4-disubstituted-1,2,3-triazoles 6.

to construct this biologically important heterocycle [15]. Synthesis of this key heterocycle by multi-component routes have attracted a large amount of attention due to their efficiency and intrinsic atom-economy [16].

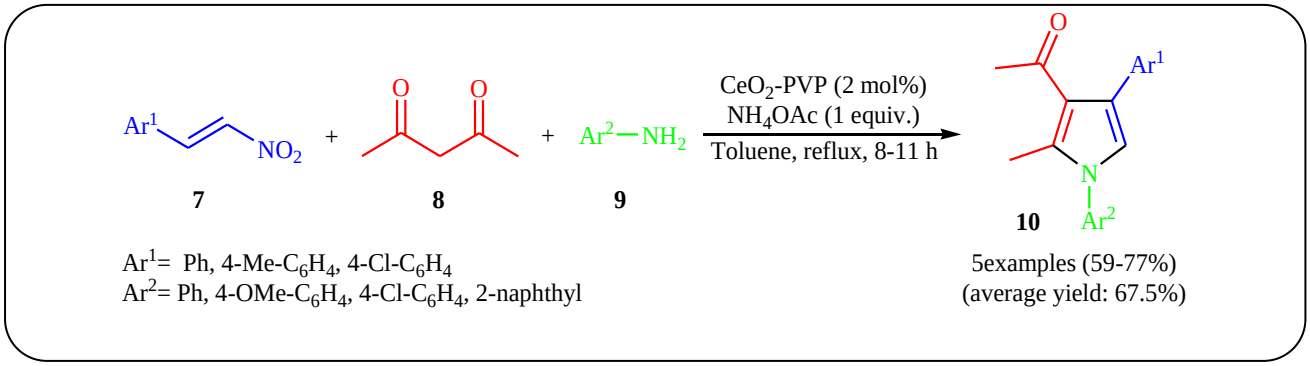
In 2016, Samai and co-workers reported a three-component reaction from nitrostyrenes **7**, pentane-2,4-dione **8** and anilines **9**, catalyzed by nano-sized CeO_2-PVP (polyvinylpyrrolidone), for the synthesis of *N*-aryl pyrrole derivatives **10** [17]. The reactions were performed in the presence of 1.0 of ammonium acetate as an additive in refluxing toluene and generally provided highly substituted pyrroles **10** in good yields (Scheme 3). The catalyst could be efficiently reused for four catalytic cycles without significant loss of its activity. It is noteworthy that CeO_2-P123 (triblock copolymer PEO_{20}-PPO_{70}-PEO_{20}) and CeO_2-17R4 (reverse triblock copolymer PPO_{14}-PEO_{24}-PPO_{14}) were also found to promote the reaction but in slightly lower yields. The authors explained this fact by the smaller size and greater surface area of CeO_2-PVP compare to CeO_2-17R4 and CeO_2-P123.

Very recently, the group of Wu developed a one-pot, four-component reaction between aromatic aldehydes **11**, malononitrile **12**, isocyanide **13**, and 2-mercaptobenzazoles **14** catalyzed by porous CeO_2 nanorod, for the synthesis of highly functionalized imino-pyrrolidine-thione derivatives **15** (Scheme 4) [18]. Among the various solvents like MeCN, MeOH, EtOH, H_2O, MeCN:H_2O (1:1), MeCN:H_2O (1:3), MeCN:H_2O (3:1); MeCN:H_2O (3:1) was the most efficient for this transformation. It should be mentioned that commercial CeO_2, granular CeO_2 NPs, fusiform CeO_2 NPs and linear CeO_2 NPs all could also be used to promote the reaction but afforded a lower yield of the final product. The results demonstrated that aromatic aldehydes bearing electron-withdrawing groups gave higher yields than those bearing electron-donating groups and 2-mercaptobenzoxazole compare to 2-mercaptobenothiazolegave gave higher yield of desired product. The mechanism proposed for this transformation is summarized in Scheme 5 and starts with the Knoevenagel condensation between the aldehyde **11** and the malononitrile **12**, leading to the formation of a gem-dicyano olefin intermediate **A**, which reacts with isocyanide **13** to furnish intermediate **B**. Its reaction with thiol **14** yields intermediate **C** that undergoes Ugi–Smiles-type rearrangement through intermediate **D** to the intermediate **E**. Finally, nucleophilic addition of the amino group onto the cyano group affords the expected product **15**.

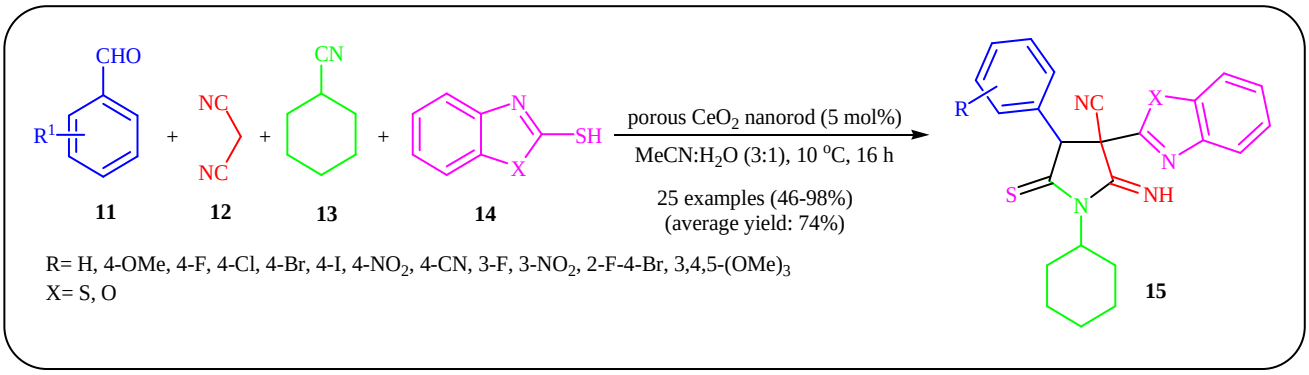
PYRIDINES

Pyridine is the most important six-membered heterocycles, present in more than one hundred currently marketed drugs [19]. Consequently, a number of methods have been reported for the synthesis of this biologically interesting *N*-heterocycle [20].

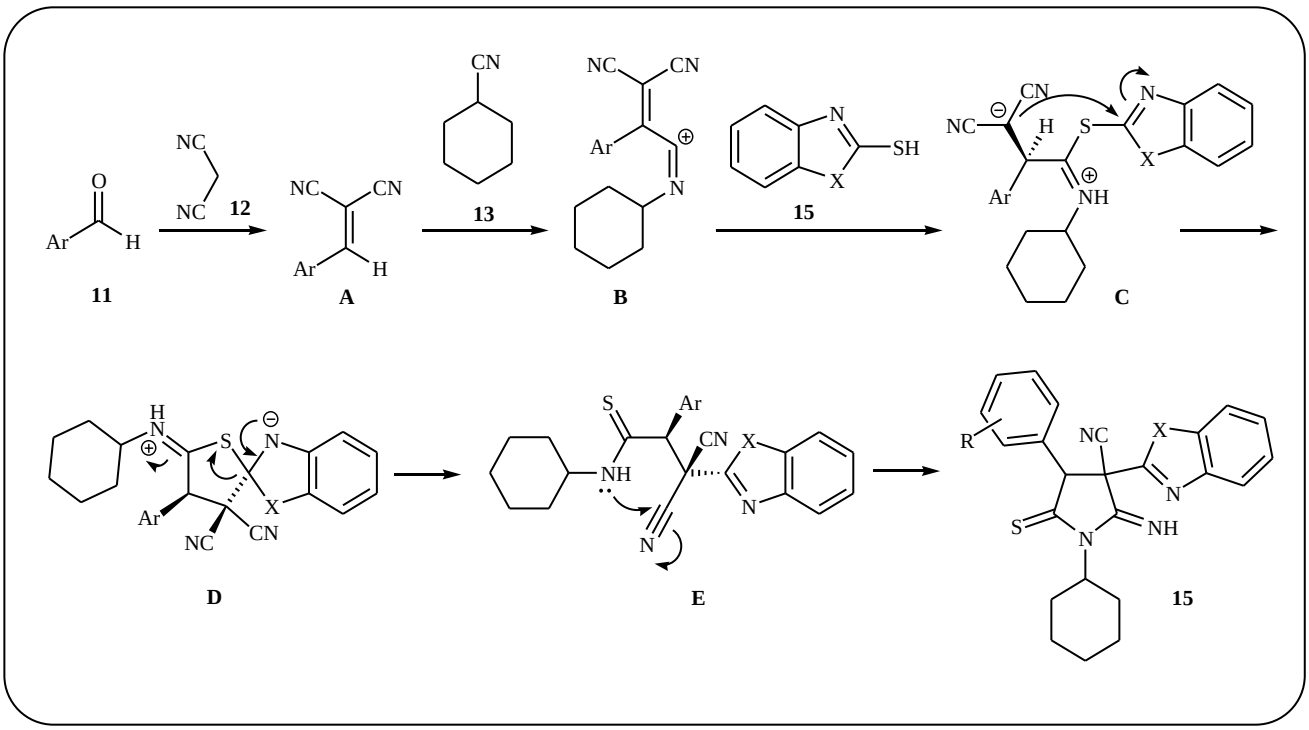
In 2013, Gawande and co-workers have synthesized a novel magnetite-based catalyst by coating Fe_3O_4 with CeO_2 nanoparticles [21]. The catalyst successfully applied in the synthesis of functionalized 1,4-dihydropyridines **19** by a one-pot four-component reaction of aromatic aldehydes **16**, β-ketoesters **17**, 5,5-dimethyl-1,3-cyclohexanedione **18**, and ammonium acetate in ethanol at room temperature (Scheme 6). The process showed very good functional group tolerance, including CN, OH, OMe, OPh, and Br functionalities that would allow further elaboration of the products. Importantly, the catalyst could be easily recycled from the reaction mixture by applying an external magnetic field without loss of catalytic activity within six cycles of reuse. Previously,



Scheme 3: Three-component pyrrole 10 synthesis from nitrostyrenes 7, pentane-2,4-dione 8 and anilines 9.



Scheme 4: Porous CeO_2 nanorod catalyzed four-component synthesis of imino-pyrrolidine-thione derivatives 15.



Scheme 5": Mechanism proposed to explain the imino-pyrrolidine-thione 15 synthesis.

the group of Naik reported the usefulness of free-ceria nanoparticles for the same reaction under solvent-free conditions [22].

Another environmentally benign procedure has been developed for the preparation of highly substituted 1,4-dihydropyridine derivatives **23**, the condensation of 5,5-dimethyl-1,3-cyclohexanediones **20**, 4-hydroxy-3-methoxy-5-((4-substituted-phenyl)-diazenyl)-benzaldehydes **21** and glycine **22** in the presence of Eu_2O_3 modified CeO_2 nanoparticles (nano-CeO_2-Eu_2O_3) as heterogeneous catalyst in water [23]. A library of (4-hydroxy-3-methoxy-5-(substituted-phenyldiazenyl)-dihydropyridineacetic acids **23** were prepared by performing all the reactions for 2-2.5 h at 80 ^oC to give a 69–91% yield (Scheme 7). The author proposed mechanism of the condensation is given in Scheme 8.

PYRIMIDINES

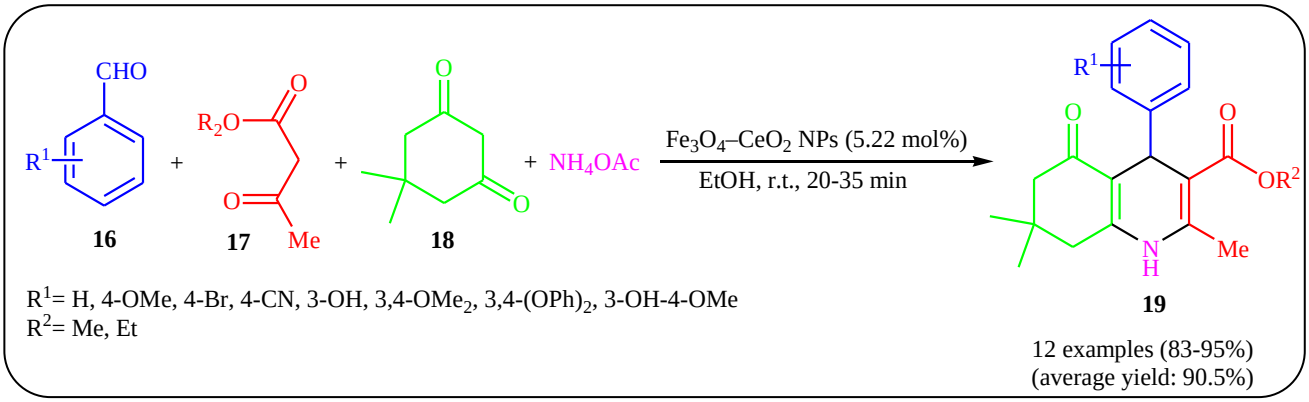
Pyrimidine is one of the most important classes of heterocyclic compounds exhibiting remarkable pharmacological activities such as antineoplastic, anthelmintic, antibacterial, antifungal, antiviral, and antiparkinson activities [24, 25]. Many commercially available drugs, including minoxidil, flucytosine, doxazosin, complera, etravirine, and rilpivirine are derived from pyrimidine core entities. The synthesis of functionalized pyrimidines through multi-component reactions has been the object of a number of studies [26], and a variety of MCR-based methods are now available. In 2005, Sabitha and co-workers used ceria nanoparticles supported on poly(4vp-co-dvb) as a heterogeneous catalyst (10 mol%) for the preparation of 3,4-dihydropyrimidin-2(1H)-ones **28** by a one-pot three-component condensation of aldehydes **25**, β-ketoesters **26** and urea **27** in moderate to excellent yields in the most environmentally benign solvent, water [27]. Various aromatic/heteroaromatic/aliphatic aldehydes, aminopyridines, and β-ketoesters were used to establish the general applicability of this synthetic process. Interestingly, the electronic character of the substituents in aromatic aldehydes had a remarkably little effect on the facility of the reaction. As shown in Scheme 9 both electron-rich and electron-poor aromatic aldehydes worked well under this reaction conditions. This methodology was also modified using β-diketone in place of the β-ketoester, providing corresponding product in good yield. The synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones using 22% Co/CeO_2-ZrO_2 nanoparticles as the heterogeneous catalyst has also been described [28]. In 2013, Albadi and Mansournezhad reinvestigated the same reaction by using CuO-CeO_2 nanocomposite as a green recyclable catalyst under aerobic condition. A series of 3,4-dihydropyrimidin-2(1*H*)-ones (10 examples) in excellent yields (up to 94%) with good functional group tolerance were obtained [29].

Recently, the group of Chandramouli used CeO_2 NPs (7-9 nm) for the synthesis of triazolo/tetrazolo[1,5-*a*]pyrimidine derivatives **32** *via* multi-component condensation reaction of aromatic aldehydes **29**, benzoylacetonitrile **30**, and 5-aminotriazole/5-aminotetrazole **31** (Scheme 10) [30]. Water was found to be the best solvent for the reaction and, among several solvents tested, EtOH, MeCN, toluene, and dioxane were found to be less effective. The reaction *did not* give any *desired product* when neat condition was used. Apparently, the outcome of the condensation was also dependent on the reaction temperature, the best results were obtained by performing the process at 80 ^oC. The optimized conditions tolerated a variety of aromatic aldehydes containing both electron-donating and electron-withdrawing substituents at *ortho*-, *meta*- or *para*-positions and provided the expected fused pyrimidines in excellent yields. The mechanism suggested by the authors is depicted in Scheme 11, and involves an initial Knoevenagel condensation between aromatic aldehyde **29** and benzoylacetonitrile **30** to give the intermediate **A**, followed by Michael addition with 5-aminotriazole/5-aminotetrazole **31** to form intermediate **B**, which then undergoes intermolecular cyclization to afford intermediate **C**. Intermolecular dehydrogenation of this intermediate affords the final product **32** with the liberation of catalyst.

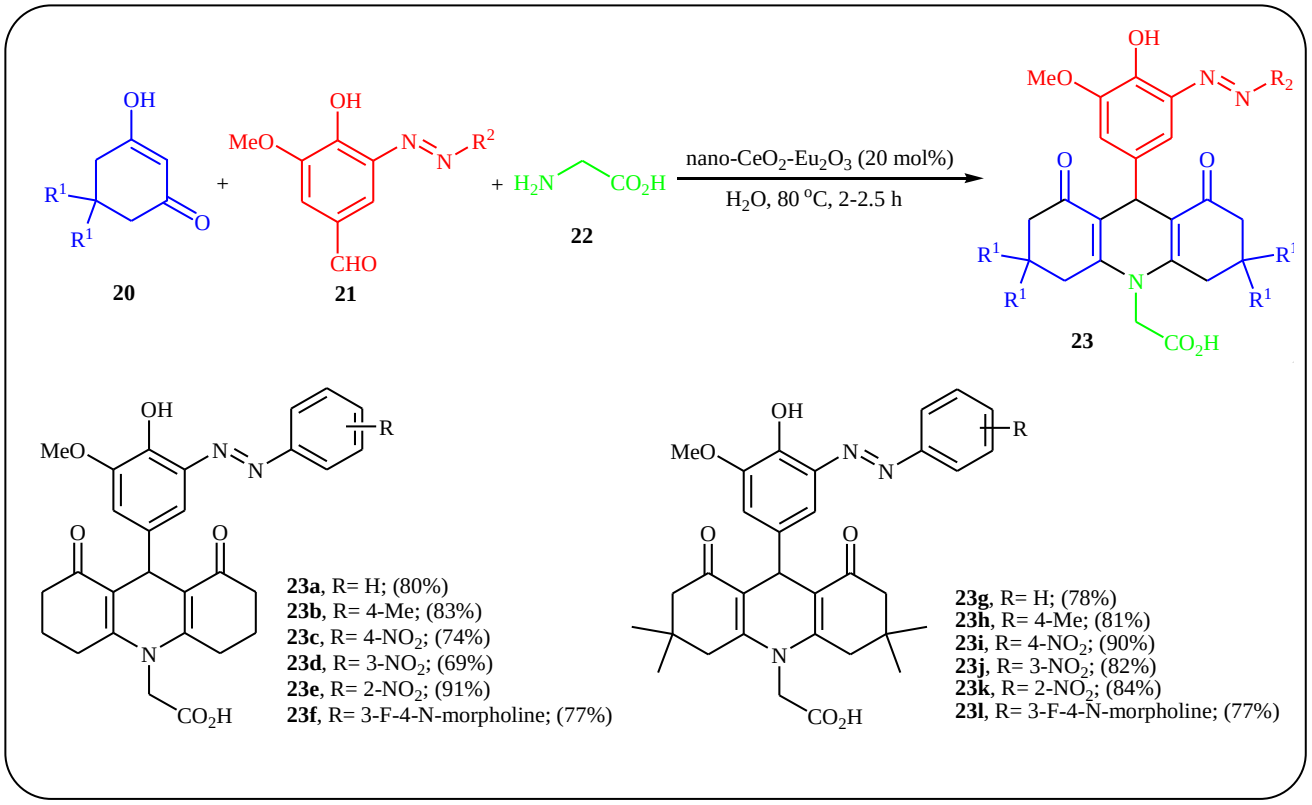
CHROMENES

The synthesis of functionalized 2-chromenes has attracted significant attention in recent years [31] as these classes of heterocyclic compounds constitute structural frameworks of several commercially available drugs and naturally occurring compounds [32].

In 2012, the group of Mishra synthesized a series of CeO_2–CaO nanocomposite oxides containing 5, 10, 20, 50 and 80 mol% of CeO_2 by the amorphous citrate method [33].



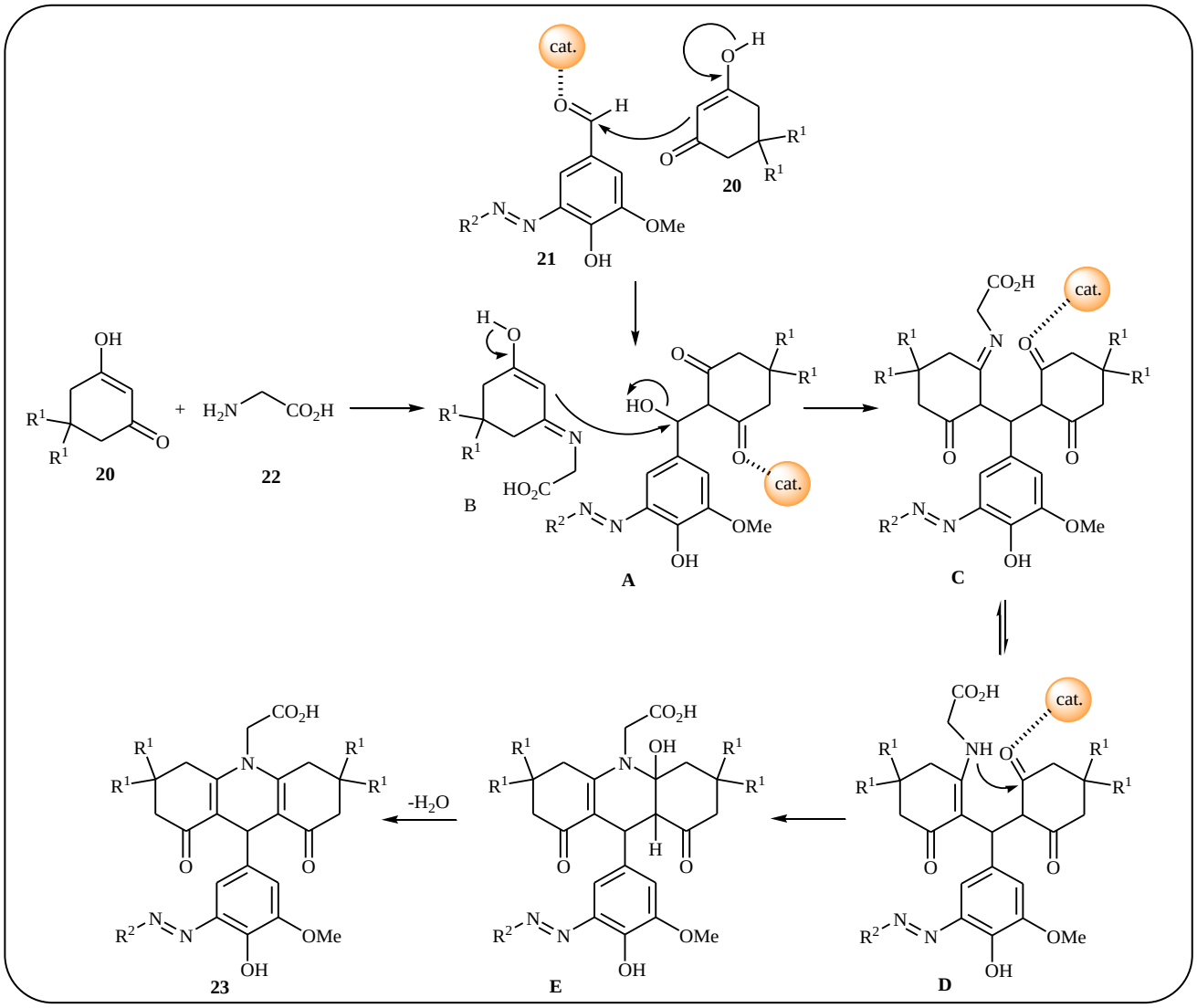
Scheme 6: Gawande's synthesis of 1,4-dihydropyridines 19.



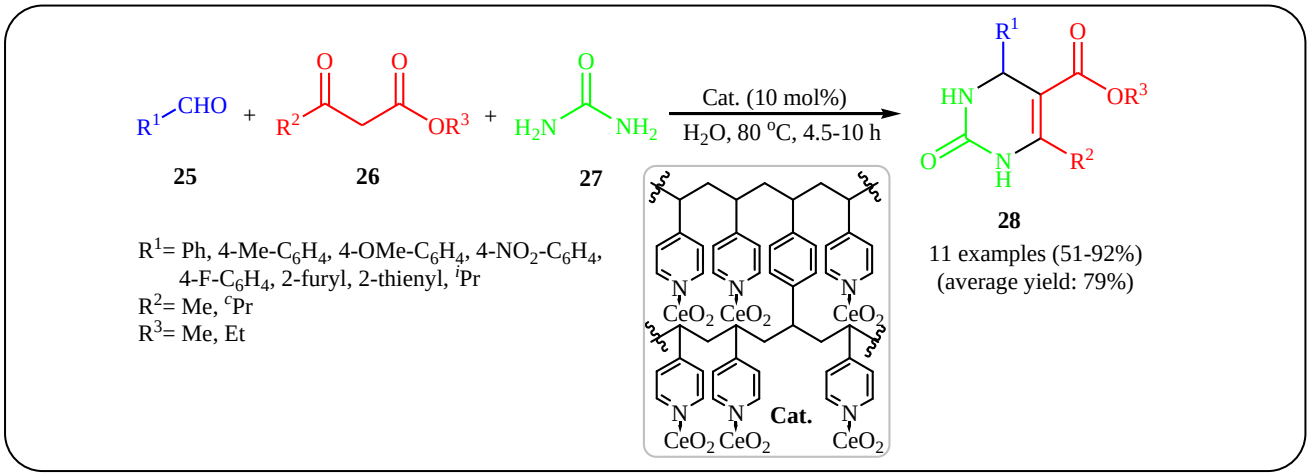
Scheme 7: Nano-CeO_2-Eu_2O_3-catalyzed four-component synthesis of 1,4-dihydropyridine derivatives 23.

The catalytic activity of these nanocomposites were investigated for aqueous phase one-pot synthesis of 2-amino-2-chromenes **35** through three-component reaction between aromatic aldehydes **33**, α-naphthol **34**, and malononitrile **12**. The results proved that among all the catalysts, the 20CeO_2–CaO exhibited a higher catalytic activity in this reaction. Under the optimized conditions (20CeO_2–CaO, H_2O, 80 °C), various electron-neutral, electron-rich and electron-poor aromatic aldehydes afforded the corresponding 2-amino-2-chromenes in good to high yields (Scheme 12). The catalyst was reusable and could be recovered and reused for three reaction runs with negligible loss of performance.

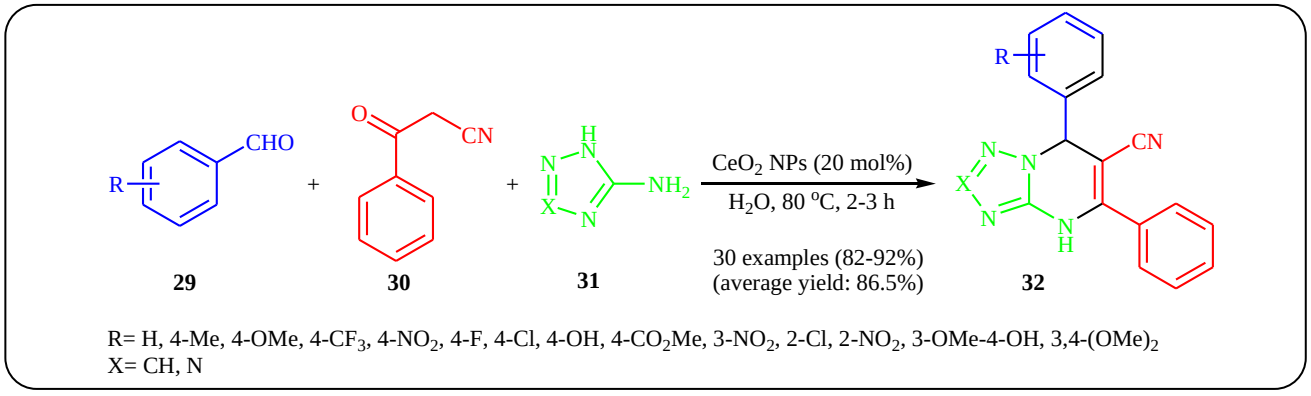
In a related investigation, Albadi and co-workers reported the use of CeO_2-CuO nanocomposite as an efficient and recyclable catalyst for the synthesis of chromene derivatives **38** *via* the one-pot three-component reaction of aromatic aldehydes **36**, resorcinol **37**, and malononitrile **12** under solvent-free conditions (Scheme 13) [34]. The reaction was performed at 80 °C,



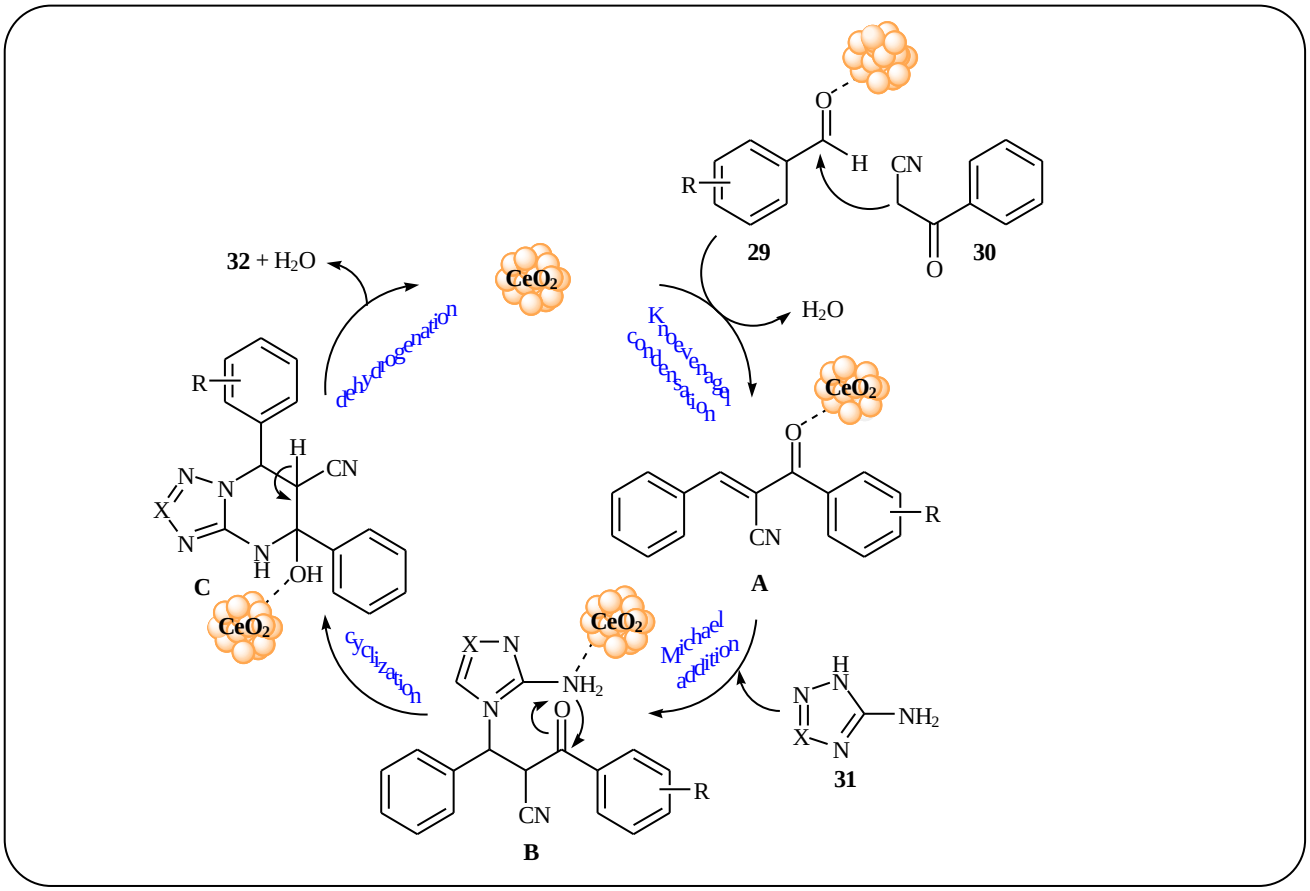
Scheme 8: Mechanism proposed for the reaction in Scheme 7.



Scheme 9: Ceria/vinylpyridine polymer nanocomposite-catalyzed synthesis of 3,4-dihydropyrimidin-2(1H)-ones 28 developed by Sabitha.



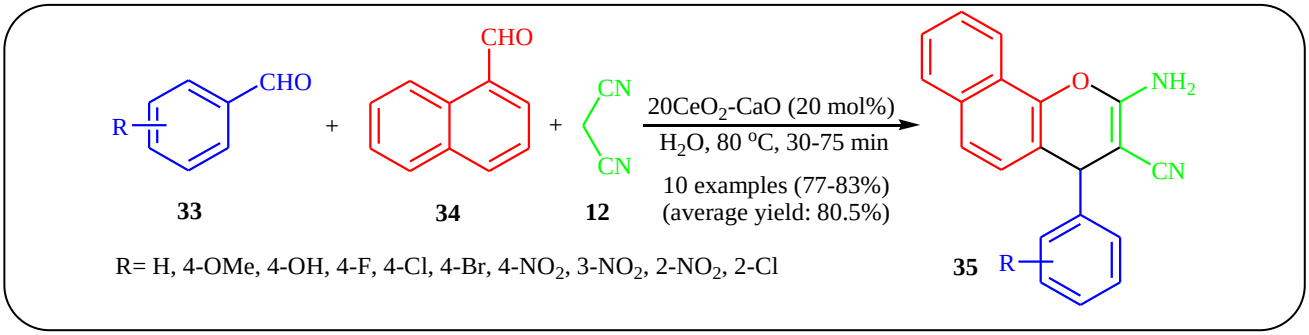
Scheme 10: CeO_2-NPs-catalyzed synthesis of triazolo/tetrazolo[1,5-a]pyrimidines 32 from aldehydes 29, benzoylacetonitrile 30, and 5-aminotriazole/5-aminotetrazole 31.



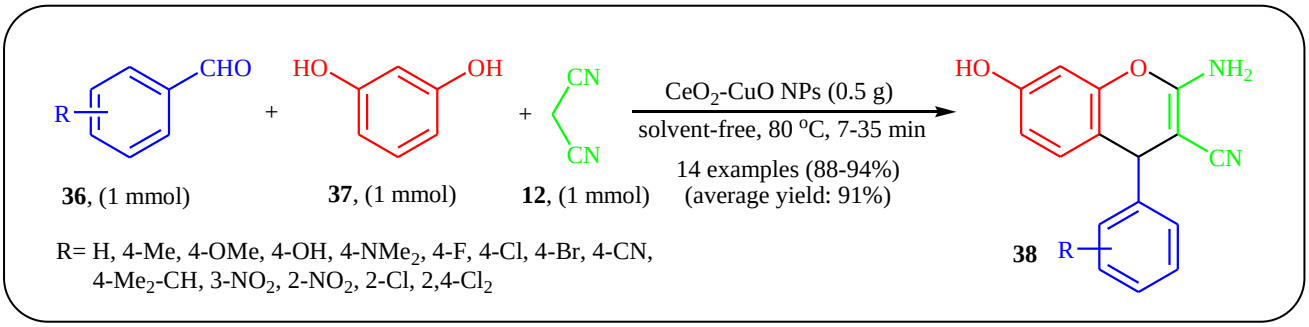
Scheme 11: Mechanistic explanation of the synthesis of triazolo/tetrazolo[1,5-a]pyrimidines 32.

tolerated a variety of sensitive functional groups (*e.g.*, nitro, cyano, amino, bromo, chloro, methoxy, and hydoxy), and generally provided the highly substituted chromenes **38** in high to excellent yields.

Recently, the group of *Chandramouli* reported an efficient synthesis of a number of 2-amino-4-(4-hydroxy-3-methoxy -5- (substituted-phenyl-diazenyl)-chromene-3-carbonitrile derivatives **40** through nano-sized CeO_2–ZrO_2 catalyzed three-component reaction between 1,3-dicarbonyl compounds **39**, 4-hydroxy-3-methoxy-5-(substituted-phenyl-diazenyl) benzaldehydes **21**, and malononitrile **12** in water medium at room temperature (Scheme 14) [35]. Other metal oxide nanoparticles were also found to promote the reaction (*e.g.*, Fe_3O_4, ZnO,



Scheme 12: Three-component synthesis of 2-amino-2-chromenes 35 catalyzed by 20CeO2–CaO nanocomposite.



Scheme 13: Three-component syntheses of chromenes 38 reported by Albadi, catalysed by the CeO2-CuO nanocomposite.

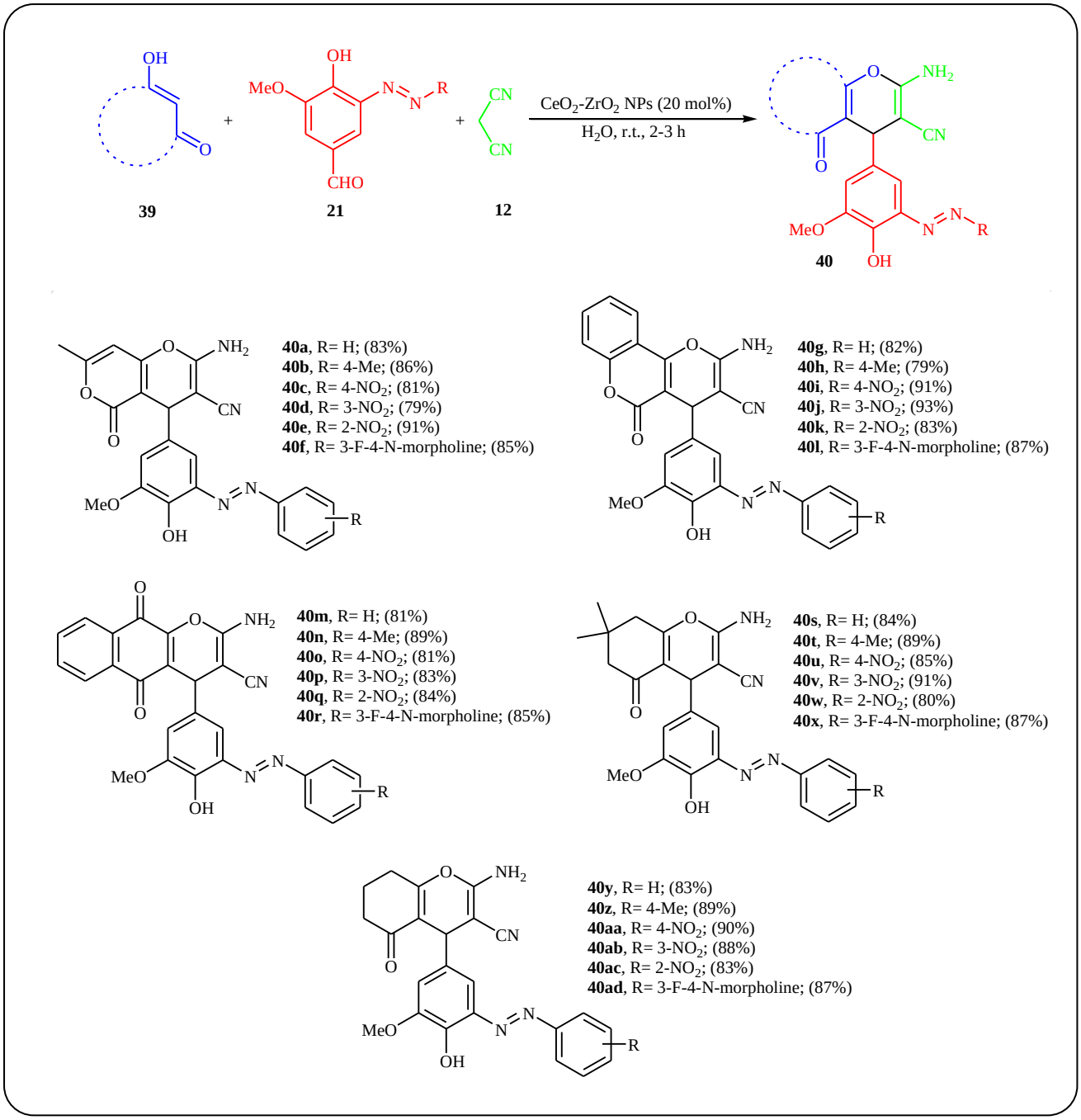
TiO_2, CeO_2); however, in lower yields. According to the author proposed mechanism, this reaction proceeded *via* a Knoevenagel condensation/Michael addition/ tautomerization/ intramolecular cyclization sequential process (Scheme 15).

QUINOZALINES

In 2014, Edayadulla and Lee explored the catalytic activity of CeO_2 nanoparticles for the synthesis of quinoxalin-2-amines **44** *via* a three-component reaction between aliphatic aldehydes **41**, 1,2-diamines **42**, and isocyanides **43**, in water at 80°C (Scheme 16) [36]. Benzaldehyde did not take part in the reaction and therefore no other aromatic aldehydes were examined in the protocol. A variety of 3,4-dihydroquinoxalin-2-amine derivatives were also successfully synthesized under standard conditions by reactions between ketones, 1,2-diamines, and isocyanides. Good to high yields, short reaction times, relatively mild reaction conditions, and reusability of the catalyst were the advantages, mentioned for this green protocol. The mechanism for this quinoxaline synthesis was proposed to be initiated by the generation of the iminium ion **A** from CeO_2NPs-promoted condensation between aldehyde **41** and 1,2-diamine **42** followed by nucleophilic addition of isocyanide **43** to this intermediate to give the intermediate **B**. intramolecular cycloaddition of **B** affords intermediate **C**, which undergoes isomerization to intermediate **D**. Finally, the oxidation of intermediate **D** affords the observed product **44** (Scheme 17).

MISCELLANEOUS REACTIONS

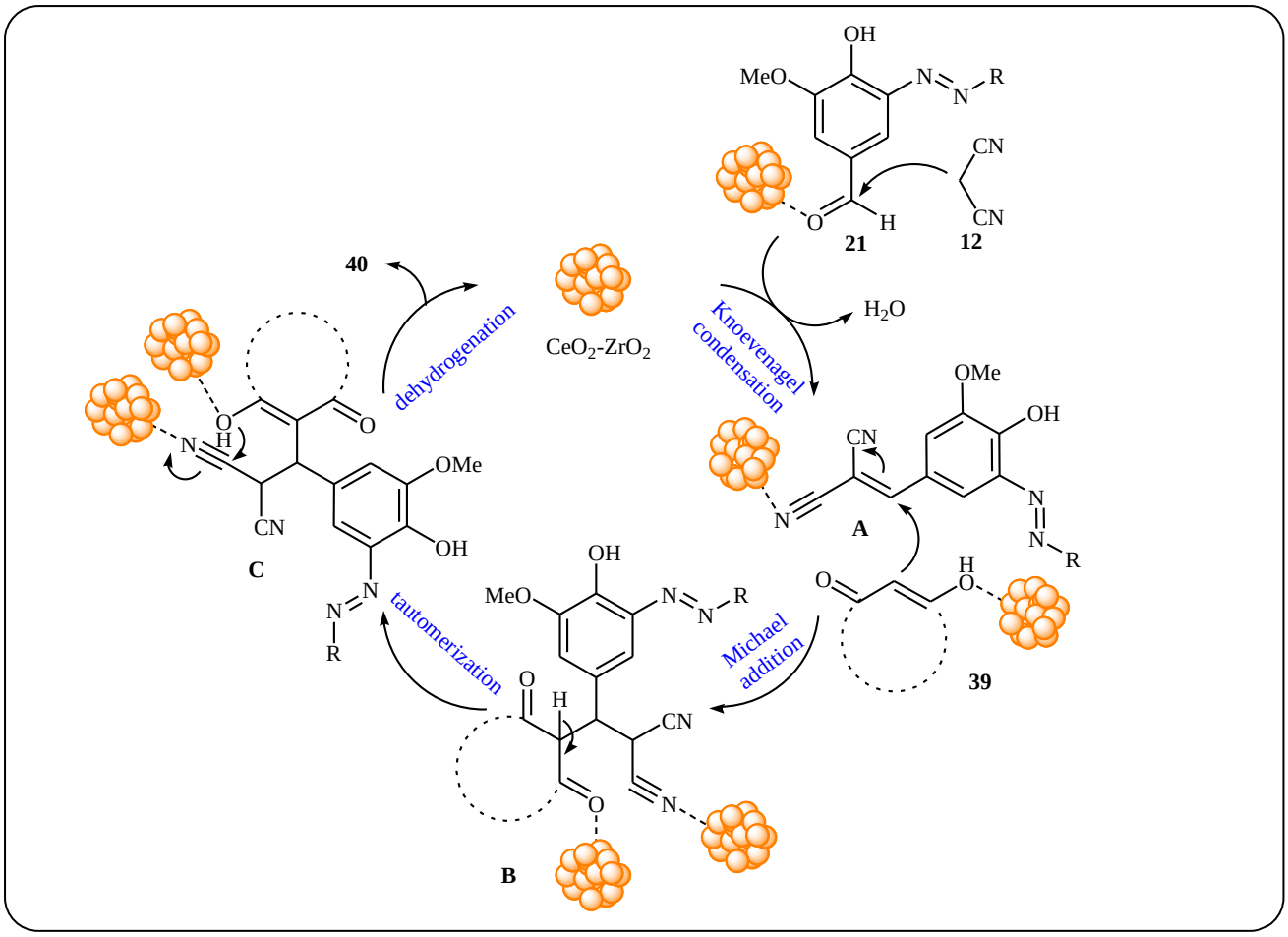
In 2013, *Albadi and et al.* have reported the synthesis of biologically important 4*H*-benzo[b]pyran derivatives **47** under solvent-free conditions using CuO–CeO_2 nanocomposite as an efficient recyclable catalyst [37]. The mixture of aromatic aldehydes **45**, 3-methyl-1-phenyl-2-pyrazoline-5-one **46**, and malononitrile **12** in 1 : 1 : 1 molar ratios in the presence of catalytic amounts of CuO–CeO_2, were heated at 80 °C to give the desired products in excellent yields (Scheme 18a). The reaction is noteworthy in that both electron-rich and electron-poor aromatic aldehydes are well tolerated. It should be noted that the catalyst could be easily recovered from the reaction mixture by a simple filtration, followed by washing with acetone to remove traces of organic compounds and drying. The separated nanocatalyst could be reused for at least eight successive times without tangible loss of its catalytic activity. A subsequent study



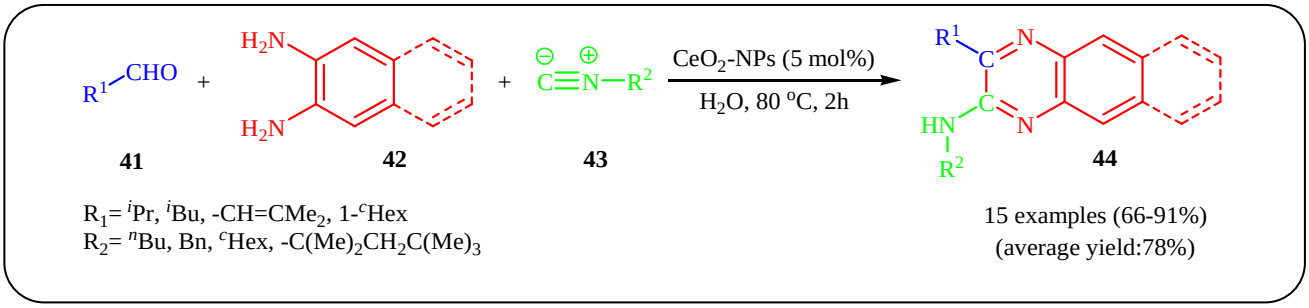
Scheme 14: Multicomponent synthesis of 2-amino-4-(4-hydroxy-3-methoxy-5-(substituted-phenyl-diazenyl)-chromene-3-carbonitrile derivatives 40 catalyzed by zirconium doped ceria nanoparticles.

by the same authors showed that 1,8-dioxooctahydroxanthenes **50** could be prepared by three-component reaction of one molecule of aromatic aldehydes **48** with two molecules of 1,3-dicarbonyl compounds **49** employing CuO–CeO_2 nanocomposite as the catalyst (Scheme 18b) [38]. This protocol afforded the optimum yield in refluxing water.

In 2015, *Safaei-Ghomi* and *co-workers* have described a synthesis of C-tethered bispyrazol-5-ols **54** by using a five-component reaction of one molecule of aromatic aldehydes **51**, two molecules of acetylenedicarboxylate **52**, and two molecules of phenylhydrazine **53** at 70 °C in water (Scheme 19) [39].



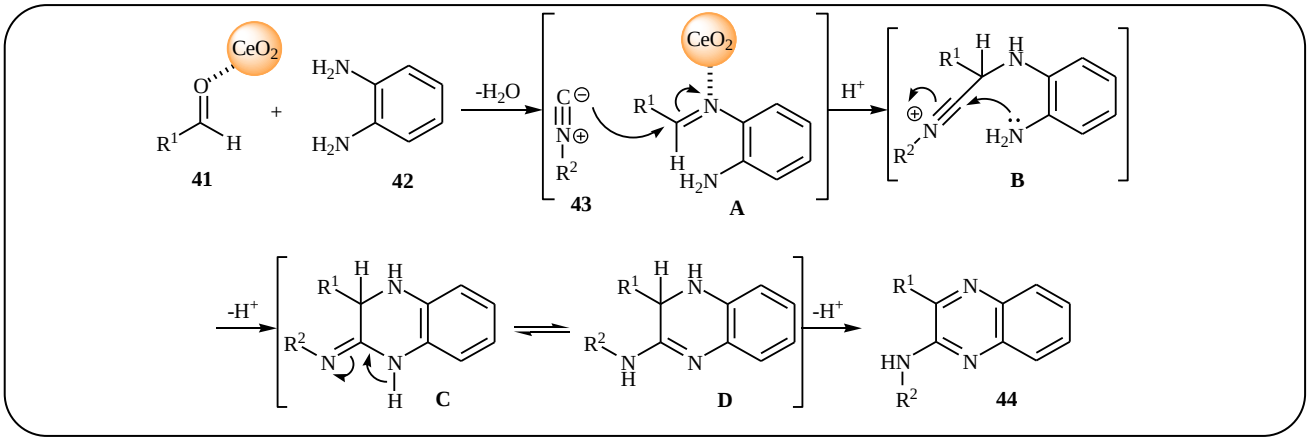
Scheme 15. Mechanistic proposal for the reaction in Scheme 14.



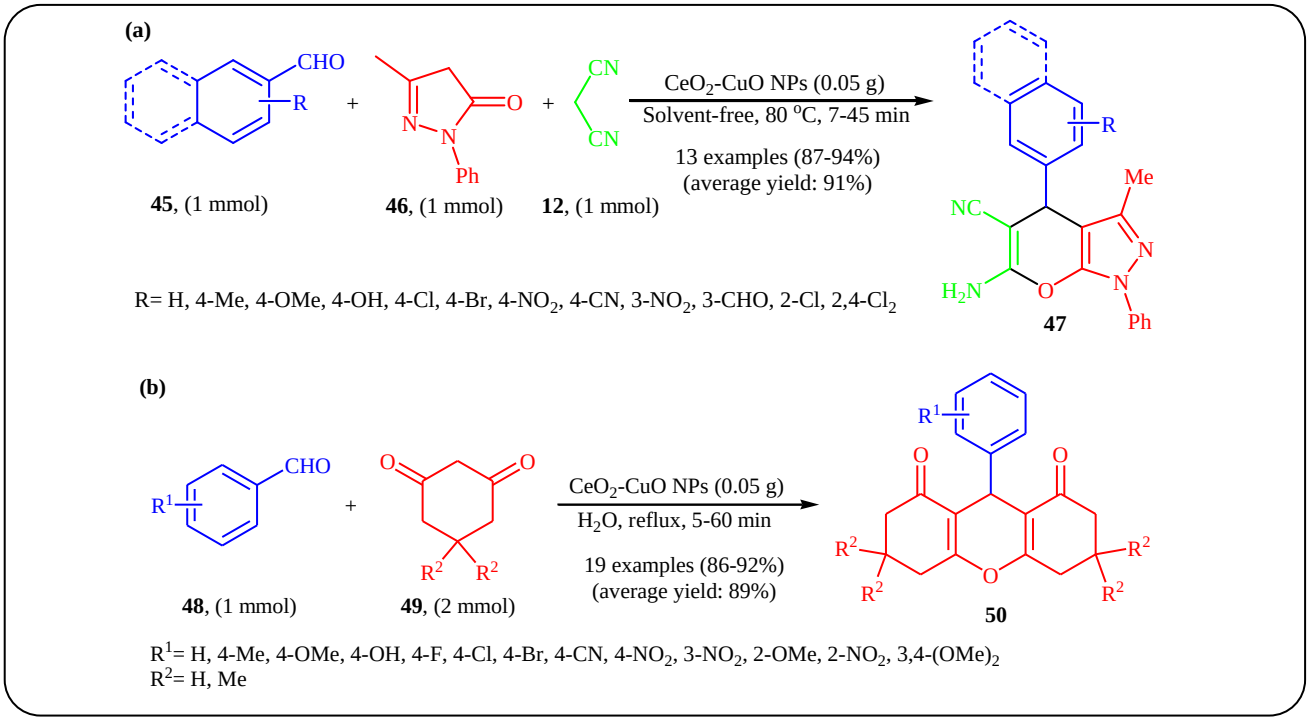
Scheme 16: CeO_2 nanoparticles-catalyzed three-component reaction between aldehydes 41, 1,2-diamines 42, and isocyanides 43.

A variety of metal catalysts such as CuO, NiO, CaO, ZrO_2, CeO_2, Al_2O_3, and Nd_2O_3 have been tested for this multicomponent reaction. Nanosized ceria has been shown as an effective catalyst for this reaction. Under optimized conditions, the corresponding C-tethered bispyrazol-5-ols **54** were obtained in high to excellent yields. The author proposed mechanism for this transformation is represented in Scheme 20.

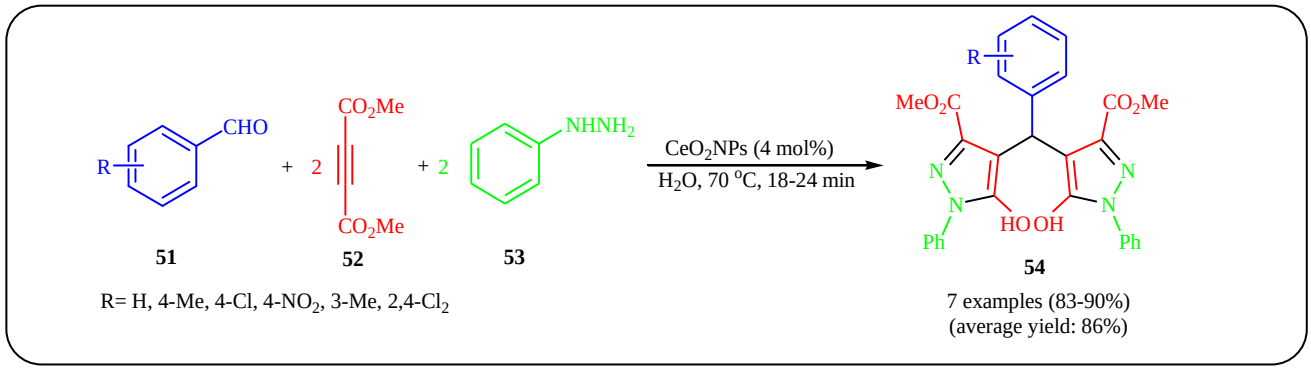
The synthesis of a range of cyclic *β*-aminoesters **58** in good to high yields (up to 85 %) was also reported by the same research team through a simple and environmentally benign three-component reaction between primary amines **55**, ethyl acetoacetate **56**, and chalcones **57** using CeO_2 NPs as an efficient heterogeneous catalyst in ethanol at room temperature (Scheme 21) [40].



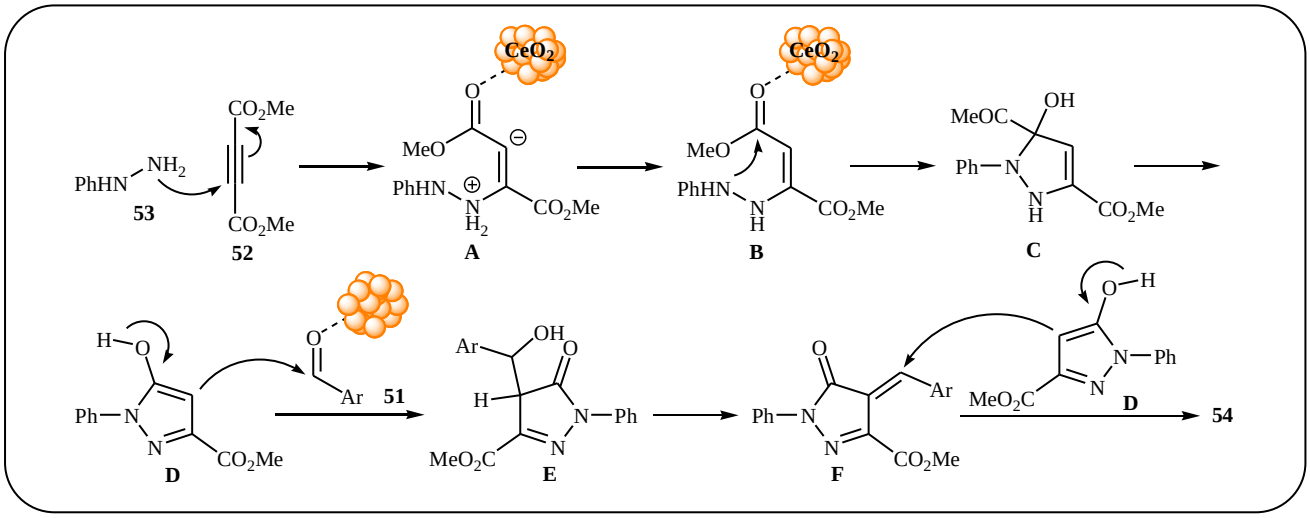
Scheme 17: Mechanism that accounts for the formation of quinoxalin-2-amines 44.



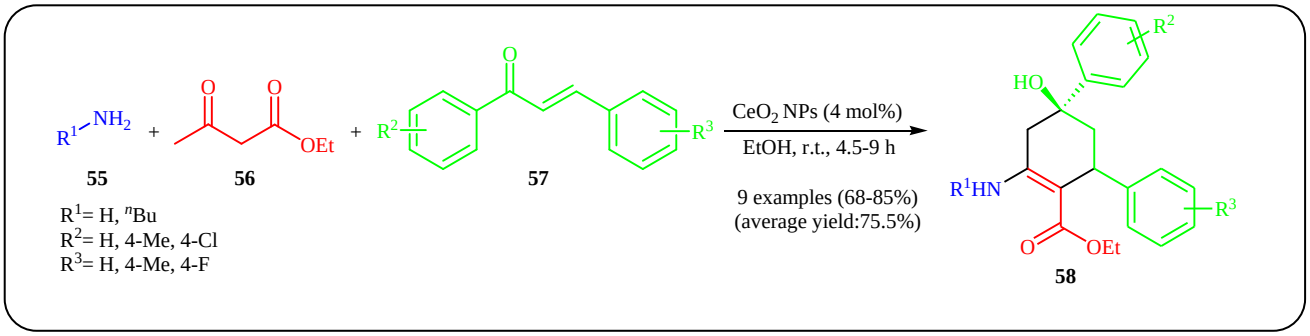
Scheme 18: Albadi's synthesis of (a) 4H-benzo[b]pyran derivatives 47; (b) 1,8-dioxooctahydroxanthenes 50.



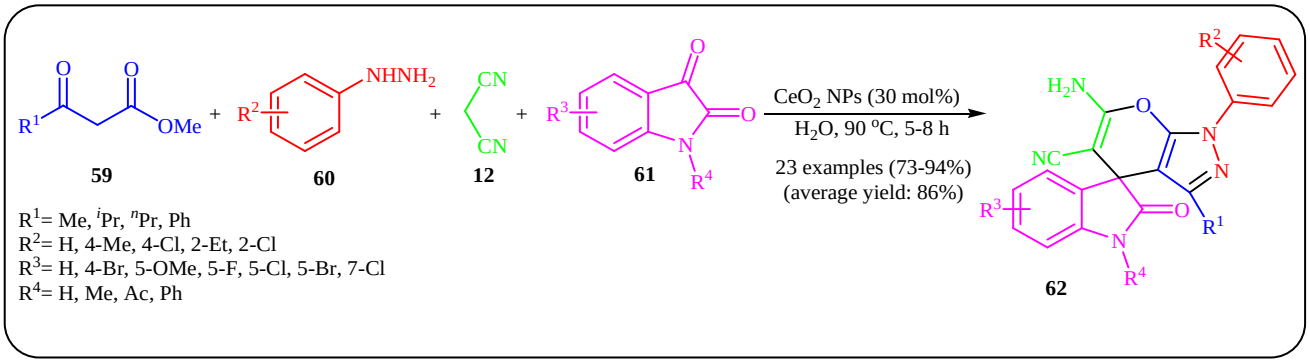
Scheme 19: Multicomponent synthesis of C-tethered bispyrazol-5-ols 54 using CeO_2 nanoparticles as catalyst.



Scheme 20: Plausible mechanism for the synthesis of C-tethered bispyrazol-5-ols 54.

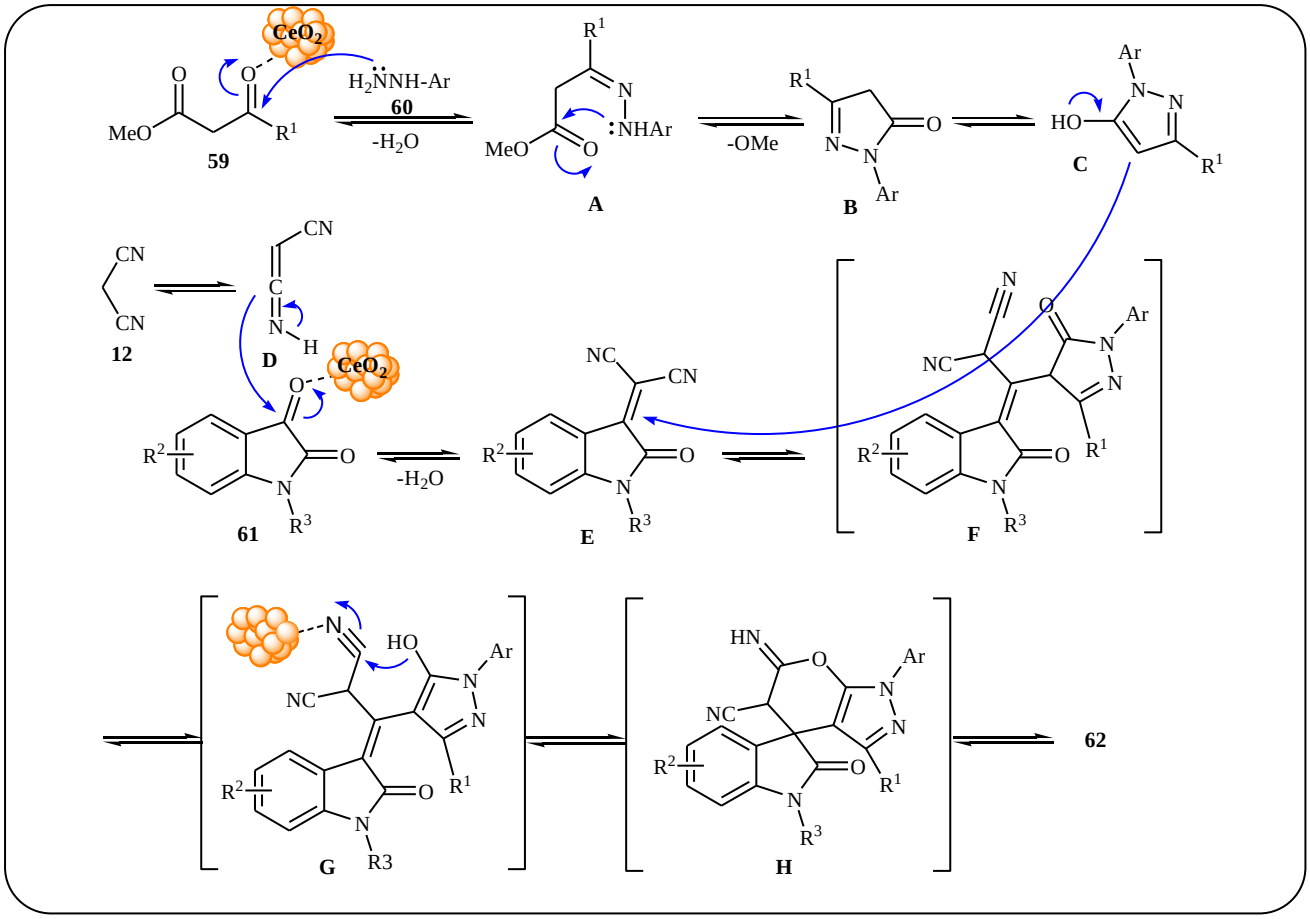


Scheme 21: CeO_2 NPs-catalyzed synthesis of cyclic β-aminoesters 58 by three-component reaction of primary amines 55, ethyl acetoacetate 56, and chalcones 57.



Scheme 22: Four-component synthesis of spiro[indoline-3,4'-pyrano[2,3-c]pyrazole] derivatives 62 catalyzed by ceria nanoparticles.

A four-component reaction of *β*-ketoesters **59**, phenylhydrazines **60**, malononitrile **12**, isatins **61** in the presence of 30 mol% of CeO_2-NPs as catalyst has been reported by Shrestha *et al*. in water at 90 ºC [41]. The protocol furnished the formation of highly functionalized and biologically interesting spiro[indoline-3,4'-pyrano[2,3-*c*]pyrazole] derivatives **62** in good to excellent yields (Scheme 22). The prepared spirooxindoles exhibit potent antioxidant and antibacterial activities. Mechanistically, this reaction proceeded *via* a condensation/ Knoevenagel reaction/ Michael reaction/ intramolecular cyclization/ isomerization sequential process (Scheme 23).



Scheme 23: Mechanism that accounts for the formation of spirooxindoles 62.

CONCLUSIONS

This Focus Review describes the recent advances on the synthesis of biologically interesting heterocyclic compounds using ceria nanoparticles as inexpensive, efficient, reusable, and environmentally sustainable heterogeneous catalyst. As illustrated, most of the reactions covered in this review have been performed in the most environmentally benign solvent, water, at room temperature. These results clearly show the potential application of CeO_2NPs-catalyzed multi-component reactions in industry. Hopefully, multi-component reactions catalyzed by CeO_2 NPs will be employed in the synthesis of complex natural and biologically important heterocyclic compounds in future studies.

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