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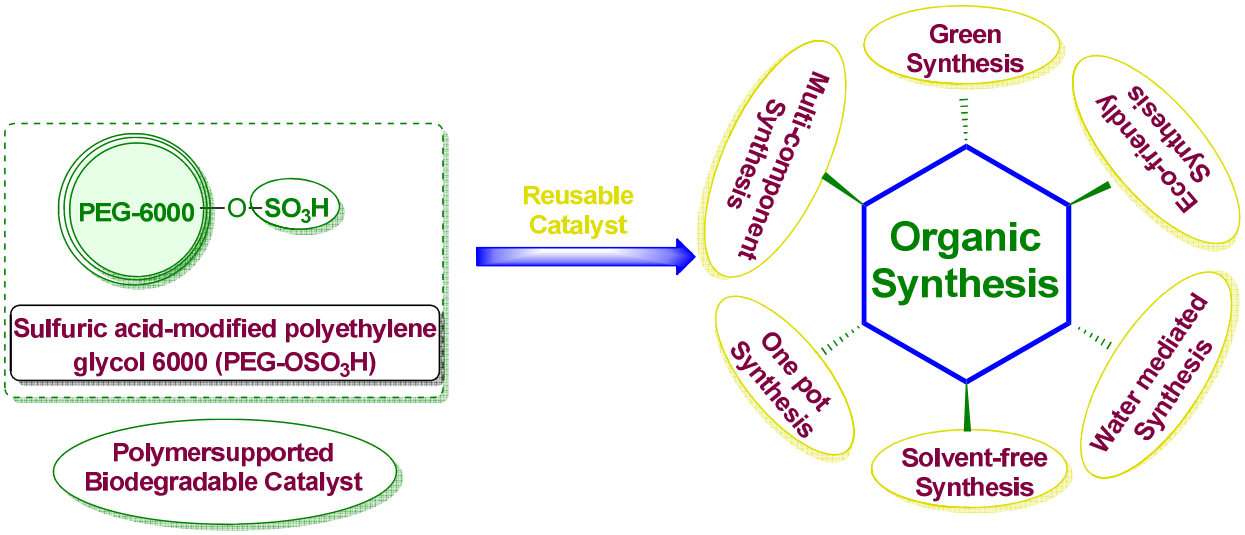

Sulfonated polyethylene glycol (PEG-OSO_3H) as polymer supported biodegradable and recyclable catalyst in green organic synthesis: Recent advances

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Abstract:

The objective of this review is to summarize some of the recent advances in a sulfuric acid-modified polyethylene glycol 6000 (PEG-OSO_3H) as a stable, recyclable and bio-degradable polymeric catalyst in organic synthesis. PEG-OSO_3H is highly efficient and eco-friendly catalyst, which catalyzed various organic reactions and could be recovered and reused several times without significant loss of its activity. In this review, preparation and application of PEG-OSO_3H in organic synthesis are investigated.

Key words:

Polyethylene glycol 6000, PEG-OSO_3H, Organic synthesis, Homogeneous catalysis, Green synthesis, Reusable catalyst, Biodegradable catalyst

Content:

1) Introduction:

Catalysis has played a significant role in reducing pollution from the chemical processes in our environment. By utilizing catalysts, organic reactions can be more efficient and selective thereby eliminating large amounts of by-products and other waste compounds.[1, 2] Catalysis is of crucial importance for the chemical industry and is used to make an enormous range of products like biologically important heterocyclic compounds and fine chemicals. It is one of the fundamental pillars of Green Chemistry[3] and considered as the most preferred and relevant technology to achieve a reduction of waste from chemical processes.

Acid catalysis is by far the most important area of catalysis employed by industries in all sectors of chemical manufacturing. The catalysts generally can be classified into two groups: homogeneous[4] and heterogeneous catalysts.[5] Homogeneous acid catalysts such as HF, HCl, CH_3COOH, HBr, CF_3COOH and H_2SO_4 are widely used in many important industrial processes, but they have some disadvantages in handling, corrosiveness, trouble work-up procedures and production of toxic waste.[6] At the end of the reaction, such acids are normally destroyed in water quenching stage and require subsequent neutralization; thus, consuming additional (alkaline) resources and producing salt waste. Hence, recyclable acid catalysts such as per fluorinated ion exchange polymers and Nafion[7, 8] were prepared by chemists to solve these problems.[9] Afterwards, solid acid zeolite,[10] solid super acid sulfated zirconia,[11] silica sulfuric acid,[12] alumina sulfuric acid,[13, 14] tungstate sulfuric acid,[15] molybdate sulfuric acid,[16] alum,[17] $ZrOCl_2.8H_2O$,[18] MCM-41- SO_3H,[19] PPA-SiO_2,[20] SiO_2-$HClO_4$,[21] SiO_2-$NaHSO_4$,[22] SiO_2-Pr-SO_3H,[23] amberlyst-15,[24] heteropoly acids[25] and montmorillonite K-10[26] were utilized in the synthesis of wide range of organic compounds. These solid acids have advantages over conventional acid catalysts such as simplicity in handling, mildness, cost-effective, selective and decreased reactor and plant corrosion problems. But the biodegradability and lower reactivity of these heterogeneous catalysts are still the major problem for organic synthesis. Thus, there is high need to develop biodegradable, polymer-supported and recyclable solid acid catalysts for the synthesis of heterocyclic compounds as well as a wide range of industrial important organic intermediates.

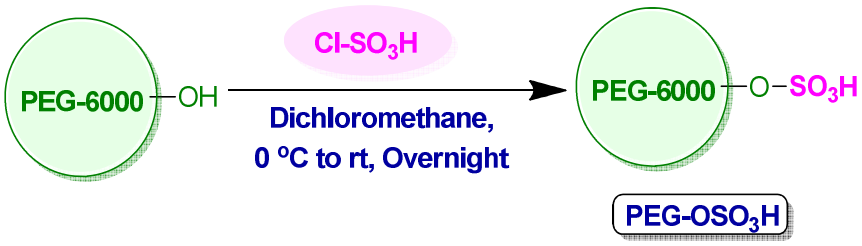
In recent years, the direction of science and technology has been shifting more towards eco-friendly, natural product resources and reusable catalysts. Thus, polymer-supported compounds used as supported catalysts, reagents and scavengers have drawn the attention of researchers.[27, 28] The utility of polymer-supported catalysts is well-recognized with their advantages like ease of workup, simple separation of products from the catalysts, economy and easily use in industrial processes.[29] The high reactivity, lack of diffusion phenomena, analytical simplicity and solubility profile of polyethylene glycols (PEGs with MW > 2,000 Da) are mostly soluble in polar solvents and insoluble in a few non-polar solvents have established them as good catalysts in homogeneous solid supported catalysis.[30] In addition, several strains of bacteria able to degrade polyethylene glycols (PEG) are reported in the literature.[31-33] Among them PEG-OSO_3H is a good example of solid supported organic acid catalyst that is functionalized with mild acidity, non-volatility and non-corrosiveness and also recognized as a good surfactant. Therefore, many

efforts have been made by researchers constantly to introduce novel recyclable, biodegradable and polymer-supported catalyzed organic synthesis by using PEG-OSO_3H, which is more efficient, economical and compatible with the environment. Also, these catalysts can be recovered and reused several times without a decrease in activity as well as its efficiency. The present article is intended to review briefly in recent research progress concerning the synthesis of different organic compounds catalyzed by PEG-OSO_3H.

2) Preparation of catalysts:

2.1) Preparation of sulfuric acid-modified polyethylene glycol 6000 (PEG-OSO_3H)[34]

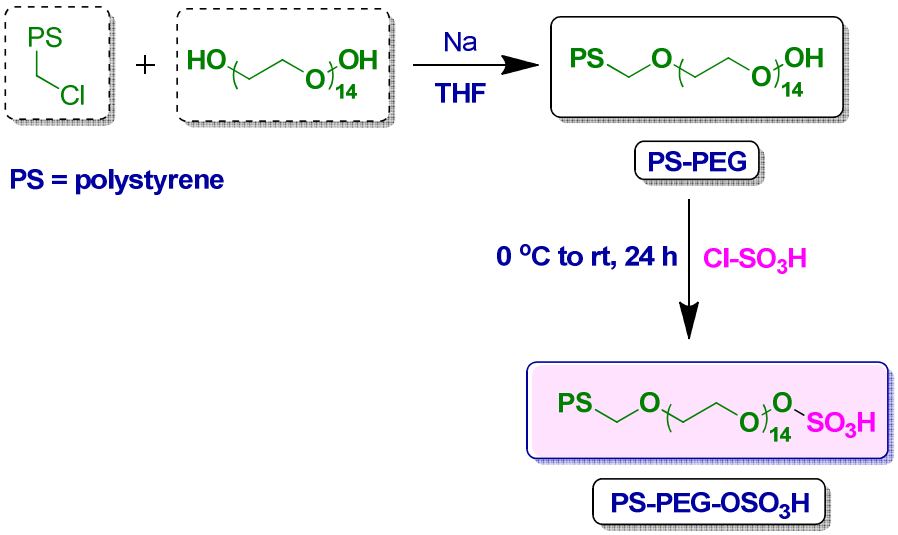
At 0 ^oC, chlorosulfonic acid (10 mmol) was added to a solution of PEG-6000 (1 mmol) in dichloromethane (10 ml), and the resulting solution was stirred at room temperature overnight. Then, the solution was concentrated under vacuum, and ether was added to it. The resulting precipitate was filtered and washed with ether three times to afford PEG-OSO_3H as a gummy solid.



2.2) Preparation of PS-PEG-bound sulfonic acid (PS-PEG-OSO_3H)[35]

Preparation of polystyrene-supported poly(ethylene glycol) (PS-PEG): Dry chloromethyl polystyrene (4.2 mmol Cl/g) (3 g, Cl 12.6 mmol) was allowed to swell in tetrahydrofuran for 1 h. Polyethylene glycol (PEG-600) (40 g, OH 134 mmol) and metallic sodium (3.0 g, 134 mmol) were added and the temperature was maintained at 80 ^oC for 35 h in an oil bath. The resulting polymer was cooled, collected by filtration; washed with methanol (60 mL), water (60 mL), and acetone (60 mL); and dried at 50 ^oC in vacuum for 12 h.

Above prepared, polystyrene-supported poly(ethylene glycol) (PS-PEG) (5 mmol) was allowed to swell in dichloromethane (50 mL) for 1 h. At 0 ^oC, chlorosulfonic acid (25 mmol) was added to the above mixture. Then the resulting mixture was stirred at room temperature for 24 h. The resulting polymer was collected by filtration; washed with dichloromethane, methanol and acetone; and dried at 50 ^oC in vacuum for 12 h.



PS-PEG-SO3H is a polystyrene-supported poly(ethylene glycol) bonded sulfonic acid, while PEG-OSO_3H is only poly(ethylene glycol) bonded sulfonic acid. In PS-PEG-SO_3H, polystyrene linker is attached, which shows better catalytic activity towards organic synthesis compared to PEG-OSO_3H. The addition of polystyrene linker in PS-PEG-SO3H, which increase the mass transfer ratio of the product from the reactants as well as increase the heterogeneous nature and stability of the catalyst.

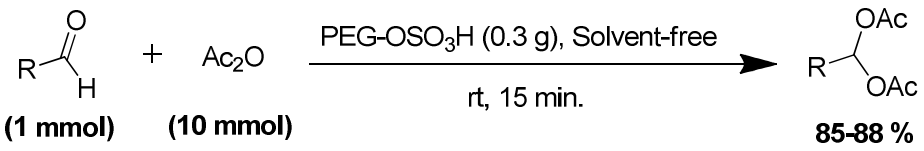
3) Various organic reactions catalyzed by sulfuric acid-modified polyethylene glycol 6000 (PEG-OSO_3H):

3.1) Solvent-free organic transformations catalyzed by PEG-OSO_3H

3.1.1) Synthesis of 1,1-diacetates from aromatic aldehydes and acetic anhydride

The synthesis of 1,1-diacetates is one of the most versatile acylalformation reactions in modern organic synthesis. Since 1,1-diacetates are stable toward a wide range of nucleophiles under neutral and basic conditions, acetylation is commonly utilized as a protecting method for carbonyl groups.[36] Moreover, they also serve as valuable precursors for the asymmetric allylic alkylation reactions[37] in natural product synthesis,[38] and for the synthesis of 1-acetoxydienes and 2,2-dichlorovinylacetates for Diels-Alder reactions.[39] Zong et al. have described an efficient and convenient protocol for the synthesis of 1,1-diacetates from aromatic aldehydes and acetic anhydride in the presence of PEG-OSO_3H as eco-friendly catalyst under mild and solvent-free conditions at room temperature, which afforded excellent yield of the product **(Scheme 1)**.[40] Here, PEG-OSO_3H acts as a catalyst and can be recovered and reused eight times without apparent loss of its catalytic activity. At the end of each run, the catalyst was recovered from the reaction mixture by addition of diethyl ether followed by a simple filtration. The recovered catalyst was dried under vacuum condition at 40 ^oC and reused. The yields remained unchanged even after the catalyst had been recycled eight times. The reaction did not take place after 4 h without the catalyst. Various solvents such as water, methanol, acetonitrile, dichloromethane and

solvent free condition were used in this transformation by the authors. However, protic solvents such as water and methanol required longer times with poor yields. Solvent-free condition was proved to be the best in terms of product yield and reaction time. The electron donating or electron withdrawing groups on the aromatic ring did not affect the yields. Aliphatic aldehyde like hexanal, can also be converted efficiently. It is important to note that in the reaction of 4-hydroxybenzaldehyde with acetic anhydride under the above conditions, both carbonyl and phenolic -OH groups were acylated. Various Lewis acids such as $Fe(NO_3)_3.9H_2O$,[41] cupric sulfate,[42] $In(OTf)_3$,[43] P_2O_5/Al_2O_3,[44] LiOTf,[45] $Bi(NO_3)_3$,[46] and $Al(HSO_4)_3$[47] were used for this synthesis, but they are not efficient as like PEG-OSO_3H in terms of product yields and reaction times. Zare and co-workers have also reported the same protocol for the chemoselective preparation of acylals from aldehydes and acetic anhydride in the presence of a catalytic amount of poly(ethylene glycol)-bound sulfonic acid (PEG-OSO_3H) at room temperature.[48] The best results were obtained, when 1.67 mol% of the catalyst was used. Increasing the amount of PEG-OSO_3H to 2.1 mol% did not improve the reaction results. Ketones don't react under these reaction conditions. By using this method, all kinds of aldehydes, including benzaldehyde, aromatic aldehydes possessing electron-releasing substituents, electron-withdrawing substituents and halogens on their aromatic rings, 2-naphthaldehyde, acid-sensitive aldehyde (furfural), bis-aldehyde (terephthaldehyde) and aliphatic aldehydes were acylated in excellent yields.



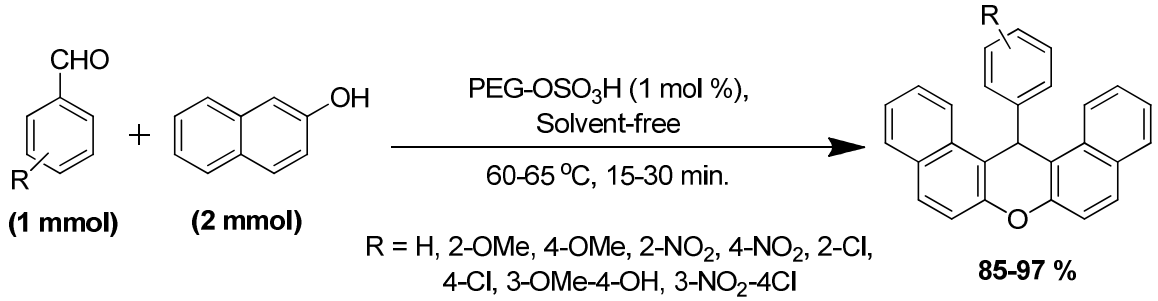
R = C_6H_5, 4-$NO_2C_6H_4$, 3-$NO_2C_6H_4$, 2-$NO_2C_6H_4$, 4-$OMeC_6H_4$, 4-BrC_6H_4, 4-ClC_6H_4, 4-OHC_6H_4, 4-MeC_6H_4, $CH_3(CH_2)_4$

Scheme 1

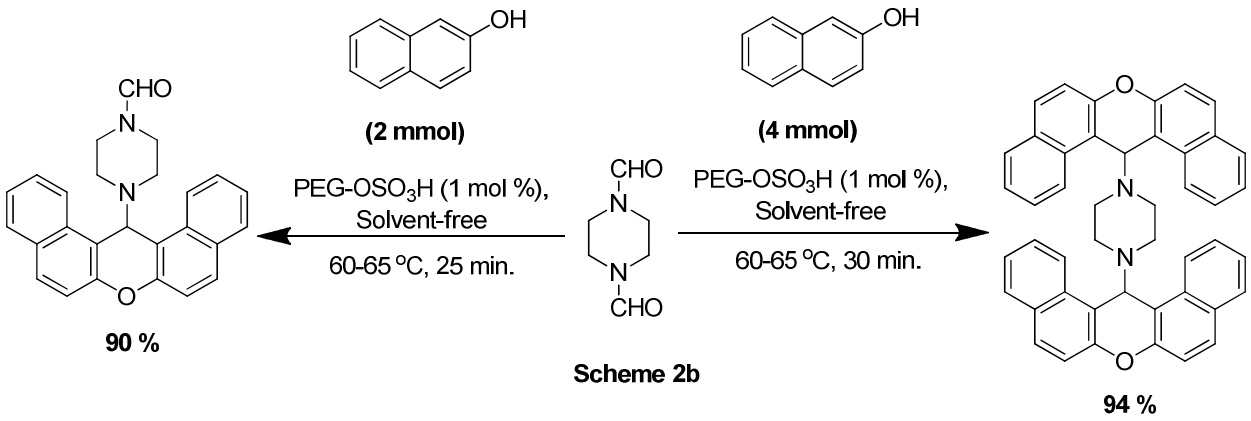
3.1.2) Synthesis of Aryl-14*H*-dibenzo[*a,j*]xanthenes

Aryl-14*H*-dibenzo[*a,j*]xanthenes are reported as important antibacterial, antiviral and anti-inflammatory agents.[49-51] The xanthene synthesis is catalyzed by some catalysts like *p*-toluenesulfonic acid,[52] sulfamic acid,[53] $AcOH/H_2SO_4$,[54] iodine,[55, 56] $K_5CoW_{12}O_{40}\cdot 3H_2O$,[57] cyanuric chloride,[58] LiBr,[59] $HClO_4\cdot SiO_2$,[60] $KAl(SO_4)_2\cdot 12H_2O$,[61] silica sulfuric acid[62] and $Yb(OTf)_3$.[63] However, there is a need to find new catalysts and green methods to minimize the drawbacks of existing methods such as poor yields, prolonged reaction times, toxic organic solvents, excess reagents, catalysts and harsh reaction conditions. Therefore, polyethylene glycol bound sulfonic acid (PEG-OSO_3H) was efficiently used by Naidu and co-workers as an efficient and eco-friendly polymeric catalyst in the synthesis of 14-aryl/heteroaryl-14*H*-dibenzo[*a,j*]xanthenes obtained from the reaction of 2-naphthol and carbonyl compounds under solvent-free conditions at 60-65 °C with short reaction time and excellent yields **(Scheme 2a-c)**.[64] After completion of the reaction, PEG-OSO_3H was extracted with water and reused after the evaporation of aqueous layer under reduced pressure. The catalyst was recovered at least three

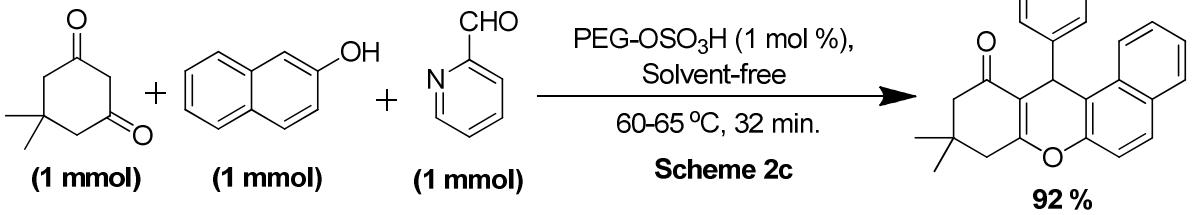
times without loss of their efficiency. Both an electron withdrawing and electron donating groups on aldehydes reacted efficiently in this protocol to afford excellent yield of the product.



Scheme 2a



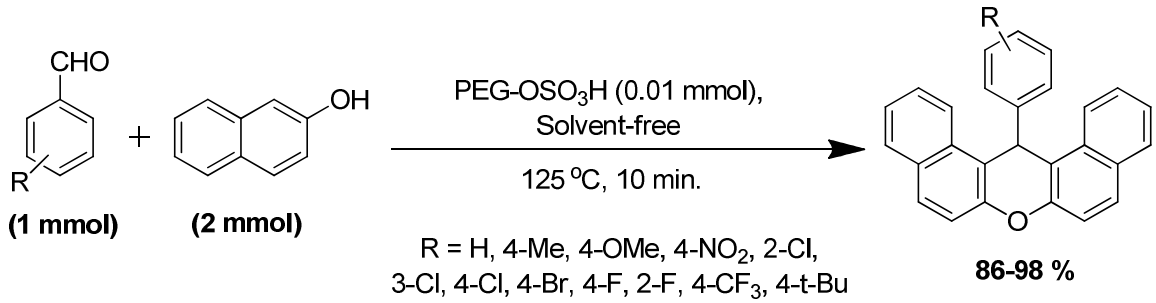
Scheme 2b



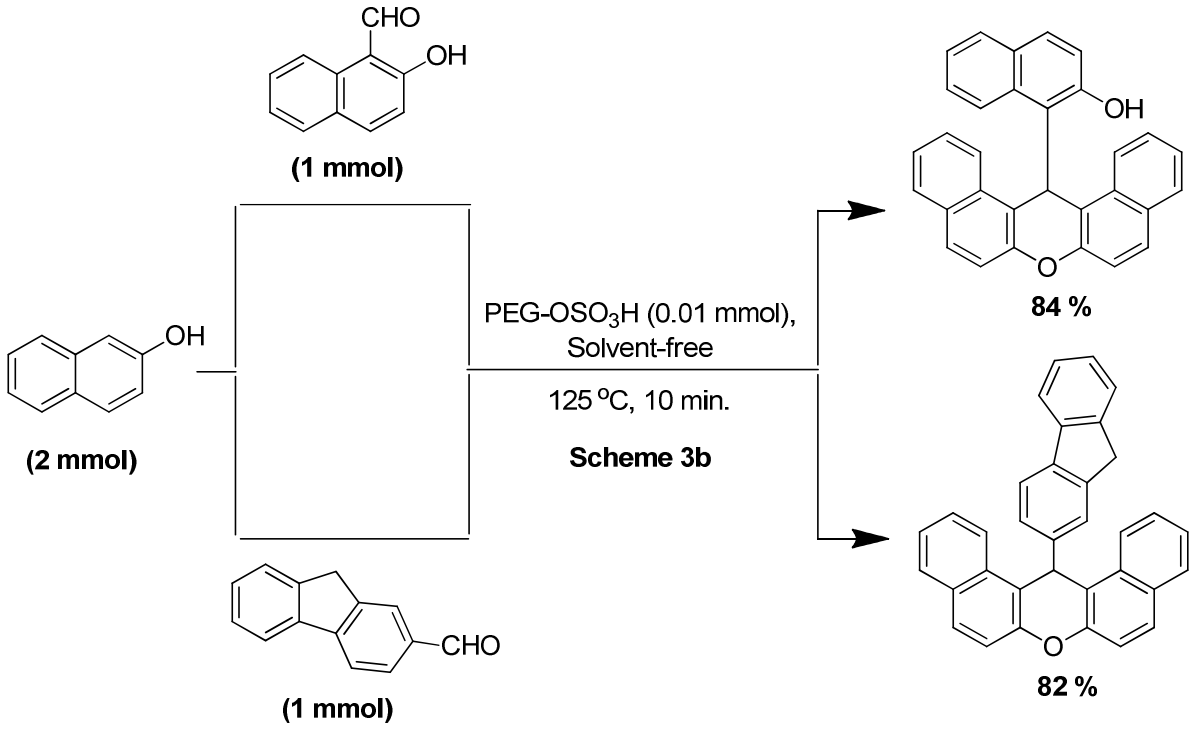
Scheme 2c

Xanthenes belong to an important class of oxygen heterocycles that are known to possess diverse pharmacological activities such as antibacterial,[65, 66] anti-proliferative,[67] anti-inflammatory,[68] and antiviral activities.[69] They have also been employed as excellent fluorescent dyes,[70] pH-sensitive fluorescent materials for the visualization of biomolecules,[71] photosensitizers in photodynamic therapy for the treatment of tumor cells,[72] and in laser technology.[73] A highly efficient, eco-friendly and high yielding methodology for the synthesis of 14-aryl-14*H*-dibenzo[*a,j*]xanthenes was developed by Prasad et al. via one-pot condensation reaction of *β*-naphthol with various aromatic aldehydes in the presence of a catalytic amount of sulfonated polyethylene glycol 6000 (PEG-OSO_3H) as a stable, recyclable and bio-degradable polymeric catalyst under solvent-free conditions **(Scheme 3a-b)**.[74] It was noted that the 1 mol% of PEG-OSO_3H was sufficient for this transformation. Moreover, the aromatic aldehydes with both electron-withdrawing and electron-

donating reacted smoothly to afford the corresponding products in excellent yields. Though, PEG-OSO_3H displayed relatively comparable reactivity to the catalysts, $HClO_4$-SiO_2 and [MIMPS]HSO_4, but it can be considered as an efficient, economical and biodegradable catalyst for the synthesis of various dibenzoxanthene analogues. After completion of the reaction, PEG-OSO_3H was extracted with water and reused after the evaporation of the aqueous layer under reduced pressure. The above sequence was repeated three times to produce product in good yields without significant loss in catalytic activity of PEG-OSO_3H.



Scheme 3a

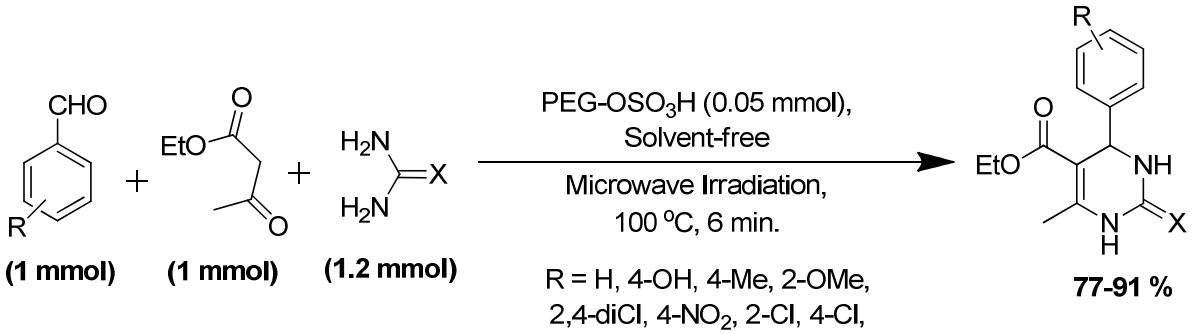


Scheme 3b

3.1.3) Synthesis of 3,4-dihydropyrimidones via Biginelli-type condensation under MWI

An efficient and environmentally friendly process was developed by Wang et al. for the synthesis of 3,4-dihydropyrimidones via the Biginelli-type condensation reaction using poly(ethylene glycol)-bound sulfonic acid (PEG-OSO_3H) as catalyst under microwave irradiation **(Scheme 4)**.[75] The PEG-OSO_3H acted simultaneously as catalyst and as solvent in the

condensation. Various solvents were tested, including toluene, acetonitrile and ethanol under microwave irradiation by the authors in this this reaction. However, under solvent-free condition best results were obtained. After completion of the reaction the catalyst could be recovered and reused several times without significant loss of their activity. The method afforded 3,4-dihydropyrimidones within a shorter period in high purities and improved yields compared with the classical solution-phase reaction.

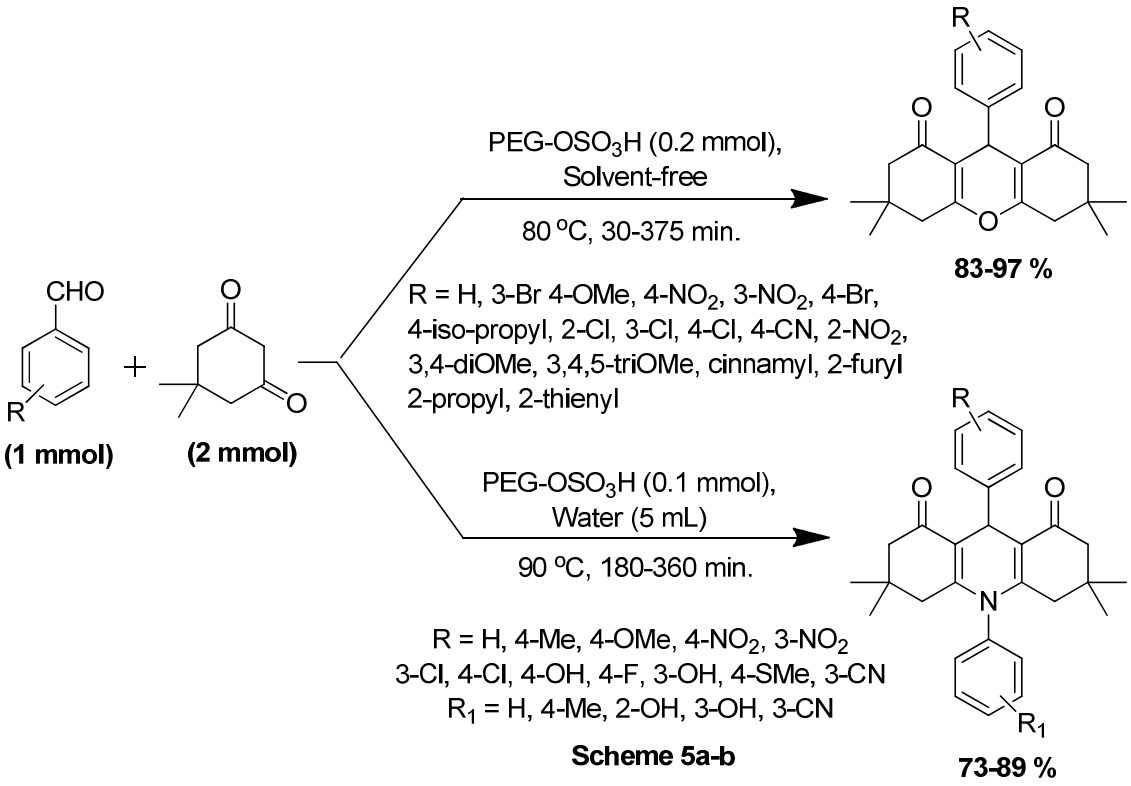


Scheme 4

3.1.4) Synthesis of 1,8-dioxo-octahydroxanthene and 1,8-dioxo-decahydroacridine derivatives

Xanthene based compounds exhibit extensive activities in pharmaceutical and biological aspects, for example antibacterial, antiviral and anti-inflammatory activities.[76] A wide range of synthetic methods have been reported for the synthesis of 1,8-dioxo-octahydroxanthene derivatives in the presence of protonic acids[77] or Lewis acids such as $InCl_3.4H_2O$,[78] $FeCl_3.8H_2O$,[79] $NaHSO_4$,[80] $NaHSO_4$-SiO_2,[81] silica sulphuric acid,[62] PPA-SiO_2[82] and Amberlyst-15.[83] In addition, acridinedione derivatives were synthesized utilizing various catalysts such as p-dodecylbenzenesulfonic acid (DBSA) under microwave irradiation,[84] Brønsted acidic imidazolium salts containing perfluoroalkyl tails[85] and 1-methylimidazolium triflouroacetate ([Hmim]TFA).[77] However, some of these methodologies have some disadvantages, such as low yields, prolonged reaction time, harsh reaction conditions and the requirement of excess of catalysts or special apparatus. Thus, a green, simple and highly efficient methodology was described by Hasaninejad and co-workers for the preparation of 1,8-dioxo-octahydroxanthene and 1,8-dioxo-decahydroacridine derivatives via one-pot multi-component domino condensation reaction of dimedone and aromatic aldehydes without/and a primary amine in the presence of sulfonated polyethylene glycol (PEG-OSO_3H) as a biodegradable and recyclable catalyst **(Scheme 5a-b)**.[86] The reactions were completed at 80 °C in water as green solvent, which afforded products in good to excellent yields. Various solvents such as chloroform, water, tetrahydrofuran, methanol, dichloromethane, ethanol, ethyl acetate as well as solvent-free condition were employed for this reaction. But excellent results were obtained under solvent free conditions and in water using 20 mol% of catalyst for the synthesis of Xanthene derivatives, while reaction in water using 10 mol% of catalyst was sufficient for synthesis of acridine derivatives. Both an electron-donating and electron-withdrawing substituent on aldehydes as

well as on aniline were equally converted into the products in terms of product yield. After completion of the reaction the PEG-OSO_3H was recovered by evaporation of water after filtration of insoluble products and reused five times without noticeable loss of its reactivity.

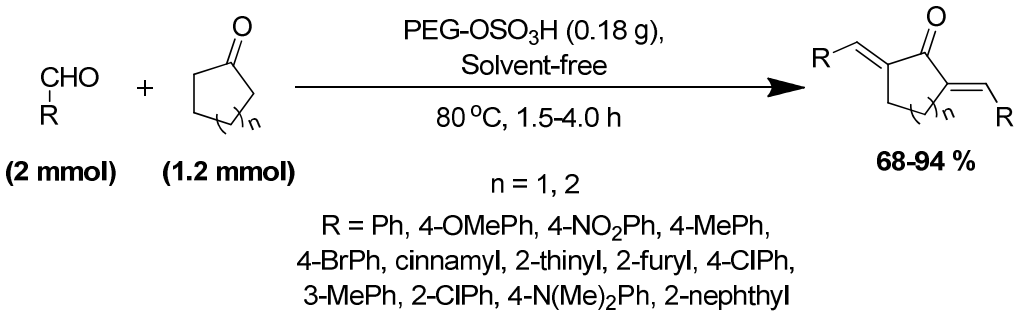


Scheme 5a-b

3.1.5) Synthesis of α,α'-bis (arylidene) cycloalkanone derivatives

Cycloalkanones are useful precursors to synthesize potentially bioactive pyrimidine derivatives,[87] 2,7-disubstituted tropones,[88] and are important intermediates to functionalize α,β-positions in organic synthesis.[89] Nasseri et al. have reported a green and efficient protocol for the synthesis of α,α'-bis (arylidene) cycloalkanone derivatives utilizing aromatic aldehydes and ketones in the presence of sulfonated polyethylene glycol 6000 (PEG-OSO_3H) as a stable, reusable and biodegradable catalyst **(Scheme 6)**.[90] Various solvents such as water, ethanol, DMSO, 1,4-dioxane, dichloromethane and toluene were examined by the authors for optimization of the reaction condition. The best result was obtained in the presence of 3 mol% of the catalyst under solvent-free conditions at 80 °C. Aromatic aldehyde with electron donating and electron withdrawing substituents showed the similar reactivity in this transformation. Moreover, Cinnamaldehyde, 2-furaldehyde and thiophene-2-carbaldehyde were also afforded the desired products in high yields. Both cyclopentanone and cyclohexanone showed the similar activity toward the condensation. In order to resumption of catalyst, water was evaporated in reduced pressure and recovered catalyst was washed by diethyl ether two times and dried. The recovered catalyst was reused 5 times without significant loss of their efficiency. The use of a nontoxic, inexpensive, easily available and recyclable catalyst makes this protocol, practical,

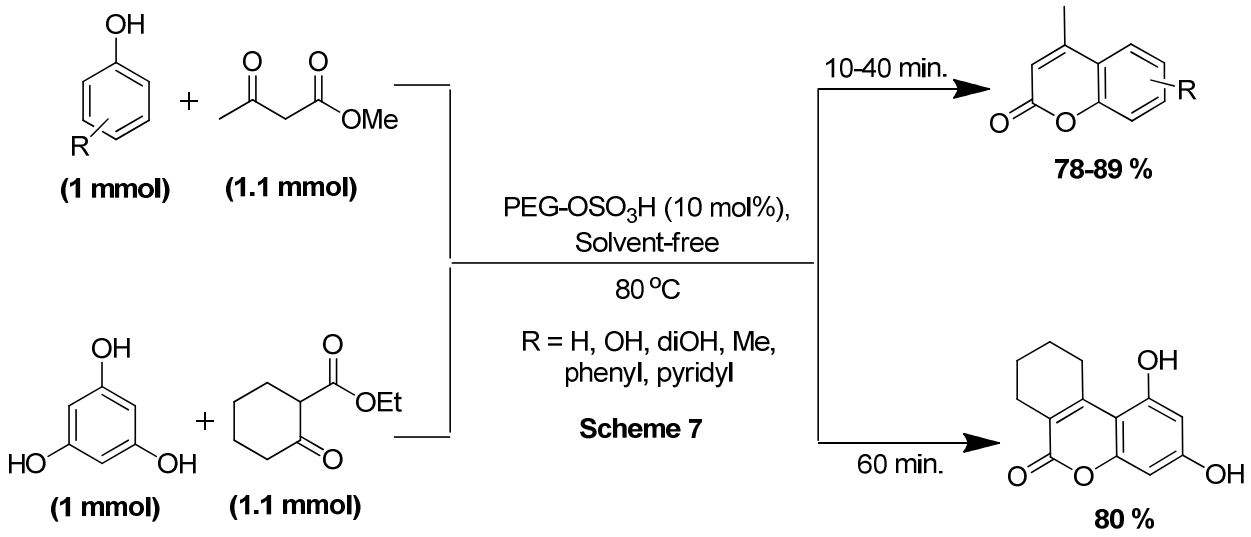
environmentally friendly and economically attractive. Several catalysts such as $RuCl_3$,[91] $FeCl_3$,[92] $SOCl_2$,[93] $Yb(OTf)_3$,[94] molecular I_2,[95] NaOAc-AcOH,[96] $Et_3N/LiClO_4$,[97] TMSCl[98] and sulfated zirconia[99] have been reported for synthesis of bis (arylidene) cycloalkanones. However, they are not efficient as like PEG-OSO_3H, in terms of product yield, reaction time and environmental friendliness.



Scheme 6

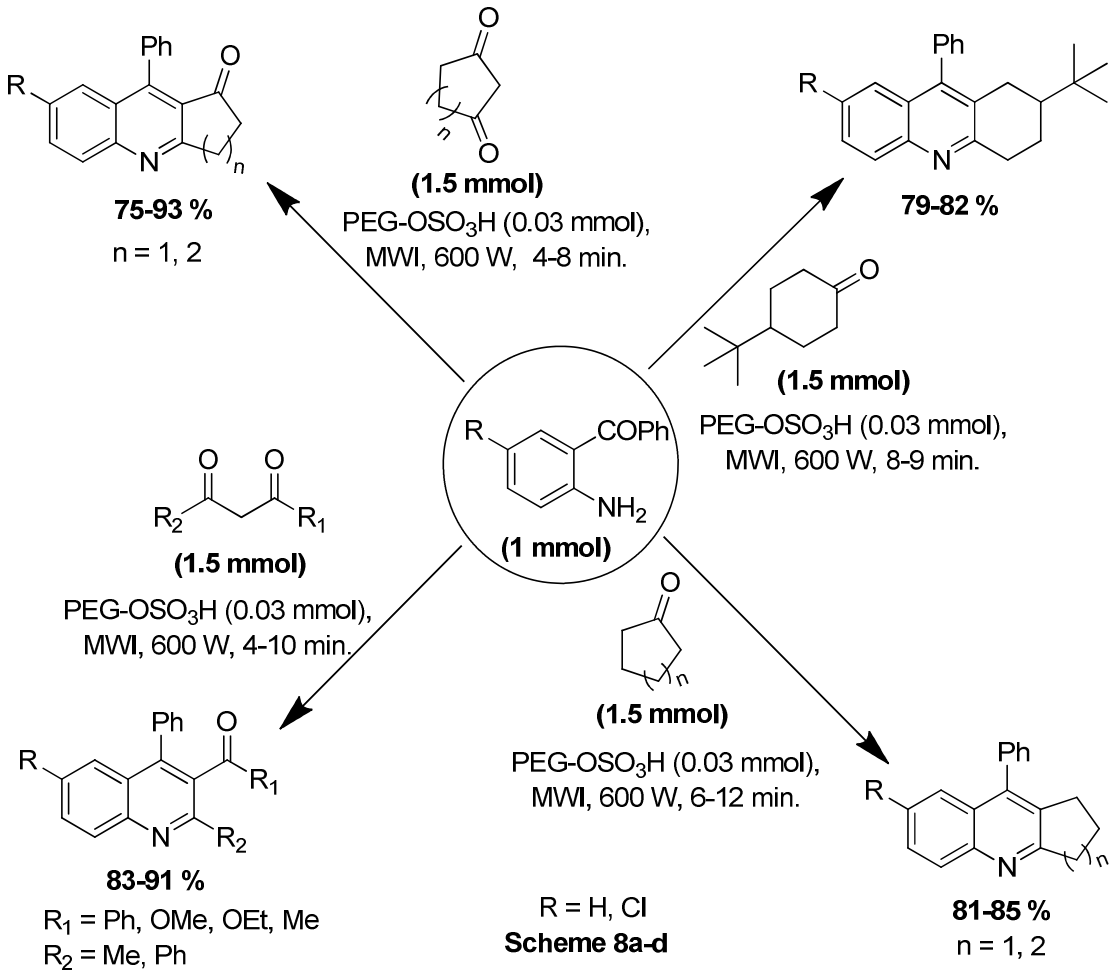
3.1.6) Synthesis of coumarin derivatives via Pechmann condensation

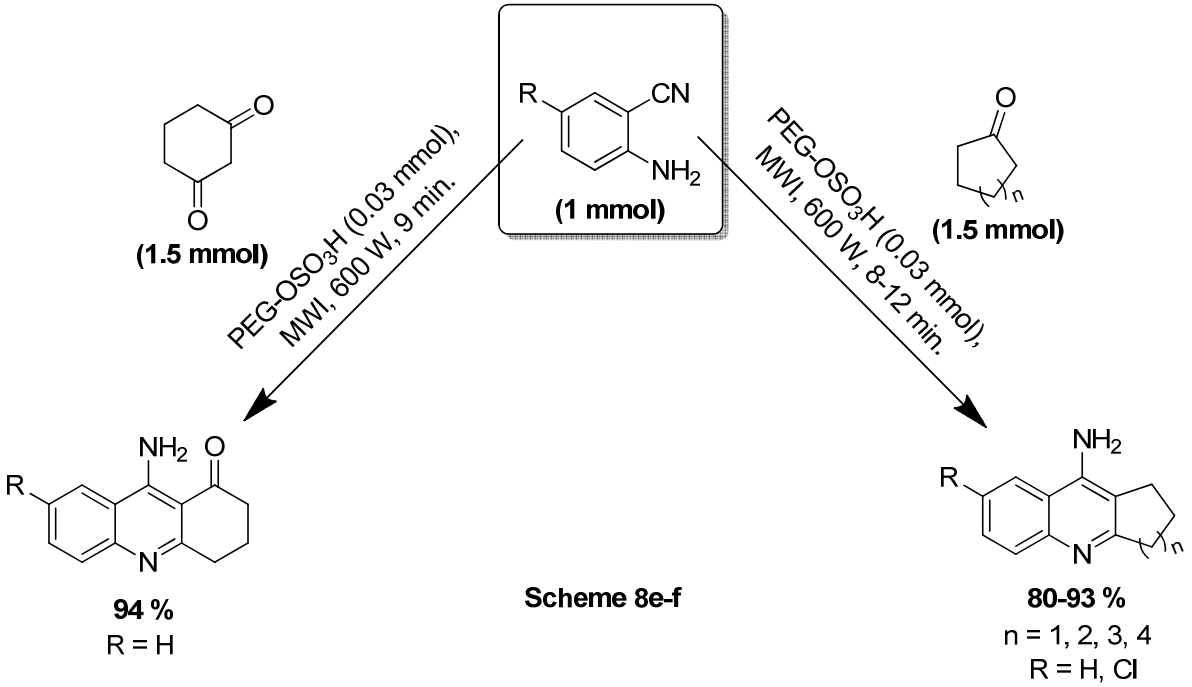
The synthesis of coumarin and their derivatives has attracted considerable attention of organic and medicinal chemists, because a large number of natural products contain this heterocyclic nucleus; most of them show wide biological activities like anthelmintic, hypnotic, insecticidal and anticoagulant properties.[100] The Pechmann reaction involves the condensation of phenols with β-keto esters in the presence of variety of acidic catalysts such as sulfuric acid, hydrochloric acid, trifluoroacetic acid, phosphoric acids, phosphorous pentoxide and Lewis acids such as $ZnCl_2$, $FeCl_3$, $AlCl_3$.[101] However, most of these methods suffer from one or more of the disadvantages such as long reaction time, vigorous reaction conditions, occurrence of side reactions, highly toxic and corrosive acidic and metallic effluent as well as poor yields of the desired product. Thus, Nazeruddin and co-workers have described a high yielding synthesis of coumarin derivatives through condensation reaction of substituted phenols and dicarbonyl compounds using PEG-OSO_3H as a biodegradable recyclable catalyst under solvent-free conditions at the 80 ^oC **(Scheme 7)**.[102] The authors have compare the activity of various catalysts such as silica sulfuric acid, $SnCl_2$, $BF_3.SiO_2$, PEG and PEG-OSO3H in Pechmann condensation of resorcinol and methyl acetoacetate in ratio (1:1.1). Excellent yield of the desired product was obtained when PEG-OSO_3H was used as a catalyst. The catalyst was successfully recovered and recycled at least for three runs without significant loss in activity.

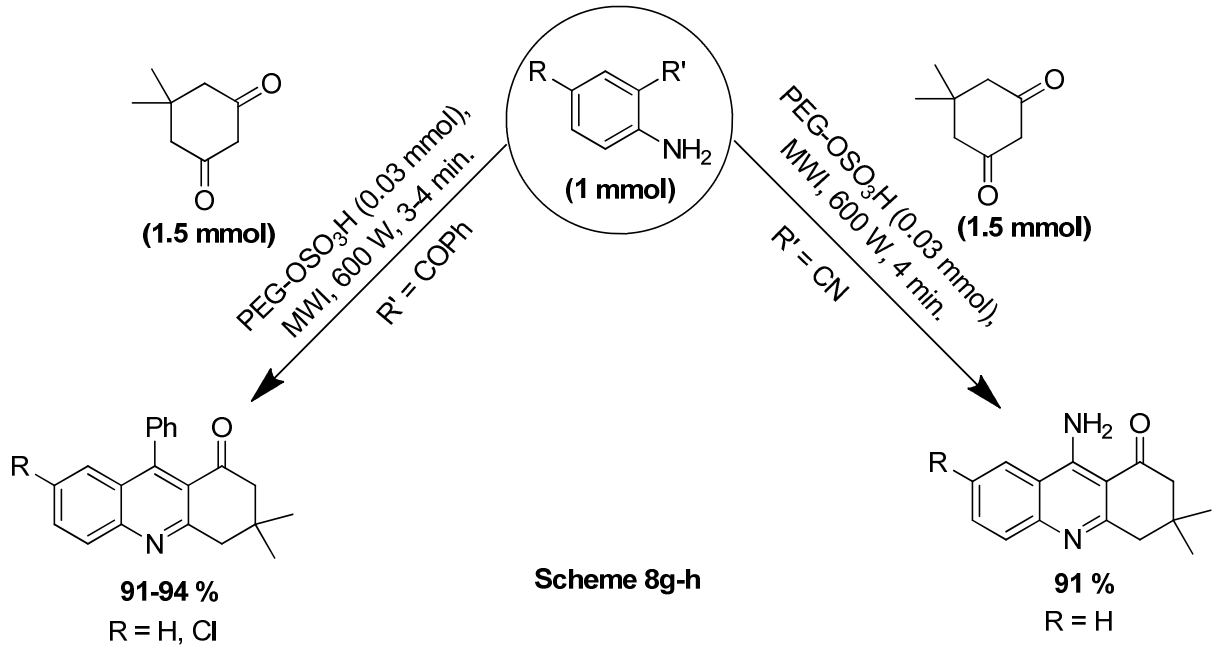


3.1.7) Synthesis of quinoline derivatives

Hasaninejad group has demonstrated sulfuric acid-modified polyethylene glycol 6000 (PEG-OSO_3H) as an efficient and eco-friendly polymeric catalyst for Friedlander synthesis of poly-substituted quinoline derivatives from *ortho*-aminoaryl ketones and carbonyl compounds possessing a reactive methylene group under microwave irradiation (MWI) and solvent-free conditions **(Scheme 8a-h)**.[103] The best results were obtained in the presence of 3 mol% of PEG-OSO_3H at 600 W (130 ^oC) of microwave irradiation. The reactions are completed in short times, and the products are obtained in good to excellent yields. Only, 28% yield of product was obtained the absent of catalyst even after 20 min. Cyclic and acyclic 1,3-diketones as well as b-ketoesters were efficiently condensed with 2-aminoaryl ketones, and the corresponding quinoline derivatives were obtained in excellent yield. After completion of each reaction, water was added to the reaction mixture and was shaken for a few minutes to dissolve PEG-OSO_3H. In order to recover the catalyst, water was evaporated under reduced pressure, and the resulting solid was washed with *t*-butyl methyl ether and dried. PEG-OSO_3H showed better efficiency towards this transformation in terms of product yield and reaction time, compared to other catalysts such as NH_2SO_3H,[104] Cellulose sulfuric acid,[105] Amberlyst-15,[106] $HClO_4$-SiO_2[107] and $BF_3{\cdot}(Et_2O)_2$.[108]

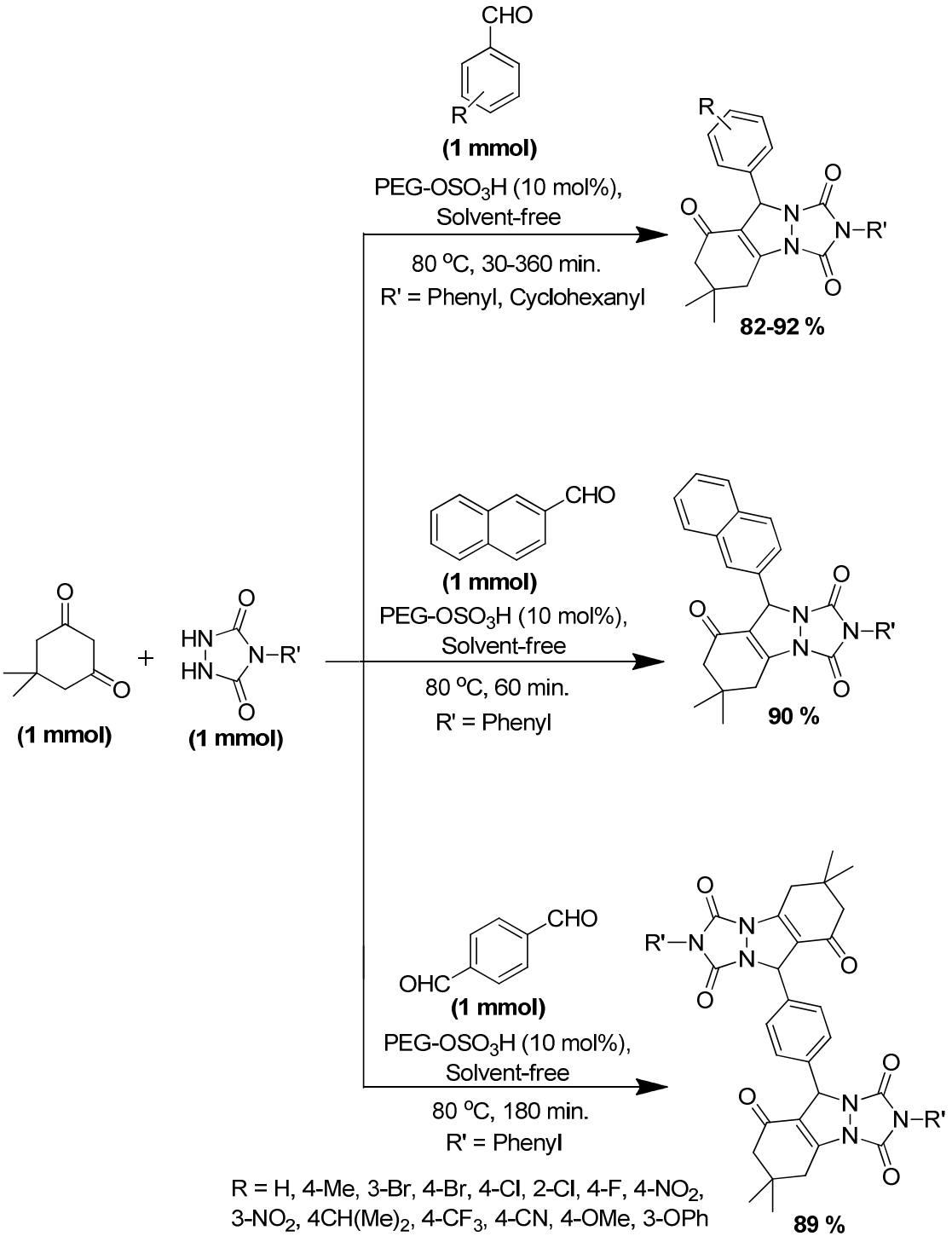




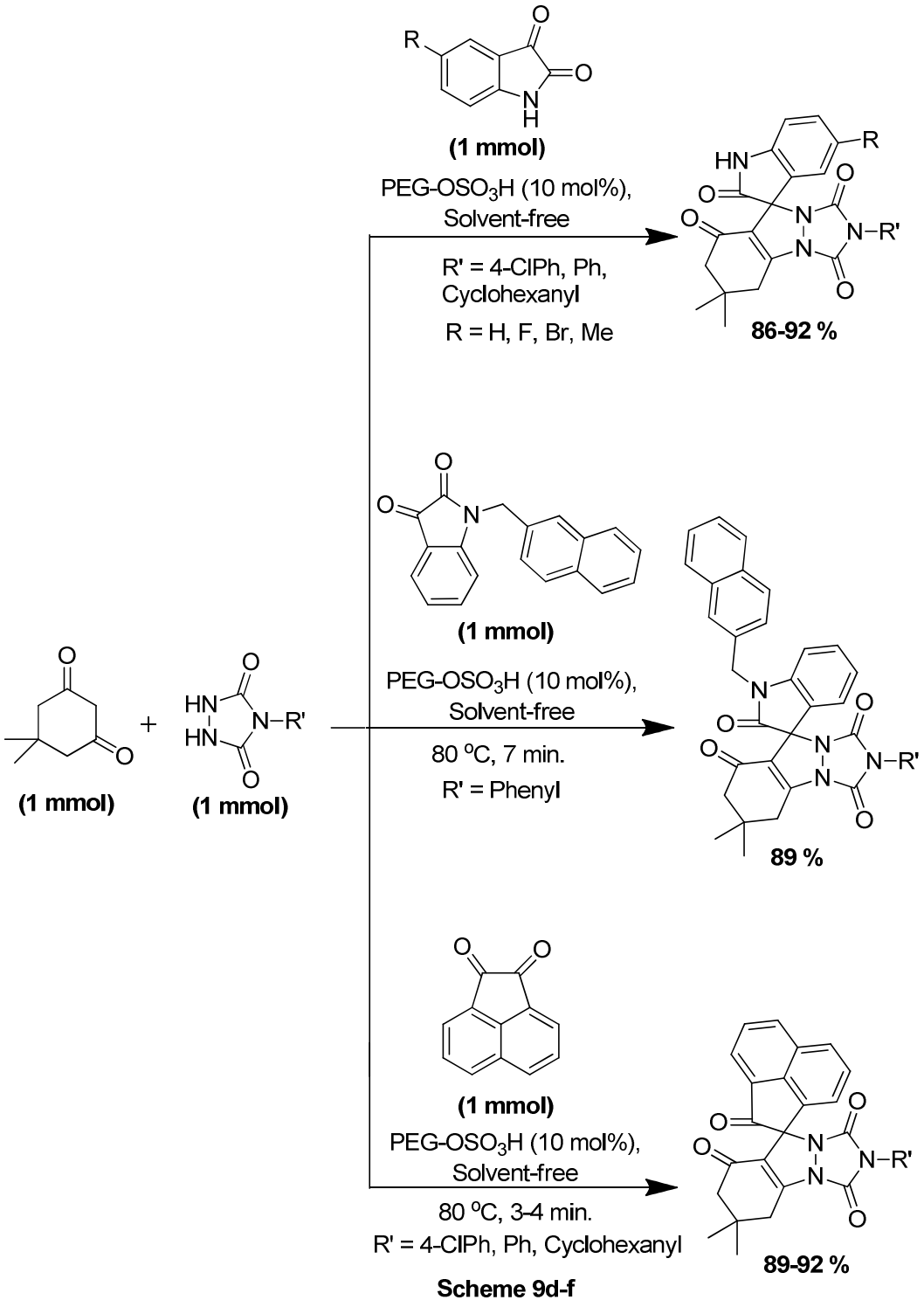


3.1.8) Synthesis of triazolo[1,2-a]indazole-trione derivatives

A green and high yielding protocol for the synthesis of triazolo[1,2-a]indazole-trione derivatives has been described by Hasaninejad and co-workers through condensation reaction between dimedone, aryl aldehydes, and ueazoles in the presence of a catalytic amount of sulfonated polyethylene glycol (PEG-OSO3H) as a highly stable and reusable eco-friendly degradable polymeric catalyst under solvent-free conditions at the 80 ^{o}C **(Scheme 9a-f)**.[109] Only, 10 mol % of PEG-OSO_3H was sufficient for this conversion. Increasing the amount of PEG-OSO_3H to more than 20 mol % showed no substantial improvement in the yield, whereas the yield decreased by decreasing the amount of the catalyst to 5 mol %. Moreover, it was observed that the reaction did not proceed efficiently in the absence of PEG-OSO_3H after a long time. The results showed that both electron-withdrawing and electron-donating substituents on aldehydes had no significant effect on the reaction yields. This procedure has also been applied successfully for the synthesis of novel spiro triazolo[1,2-a]indazole-tetraone derivatives via a condensation reaction between dimedone, terphthaldehyde, and 4-phenylurazole.



Scheme 9a-c

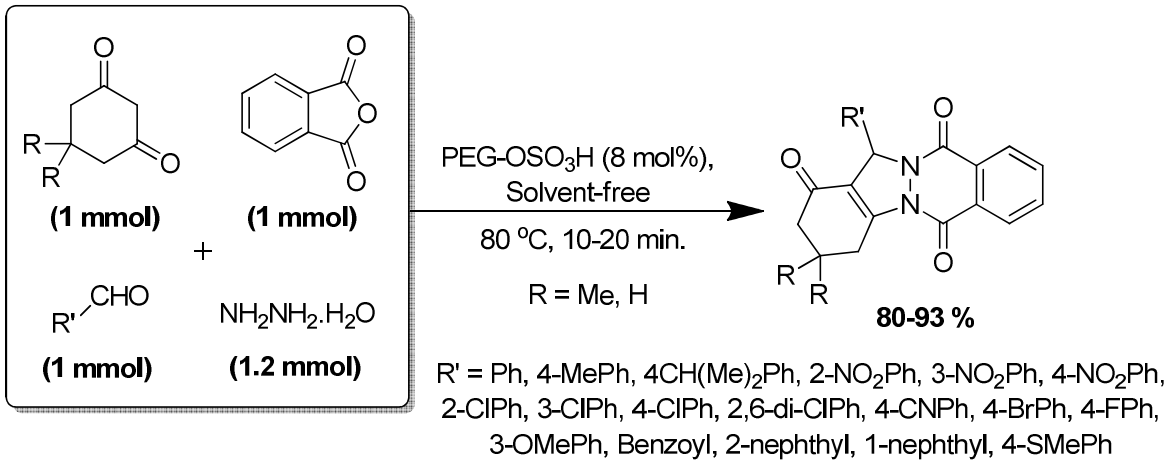


Scheme 9d-f

3.1.9) Synthesis of 2*H*-indazolo[2,1-b]phthalazine-1,6,11(13*H*)-trione derivatives

A green practical method for the efficient synthesis of 2*H*-indazolo[2,1-b]phthalazine-1,6,11(13*H*)-trione derivatives using sulfuric acid-modified polyethylene glycol-6000 (PEG-OSO_3H) as an eco-friendly polymeric catalyst from the four-component condensation reaction of

phthalic anhydride, hydrazinium hydroxide, 1,3-cyclohexanedione or 5,5-dimethyl 1,3-cyclohexanedione (dimedone) and aromatic aldehydes under solvent-free conditions at 80 ^{o}C **(Scheme 10)**.[110] Only, 8 mol % of catalyst was sufficient for this conversion. The reaction did not proceed at all in the presence of PEG alone with different molecular weights such as PEG-400, PEG-4000, PEG-6000 and PEG-10000. Also the reaction was examined in the presence of different molecular weight of PEG-OSO_3H. It is important to note that $PEG_{(6000)}$-OSO_3H was the best catalyst and the yield of product in the presence of this catalyst is high. Aromatic aldehydes bearing electron donating and electron withdrawing substituents gave the desired products in high yields. After completion of each reaction, water was added to the reaction mixture and was shaken for a few minutes to dissolve PEG-OSO_3H. The crude product was filtered and recrystallized from hot ethanol for more purification. In order to recover the catalyst, water was evaporated under reduced pressure, and the resulting solid was washed with *t*-butyl methyl ether, and dried. The recovered catalyst was reused several times without loss of their efficiency.



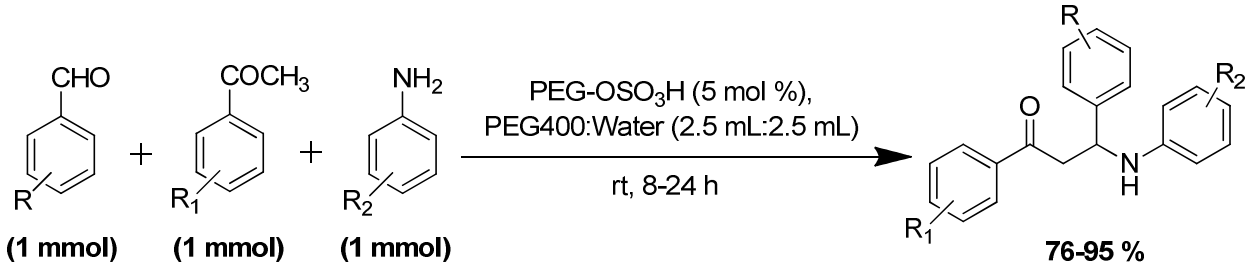
Scheme 10

3.2) Water mediated organic reactions catalyzed by PEG-OSO_3H

3.2.1) Synthesis of β-amino carbonyl compounds via the Mannich reaction

The Mannich reaction is an important carbon-carbon bond forming reaction in organic synthesis for the preparation of β-amino carbonyl compounds constitute various pharmaceuticals, natural products, and versatile synthetic intermediates used for the synthesis of amino alcohols, peptides and lactams, and as precursors for optically active amine acids.[111] Sulfuric acid-modified polyethylene glycol 6000 (PEG-OSO3H) as an efficient and recyclable catalyst for the synthesis of β-amino carbonyl compounds via the Mannich reaction between aldehydes, aromatic ketones and aromatic amines at room temperature using PEG400-H_2O (1:1) as environment-friendly solvents, which was disclosed by Wang et al. **(Scheme 11)**.[112] The authors have employed various solvents such as ethanol, dichloromethane, water, acetonitrile, toluene, PEG 400 and PEG400-H_2O. Interestingly, the best result was obtained, when the mixture of PEG400-H_2O

(V:V = 1:1) as the solvent. It was found that 5 mol% of PEG-OSO_3H was sufficient and excessive amount of catalyst did not increase the yield. This method is bestowed with several unique merits, such as high conversions, simplicity in operation, cost efficiency, inexpensive catalyst and used PEG400-H_2O as green solvents. In order to recover the catalyst, H_2O was evaporated from the filtrate under reduced pressure, giving a mixture of PEG-OSO_3H with PEG-400. Then hot water (2 mL) was added and the solution was cooled to room temperature to give the pure PEG-OSO_3H. The recovered catalyst was reused seven times without loss of their efficiency. PEG-OSO_3H showed better reactivity towards this synthesis in terms of reaction times and product yields compared to other catalysts such as $CeCl_3.7H_2O$,[113] proline,[114, 115] Bronsted ionic liquids,[116, 117] $Bi(OTf)_3$,[118] SmI_3,[119] $Zn(OTf)_2$[120] and $InCl_3$.[121, 122]



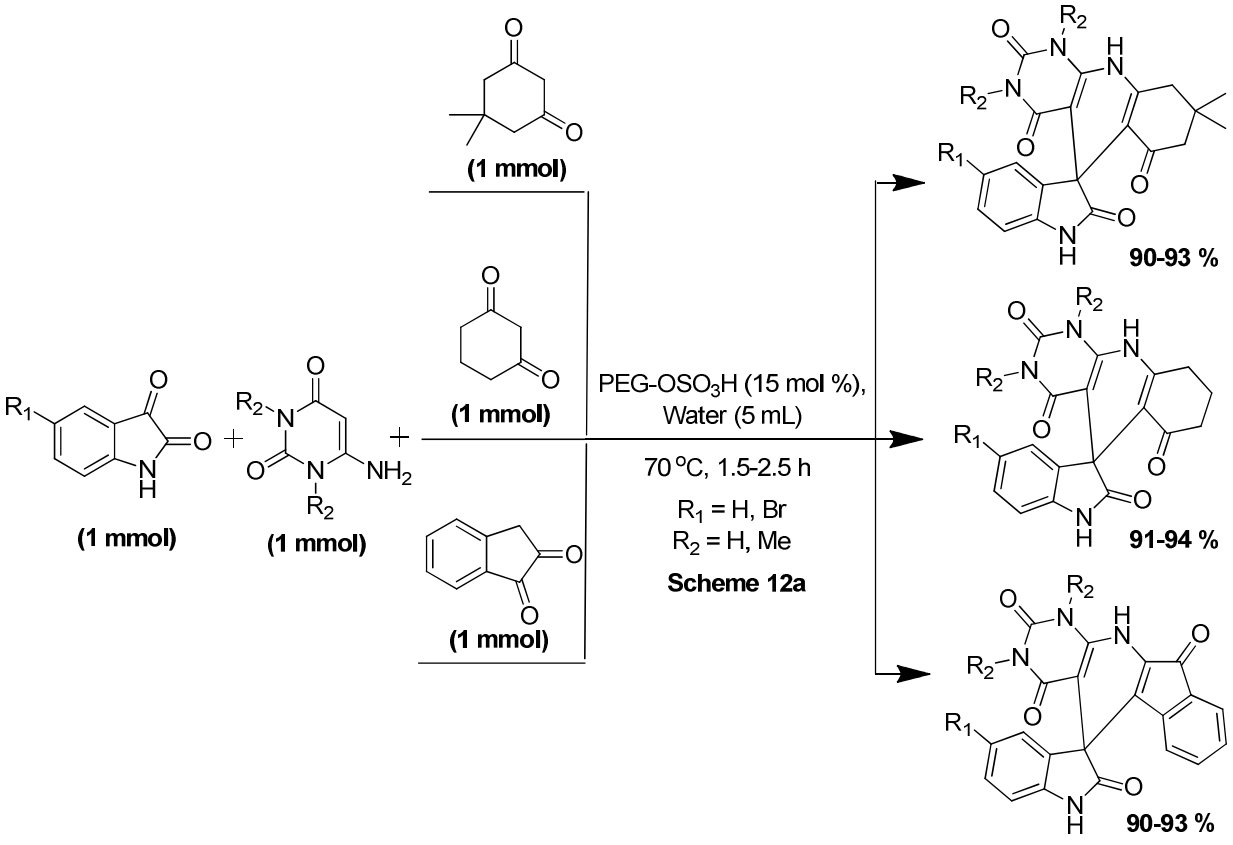
R = H, 4-OMe, 4-Me, 4-NO_2, 4-Cl, 4-F, C_6H_5
R_1 = H, 4-Me, 4-NO_2, 4-Cl
R_2 = H, 4-OMe, 4-Me, 4-NO_2, 4-Cl, 4-Br

Scheme 11

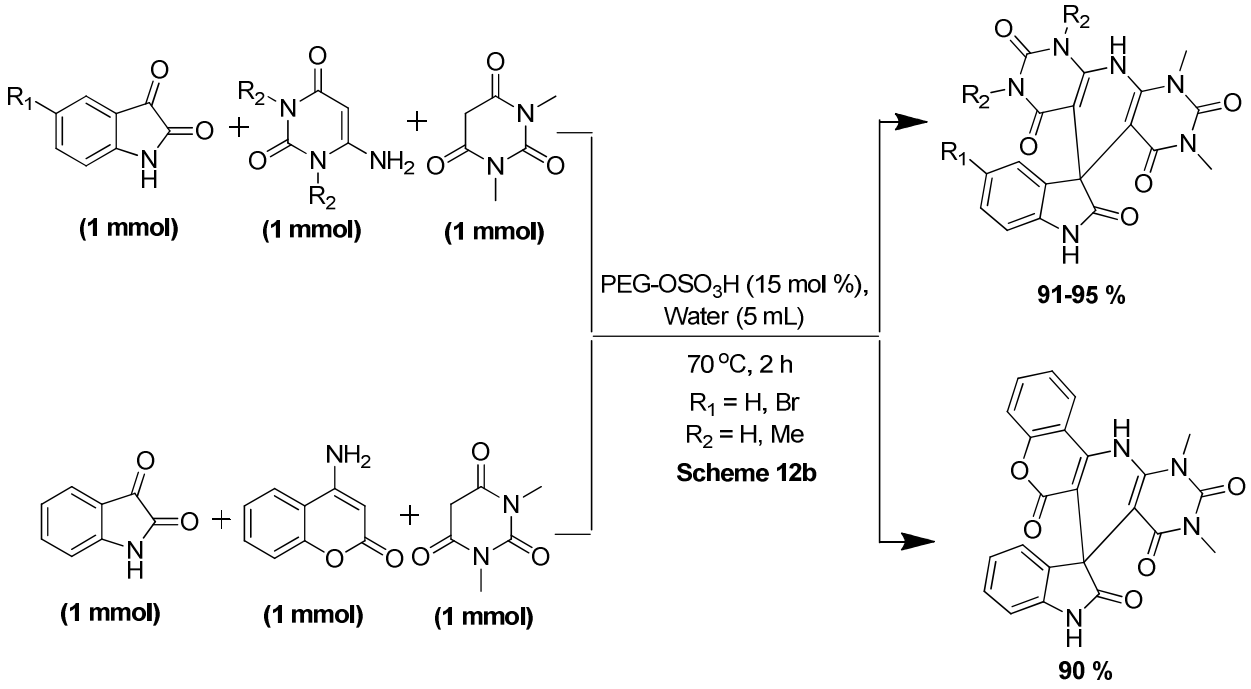
3.2.2) Synthesis of uracil and coumarin fused spirooxindole derivatives

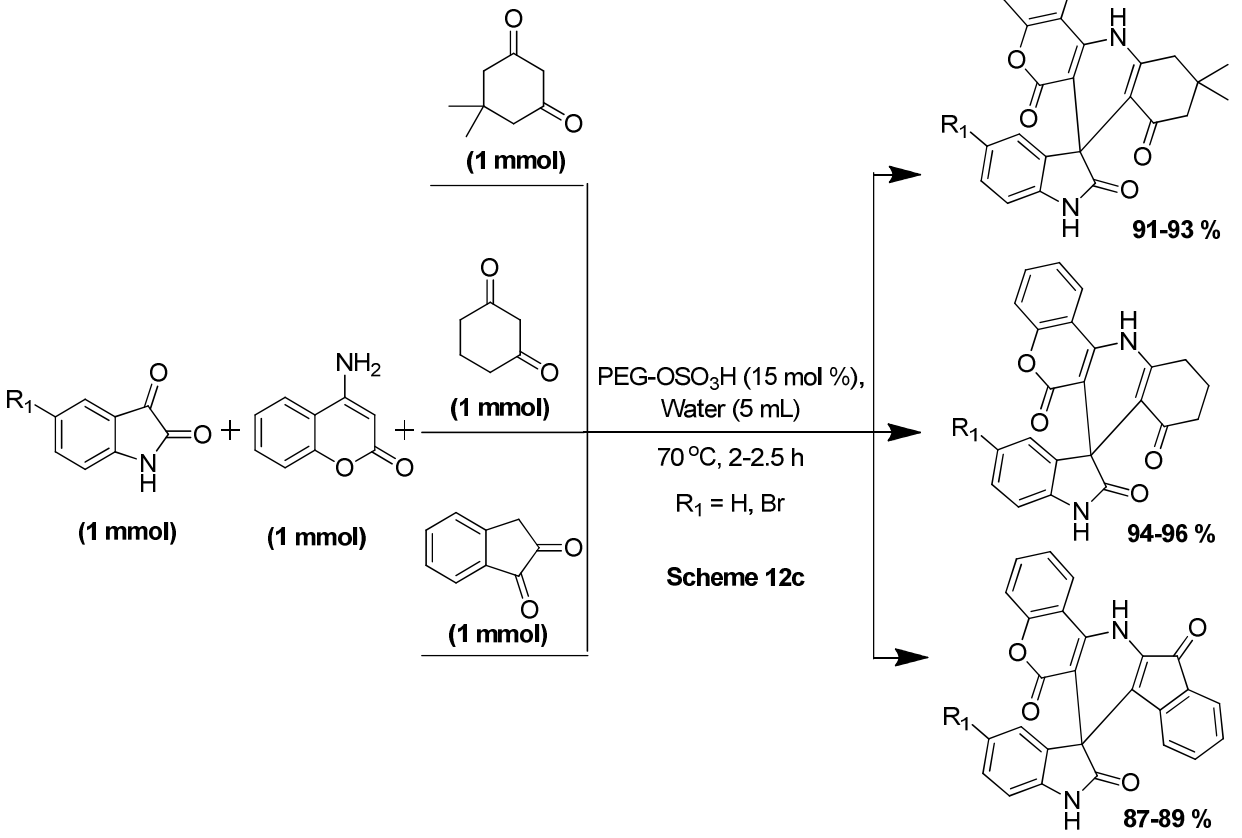
Naturally occurring heterocyclic compounds containing coumarin and uracil core are one of the most active classes of compounds possessing a wide spectrum of biological activity.[123] Highly efficient and practical heteroannulation protocol has been developed by Paul and co-workers for the synthesis of a library of uracil and coumarin fused spirooxindole derivatives in the presence of PEG-OSO_3H as a heterogeneous catalyst. The reaction was carried out in one-pot three-component domino coupling of 1,3-diketo compound (cyclohexane-1,3-dione, indane-1,3-dione, dimedone, and 1,3-dimethylbarbituric acid), 6-aminouracil/4-aminocoumarin, and isatin/5-bromoisatin, which afforded highly substituted uracil and coumarin fused spirooxindole derivatives **(Scheme 12a-c)**.[124] Lewis acid catalysts like nano aluminum oxide, $H_6P_2W_{18}O_{62}.18H_2O$, SiO_2, acetic acid, I_2, p-TSA, L-proline, DABCO, piperidine, lactic acid and CF_3CO_2H were also employed by the author in the synthesis of uracil fused spirooxindoles. However, lower or no product yield was observed in all these cases. Various solvents such as ethanol, acetonitrile, dimethylformamide and water were also examined for the synthesis of uracil fused spirooxindoles. However, desired product was obtained in water at 70 ^oC within short reaction time. Due to the unavailability of activation energy, the progress of the reaction was very slow at a temperature below 70 ^oC and at a higher temperature there might be some sort of polymerization of the intermediates or starting materials which lowered the yield of the

targeted molecule. This also revealed that the quantity of the catalyst played a vital role in synthesizing the product. An increase in the amount of PEG-OSO_3H from 5 to 15 mol % increased the yield of the desired product to 67-94%. Under optimized reaction condition coumarin fused spirooxindoles were also synthesized efficiently. The catalyst was recovered in excellent yield and reused six times without loss of their efficiency. The authors have proposed reaction mechanism and according to them the catalyst is accompanied by inherent Brønsted acidity of SO_3H groups, which are capable of bonding with the carbonyl oxygen of the isatin assisting the nucleophilic attack by the 1,3-diketo compound and in turn facilitates the formation of intermediate through activation of reactants. Then the obtained intermediate is attacked by the α-position of the amine functionality of a hetero aryl amine with the formation of another intermediate. Finally, the nucleophilic attack by the nitrogen atom of the amine group and elimination of water leads to the formation of the desired coumarin and uracil fused spirooxindole derivatives. The aqueous reaction medium, dual role of the polymer supported catalyst PEG-OSO_3H in aqueous media, easy recovery of the catalyst, and high yield make the protocol attractive, sustainable, and economic.



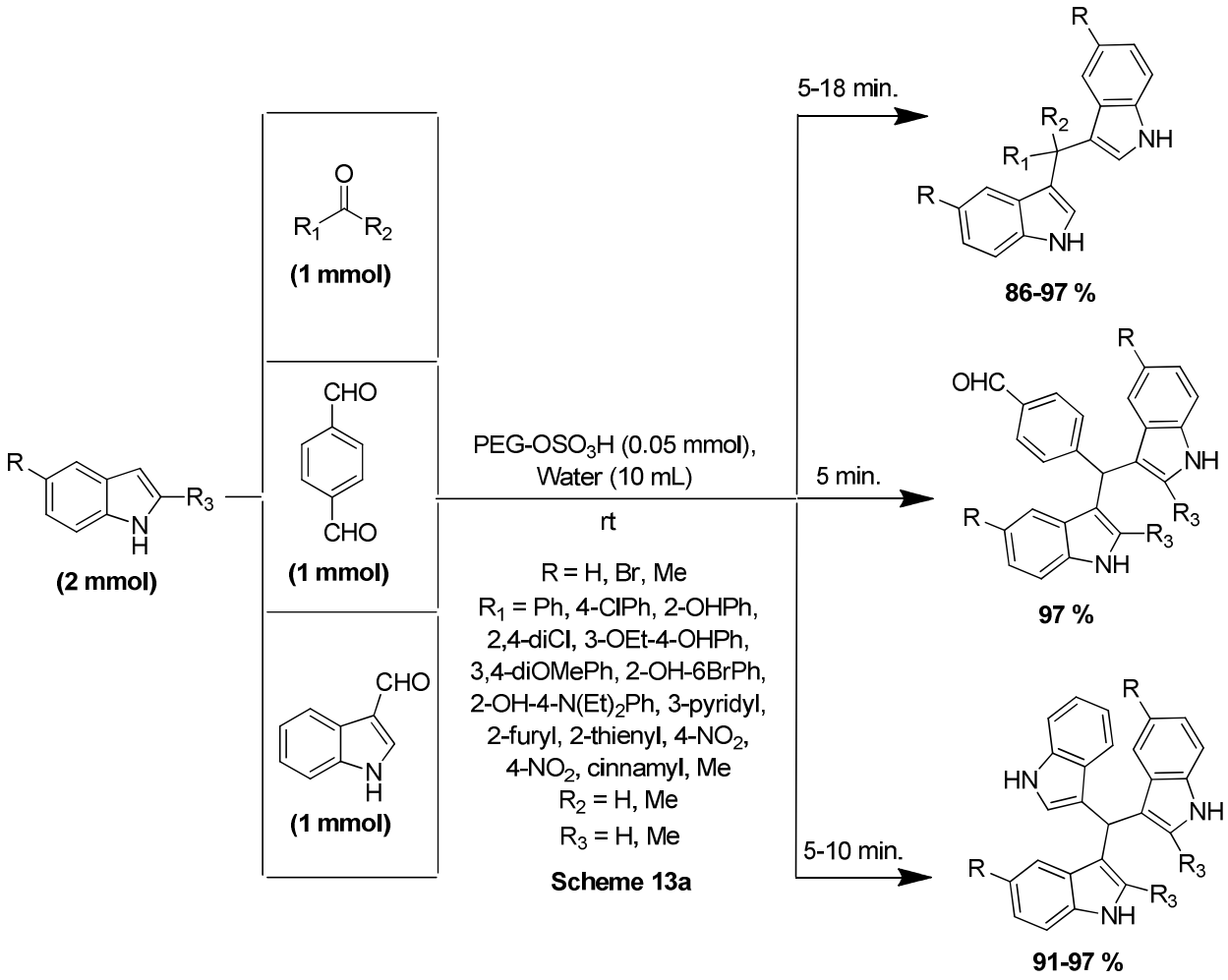
Scheme 12a



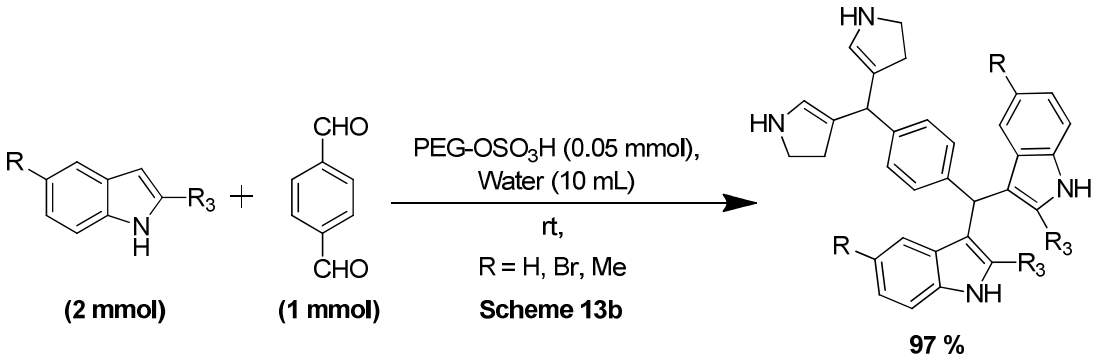


3.2.3) Synthesis of bis-indolyl and tris-indolyl methane derivatives

Indoles are privileged heterocyclic rings, and many biologically active and natural products are 3-substituted indoles.[125, 126] Rani et al. have reported facile, efficient, and green synthesis of bis-indolyl and tris-indolyl methanes trough one-pot condensation of indole with structurally diverse aldehydes and ketones in the presence of poly(ethylene glycol)-bound sulfonic acid (PEG-OSO_3H) as catalyst at room temperature **(Scheme 13a-b)**.[127] Electron deficiency and the nature of substituents on the ring of aldehydes didn't show any obvious effects on this conversion. An electron-rich as well as electron deficient aldehydes reacted with indoles with equal ease to give the products in excellent yields. It is noted that in water the catalytic activity of PEG-OSO_3H was increased, because of the increase in solubility. Unfortunately, in this conversion the use of recycled PEG-OSO_3H resulted in a significant loss of its activity. The reaction of indole with aldehydes proceeded through the successive intermediates of related carbinols. The sulfonic acid groups on the PEG are involved in a salt formation with indolylcarbinols. Because of their instability in acidic conditions, the indolylcarbinols lose water, generating the salts of indoleninium species, which act as electrophiles toward a second molecule of indole, giving the corresponding bis-indolyl methanes or tris-indolyl methanes respectively.



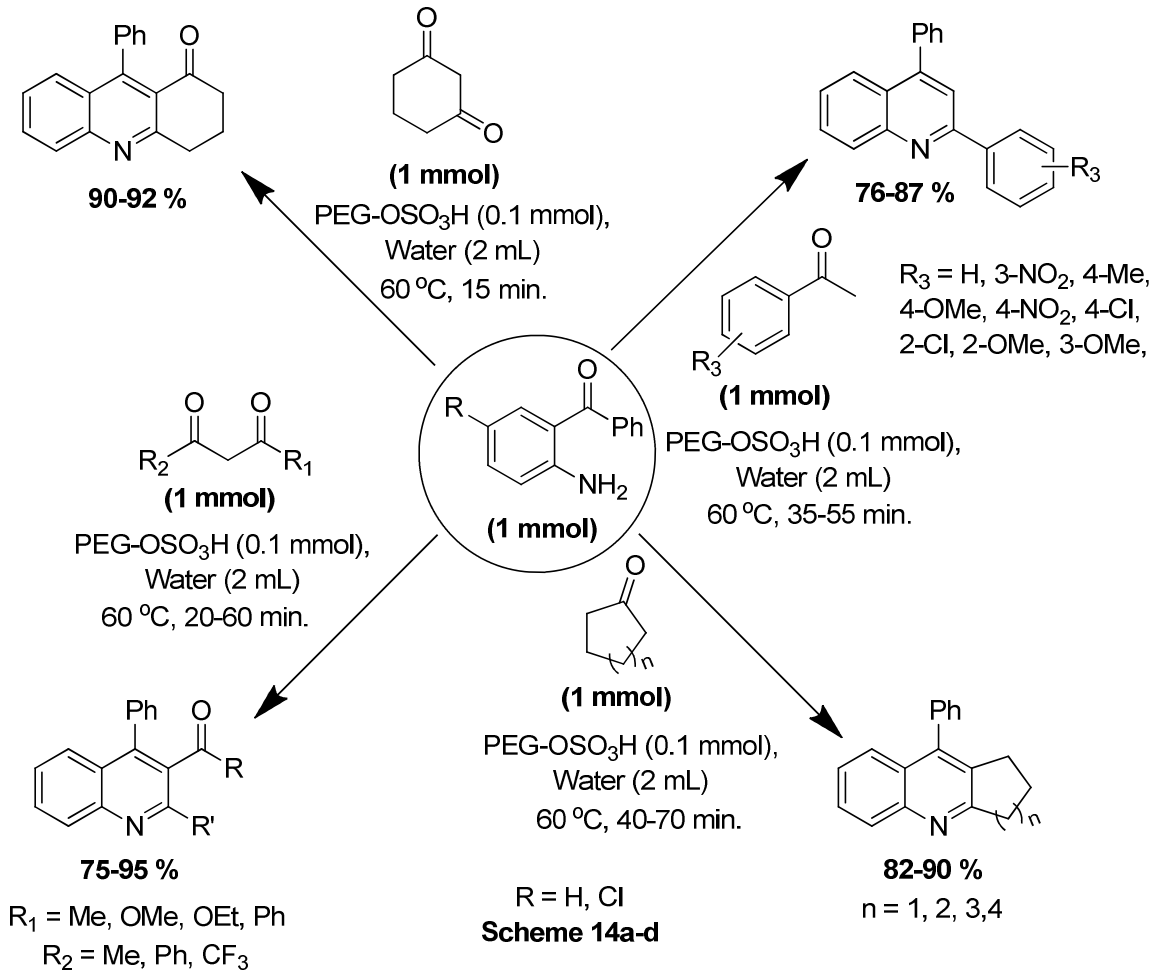
Scheme 13a



(2 mmol) (1 mmol) **Scheme 13b**

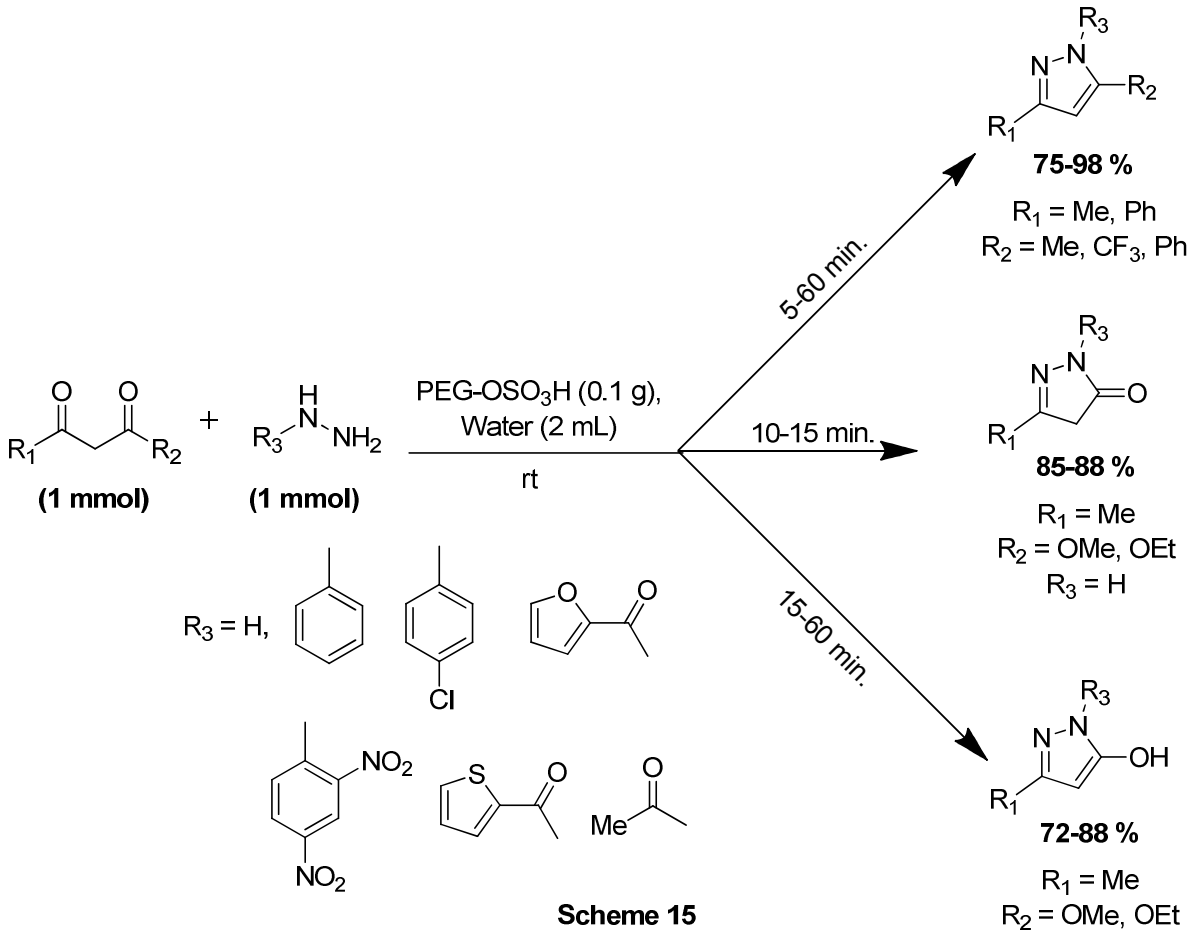
3.2.4) Synthesis of quinoline derivatives

Nasseri and coworkers have described a convenient and efficient methodology for the synthesis of quinoline derivatives through one-pot condensation of *ortho*-aminoaryl ketones and carbonyl compounds catalyzed by PEG-OSO_3H as a recyclable biodegradable catalyst in water as a green solvent **(Scheme 14a-d)**.[34] The compounds were isolated by simple filtration in a high purity form. This reaction was carried out in various solvents, with PEG-OSO_3H (0.2 g or 0.1 mmol H^+) as a catalyst, at 60◦C. The reaction proceeded perfectly in polar solvents such as water and ethanol, but the yield of product decreased when the reaction was carried out in non-polar solvents. It is important to note that in the absence of the catalyst, the reaction at the same condition gave quinoline in very low yield. Also, the reaction time of 2-aminobenzophenone and dicarbonyl compounds were longer than those of 2-amino-5-chlorobenzophenone. This behavior could result from the more reactivity of 2-amino-5-chlorobenzophenone by electron-donating group (Cl). Moreover, the reaction of cyclic diketones took place faster than open chain analogues. The aromatic carbonyl derivatives having an electron-donating substituent were highly reactive and gave the products in excellent yields. When the aromatic carbonyl compounds containing electron-withdrawing group was used, the reaction time was longer. In comparison with other catalysts such as $Ag_3PW_{12}O_{40}$, $HClO_4/SiO_2$, $Zr(HSO_4)_4$, $Y(OTf)_3$, $NaHSO_4/SiO_2$, Amberlyst-15 and HCl were employed for the synthesis of quinoline from *ortho*-amino benzophenone and carbonyl compound, but PEG-OSO3H showed a much higher activity.



3.2.5) Synthesis of pyrazolo derivatives

The development of new methodologies for the synthesis of pyrazoles is a subject of continuous interest to synthetic organic/medicinal chemists as pyrazole and their derivatives have versatile biological activities.[128] A versatile, alternative and environmentally benign strategy was reported by Nasseri's group for the synthesis of a series of pyrazoles through one-pot condensation involving dicarbonyl compounds and hydrazines/hydrazides in water using PEG-OSO_3H as an acidic catalyst **(Scheme 15)**.[129] In absent of catalyst the reaction proceeded poorly. The reaction proceeded perfectly in polar solvents such as water, ethanol, methanol, DMSO and acetonitrile, while the yields decreased when the reaction was carried out in non-polar solvents like toluene, dichloromethane, n-hexane and chloroform. However, the best result was obtained in water in terms of product yield and reaction time. The reaction time of hydrazides and 1,3-dicarbonyl compounds was longer than those of hydrazines. This behavior could result from the low reactivity of hydrazides. A series of different substituted diketones, including electron-withdrawing or electron-donating groups, and different substituted β-ketoesters were used in this reaction makes this protocol have wide synthetic utility.

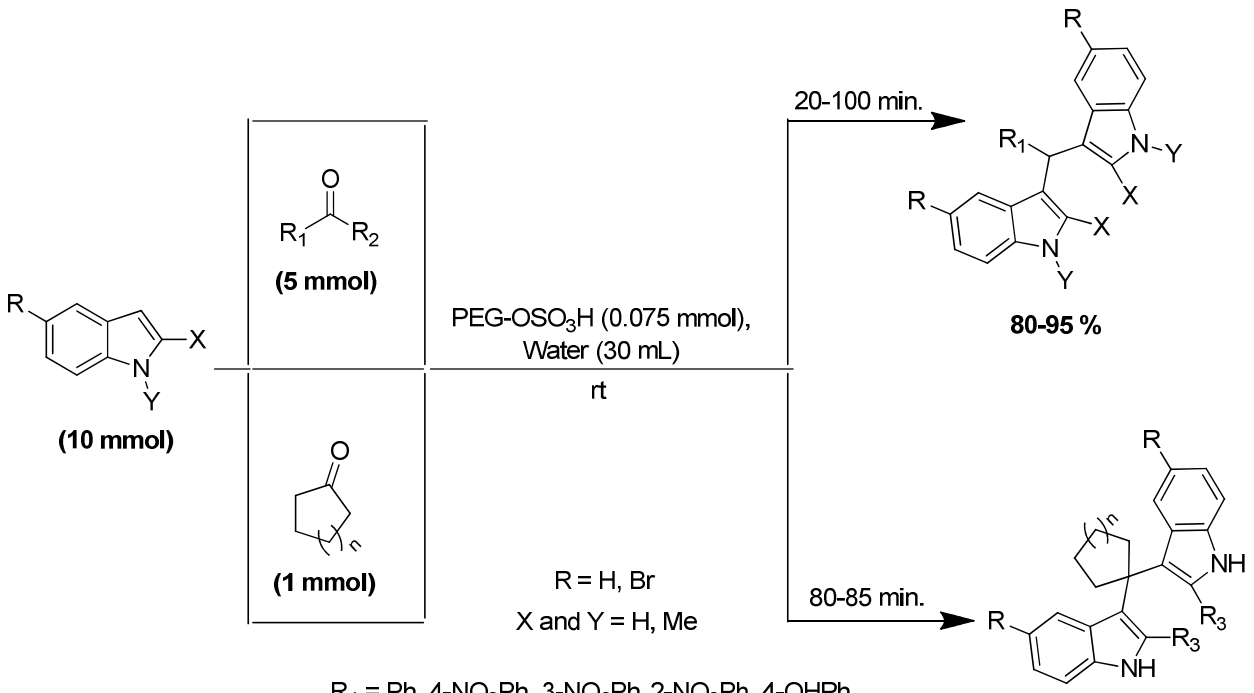


Scheme 15

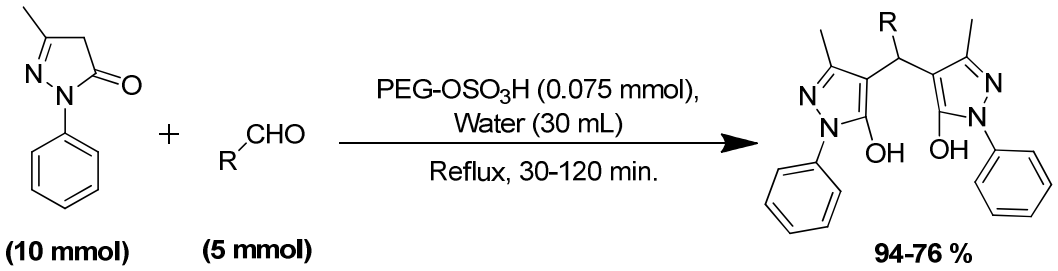
3.2.6) Synthesis of bis(indolyl)methane and 4,4′-(arylmethylene)-bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ol) derivatives

Hasaninejad et al. have discovered a green, simple and highly efficient methodology for the synthesis of bis(indolyl)methane and 4,4′-(arylmethylene)-bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ol) derivatives via condensation of indoles or 1-phenyl-3-methylpyrazol-5-one with carbonyl compounds catalyzed by poly(ethylene glycol)-bound sulfonic acid (PEG-OSO_3H) in water affords the title compounds in high yields and relatively short reaction times **(Scheme 16a-c)**.[130] The optimized reaction conditions were screened by allowing the reaction to proceed and using different amounts of the catalyst in aqueous media. However, the best results were obtained when PEG-OSO_3H was used as a catalyst. Moreover, it was observed that the reaction did not proceed at all in the absence of PEG-OSO_3H. Various solvents were also examined by the authors for optimize reaction condition, only water showed better activity comparabel to others. No significant loss of the product yield was observed, when PEG-OSO_3H was used after two times of recycling. These methods have several unique merits, such as high yields, relatively short reaction times, efficiency, generality, recyclability of the catalyst, scalability of the methods, the use of a small amount of the catalyst, simplicity in operation, low cost and the use

of water as solvent. To put it differently, the method significantly contributes to the practice of green chemistry.



Scheme 16a-b

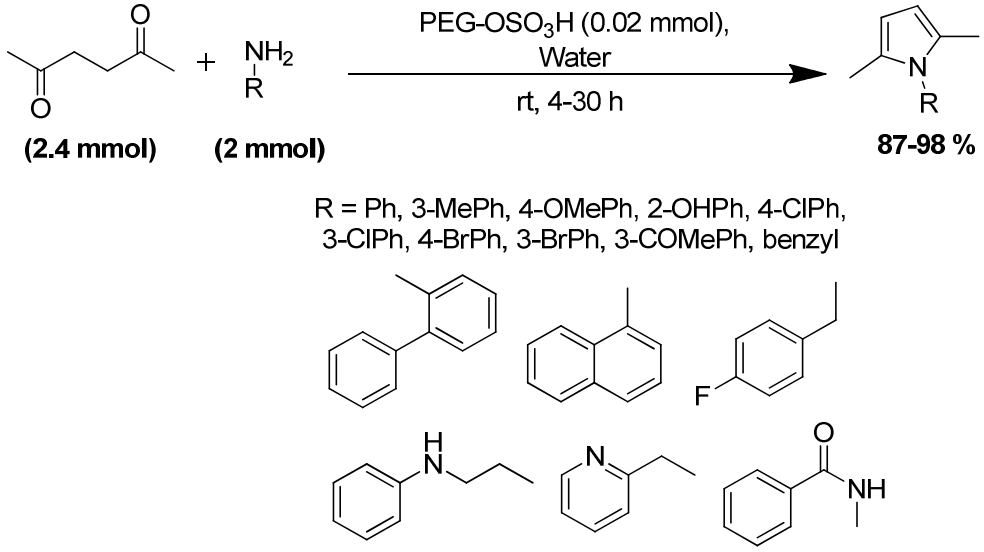


Scheme 16c

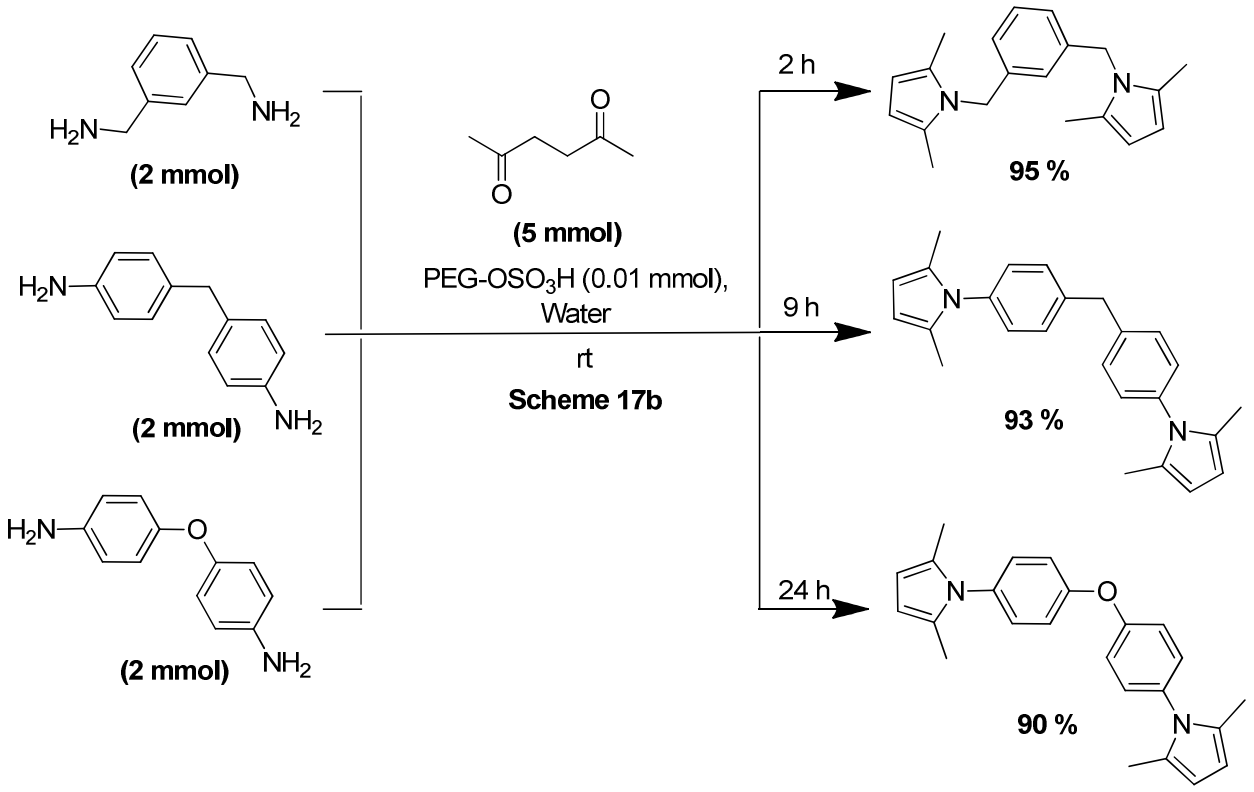
3.2.7) Synthesis of pyrrole derivatives (Paal-Knorr pyrroles synthesis)

The pyrrole ring system is a useful structural element in medicinal chemistry18 and has found broad application in drug development as an antibacterial, antiviral, anti-inflammatory, antitumor, and antioxidant agent.[131] Jafari and co-workers have described high yielding synthesis

of pyrrole derivatives (Paal-Knorr pyrroles synthesis) utilizing condensation of various amines and 2,5-hexadione in the presence of 1 mol% of Poly(ethylene glycol)-bounded sulfonic acid (PEG-OSO_3H) as a solid recyclable catalyst. The reaction was carried out in water as greener solvent at room temperature **(Scheme 17a-b)**.[132] In addition, bispyrroles were synthesized in excellent yields via this eco-friendly and green methodology. The method is easy, simple, cost-effective, chemoselective, and environmentally benign that introduces a beautiful example of click chemistry in water. The reaction in the presence of triton X-100, cetyl trimethylammonium bromide (CTAB), sodium dodecyl sulfate (SDS), and lithium dodecyl sulfate (LiDS) did not proceed to completion even after 24 h. All the reactions proceeded well enough and delivered excellent yields with a range of aliphatic and aromatic amines containing electron donating and electron withdrawing groups. In all the cases, the pure product was isolated by a simple filtration without using any chromatography reaction work-up. The reactivity of aliphatic amines were more than aromatic amine towards this reaction. The catalyst could be used at least for four successive times without any reduction in its efficiency. The reusability of the catalysts and solvent free condition are the most important benefits, which makes this protocol green and clean.



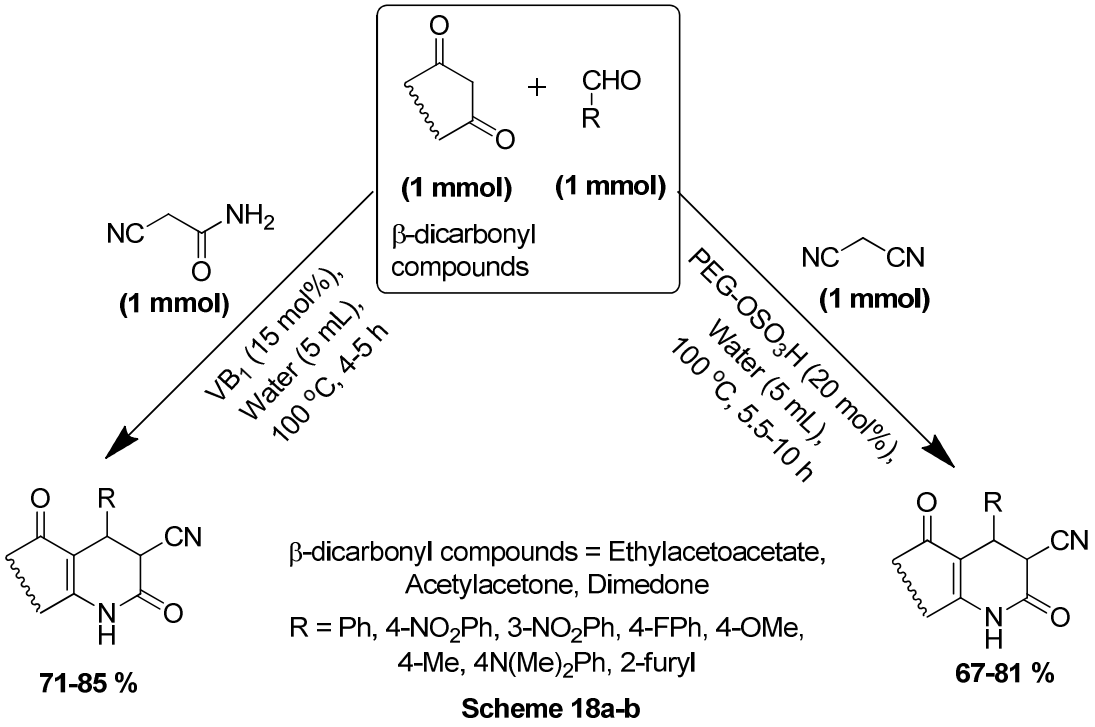
Scheme 17a



3.2.8) Synthesis of 3,4-dihydropyridin-2-one derivatives

In recent years, much attention has been devoted toward dihydropyridin-2-one derivatives due to their significant therapeutic and biological activities, such as antibacterial,[133] antifungal,[134] and antitumor,[135] also served as HIV-1 specific reverse transcriptase inhibitors.[136] Two highly efficient, green one-pot methodologies have been developed by the Pradhan and co-workers for the synthesis of 3,4-dihydropyridin-2-one derivatives from different starting materials such as aldehyde, cyanoacetamide or malononitrile, and 1,3-dicarbonyl compounds in the presence of two specific catalysts, vitamin B1 (VB1) and PEG-OSO_3H **(Scheme 18a-b)**.[137] The reaction was carried out at 100 ^oC in presence of water as a solvent. A wide range of catalysts including $ZnCl_2$, $MgCl_2$, SiO_2, Al_2O_3, alum, I_2, p-toluene sulfonic acid (p-TSA), CH_3COOH, PEG-OSO_3H and VB1 were employed by the authors for optimization of reaction catalyst. However, PEG-OSO_3H showed better efficiency comparable to others. It was evident that the reaction proceeded very slowly in the absence of catalyst and the expected product was isolated in a very small quantity after heating the reaction mixture for about 24 h at 100 ^oC. Various solvents such as THF, toluene, water, acetonitrile, methanol and ethanol were employed in this reaction. It was evident that the polar solvents afforded better yield than the nonpolar ones and in case of both the synthetic protocols water showed superiority over the other solvents. Moreover, the reaction can be scaled up to 10 mmol scale. In large scale preparation, the authors have successfully recycled both the catalysts in five new batches of reactions with almost same catalytic activity. This three component coupling reaction involves mild polymer supported acid catalyzed

Knoevenagel condensation, Michael addition, and then intra molecular cyclization for the formation of 4*H*-pyran intermediate. Subsequently, this intermediate undergoes PEG-OSO_3H catalyzed sequential ring opening and closing involving hydration and dehydration of the 4Hpyran nucleus to form 3,4-dihydropyridin-2-one derivatives in aqueous medium.

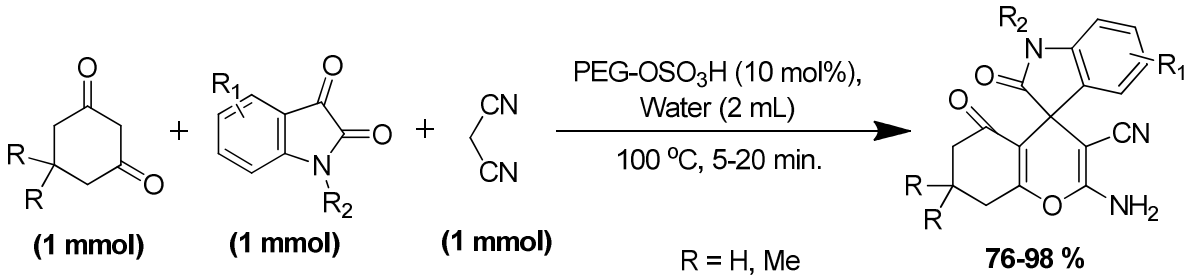


Scheme 18a-b

3.2.9) Synthesis of oxindole derivatives

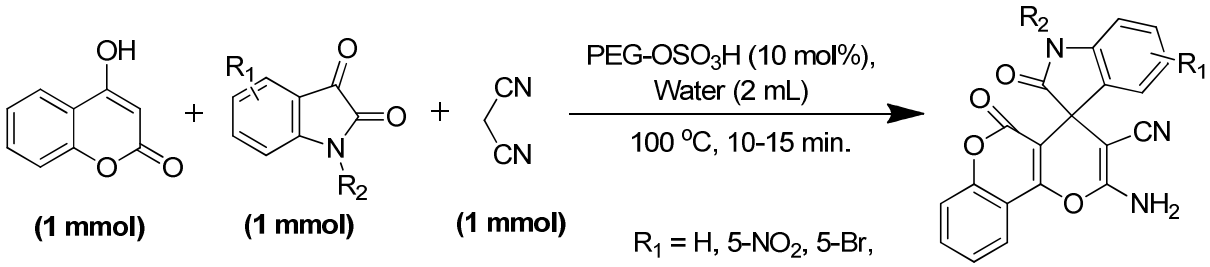
The indoline and oxindole structures are important components of a large number of natural products and medicinal agents with good biological activity.[138-140] Nasseri and co-workers have displayed a versatile, novel, and environmentally benign strategy for synthesis of oxindoles via one-pot reaction of malononitrile, 1,3-dicarbonylcoumarin or 4-hydroxycoumarin derivatives, and isatins in the presence of sulfonated poly(ethylene glycol) (PEG-OSO_3H) was used as inexpensive and recyclable acidic catalyst in water, which afforded excellent yields of the products **(Scheme 19a-b)**.[141] Only, 10 mol% catalyst at 100 °C was selected as the best conditions for synthesis of oxindole. With decreasing temperature, the solubility of isatin and the catalyst decreased, therefore the rate of the reaction and the yield of the product decreased. This new protocol totally avoids the use of organic acids and toxic or expensive solvents. Various solvent such as water, ethanol, methanol, ethyl acetate, DMSO, DMF, dichloroethane, tetrahydrofuran, chloroform, dichloromethane and solvent-free conditions. However, excellent yield was observed in water with short reaction time. Different catalysts such as SiO_2, Acidic Al_2O_3, Basic Al_2O_2, MgO, CaO, CdO, $NbCl_5$, $ZrCl_4$, $SnCl_2.2H_2O$ and $FeCl_3$ were also examined by the authors in this synthesis. However, PEG-OSO_3H gave better results compared to others in terms of reaction time and product yield. No electronic effect of substituents on isatin was observed in the yield of the product. The procedure has several advantages, including

inexpensive and readily available catalyst, mild reaction conditions, high yields of the products, and simple experimental and isolation procedures.



R = H, Me
R_1 = H, 5-NO_2, 5-Br, 5-Me, 5-OMe, 4-Me, 6-Me
R_2 = H, CH_2Ph

Scheme 19a



R_1 = H, 5-NO_2, 5-Br, 5-Me, 4-Me, 6-Me
R_2 = H, Me, Et, CH_2Ph

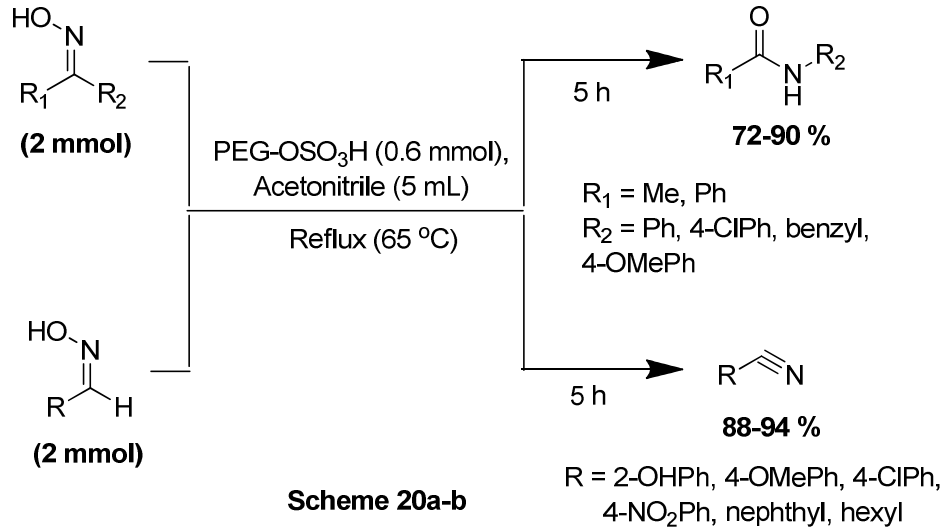
Scheme 19b

3.3) Organic solvents mediated organic reactions catalyzed by PEG-OSO_3H

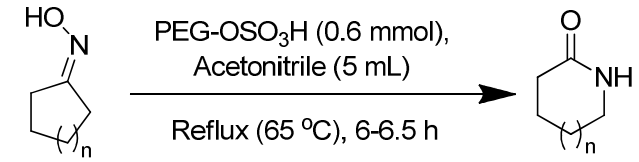
3.3.1) Synthesis of ketoximes and aldoximes via Beckmann rearrangement

Beckmann rearrangement was carried out using various catalysts such as, chlorosulfonic acid,[142] silica sulfate,[143] sulfamic acid,[144] cyanuric chloride,[145, 146] chloral,[147] anhydrous oxalic acid,[148] and P_2O_5.[149] The drawbacks in such methods are the use of toxic solvents, expensive reagents, production of considerable amounts of by-products, long reaction time, and low yields. Also, the conventional Beckmann rearrangement usually requires relatively high temperature and strong Bronsted or Lewis acids such as concentrated sulfuric acid, phosphorus pentachloride in diethyl ether, and hydrogen chloride in acetic anhydride, which lead to large amount of waste and serious corrosion problems.[150] Therefore, Wang and co-workers have reported an efficient process for the conversion of a variety of ketoximes and aldoximes into their corresponding amides and nitriles via Beckmann rearrangement in the presence of PEG-OSO_3H with high yields **(Scheme 20a-c)**.[151] The authors have examined various solvents such as carbon tetrachloride, acetone, acetonitrile, dichloromethane, toluene and THF. However the best results

were obtained in acetonitrile and toluene. Moreover, in acetone and dichloromethane reaction did not proceed efficiently. The probable reason behind this result is that the Beckmann rearrangement needs higher temperature, acetonitrile was the best solvent for this conversion. Aromatic aldoximes with electron withdrawing and electron donating groups converted efficiently into their corresponding nitriles efficiently. Not only aromatic but also aliphatic oximes were smoothly rearranged under given conditions. In the case of unsymmetrical oximes the reaction of the Beckmann rearrangement was selective and only one amide was produced. The catalyst was recovered at least four to five times without loss of their efficiency. This method has advantages of high conversion, high selectivity and simple work-up procedure.



Scheme 20a-b

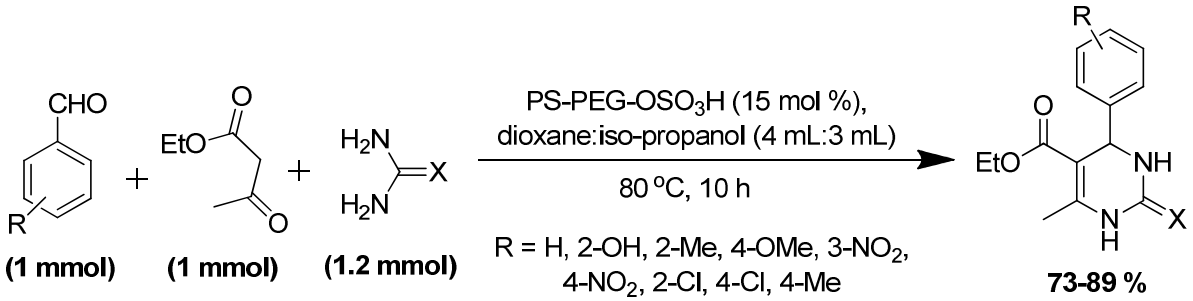


Scheme 20c

3.3.2) Synthesis of 3,4-dihydropyrimidinone derivatives

The considerable interest for 3,4-dihydropyrimidinone (DHPM) type products stems from their wide range of biological activities as calcium channel blockers, antihypertensive agents, α_{1a} adrenergic antagonists and neuropeptide Y antagonists.[152] Quan and co-workers have developed polymer bound sulfonic acid on polystyrene-poly(ethylene glycol) (PS-PEG) resin (PS-PEG-OSO_3H) for the synthesis of 3,4-dihydropyrimidinones via Biginelli-type reaction utilizing various aldehydes, ethyl acetoacetate and urea or thiourea in dioxane and *iso*-propanol as a solvent at 80 °C for 10 h, which afforded excellent yield of the product **(Scheme 21)**.[35] Various solvents were tested including DMF, MeCN, ethanol, toluene, dioxane, and *iso*-propanol, which

afforded average yield of the product. Finally, the authors have identified a mixture of 4 mL dioxane and 3 mL iso-propanol as the most efficient solvent to afford a product in the high yield. Aldehydes with electron withdrawing and electron donating groups reacted equally to afford the desired 3,4-dihydropyrimidines in high yield. The catalyst can be easily recycled and reused six times with significant loss of their activity. Conventional homogeneous acid catalysts have some limitation such as strongly acidic conditions, the low yield of the products and difficult isolation process. While PS-PEG-OSO_3H showed better reactivity, efficiency and recoverability to solve above problems in this synthesis.

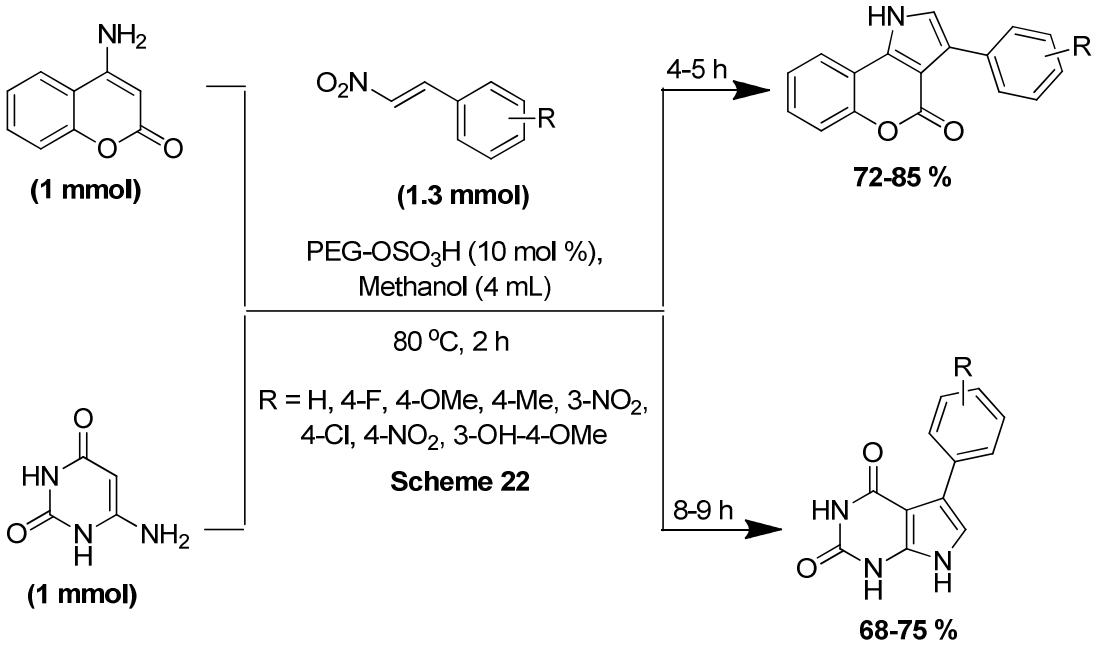


Scheme 21

3.3.3) Synthesis of coumarin and uracil fused pyrrole derivatives

Coumarin and uracil fused heterocycles are one of the most active classes of compounds possessing a wide spectrum of biological activity.[123, 153, 154] Many of the coumarin fused heterocycles shows antitumor,[155] antibacterial,[156] antifungal,[157] anticoagulant,[158] anti-inflammatory[159] and antiviral[160] activities. Paul el al. have described an another protocol for the efficient, simple and convenient synthesis of coumarin and uracil fused pyrrole derivatives using a biodegradable, polymer supported catalyst, PEG-OSO_3H via two component coupling of 4-aminocoumarin or 6-aminouracil and α,β-unsaturated nitroalkene in methanol at 80 °C **(Scheme 22)**.[161] The authors have applied a wide variety of Lewis acids such as $ZnCl_2$, $AlCl_3$, I_2, $FeCl_3$, $InCl_3$, p-toluenesulphonic acid (p-TSA) and polymer-supported PEG-OSO_3H in this reaction. It was evident that with the use of $ZnCl_2$ and $AlCl_3$ the product was formed in poor yields. Whereas using $FeCl_3$, $InCl_3$ and p-TSA the product was obtained in moderate yields. However, PEG-OSO_3H showed better results as compare to others. Various solvents such as methanol, dioxan, DMSO, DMF, glycol, nitro methane and acetonitrile were screened for this two component coupling reaction. The best result was observed in methanol. It is important to note that 10 mol % of catalyst was efficient for this transformation. It was found that nitro olefins bearing an electron-donating group in the benzene ring gave the corresponding pyrroles in good yield compared to electron-withdrawing groups in the benzene ring. The mechanism of this reaction shows that PEG-OSO_3H catalyze the Michael addition of 4-aminocoumarin or 6-aminouracil to α,β-unsaturated nitro alkenes. The nucleophilic attack at the β position of the α,β-unsaturated nitro alkenes is enhanced by PEG-OSO_3H may be due to the polarization of the π-electron cloud

towards the nitro group of α,β-unsaturated nitro alkenes. Then the Michael adduct is attacked by the nitrogen atom of the amine group, with the formation of the five member ring. Finally, the elimination of water and nitroxyl molecules leads to the formation of the desired pyrroles. Furthermore, the reaction was scaled up to the 10 mmol scale; excellent results were still obtained in similar condition. After completion of each reaction, methanol was evaporated and water was added to the reaction mixture. In order to recover the catalyst, water was evaporated under reduced pressure, and the resulting solid was washed with diethyl ether, and dried under reduced pressure. The catalyst was recovered at least five times without loss of their efficiency.

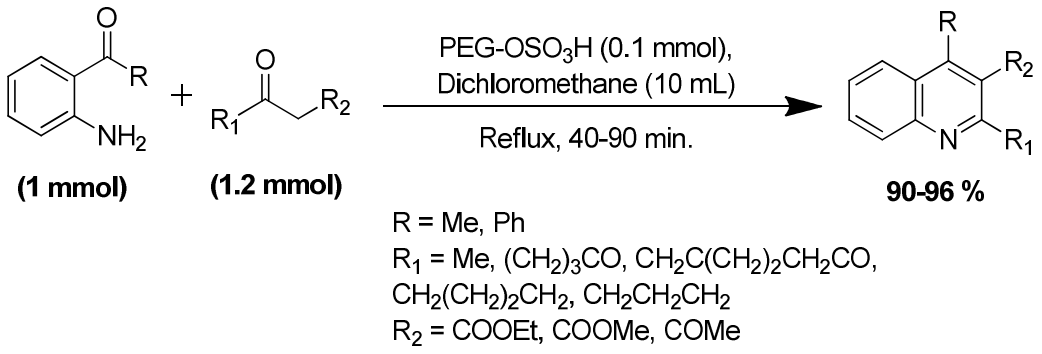


Scheme 22

3.3.4) Synthesis of polysubstituted quinoline derivatives

Quinolines and their derivatives are very important compounds because of their wide occurrence in natural products[162] and their interesting biological activities as antimalarial, anti-inflammatory, antiasthmatic, antibacterial, antihypertensive, and tyrosine kinase-inhibiting agents.[163-165] Zhang et al. have reported condensation of 2-Aminoarylketones and α-methylene ketones in the presence of 10 mol% of poly(ethylene glycol) (PEG)-supported sulfonic acid (PEG-OSO_3H) under mild reaction conditions to afford the corresponding polysubstituted quinoline derivatives in excellent yields **(Scheme 23)**.[166] Different solvents such as methanol, Et_2O, acetonitrile and dichloromethane were examined by the authors. However, the best results were obtained when the reaction was carried out in dichloromethane at reflux temperature for 40 min in the presence of 10 mol% of PEG-OSO_3H. Furthermore, the condensation in the presence of concentrated H_2SO_4 afforded product in only lower yield. A possible mechanism for the synthesis of quinolines using this method followed mechanism of simple Friedlander synthesis. Wide range of cyclic and acyclic ketones were employed in this reaction and they all converted efficiently

into the products. After finishing the condensation reaction, dichloromethane was evaporated, and the PEG-OSO_3H was readily recovered by precipitation with cold diethyl ether, followed by filtration and washing with diethyl ether. The recovered catalyst was used four to five times without loss of their efficiency. It should be noted that when the catalytic activity of polymeric sulfonic acid decreased, the resin could be treated with concentrated HCl again to keep its catalytic activity. Lewis acids such as $FeCl_3$,[167] $Mg(ClO_4)_2$,[168] $BiCl_3$,[169] $SnCl_2$,[170] $Bi(OTf)_3$,[171] $Sc(OTf)_3$,[172] $Y(OTf)_3$[173] and I_2[174] have been found to be effective for this conversion. But they showed relatively poor efficiency compared to PEG-OSO_3H in terms of product yield and reaction time. From the practical point of view, the catalyst is inexpensive, nontoxic, and readily available, and the reaction proceeded in shorter time makes this method green and clean.

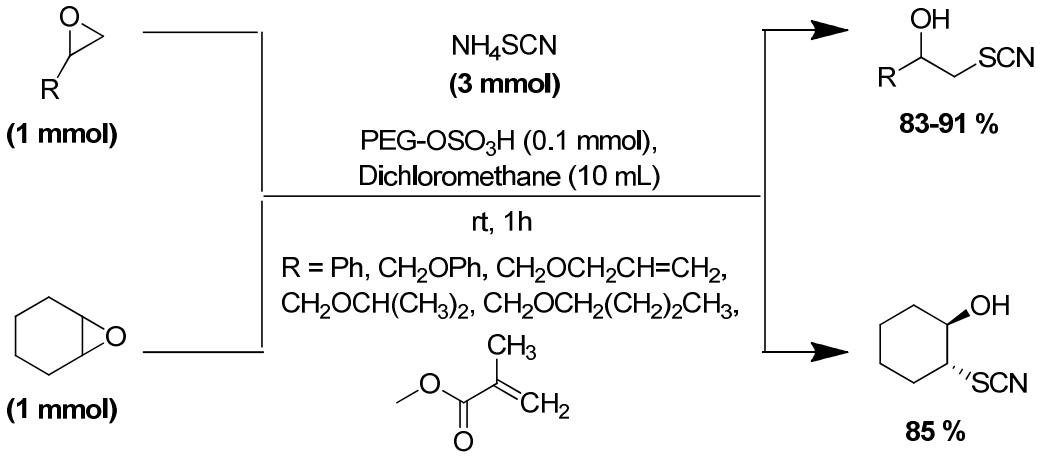


Scheme 23

3.3.5) Synthesis of thiocyanohydrin derivatives

Kiasat et al. have discovered an efficient protocol for the regioselective ring opening of epoxides by thiocyanate ion to give thiocyanohydrins as key intermediates utilizing poly(ethylene glycol)-bound sulfonic acid (PEG-OSO_3H) as green and biodegradable polymeric phase-transfer catalyst **(Scheme 24)**.[175] Different types of oxiranes, except styrene oxide, carrying activated and deactivated groups were cleanly, easily, and efficiently converted to the corresponding β-hydroxy thiocyanates as exclusive and virtually pure products. It is noteworthy that no evidence for the formation of thiirane as by-product of the reaction was observed, and the products were obtained in pure form without further purification. Epoxides carrying electron-withdrawing groups reacted under similar reaction conditions, and their corresponding β-hydroxy thiocyanates were produced in excellent yields and regioselectivity. In these cases, with the attack of the thiocyanate ion on the less substituted oxirane carbon, the regioselectivity was reversed and β-hydroxy thiocyanates (I) were obtained. It is shown that, for epoxides carrying electron-donating groups, it is the electronic factor that predominates, and the thiocyanate ion attacks predominantly at the secondary carbon atom of the epoxide ring, a fact that is reasonably well established.[176] In contrast, in epoxides carrying electron-withdrawing groups, it is the steric factor in that predominates and the nucleophilic attack of thiocyanate ion is strongly favored on the less substituted carbon of epoxides. Also in the case of cyclohexene oxide, the stereochemistry of the ring-opened product was found to be *trans*. It seems that this polymeric

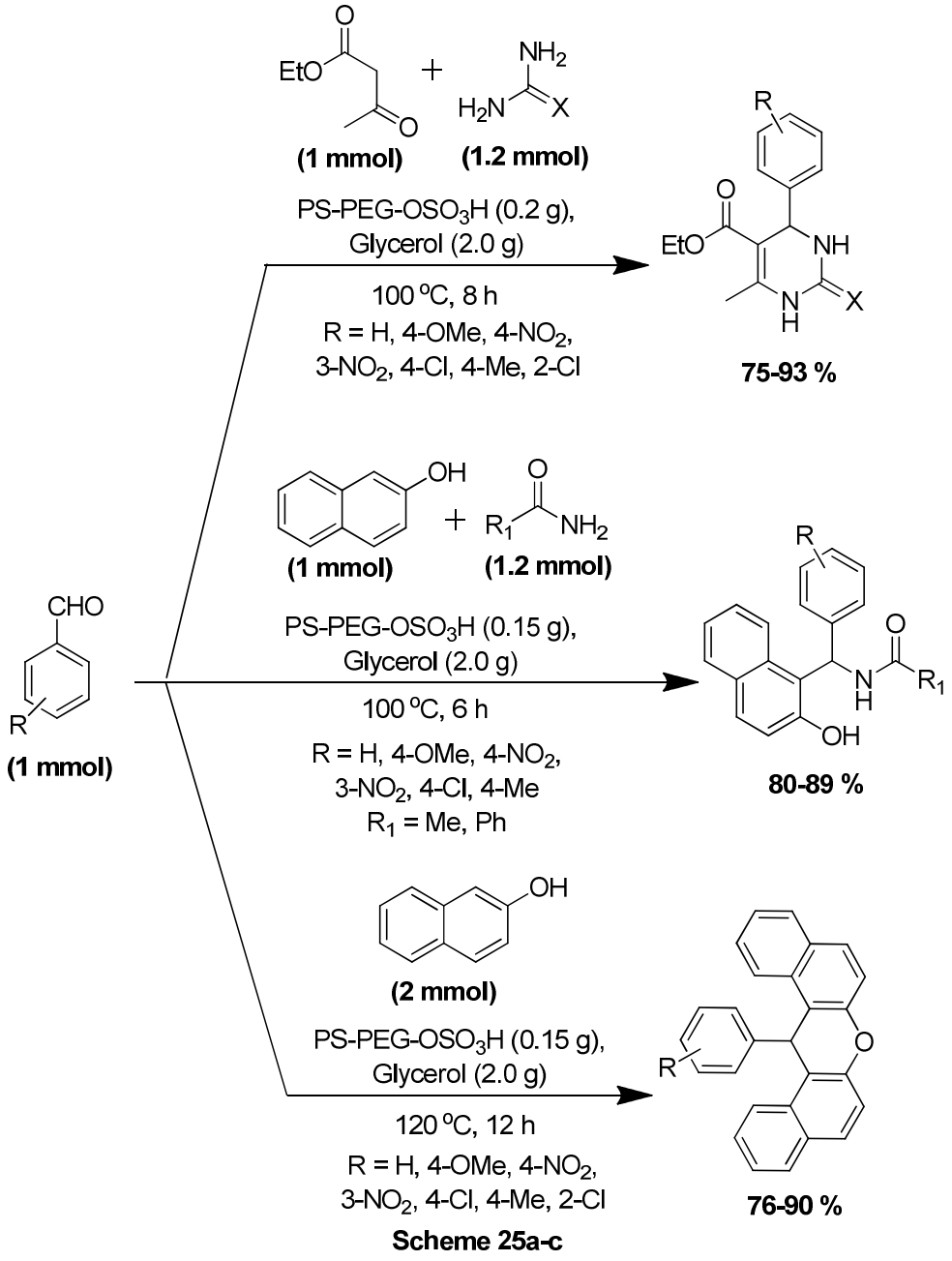
catalyst forms a complex with cation, much like crown ethers, and this complex causes the anion to be activated. In addition, polymeric catalyst, probably can be facilitated the ring opening of the epoxide by hydrogen bonding. The reaction did not complete after 5 h, and was contaminated by diol and thiirane formation in the presence of catalysts such as tetrabutylammonium bromide (TBAB) as anonacidic phase transfer catalyst, silica sulfuric acid (SSA) and Dowex resin SO_3H, however excellent result was obtained in PEG-OSO_3H.



Scheme 24

3.3.6) Synthesis of 3,4-dihydropyrimidinones, amidoalkyl naphthols, and dibenzoxanthenes

Quan's group have discovered an efficient, green and recyclable catalyst system as glycerol and PS-PEG-OSO_3H in the multicomponent reactions for the synthesis of 3,4-dihydropyrimidinones, amidoalkyl naphthols, and dibenzoxanthenes at 100 ^oC within 6 to 8 hours **(Scheme 25a-c)**.[177] The 3,4-dihydropyrimidinone derivatives were synthesized using various acid catalysts such as p-toluene sulfonic acid (p-TSA), poly(ethylene glycol)-supported sulfonic acid (PEG-OSO_3H), PS-PEG-OSO_3H and acetic acid. However, best results were obtained in PS-PEG-OSO_3H. When this reaction was performed without any catalyst, the product was obtained with 20% yield. The combination solvent system of equal amounts of glycerol with water and pure water were also tested by the authors as the reaction solvents, but only glycerol showed higher activity towards this transformation. For the synthesis of amidoalkyl naphthols solvents like PEG-400, water and 1,2-dichloroethane and glycerol were studied by the authors. This reaction could also be carried out in PEG-400 and 1,2-dichloroethane to give the products in good yield. Compared to the reaction in 1,2-dichloroethane, the reaction in glycerol has the advantages of easy isolation of products, good recyclability, and environmental friendliness. In the synthesis of dibenzoxanthenes, p-TSA, PEG-OSO_3H, and PS-PEG-OSO_3H all were shown to be greatly effective. Though this reaction can also be performed in 1,2-dichloroethane or under solvent-free conditions, the product separation and the catalyst recycling is difficult. At the end of the reaction, because glycerol and PS-PEG-OSO_3H are not soluble in the organic phase, the product can be easily extracted with ethyl acetate. After simple filtration and washing with ethyl acetate and ether, the recycled PS-PEG-OSO_3H was used directly in the next run. The yields obtained after five cycles were comparable to those of fresh glycerol and PS-PEG-OSO_3H.

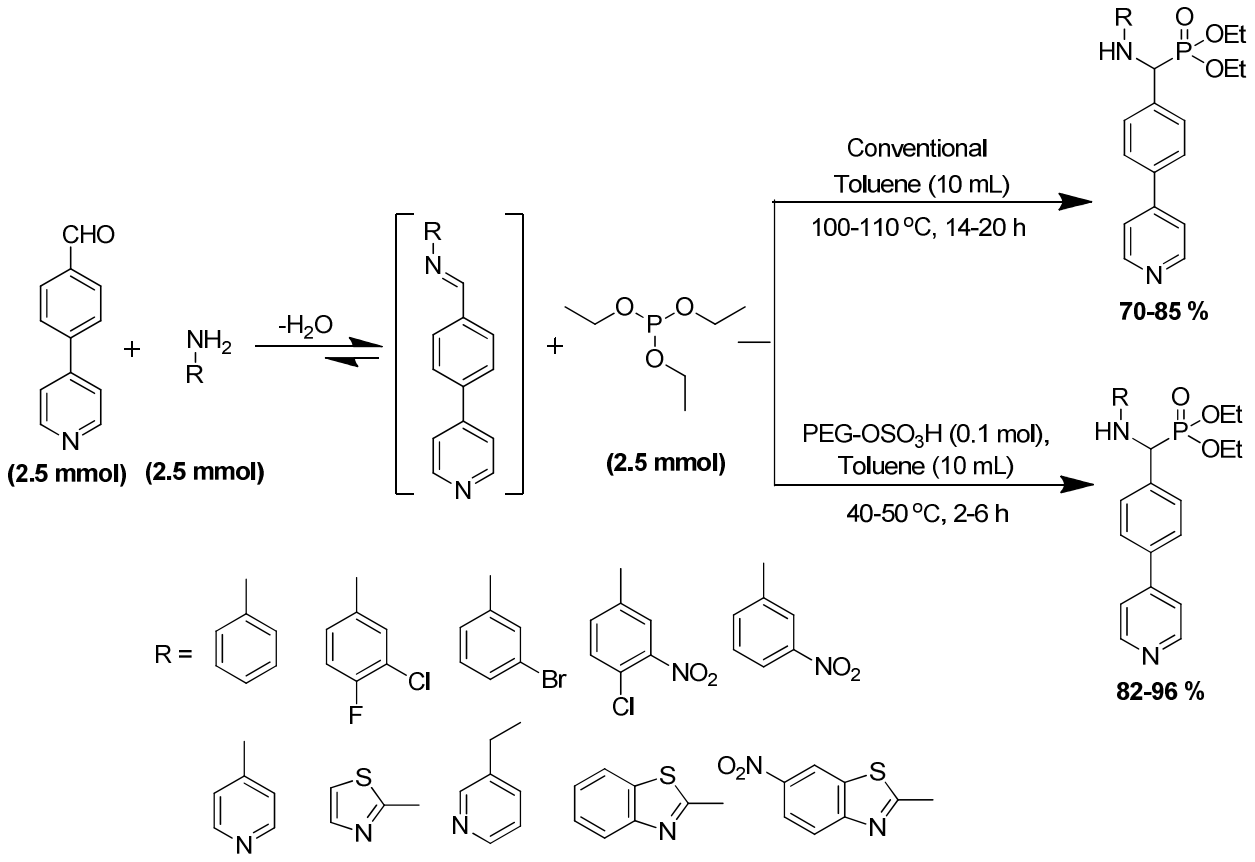


Scheme 25a-c

3.3.7) Synthesis of α-aminophosphonate derivatives

α-Aminophosphonates are an important class of bioactive molecules. Their use as peptide mimics,[178] enzyme inhibitors,[179] antibiotics[180] and anti-HIV,[181] anti-cancer[182] and thrombotic[183] agents has proved their vast potentiality both as direct drugs and as drug precursors for several disease manifestations. Reddy and co-workers have reported one pot three-component PEG-OSO_3H catalyzed Kabachnike Field's reaction of 4-(Pyridin-4-yl)benzaldehyde and triethyl phosphite with various primary amines afforded α-aminophosphonates with high yield **(Scheme 26)**.[184] These new series of α-aminophosphonates (4aej) were evaluated for their anti-tumor

activity on human chronic myeloid leukemia cells (K 562), human colon carcinoma cells (Colo 205) and showed moderate activity. The authors have proposed reaction mechanism and according to that the corresponding imine intermediate was formed from the reaction of aldehyde and amines and in the second step subsequent addition of Phosphite to the C=N bond of the imine occurs to from the corresponding α-aminophosphonates. However, this one-pot synthesis is not straightforward, because of the formation of water molecule during imine formation in the first step hydrolyzes theimine intermediate and thus retards the forwarded process of the reaction. This drawback is minimized by the use of PEG-OSO_3H catalyst which traps the released water and subsequently drive the reaction forward. In conventional preparation in refluxing toluene even after 14-20 h of reaction, only unsatisfactory product yield (70%) was observed. When the same reaction was performed in the presence of PEG-OSO_3H as catalyst at 40-50 ^oC for the duration of 2 h 96% yield of the product was obtained.

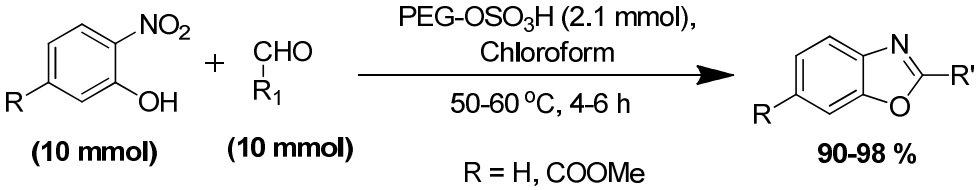


Scheme 26

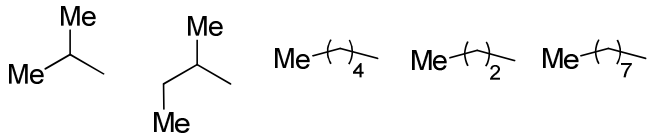
3.3.8) Synthesis of benzoxazole derivatives

Chikhale et al. have developed highly efficient, simple and rapid protocol for the preparation of various 2-aminobenzoxazoles via three different methods in the presence of catalytic amount of poly(ethylene glycol)-bound sulfonic acid (PEG-OSO_3H) **(Scheme 27a-c)**.[185] In first method, substituted benzoxazole derivatives were synthesized from the *ortho*-nitro phenols and substituted aldehydes in minimum amount of chloroform at 50-60 ^oC for 4-6 h. In second

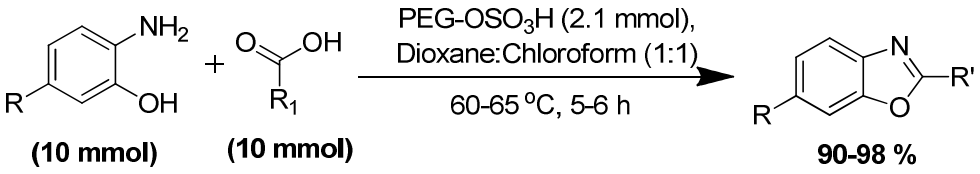
method, substituted benzoxazole derivatives were synthesized from the substituted *ortho*-amino phenols and substituted benzoic acids in Dioxane:Chloroform (1:1) at 50-60 ^{o}C for 5-6 h. In the third method, substituted 2-aminobenzoxazoles were synthesized from the substituted phenylurea from parent anilines using potassium cyanate and concentrated HCl, which was then reflux in chloroform at 80-90 ^{o}C for 6-7 h. It was found that use of nearer 2.1 mmol of catalyst gave optimum results. A wide range of aldehydes and acids used for the synthesis of 2-substituted benzoxazole derivatives makes it has a wide synthetic utility. PEG-OSO_3H is found to be an economical and reusable catalyst with low catalytic loading. It was found that up to three cycles the catalytic activity provided a good yield of the reaction product, while conventional catalysts could not be recovered and reused.



R = Ph, 2,4-diOMePh, 4-OMePh, cyclohexyl, 2-OHPh



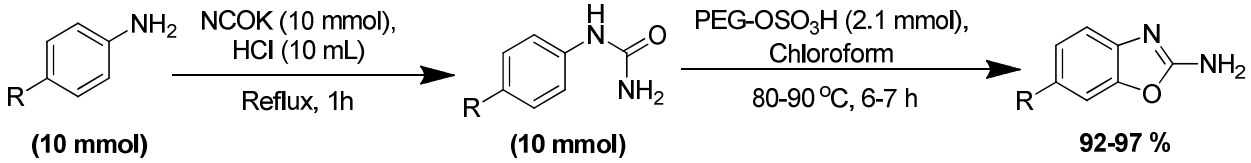
Scheme 27a



R = H, Me, Cl, F

R = Ph, 3,4-ClPh, 4-ClPh, 4-BrPh, 4-CNPh, 4-OMePh, 2-OMe

Scheme 27b

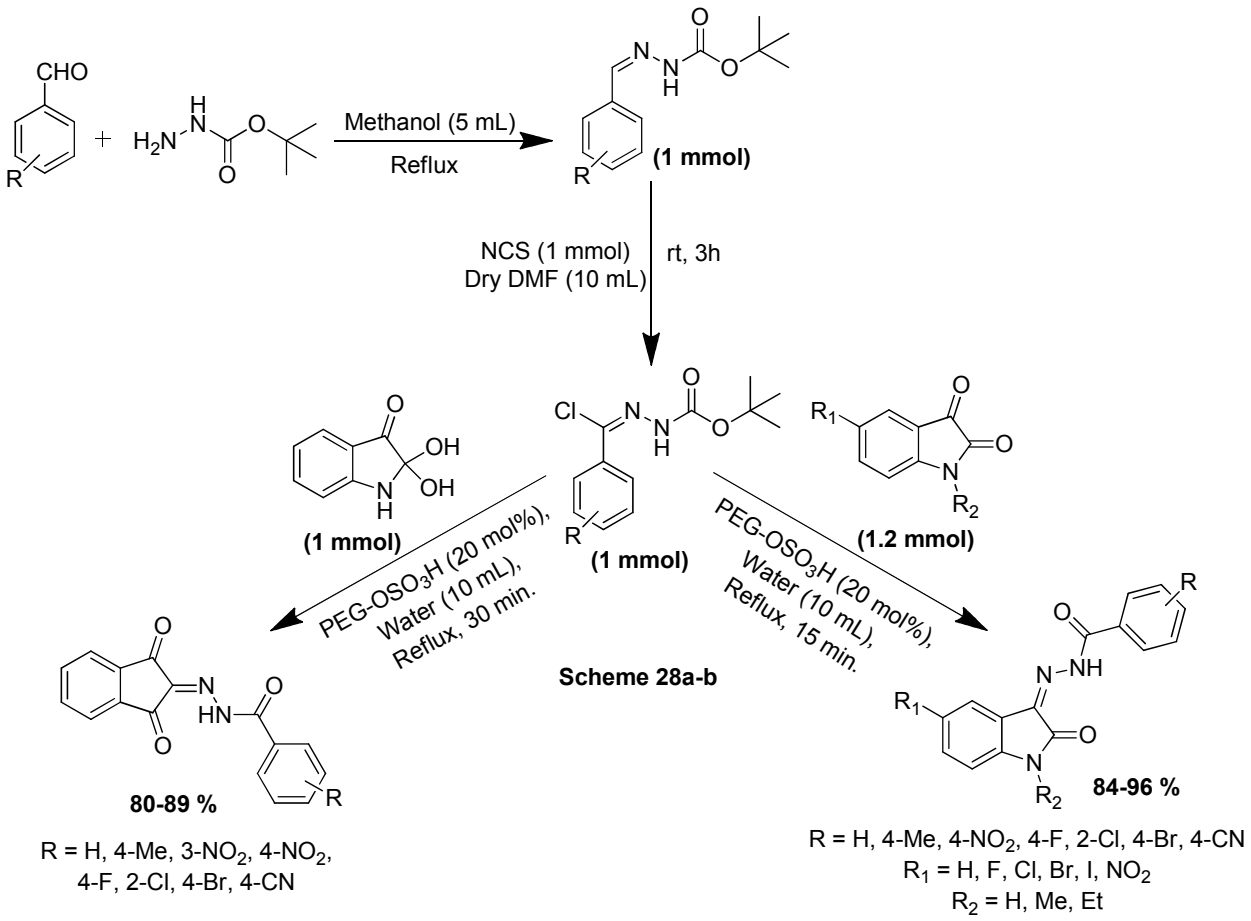


R = H, Me, Cl, Br, NO_2

Scheme 27c

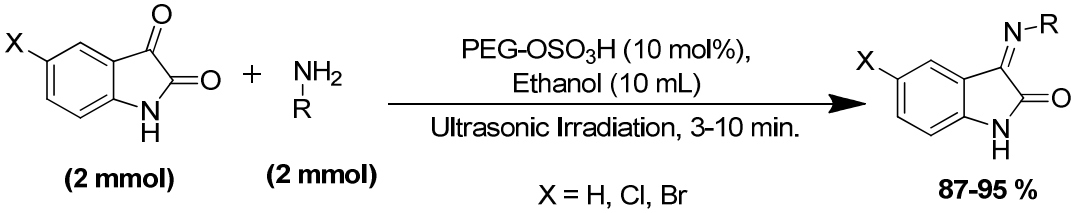
3.3.9) Ninhydrin and isatin based hydrazine derivatives

Debnath and co-workers have synthesized a series of biologically important ninhydrin and isatin based hydrazones by utilizing N'-(chloro-aryl-methylene)-tert-butylcarbazates with ninhydrin and isatins in the presence of PEG-OSO_3H as catalyst in water under reflux condition **(Scheme 28a-b)**.[186] The dual characteristic of PEG-OSO_3H as a Brønsted acid as well as a phase-transfer catalyst is successfully exploited in this synthesis. The authors have tested several Brønsted catalysts such as HCl, p-TSA, and acetic acid along with some organo-acid catalysts such as lactic acid, formic acid, and citric acid in water. In all these cases, the desired product was isolated with unsatisfying yield. On varying the percentage of catalyst load (10-25 mol%), maximum yield of the product (95%) was obtained at 20 mol%. The catalyst was recovered and reused at least five times without loss of their efficiency. In order to recover the catalyst, methanol and water were evaporated under reduced pressure, and the resulting gummy mass was washed with diethyl ether, and dried. The recovered catalyst was reused directly for a new reaction cycle. Reduced reaction time, operational simplicity, excellent yields of the products with high purity, and more importantly, easy recoverability, and reusability of the homogeneous polymeric catalyst make the reaction an attractive, economic, and sustainable green synthetic methodology.

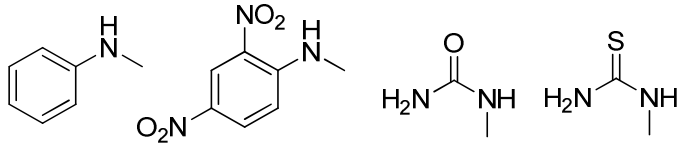


3.3.10) Synthesis of Schiff and Mannich bases of isatin derivatives

Schiff bases are used as important precursor for the synthesis of several industrial and biologically active compounds via ring closure, cycloaddition and replacement reactions.[187] Schiff and Mannich bases of isatin derivatives possesses variety of biological activities like antibacterial,[188] antifungal,[189] anticonvulsant,[190] anti-HIV[191] and antidepressant.[192] Abaszadeh et al. have discovered an efficient and green protocol for the synthesis of Schiff and Mannich bases of isatin derivatives using condensation reaction of amines, hyrazines, thiosemicarbazide and semicarbazide with isatin derivatives, in the presence of catalytic amounts of PEG-OSO_3H, under ultrasonication in ethanol at the 80 ^oC **(Scheme 29)**.[192] The authors have carried out this reaction in different solvents such as ethyl acetate, ethanol, chloroform and acetonitrile, and the best results in terms of reaction time and yield of the products, were obtained in ethanol. In addition, the best catalyst loading was found in 10 mol %, which gave an excellent yield of product within a short period of time. The authors have described a probable mechanism for the formation of the product shows that the nucleophilic attack of the NH_2 group of the amines, hyrazines, thiosemicarbazide and semicarbazide on the carbonyl group of isatin was enhanced by PEG-OSO_3H. High conversions, short reaction times and a cleaner reaction conditions are the added advantages of this method.



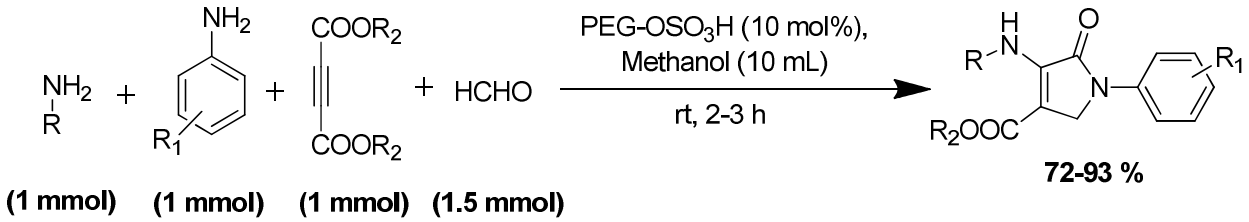
R = Ph, 4-ClPh, 4-BrPh, 4-MePh, 4-OMePh,1-naphthyl, NH_2



Scheme 29

3.3.11) Synthesis of dihydropyrrolone derivatives

Shuanbao et al. have discovered an efficient synthesis of dihydropyrrolone derivatives in high yields through reaction of two same or different primary amines, but-2-ynedioates and formaldehyde in the presence of sulfuric acid-modified polyethylene glycol 6000 (PEG-OSO_3H) in methanol at room temperature **(Scheme 30)**.[193] Various solvents such as methanol, dichloromethane, acetonitrile, DMSO, ethanol and water were examined by the authors in this synthesis. However, the reaction in methanol was efficiently undergoing and afforded product in excellent yield. Various aromatic amines with electron donating and electron withdrawing groups were converted efficiently into the products in high yield. The catalyst was recovered six times without significant loss of their efficiency.



R = Ph, 4-ClPh, 3-MePh, 4-OMePh, 4-NO_2Ph, CH_2Ph, Cyclohexanyl, n-C_4H_9

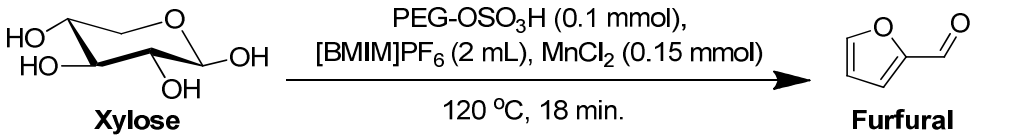
R_1 = H, 4-Cl, 3-Me, 4-OMe, 4-Br

R_2 = Me, Et

Scheme 30

4) Conversion of biomass into furfural derivatives catalyzed by PEG-OSO_3H

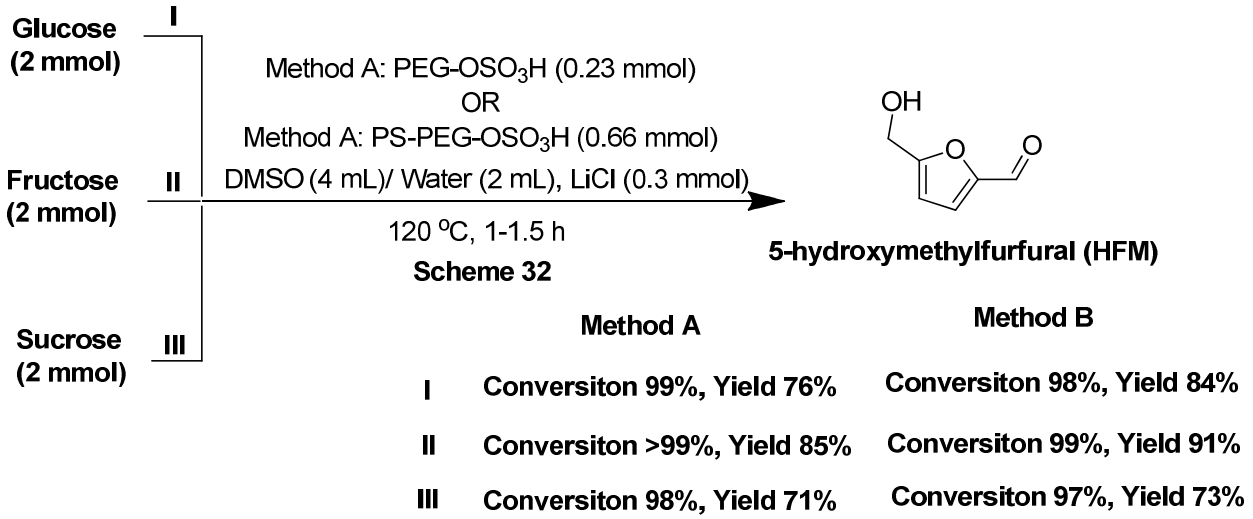
Zhang and co-workers have described the dehydration of biomass to furfural using polymer bound sulfonic acid (PEG-OSO_3H) as an efficient and bio-degradable catalyst **(Scheme 31)**. This reaction was catalyzed by a co-catalyst system of PEG-OSO_3H (0.3 g, 0.1 mmol –OSO_3H) and $MnCl_2$ in 1-butyl-3-methylimidazolium hexafluorophosphate ([BMIM]PF_6).[194] The other co-catalysts such as $SnCl_2$, $MnCl_2$, $AlCl_3$, $FeCl_3$, CuCl, $CuCl_2$, KCl, NaCl, $ZnCl_2$, LiCl, KF, NaF, $BiCl_3$, $NiCl_2$, $BaCl_2$, $CoCl_2$, $CdCl_2$ and $CrCl_3$ were also examined by the authors for this transformation. However, the furfural yield is improved, when MnCl2 is added to the reaction mixture as a co-catalyst. The catalyst was mild, non-volatile, and non-corrosive and can be recycled multiple times (>10) without an intermediate regeneration step and no significant leaching of –OSO_3H groups. Different solvents likes [BMIM]PF_6, glycerol, PEG-400 and water were also examined by the authors for the optimization of the reaction condition. However, [BMIM]PF_6 showed an excellent activity towards this reaction in terms of product yield. Here, Xylose, Ribose and Arabinose were taken as biomass. Best conversion of furfural was obtained from the Xylose. This reaction was also catalyzed by Con. H2SO4, but it was not showed better efficiency as compared to PEG-OSO_3H.



Scheme 31

Zhang et al. have also reported green synthesis of 5-hydroxymethylfurfural (HMF) from carbohydrates such as monosaccharides, disaccharides and polysaccharides using PEG-OSO_3H or PS-PEG-OSO_3H as reusable and bio-degradable catalysts in a DMSO/H_2O reaction system **(Scheme 32)**.[195] Glucose or glucose-based carbohydrates were efficiently transformed into HMF co-catalyzed by polymer bound sulfonic acids with LiCl. It displayed high activity and good

yield. For glucose, the yield of HMF can mount to 86% in DMSO/H_2O mixed systems. Compared to PEG-OSO_3H, PS-PEG-OSO_3H showed better activity for this reaction.



Scheme 32

	Method A	Method B
I	Conversiton 99%, Yield 76%	Conversiton 98%, Yield 84%
II	Conversiton >99%, Yield 85%	Conversiton 99%, Yield 91%
III	Conversiton 98%, Yield 71%	Conversiton 97%, Yield 73%

5) Conclusion:

Compared with liquid homogeneous acid catalysts, solid acid catalysts have distinct advantages in recycling, separation, and environmental friendliness. Here, we gave an overview on the application of sulfonated polyethylene glycol (PEG-OSO_3H) as a biodegradable and heterogeneous catalyst in organic synthesis. PEG-OSO_3H with mild acidity has shown excellent activity in various organic reactions especially heterocyclic synthesis. It is important to note that the most of the synthesis catalyzed by PEG-OSO_3H was under solvent free conditions. In addition, the use of water as a medium for some organic reactions catalyzed by PEG-OSO_3H, makes these protocols green, clean and environmentally friendly. Excellent accessibility, inexpensive, biodegradable and many reactive sites are significant properties of this catalyst. PEG-OSO_3H was proved to be a recyclable, green, and highly effective solid acid catalyst in a wide range of organic synthesis.

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