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Review

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Recent advances in novel catalytic synthetic methodologies towards the construction of the coumarin nucleus: a review

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Abstract

This review summarizes the recent advances in the methodological development for the construction of coumarin nucleus. Various synthetic strategies involving the catalytic applications of Bronsted acids, natural acids, basic media, nanoparticles, visible light, ultrasonic waves and microwaves etc. have been reviewed in this article, reported since 2020.

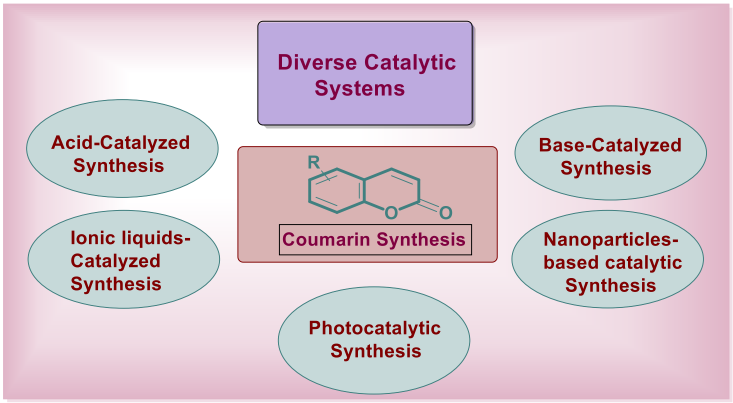

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Table of Contents

1. Introduction

Heterocyclic moieties have been found integral part of several natural and synthetic drugs.[1, 2] Coumarins are naturally occuring oxygen-containing heterocyclic compounds (lactones), which belongs to the class of secondary metabolites. It is also known as 2*H*-1-benzopyran-2-one or 1,2-benzopyrone as it contains fused benzene and pyrone rings (Figure 1).[3, 4]

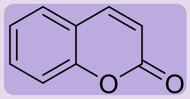

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Figure 1. General structure of coumarin.

Coumarins possess a variety of biological and pharmacological activities.[5] Coumarins and their derivatives have found growing curiosity due to their anti-bacterial, anti-HIV, anti-fungal, anti-oxidant, anti-helmintic and anti-cancer activities.[6-11] Coumarins such as osthol **4** has been depicted to induce apoptosis and inhibit cancer cell growth. Similarly, some derivative of coumarin (such as Esculetin **7**) can scavange free radicals ultimately decreasing oxidative stress. The pharmacologic profile of these biological scaffolds includes anti-bacterial (armillarisin A) **5**, anti-tumor (osthol), **4** anti-coagulant (warfarin) **3**, immunosuppressive (scoparone) **2**, anti-oxidant (esculetin) **7** and anti-HIV (calanolides) **6** properties (Figure 2).[12] Owing to their high fluorescence quantum efficiency,[13, 14] the coumarins analogues are widely employed as fluorescent probes, sensors dyes and imaging agents. Nowadays, coumarin based probes are being used in monitoring water pollution and for locating the tumor lesions. For example, 4-methyl-7-(vinyloxy)-2*H*-chromen-2-one is a fluorescent probe comprising of coumarin nucleus as a fluorophore (Figure 3).[15]

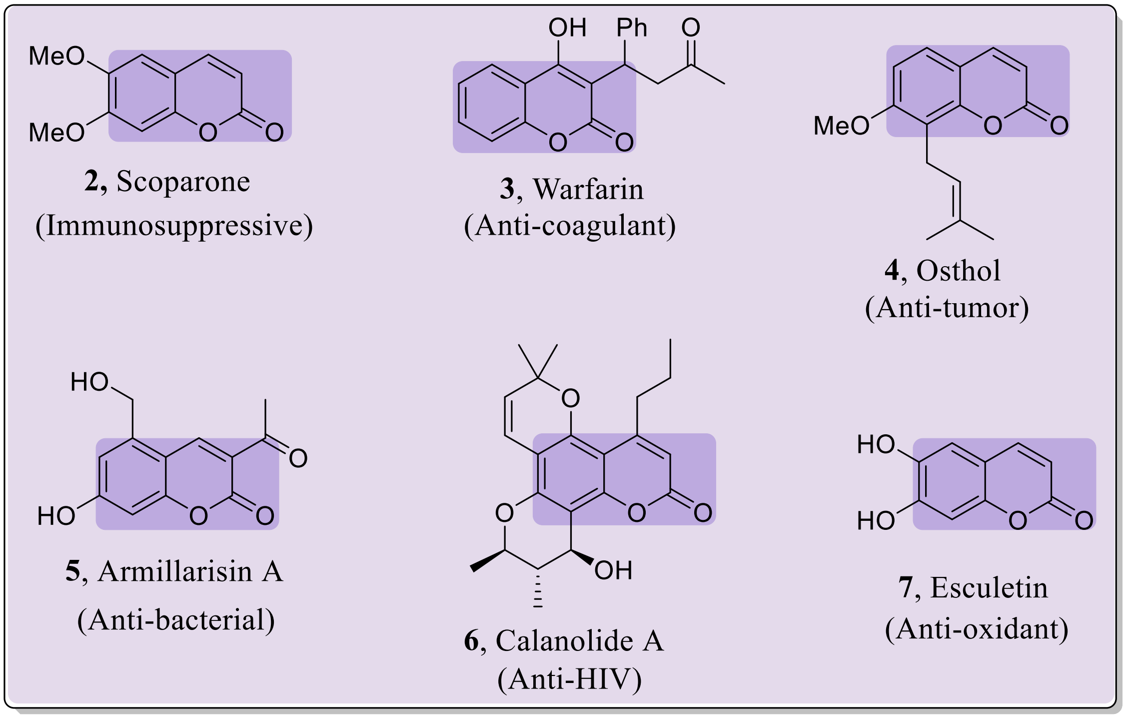


Figure 2. Structures of some biologically active coumarin based molecules.

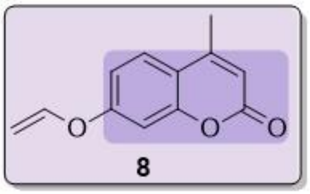


Figure 3. Structure of Fluorescent probe comprising coumarin nucleus.

Coumarin derivatives have gained considerable attention of many medicinal and organic chemists due to the presence of this heterocyclic core in natural products.[16] Besides their medicinal uses, coumarins are widely used as additives in food industry (6-methylcoumarin is mostly used in different vanilla compositions).[17] Coumarins have also found applications in cosmetics, optical and agricultural field as insecticides.[18]

Coumarins have been prepared by various methods such as Reformatsky, Knoevenagel, Pechmann, intermolecular carbochlorocarbonylation, Wittig and Claisen reactions.[19-23] Among all, Pechmann reaction is characterized by its pervasive applications in the construction of coumarin core structure.[25] In the past, initially introduced reactions have gone through rapid development and have been applied for the synthesis of many bioactive compounds as previously used synthetic methodologies were observed to suffer from some drawbacks i.e., use of unsafe solvents, low yield due to side products and long reaction time.[24] Some of the employed catalysts have multiple demerits; such as sulfuric acid, trifluoroacetic acid, phosphorous pentoxide and [bmim]Cl.2AlCl$_3$ have to be used in excess quantities i.e., 10-12 equiv., 3-4 equiv., 5 equiv. and 1.1 equiv. respectively and their waste products are not safe for humans.[25]

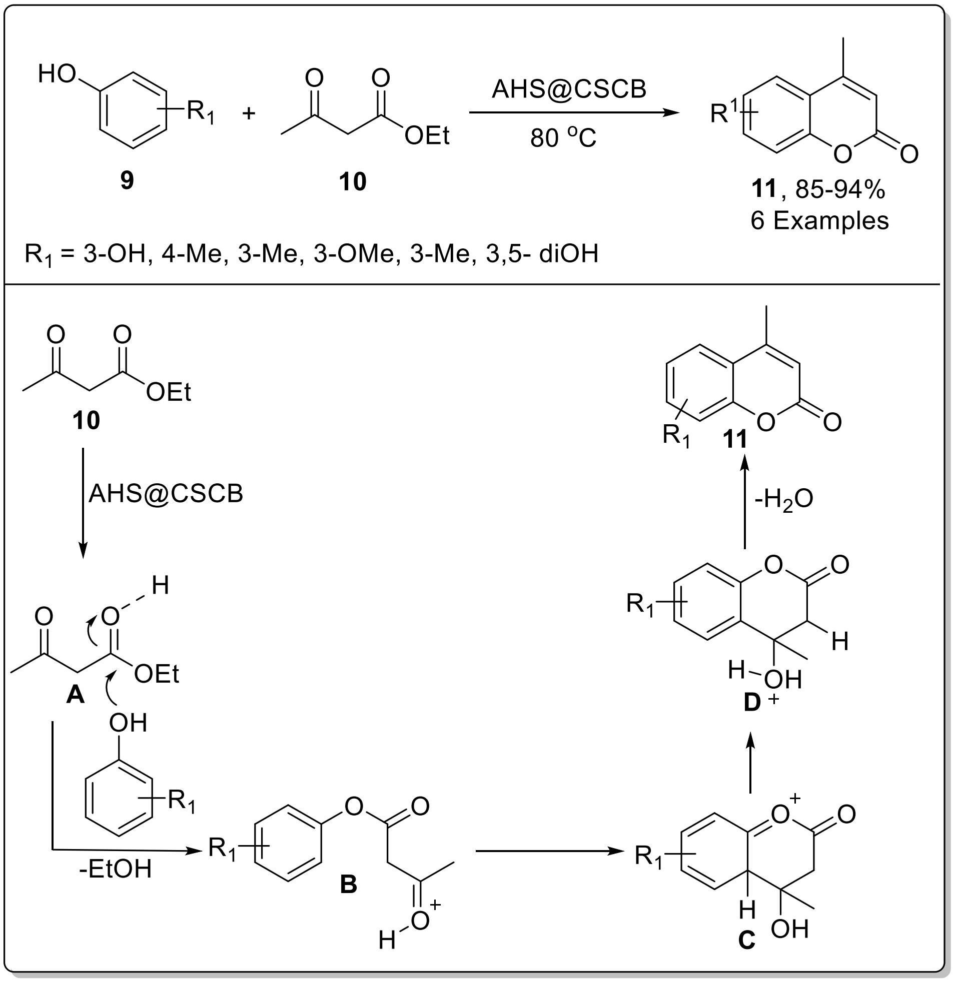
Literature survey reveals that coumarin based molecules have been reviewed widely focusing on their method development and synthetic applications.[26-31] In this review, we have particularly focused on the recently established novel methods developed by various research groups involving the construction of coumarin nucleus, reported within 2020-2025.

2. Construction of the Coumarin Nucleus Using Several Catalytic Strategies

2.1. Acid-Catalyzed coumarin synthesis

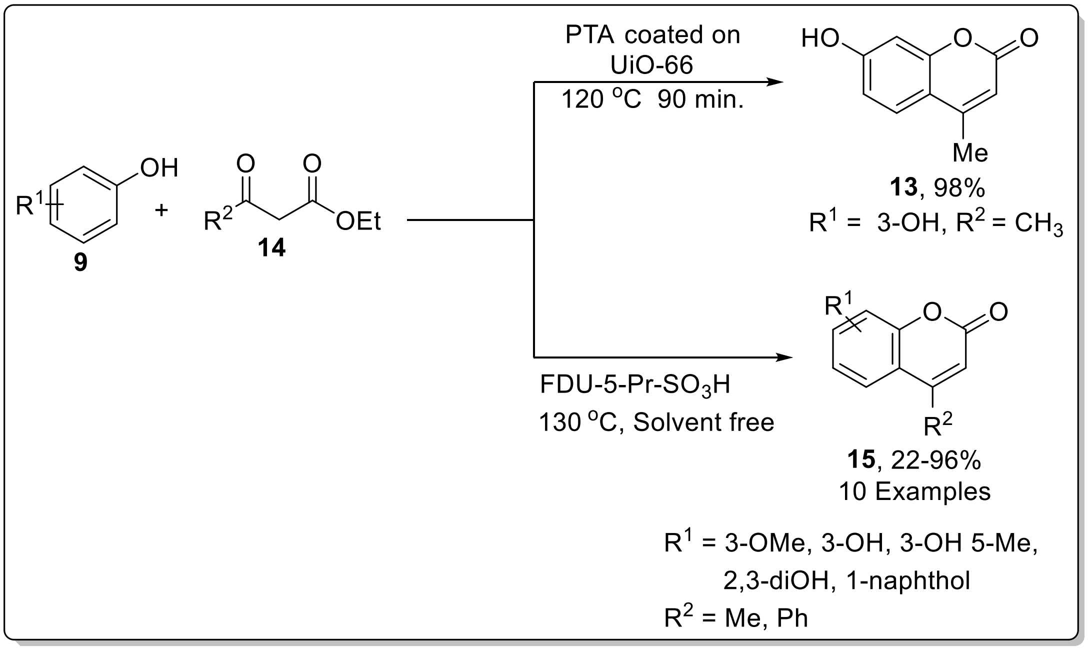
2.1.1. Bronsted acids-mediated synthesis of coumarin. Bronsted acids have been extensively employed towards the formation of C-C bonds. They are involved in promoting nucleophilic addition reactions by activating the alkene, alkyne, hydroxyl groups, imine functionalities to afford the corresponding carbocations and oxonium salts.[32] Hence, Rostami and Zare introduced a new acidic catalyst by utilizing carbonized waste product of sugar production as a carbon bed for dual Bronsted acidic media. The hydrogen sulfate was immobilized as a result of treatment of 3-aminopropyltriethoxysilane and carbonized baggase and sulfuric acid induced sulfonation of amine groups. As a result, ammonium hydrogen sulfate immobilized on carbonized sugar cane bagasse (AHS@CSCB) was synthesized which acted as a green, efficient, thermally stable, inexpensive, and non-metal catalyst. The synthesized solid acidic catalyst was employed for the synthesis of xanthenes, dicoumarols and coumarins. For the coumarins synthesis, ethyl acetoacetate **10** was reacted with substituted phenols **9** via Pechmann reaction under the presence of various solvents such as water, ethanol and solvent-free medium at different temperatures and as well as under reflux conditions while using AHS@CSCB as a catalyst (Scheme 1)[33]. The outcomes revealed that substituted coumarins can be prepared in efficient yields (85-94%) by employing solvent-free conditions at 80 °C by using AHS@CSCB (10 mg) as a catalyst. The plausible mechanism of this reaction involved the activation of carbonyl groups of ethyl acetoacetate by the prepared acid catalyst i.e., AHS@CSCB, followed by nucleophilic reaction with substituted phenols to synthesize the target molecules. By employing the optimized conditions, reaction between 4-hydroxy coumarin and substituted benzaldehydes led to the synthesis of several biscoumarin derivatives **11** in efficient yields.

A solvent free and facile synthetic methodology for the construction of 7-hydroxy-4-methyl coumarin **13** was explored by Alshorifi *et al*. in 2022. The targeted coumarin derivatives and dihydropyrimidinones were synthesized by employing a new reusable catalyst UiO-66 (Zr) impregnated with phosphotungstic acid (PTA) (Zr-based MOFs of UiO-family UiO = University of Oslo). Optimization of reaction was done by reacting the various phenols **9** with ethyl acetoacetate **14** on different parameters i.e., ethyl acetoacetate-resorcinol mole ratio, reaction time, temperature and amount of catalyst (Scheme 2).[34] The results revealed that maximum yield (98%) of coumarin derivative **13** was obtained in 90 minutes by using 2:1 mole ratio of β-keto ester and phenol in the presence of 7 mg of mentioned catalyst (50 wt%) at 120 ^{o}C temperature. Furthermore, the PTA coated on UiO-66 (Zr) is a reusable catalyst with greater surface area and stability as it displayed high activity even after four runs.



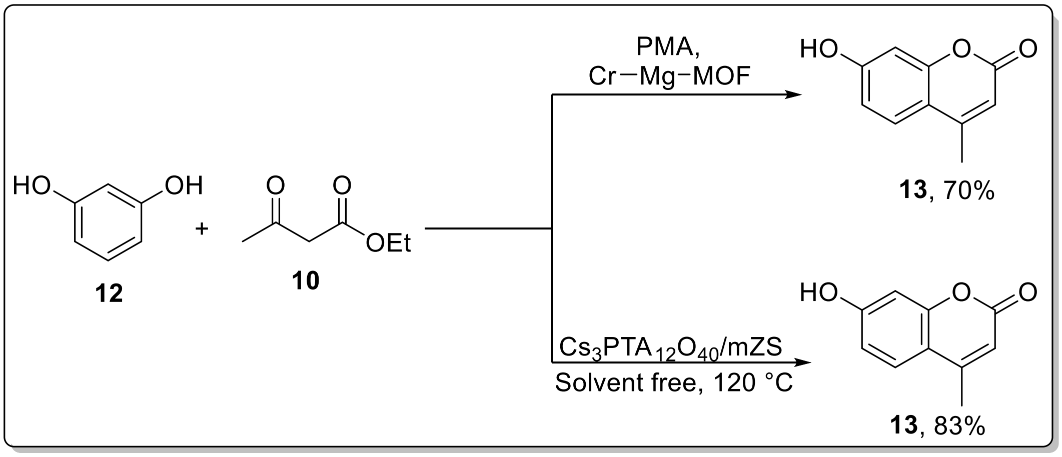
Scheme 1. Synthesis of coumarin **11** by using AHS@CSCB.

Building upon the work by Alshorifi *et al.*, Gonzalez-Carrillo and coworkers developed a new catalyst for Pechmann reaction to synthesize the substituted coumarin **15** under solvent free conditions. Substituted coumarins were synthesized by reacting various phenols **9** with β-keto ester **14** in the presence of FDU-5-Pr-SO_3H (propylsulfonic acid supported on flourodeoxyuridine-5) (Scheme 2).[35] FDU-5-Pr-SO_3H was synthesized by the co-condensation of MPTES [(3-mercaptopropyl)-triethoxysilane] and TEOS (tetraethoxysilane). The optimization process elaborated the influence of the phenol:ethylacetoacetate molar ratio, catalyst loading, reaction time and reaction temperature. The catalyst loading of 1.65 mol %, 130 °C temperature and 1:1.5 molar ratio of reactants was found as optimum conditions to generate the maximum yield up to 97%. Substituted phenols were made to react with diversely substituted dicarbonyl compounds to afford several coumarin derivatives **15** in low to remarkable yield range (22-97%). Low molar equivalents of reactants, high TOF and short duration of reaction are some of the significant merits of this catalytic protocol to construct the coumarin nucleus.



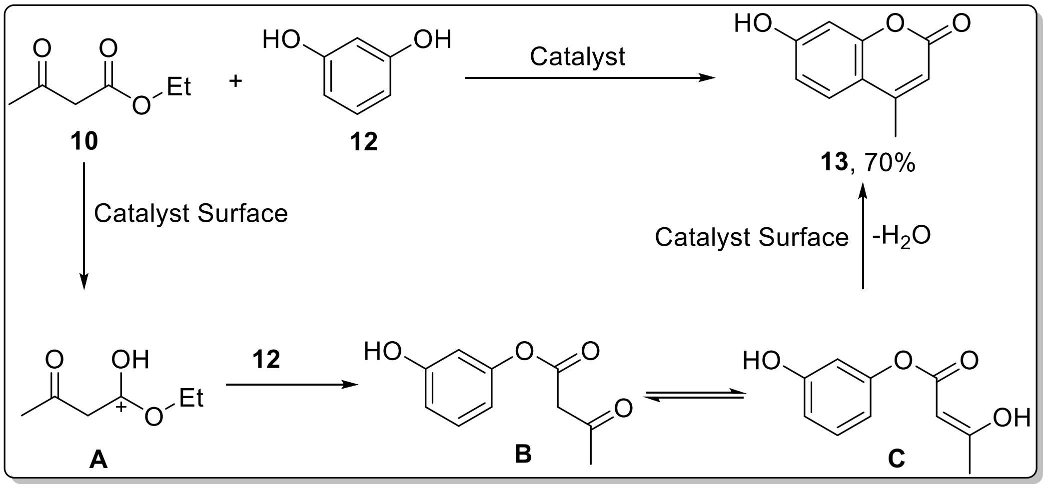
Scheme 2. Synthesis of coumarin derivatives **13** and **15** by PTA coated on UiO-66 (Zr).

Due to large surface area and adaptive pore size, metal organic frameworks (MOF) act as efficient catalysts and can also employed as a support to anchor other active catalysts.[36] In this regard, Salama *et al*. reported the synthesis of coumarin nucleus via Pechmann condensation between phenols and β-keto esters in good yield without using any solvent in the presence of phosphomolybdic acid (PMA) supported on bimetallic Cr–Mg-MOF (chromium magnesium metal organic framework) (Scheme 3).[37] The utilization of doping magnesium ion resulted in the increased surface area and enhanced adsorption performance of Cr-Mg-MOF. To optimize the reaction conditions, ethyl acetoacetate **10** was subjected to react with resorcinol **12** to synthesize the 7-hydroxy-4-methylcoumarin **13** by utilizing the catalytic activity of PMA/Cr–Mg-MOF. The reaction was also optimized with respect to different parameters viz. different temperatures, catalyst loadings and rection time to obtain the maximum yield of targeted derivatives. The results showed that the 70% yield of target molecule was obtained within 2 hours by using 0.05 g of catalyst at 120 °C.



Scheme 3. Synthesis of coumarin core **13**.

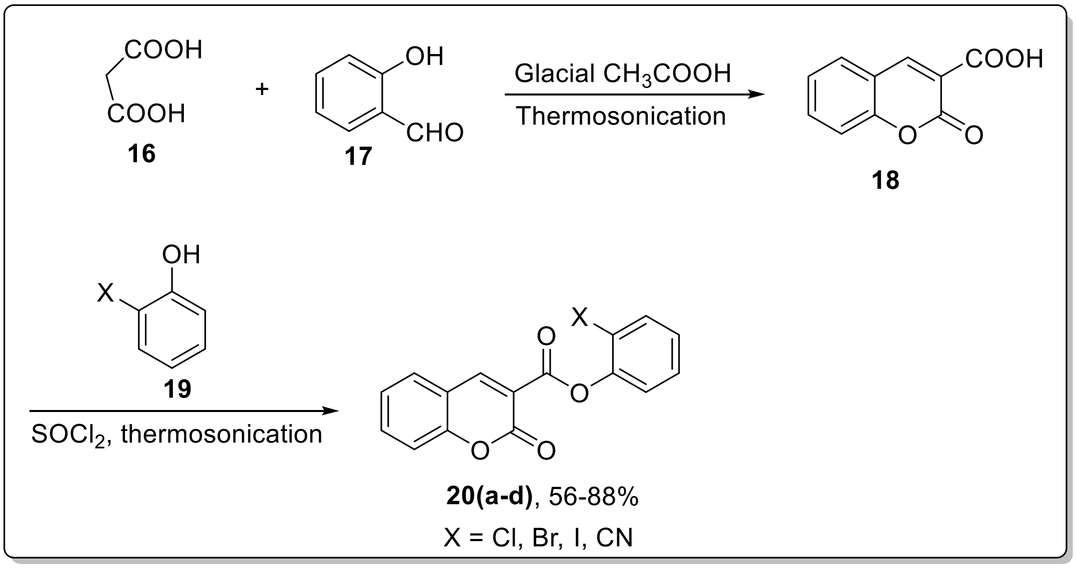
In a similar manner, Ibrahim *et al*. also studied the catalytic effect of cesium salt of phosphotungstic acid (PTA) impregnated with zirconia–silica (mesoporous composite) on the solvent free synthesis of 7-hydroxy-4-methyl coumarin **13** from resorcinol **12** and ethyl acetoaetate **10** (Scheme 3).[38] By working on the model reaction, it was observed that the activity of said catalyst was affected by the exchangeable amount of Cs with PW on the Zr-SiO_2 support, which in turn was affected by the acidity of the catalyst. It is a facile and green approach as Cs_3-$PTA_{12}O_{40}$/Zr-mSiO_2 was not observed to lose its activity even after the fifth cycle of use, thereby resulting in good yield of target molecule **13** (83%). Moreover, the generated catalyst was designed to adsorb the methylene blue (organic dye) from aqueous solution to lessen its possible detrimental health effects on society. The reaction mechanism involved the activation of carbonyl functionality of ethylacetoacetate by the Bronsted acid catalyst. The activated electrophilic center of ethyl acetoacetate was then attacked by nucleophilic -OH of resorcinol followed by cyclization via intermolecular condensation to achieve the targeted coumarin derivative **13** (Scheme 4).



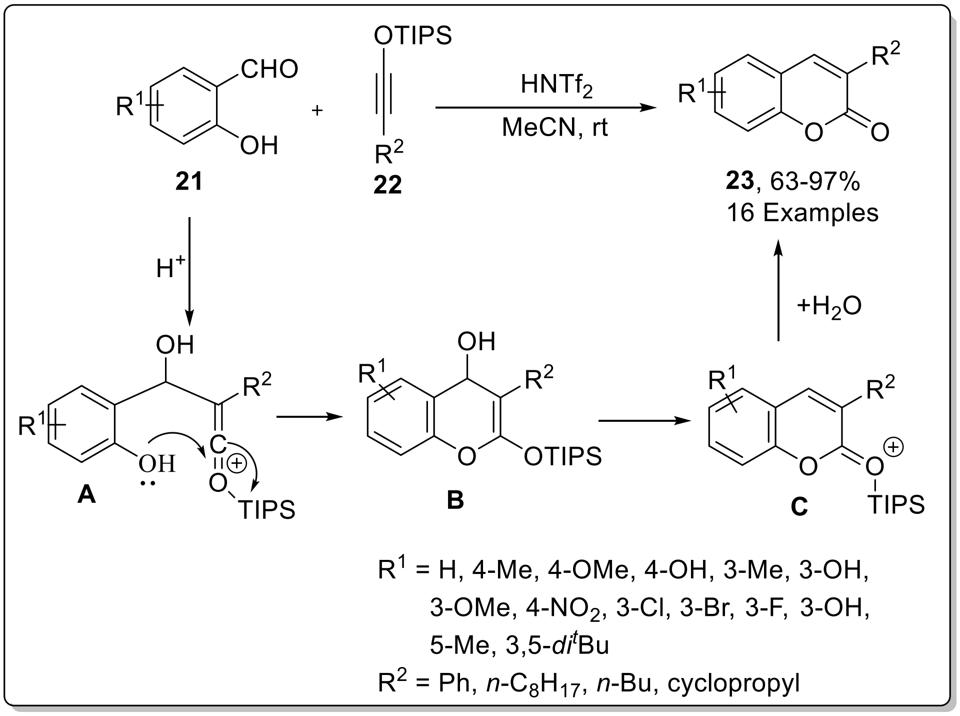
Scheme 4. Plausible mechanism for the synthesis of coumarin core **13**.

In the next year, Hammoodi carried out the synthesis of coumarin derivatives **20**(**a**-**d**) by treating salicylaldehyde **16** with malonic acid **17** via thermosonication-mediated Knoevenagel reaction, utilizing the catalytic role of glacial acetic acid. The resulting coumarin-3-carboxylic acid **18** was made to react with substituted phenols **19** to attain the targeted esterified coumarin derivatives in 56-88% yield (Scheme 5).[39] The synthesized coumarin derivatives **20**(**a**-**d**) were subjected to cancer cell lines to determine their inhibition potential in comparison to standard. Among the synthesized derivatives, 2-chloro substituted coumarin derivative exhibited the safe profile, thereby signaling its potential usage towards the development of anti-tumor agents.

Hui and Jianwei introduced a new approach for the acid catalyzed synthesis of coumarins from siloxyalkynes and salicylaldehydes. In the presence of the superior $HNTf_2$ catalyst (bis(trifluoromethane)sulfonimide), a wide range of coumarins **23** were efficiently synthesized by reacting substituted aromatic aldehyde **21** with siloxy alkyne **22**. Siloxy alkyne was used as the model alkyne, which could be easily prepared from 1-hexyne in a single step (Scheme 6).[40] The reaction between salicylaldehydes and siloxyalkynes can be regarded as [4+2] cyclization. Among them, the Brønsted acid $HNTf_2$ exhibited the best performance (40% yield). Interestingly, the use of MeCN dramatically improved the yield of the desired coumarin **23** up to 93%. The proposed mechanism consists of acid-catalyzed activation of salicylaldehydes followed by addition to siloxy alkyne resulting in silyl ketenium moiety **A**. Next, silyl ketene acetal **B** was synthesized from silyl ketenium **A** via intramolecular cyclization. Further, silyl ketene acetal **B** furnishes **C** via subsequent protonation and dehydration followed by addition of water molecule to give target molecule **23** (Scheme 6).

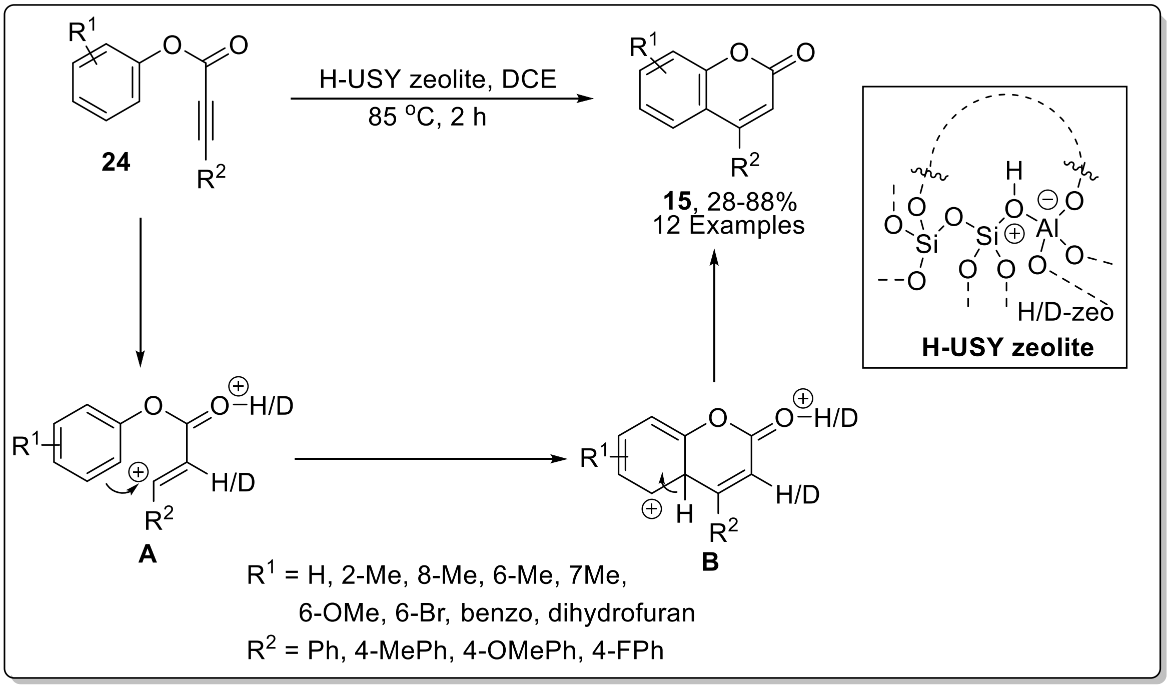


Scheme 5. Synthesis of coumarin derivatives **20**(**a**-**d**).



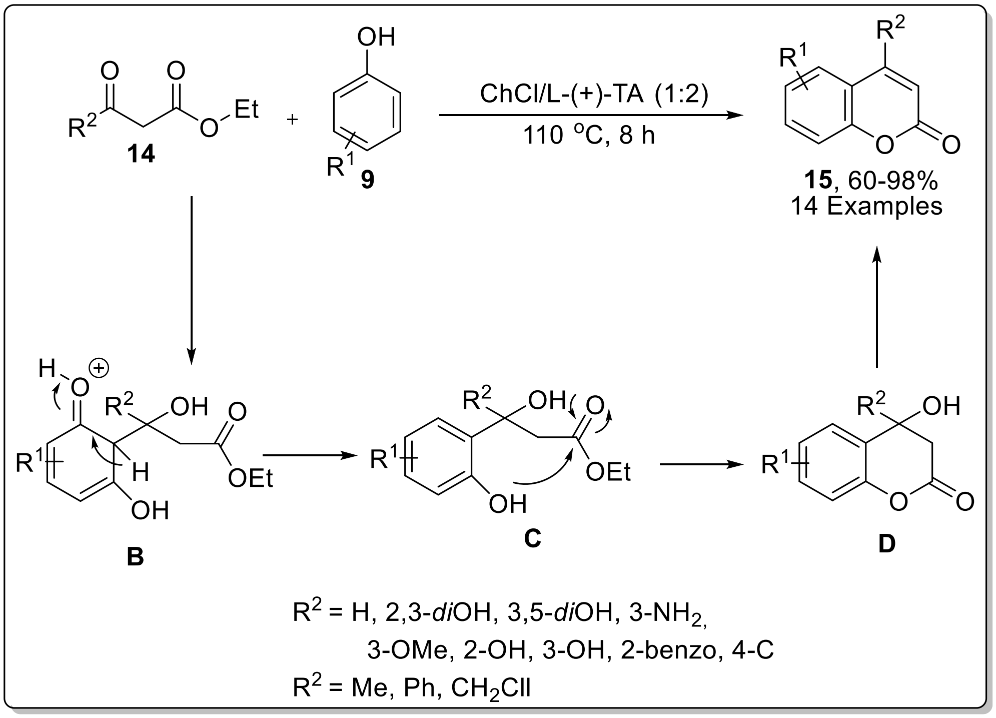
Scheme 6. Synthetic approach for coumarin synthesis **23** by using $HNTf_2$ catalyst.

2.1.2. Acidic zeolites-mediated synthesis of coumarin. Zeolites, with their distinct structural attributes and tunable acidic properties, emerged as efficient catalyst for the construction of diverse organic frameworks. In this regard, Zaitceva *et al*. in 2020 introduced a novel acid catalyzed synthetic protocol for synthesis of coumarin core by employing acidic zeolites (H-USY zeolite) (ultrastable Y). Among zeolites, faujasites efficiently helps the intramolecular cyclization of phenyl propynoates **24**, resulting in substituted coumarins **15** (Scheme 7).[41] Zeolites consist of large surface to volume ratio because of cage-like pores and were found greener and efficient substitute to acidic medium. Interestingly, 3-phenylpropynoates having electron-rich group and the ester moiety with electron-poor substituents afforded the corresponding coumarins in excellent yields (up to 88%). The mechanism of coumarin synthesis involves the deprotonation of phenyl propynoates **26** with acidic zeolite which provides intermediate **A**. The cyclization of intermediate **A** leads to cyclized product **B**, furnishing coumarin core **15**.



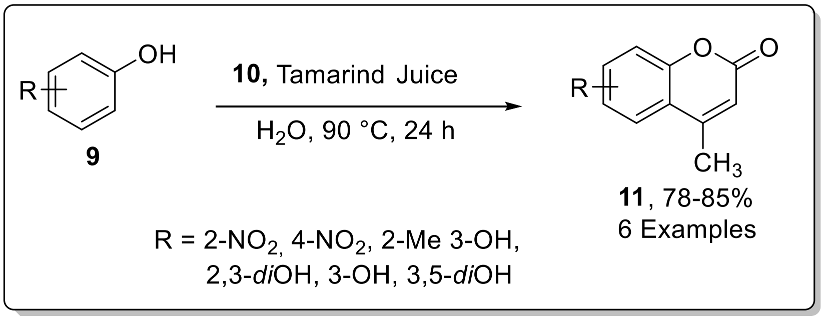
Scheme 7: Zeolite-mediated synthesis of coumarin **15**.

2.1.3. Acid-catalyzed DES-mediated coumarin synthesis. DES (deep eutectic solvents) are ionic fluids composed of more than one substance having ability of self-association to make a eutectic mixture. Eutectic mixture has melting point lower than melting points of each substance and mostly exist as liquid at temperature lower than 150 °C.[42] Herein, Ishfaq and Rashid reported an efficient and green synthetic strategy for the construction of functionalized coumarins via the Pechmann condensation. Pechmann condensation reaction was optimized by using an inexpensive, reusable and biodegradable deep eutectic solvent (DES). The catalyst comprises of *L*-(+)-tartaric acid and choline chloride in a ratio of 2:1. 98% yield of functionalized coumarin **15** was obtained by reacting β-keto esters **14** and substituted phenols **9** at 110 °C within 10 min. in the presence of this catalyst (Scheme 8).[43] As per the mechanism, DES-mediated activation of carbonyl group of ethyl acetoacetate took place, which was then attacked by resorcinol provides intermediate **A**. Next, the synthesized intermediate aromatized to generate another intermediate **B** followed by the attack of phenolic group on the carbonyl carbon in conjugation with dehydration, resulted in the synthesis of 7-hydroxy-4-methyl coumarin **15** (Scheme 8). The results demonstrated the dual character of DES (solvent and catalyst) very well. Moreover, no remarkable drop down in product yield was observed even after reuse of catalyst for four time.



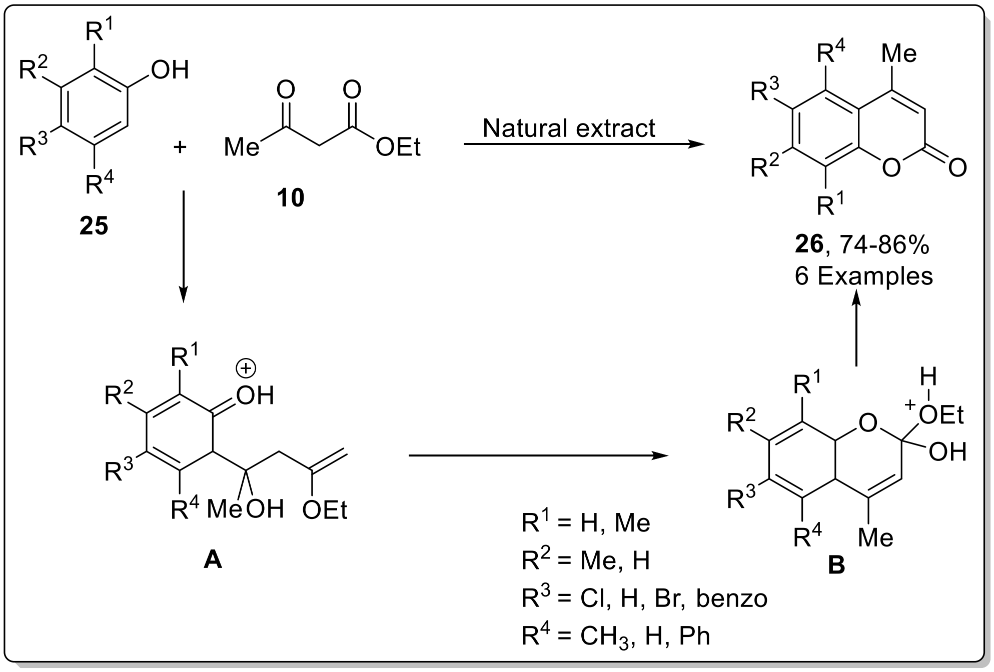
Scheme 8. Coumarin synthesis in the presence of DES.

2.1.4. Natural acids-mediated synthesis of coumarin. Now a days synthetic chemists are focusing their attention towards the development of non-toxic and eco-friendly protocols for synthesis of medicinally important heterocyclic molecules.[44] The use of waste waters from industrial and agricultural processes, vegetable juices and fruit juices (being non-toxic, easily available and environmentally benign) have become natural catalytic choices for chemists towards the synthesis of heterocyclic compounds.[45] In this regard, Navale *et al*. recently established a green and efficient synthetic route for synthesis of substituted coumarin **11** by using a natural extract, tamarind juice (Scheme 9).[46] The reactions of various phenols **9** with ethyl acetoacetate (EAA) **10** was carried out at 90 °C in aqueous condition using the catalytic role of tamarind juice. Optimum catalytic concentration for Pechmann reaction was found to be 20 mol% tamarind juice. Eco-friendly, economical, good yields (78-85%) and easy work up are prominent merits of this approach.



Scheme 9. Synthesis of coumarin **11** by using natural product.

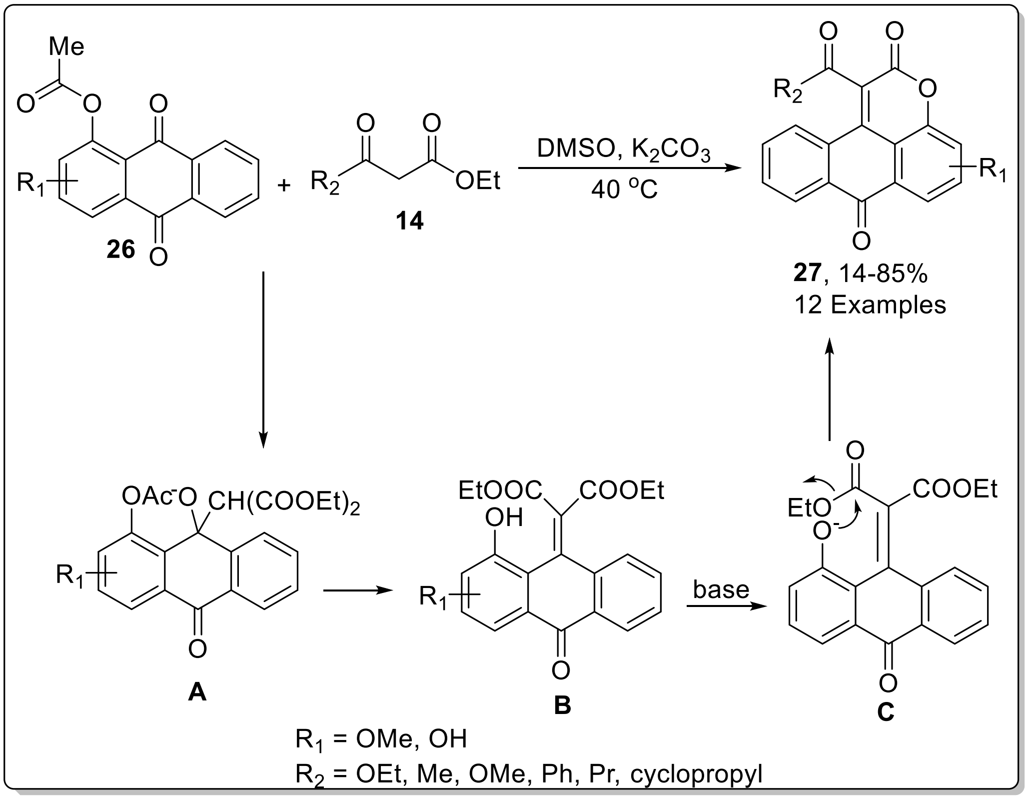
Gulati *et al*. introduced bio catalysts (*Citrus limon* L. juice, *Vitis vinifera* L. juice and banana peels extract) for the preparation of substituted coumarins **25** from substituted phenols **24** and ethyl acetoacetate **10**. *Citrus* *limon* L. Juice comprises ascorbic acid as well as citrus acid while tartaric acid is present in *Vitis vinifera* L. Juice. Research work of Gulati *et al*. revealed that acidic media present in natural extracts of fruits could be used as catalyst to obtain good yields (74-86%) of coumarin derivatives. The significant merits of the developed protocol involved the utilization of neat conditions, non-virulent side products, easily accessible precursors and facile reaction conditions (Scheme 10).[47] The plausible mechanism of this reaction involved the formation of ring via transesterification followed by nucleophilic addition of substituted phenols which led to the synthesis of targeted coumarin scaffolds **26** upon elimination of water. Synthesized coumarin compounds were determined to exhibit a variety of pharmacological activities such as herbicidal (against *Raphanus sativus* L.), anti-fungal (against *R. Solani* and *C. gloeosporioides*) and anti-bacterial activities (against *E. cartovora* and *X. citri*). Coumarin derivatives substituted with chloro, bromo and methyl groups on aromatic ring illustrated significantly potent pharmaceutical activities.



Scheme 10. Coumarin synthesis in the presence of biocatalyst.

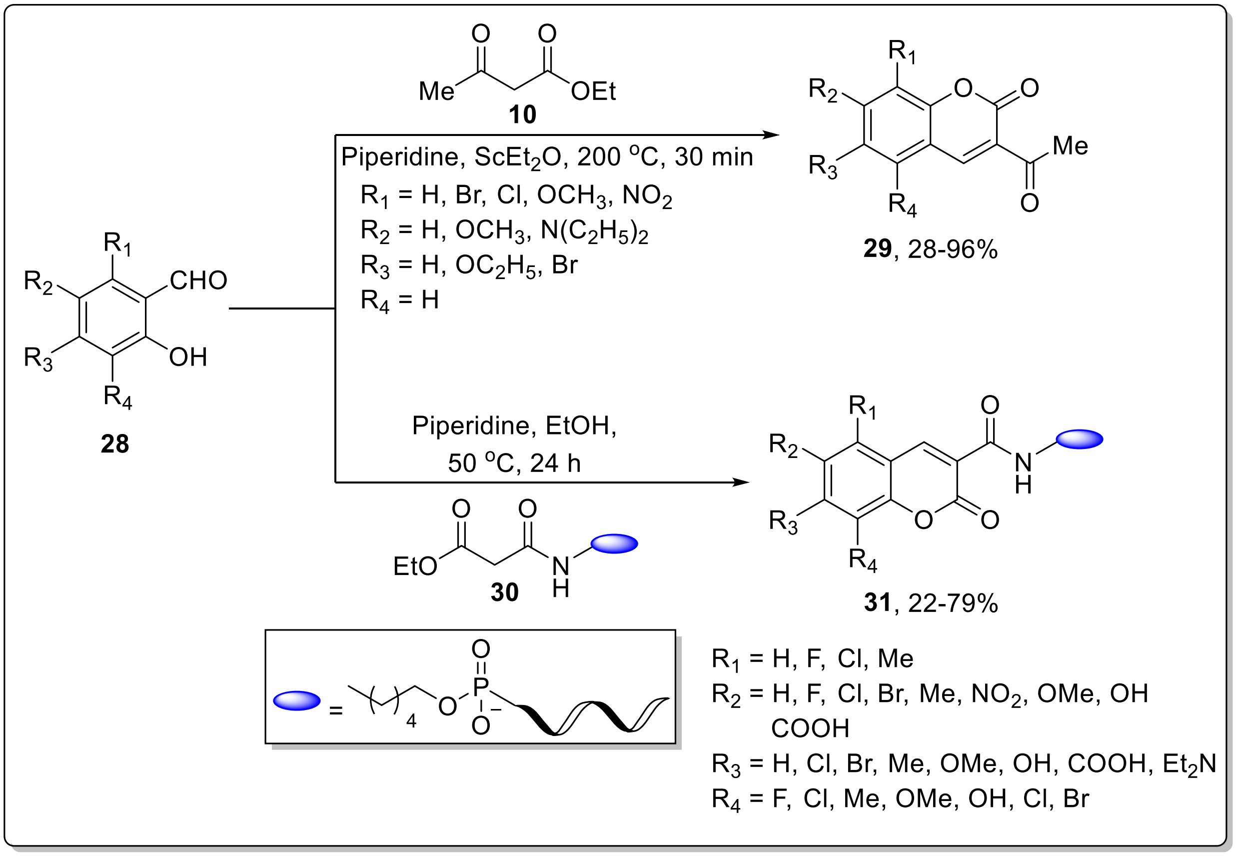
2.2. Base involving catalytic systems for the synthesis of coumarins

2.2.1. K_2CO_3-mediated synthesis of coumarin. Several organic transformations involve the catalytic role of several bases, thereby resulting in facile generation of targeted molecules.[44, 48] Tan *et al*. developed one-pot synthetic route for derivatives of anthrone lactone by Knovenagel condensation utilizing potassium carbonate. Generality and scope of this one pot protocol were explored by reacting various dicarbonyl substrates **14** with 1-acetyloxyanthraquinone series **26** in basic media while lower to good yields (23-85%) of anthrone lactones **27** were obtained. It was inferred that product yields depend upon the nature of substitution. This strategy can be useful tool for the synthesis of core structure of aspergiolide that is a medicinally important marine natural compound (Scheme 11).[49] The proposed mechanism for the synthesis of 9-anthrone lactone derivatives include the base-mediated generation of anion from diethyl malonate. Next, the carbanion attack on position 9 of anthraquinone followed by migration and elimination of acetyl group provides **B**. Further, base-mediated ionization of **B** yields **C** which upon intramolecular nucleophilic addition with ester group and removal of ethoxy group results in final compound **27**.



Scheme 11: K_2CO_3-mediated synthesis of coumarin.

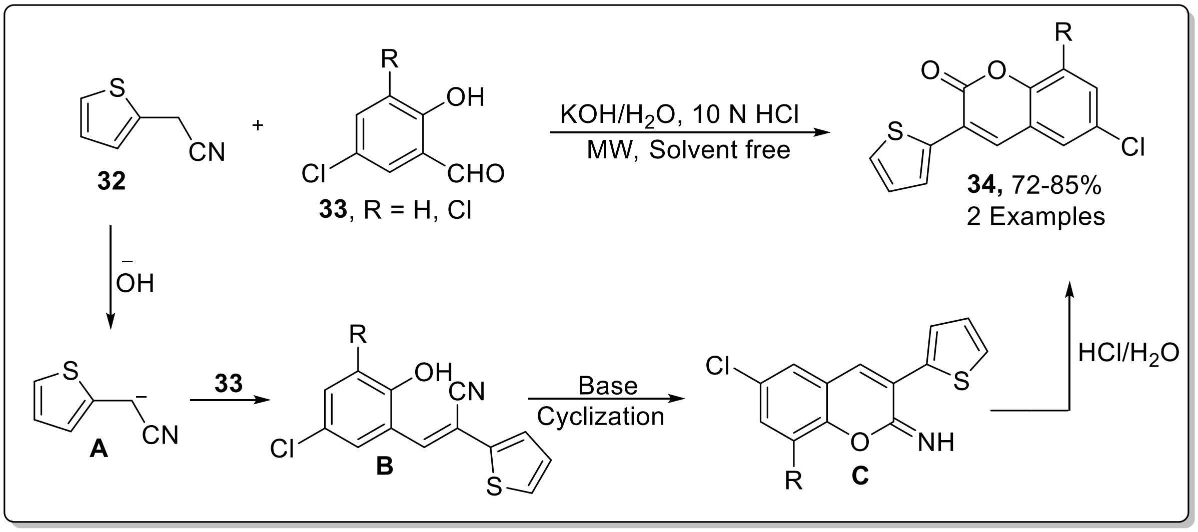
2.2.2. Pyridine-mediated synthesis of coumarin. Özsırkıntı *et al.* developed an efficient and green methodology for constructing 3-acetyl and 4-methyl coumarins in good yields. In this regard, 3-acetyl coumarins **29** were synthesized in 28-96% yield range, by reacting ethyl acetoacetate **10** and substituted salicylaldehydes **28** with the addition of few drops of piperidine in supercritical diethyl ether. The method effectively provided coumarin derivatives possessing photophysical and biological significance via a novel and promising methodology. The developed approach was also employed for the synthesis of β-methylumbelliferone in high yield (Scheme 12).[50] The development of DNA-encoded libraries (DELs) has become a tremendous approach for drug discovery. The synthesis was carried out via Knoevenagel condensation to synthesize coumarin conjugated oligonucleotide library. The synthesis was performed by reacting NHS-ester conjugated DNA **30** with substituted salicylaldehydes **28** in the presence of piperidine in ethanol. The final products **31** were obtained in low to high (22-79%) yields. The developed protocol was further applied to synthesize a model DNA hairpin consisting of coumarin. The method exhibited a wide substrate scope with substitutions being introduced to 5-, 6-, 7- and 8- position of coumarin except hydroxy group (Scheme 12).[51]



Scheme 12. Coumarin synthesis in the presence of piperidine.

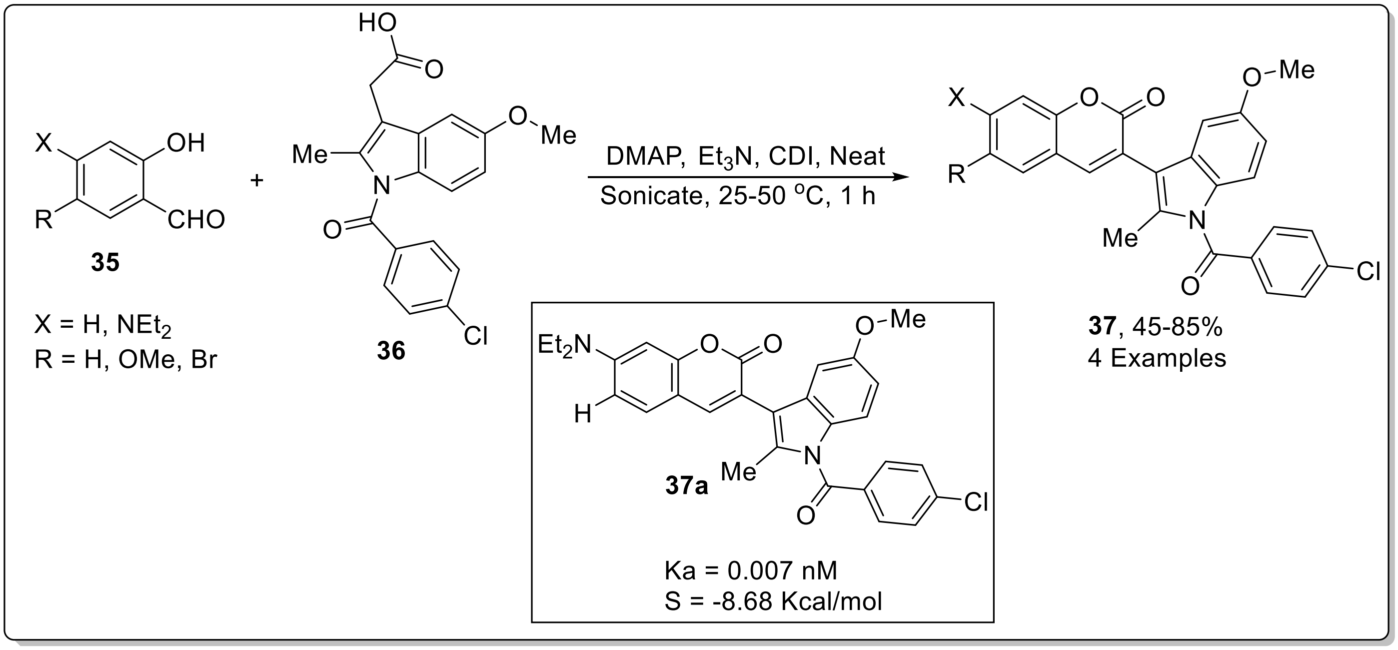
2.2.3. Base-catalyzed Microwaves-assisted synthesis of coumarin. Microwave irradiation and sonication has gained significant admiration in the past few years as a powerful tool for efficient and rapid synthesis of a variety of organic compounds due to selective absorption of electromagnetic radiation by reacting molecules.[52] Owing to increased reaction rate and improved product yields, radiation-assisted organic synthesis has become successful tool for the formation of carbon-heteroatom bonds.[53, 54]

In this regard Kumar *et al*. reported a synthetic protocol for the solvochromism-based derivatives of thiophene-coumarin known as CTFTs (coumarin thiophen fluorescent tags) using microwave radiation and solvent-free approach. The CTFTs were synthesized by treating substituted salicylaldehydes **33** with the 2-(thiophen-2-yl) acetonitrile **32** under microwave irradiation conditions by using potassium hydroxide as catalyst. As a result, CTFTs **34** were furnished in good to excellent yields i.e., 72-85%. These CTFTs exhibit remarkable solvochromatic behavior upon dissolution in polar aprotic and protic solvents. The resulting greenish blue and cyan blue organic fluorophores can be utilized in electroluminescent diodes as emitting materials. By employing powder dusting protocol, CTFTs can be utilized for the visualization of LFPs (latent fingerprint applications). The obtained results indicated that the CTFTs can be utilized as remarkable small organic fluorescent tags for LFPs and flat-panel displays (Scheme 13).[55]



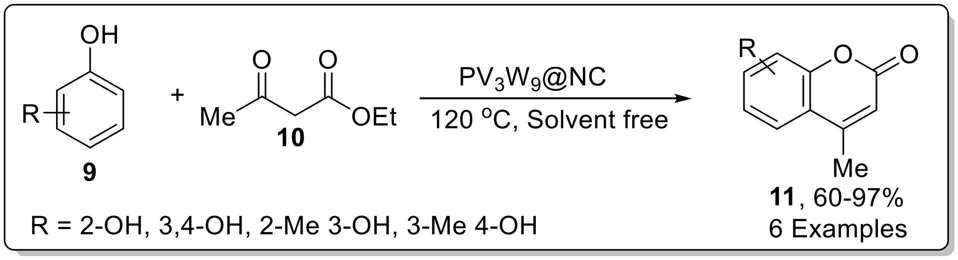
Scheme 13. Synthesis of coumarin derivatives under microwave-irradiation.

2.2.4. Base-catalyzed Ultrasonic-assisted synthesis of coumarin. An ultrasonic-assisted, facile synthesis of substituted coumarin-indomethacin hybrids (Coum-IDM) was carried out by Wet-osot *et al*. in 2021 (Scheme 14).[56] The rapid dehydrative cyclization reaction between substituted salicylaldehydes **35** and CDI-activated indomethacin **36** in the presence of dimethyl aminopyridine (DMAP), triethyl amine (Et₃N) and neat conditions at 25-50 °C sonication for 1 hour furnished coumarin-indomethacin derivatives (Coum-IDM) **37** in 45-85% yields. The synthesized derivatives were subjected to in-vitro evaluation for the presence of COX-2 against three cancer cell lines and two normal cell lines followed by in-silico study i.e., molecular docking. Among the synthesized derivatives, the compound **37a** exhibited the highest binding affinity of -8.68 Kcal/mol, thereby making it a potential inhibitor of COX-2. The analysis of photophysical properties of synthesized compounds was also carried out indicating the potential of **37a** to act as a good fluorescent probe for monitoring the inflammation process.



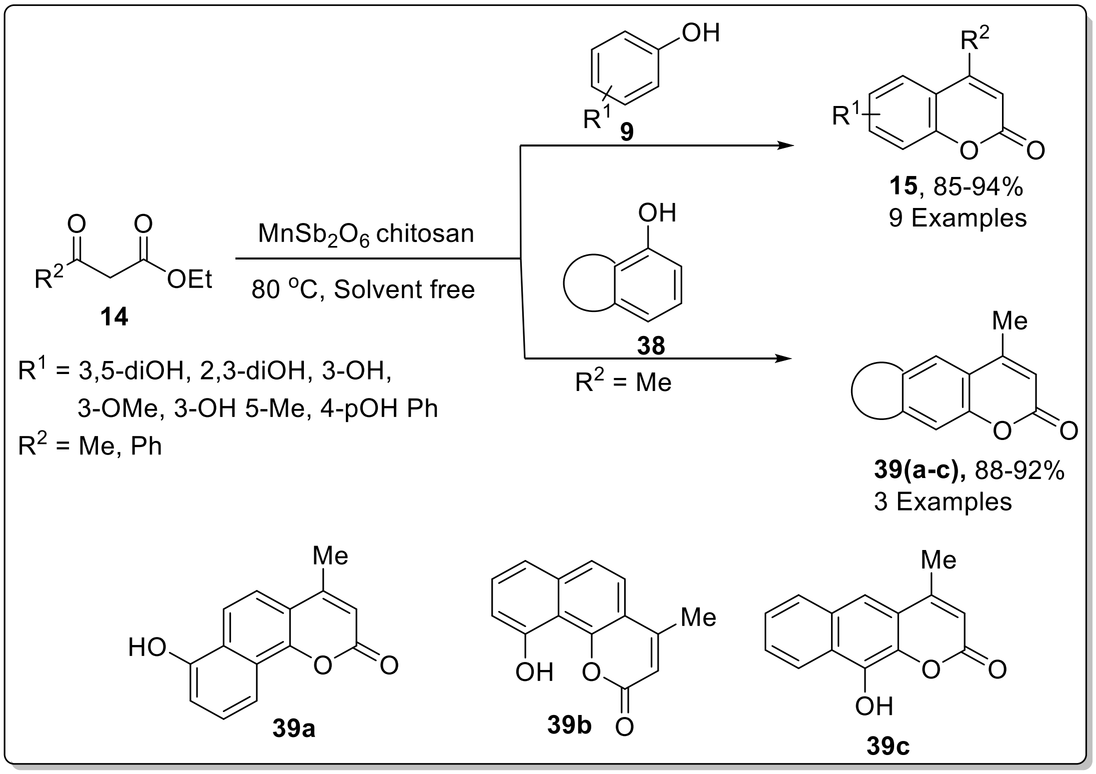
Scheme 14. Synthetic protocol for substituted coumarin by using ultrasonic waves.

2.3. Nanoparticles-based catalytic systems for coumarin synthesis. Metal nanoparticles scattered over carbon material and on the surface of oxides lead to the generation of several efficient catalysts.[57] Nanoparticles based catalytic systems are generally preferred due to their increased surface area, facile recovery and reusability.[58] In recent times, utilization of nanoparticles based catalytic systems has gained significant importance in several organic reactions.[59] Ramalingam *et al*. introduced solvent-free reaction for the synthesis of coumarin by using trivanado phosphotungstate loaded *N*-doped carbon (PV_3W_9@NC) catalyst. The methyl octyl imidazolium trivanado phosphotungstate (a hybrid material) was utilized as precursor to prepare this catalyst by hydrothermal method. It was found that PV_3W_9@NC showed excellent catalytic activities towards Pechmann condensation for coumarin synthesis. (Scheme 15).[60] In this solvent free synthetic strategy, various substituted phenols **9** were made to react with ethylacetoacetate **10** to obtain respective coumarin derivatives **11** in 60-97% yield range at 120 °C.



Scheme 15. Synthesis of coumarin derivatives in the presence of PV_3W_9@NC.

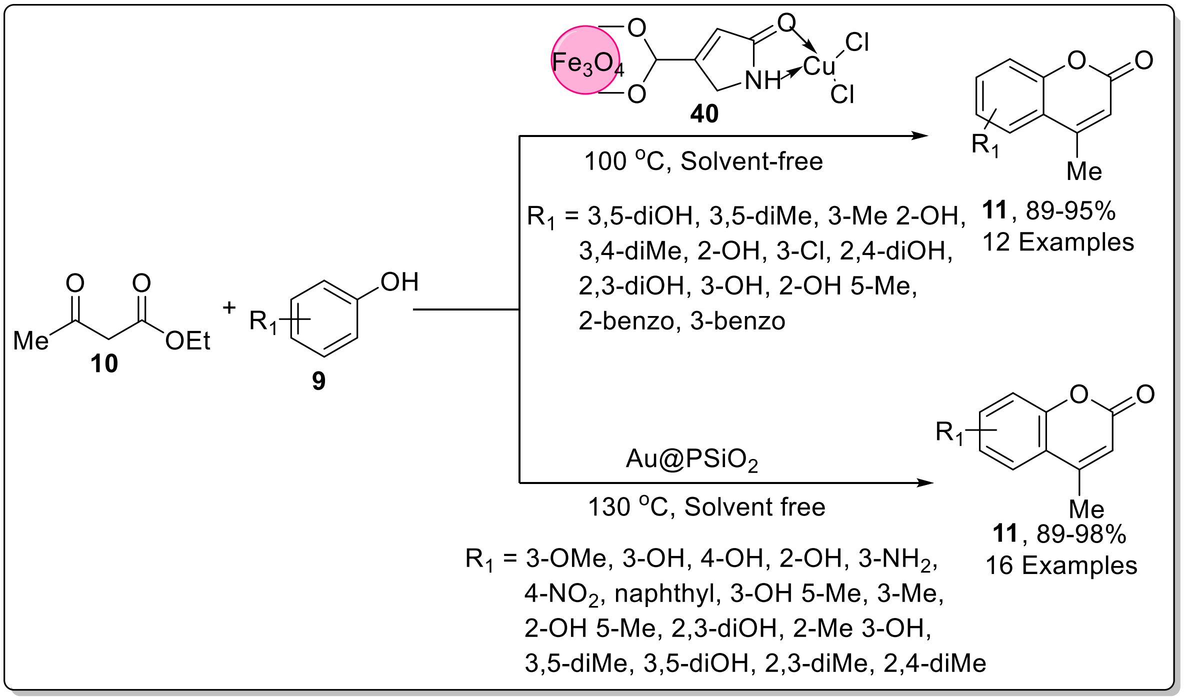
Bahramnezhad *et al*. designed $MnSb_2O_6$-chitosan nanocomposites as efficient catalyst for the solvent-free synthesis of coumarin through one pot MCR between enolizable ester **14** and various phenols **9**/**38**. Good yield of desired coumarins **15** and **39(a-c)**, short reaction time, simple work-up and eco-friendly factors are few merits of the employed methodology (Scheme 16).[61] In their synthetic methodology, ethyl acetoacetate **14** was subjected to react with phloroglucinol. The effect of different amount of catalyst, β-keto esters and various solvents has been studied. Poor yield was obtained in the presence of solvent like DMSO and water while good to excellent yields (88% to 94%) were obtained in solvent-free conditions. Research group of Ghazanfari evaluated the anti-bacterial activity of the products, and the coumarin derivatives showed significant anti-bacterial activities against *Escherichia coli* and *Staphylococcus aureus.*



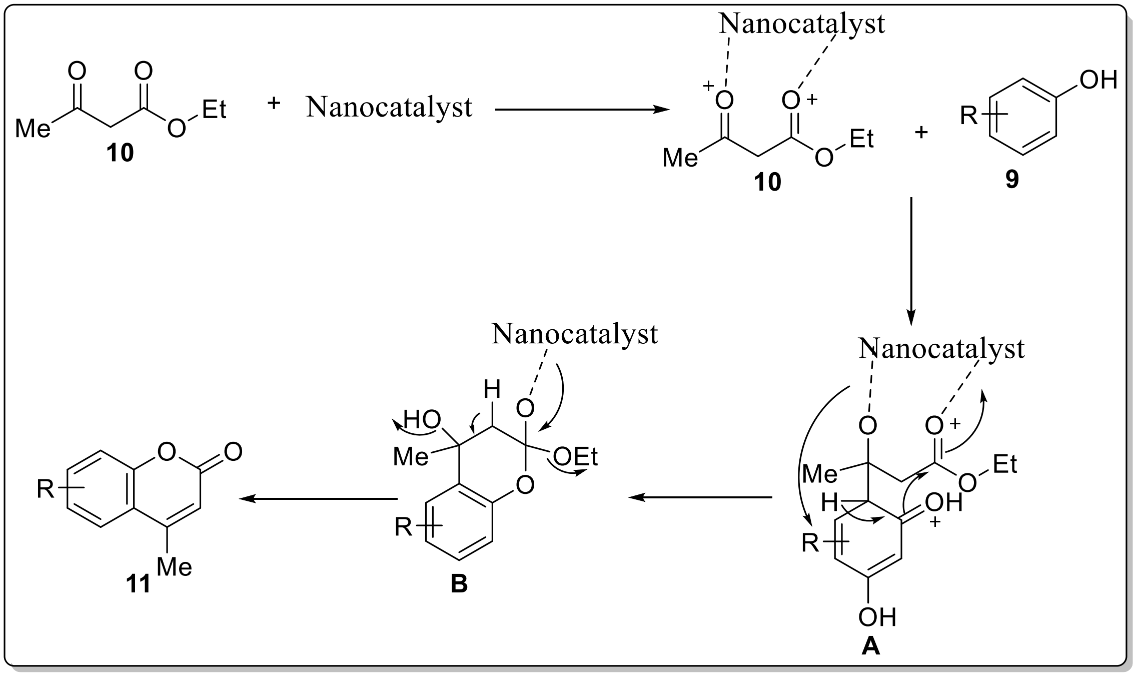
Scheme 16. Synthetic approach for coumarin by using $MnSb_2O_6$-chitosan nanocomposites.

Yuan and Mohammadnia reported the novel solid state synthetic strategy for synthesis of substituted coumarins via Pechmann condensation. In this regard, a magnetic nano catalyst (Cu(II)-OHPC-Fe_3O_4) **40** was developed that was a Fe_3O_4 nanoparticles based compound incorporated with 5-oxo-4,5-dihydro-pyrrole-3-carboxylic acid organic moiety. To obtain the desired coumarin **11**, one pot reaction between ethyl acetoacetate **10** and substituted phenols **9** was conducted by using the developed heterogenous nanocatalyst **40** (Scheme 17).[62] The obtained results revealed the green nature of (Cu(II)-OHPC-Fe_3O_4) catalyst which can be reused without much loss of its activity, thereby resulting in remarkable yields (89-95%) of target molecules within short duration. Facile availability, increased surface area, enhanced thermal and chemical stability are some other merits of the developed heterogeneous nanocatalyst involving synthetic approach.

Similarly, in 2020, Yaghoobi and co-workers worked on the synthesis of a new heterogenous Au based nano catalyst supported on porous SiO_2. In this context, a gold supported nanoparticles was employed in Pechman reaction by treating different phenols **9** with ethyl acetoacetate **10**. It was inferred that excellent yield (up to 98%) of substituted coumarin **11** was obtained by using Au-catalyst supported on porous SiO_2 (Au@pSiO_2) at 130 °C under solvent free conditions (Scheme 17).[63] The employed protocol was determined to be significantly efficacious in terms of low pollution, catalytic recyclability, non-toxic and facile operation. Other merits of this reaction include rapid access to products with simple workup. The proposed mechanism for the employed protocol involved the activation of ethyl acetoacetate by Au@pSiO_2 catalyst followed by the nucleophilic attack of phenols. The two reactants were joined together via transesterification and concurrent removal of water to synthesize coumarin scaffold (Scheme 18).

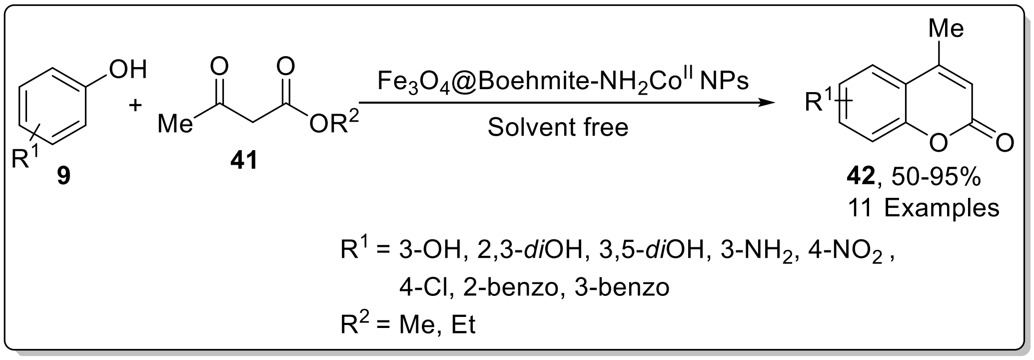


Scheme 17. Synthesis of coumarin nucleus in the presence of nanoparticles of Cu(II)-OHPC-Fe_3O_4.

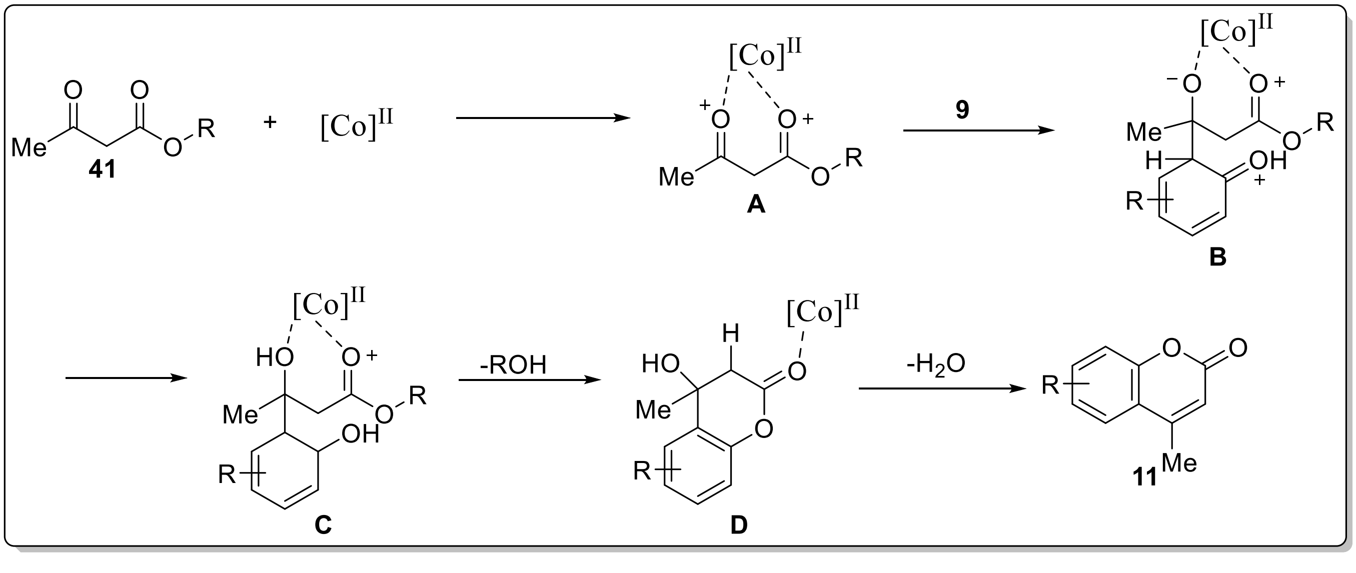


Scheme 18. Mechanistic details for the synthesis of coumarin nucleus in the presence of nanoparticles,

A novel solventless synthetic strategy for attaining substituted coumarins via Fe_3O_4@Boehmite-NH_2-Co^{II} nanoparticles (Co^{II} supported on aminated iron oxide @ Boehmite NPs) was carried out by Somayeh *et al*. In their synthetic methodology, various substituted phenols **9** were made to react with β-keto esters **41** to furnish coumarin derivatives **11** in the presence of non-toxic, easily available and inexpensive nanocatalyst (Scheme 19).[64] To study the effect of solvent on the reaction time and yield, a screening operation was conducted with different solvents such as MeOH, EtOH, DMF, H_2O and MeCN. The screening results revealed that the reaction resulted in efficient yield of targeted coumarin derivative in solvent-free conditions. Additionally, 66 mol% of Fe_3O_4@Boehmite-NH_2-Co^{II} nano catalyst afforded the excellent yield (up to 95%) of targeted coumarin derivatives by employing phenolic precursor substituted with electron donating groups. The developed catalyst was observed to retain the catalytic efficacy even in the 6th run. The plausible mechanism of the developed protocol involved the activation of keto functionality of ethyl acetoacetate by the Fe_3O_4@Boehmite-NH_2-Co^{II} NPs catalyst proceeded by nucleophilic attack via OH of substituted phenols **9** which resulted in intermediate **B**. The intermediate **B** underwent aromatization and transesterification which resulted in ring closure followed by subsequent elimination of alcohol, giving rise to intermediate **D**. The intermediate **D** then ultimately led towards the synthesis of coumarin heterocycles **11** via elimination of water (Scheme 20).



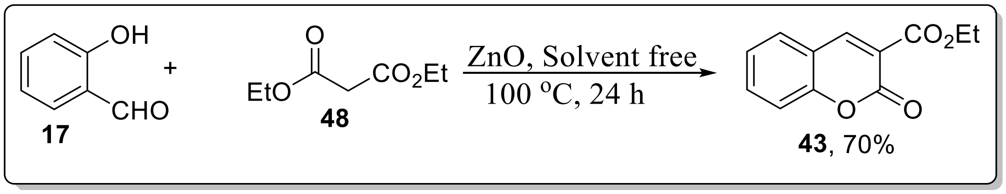
Scheme 19. Synthetic approach for coumarin by using iron-based nanoparticles.



Scheme 20. Synthetic approach for coumarin by using iron-based nanoparticles.

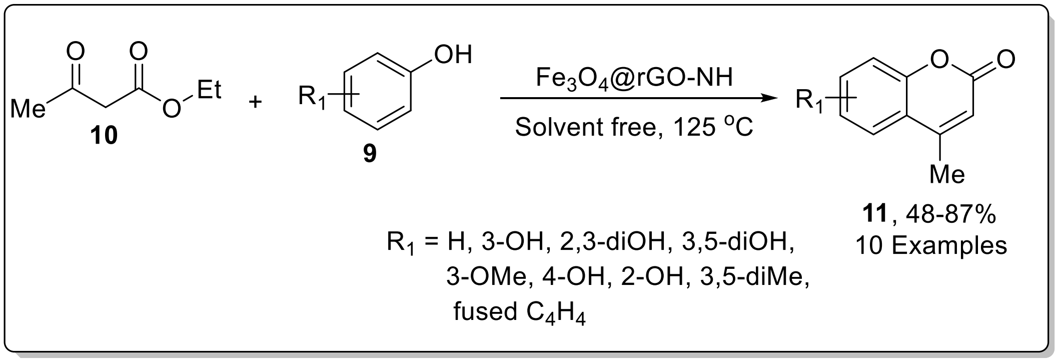
In several chemical industries, heterogeneous catalysts are preferably employed due to their facile isolation and recyclability. Shakil and co-workers reported the synthesis of coumarin scaffolds by employing the catalytic role of ZnO catalyst via a scalable method. Research group of Steven synthesized different morphologies of ZnO by changing solvents under solvothermal method. The synthesis of ethyl 2-oxo-2*H*-

chromen-3-carboxylate (coumarin) **43** was accomplished from the treatment of *o*-hydroxybenzaldehyde **17** and diethyl malonate **48** via the Knoevenagel condensation reaction in the presence of different morphologies of ZnO (Scheme 21).[65] It was inferred that the best yield of coumarin scaffold (70%) was obtained by using 8.2 mg of ZnO (synthesized by methanol). The enhanced catalytic activity of ZnO in methanol was attributed to its moderate basicity and textured properties (enhanced surface area, pore size and volume).

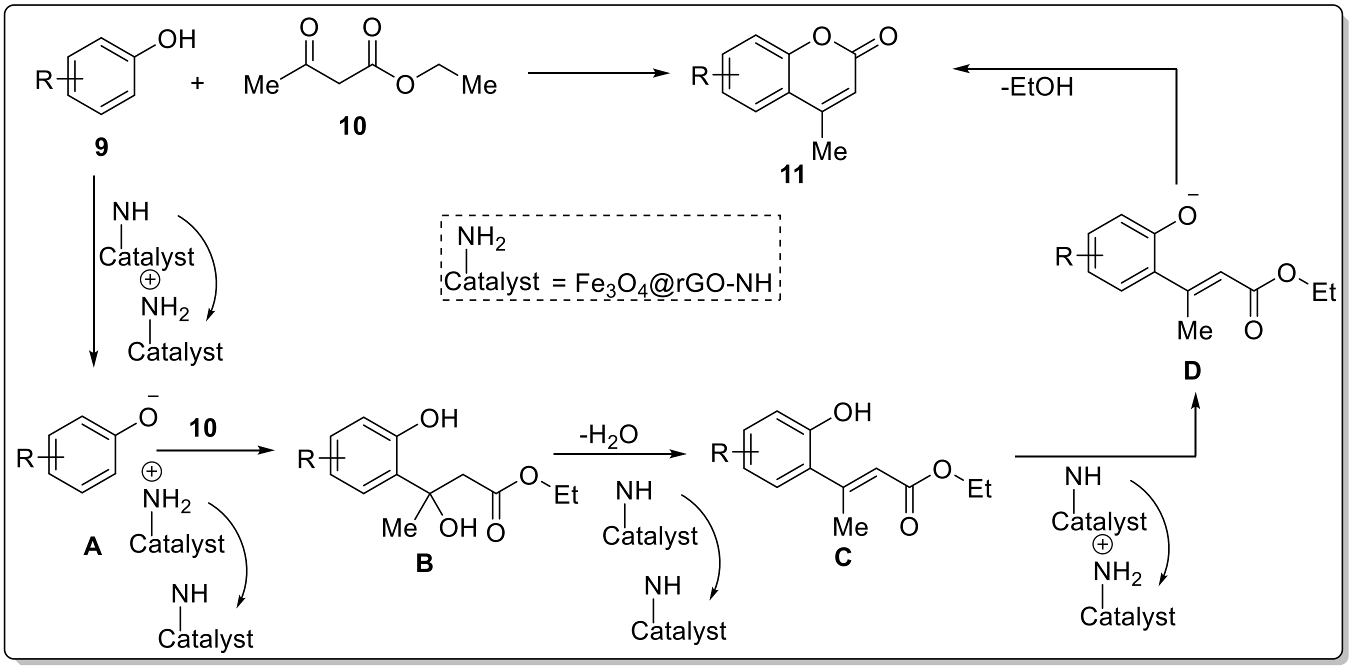


Scheme 21. Coumarin synthesis using ZnO.

In 2023, Rezaei-Seresht *et al*. reported the preparation of heterogeneous catalyst constituting reduced graphene oxide functionalized with piperazine adorned with iron oxide nanoparticles (Fe_3O_4@rGO-NH). The synthesized magnetic heterogeneous catalyst was then employed in the Pechmann reaction for the synthesis of coumarin scaffolds. In this regard, substituted phenols **9** were made to react with ethyl acetoacetate **10** in the presence of synthesized Fe_3O_4@rGO-NH magnetic catalyst under neat conditions to attain coumarin derivatives **11** in 48-87% yield range (Scheme 22).[66] Owing to the magnetic nature of catalyst, it was easily separable to determine its reusability within the Pechmann reaction. The plausible mechanism of this reaction involved a chain of proton addition and deprotonation steps involving the catalytic role of prepared catalyst or its conjugate acid in each step, via H^+ transfer process (Scheme 23).



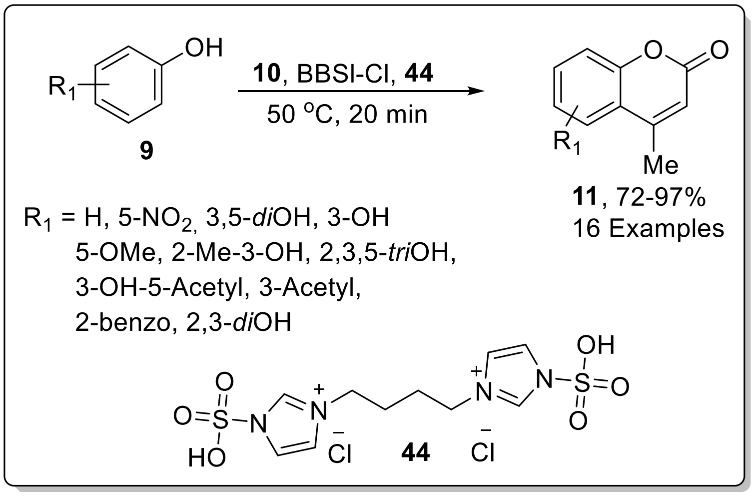
Scheme 22. Synthetic approach for coumarin by using iron-based nanoparticles.



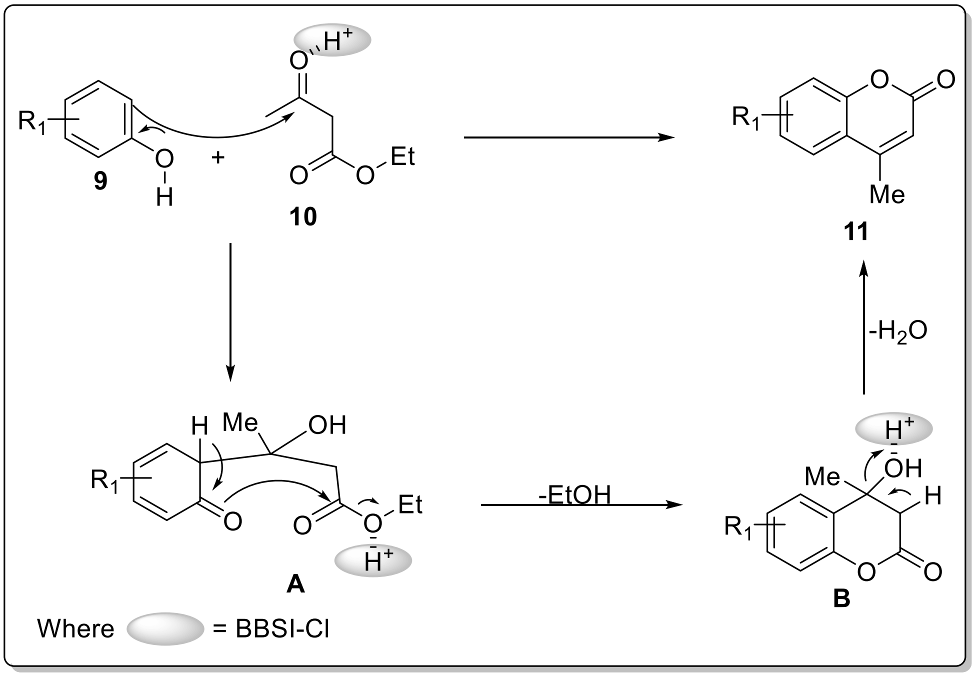
Scheme 23. Mechanism for the synthetic approach for coumarin by using iron-based nanoparticles.

2.4. Ionic liquids-mediated synthesis of coumarins.

Ionic liquids are compounds composed of ions and have melting points less than 100 ºC. In addition to acidic and basic mediums, ionic liquids being used as electrolytes are also considered as powerful solvents for organic reactions. Owing to special properties of ionic liquids such as their good solvating ability, non-inflammability, negligible vapor pressure, environment friendly medium, easy recycling and high thermal stability, these have attained the attention of organic chemists. As ionic liquids act as a reaction medium and catalyst with high activity that's why ionic liquids have become an important tool in modern chemistry. Khaligh *et al*. used an ionic liquid catalyst which showed solvent-catalyst dual activity. In this regard, various substituted coumarin **11** were efficiently synthesized by reacting the substituted phenols **9** with ethyl acetoacetate **10** in the presence of 1,10-butylenebis(3-sulfo-3*H*-imidazol-1-ium) chloride (BBSI-Cl) **44**. At room temperature, without using catalyst, reaction between ethyl acetoacetate **10** and 5-methoxy-benzene-1,3-diol yielded coumarin in traces. However, addition of BBSI-Cl as a catalyst at high temperature of 50 ºC leads to augmented yield of up to 97% (Scheme 24).[67] Aforesaid catalyst is a recyclable and show good catalytic activity even after 4 runs. Moreover, the use of ionic liquids as catalyst also decreases the reaction time providing high yields. The proposed mechanism involved the reaction of ethyl acetoacetate **10** and **9** in the presence of BBSI-Cl, providing intermediate **A** and **B** which underwent rearrangement to form coumarin core **11** (Scheme 25).

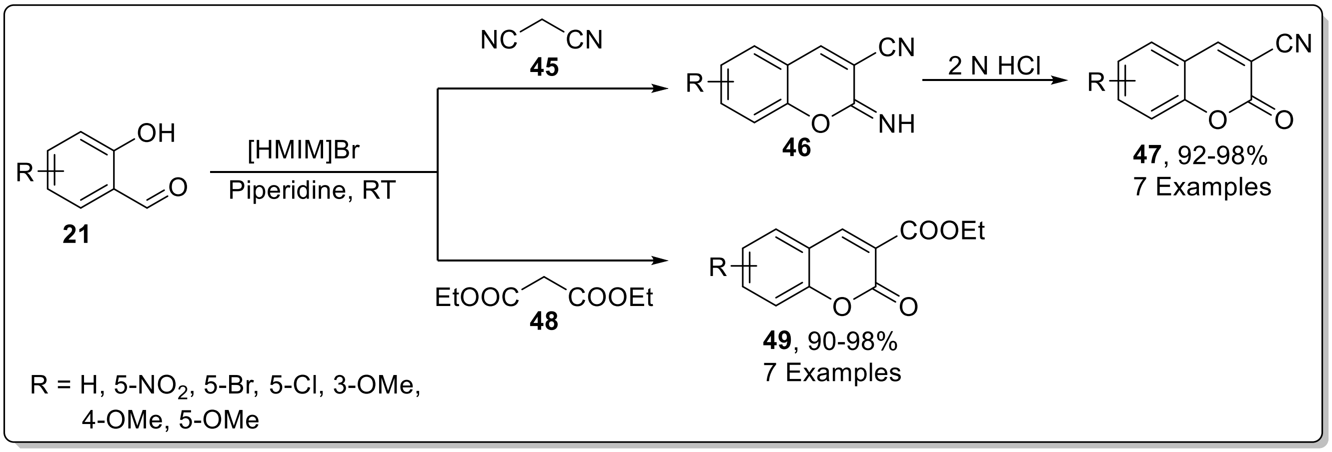


Scheme 24. Coumarin synthesis using ionic liquid.



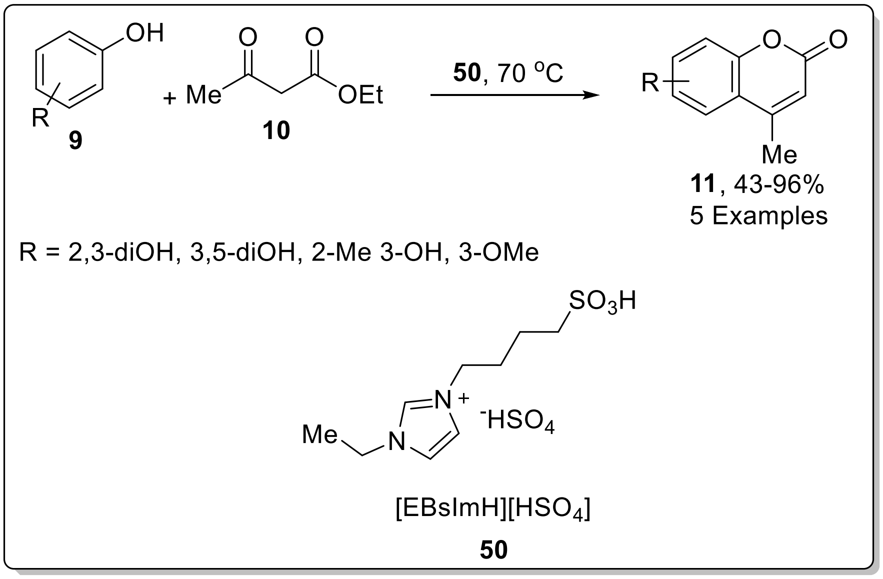
Scheme 25 BBSI-Cl mediated synthesis of coumarin core.

Keeping in view the merits of liquid ionic medium, Dinparast *et al*. in 2019, introduced a novel ionic liquid catalyst to mediate the synthesis of substituted coumarins **47** and **49** with excellent yields (upto 98%) using a one-pot protocol under green conditions with short reaction time. Using 1-hexyl-3-methylimidazolium bromide [[HMIM]Br] as a reaction medium and a substitute for common toxic solvents, reaction conditions were optimized at different temperature conditions, whereby room temperature was selected as optimum temperature (Scheme 26).[68] 3-Cyano coumarin **47** and 3-diethyl carboxylate coumarin **49** were obtained by reacting various substituted hydroxy aldehydes **21** with malononitrile **45** and diethylmalonate **48**, respectively**.** Interestingly, in the presence of the above-mentioned ionic liquid, the reaction proceeded very rapidly at room temperature. Inhibitory activities of coumarin derivatives against acetylcholinesterase and tyrosinase were also assessed which were found moderate as compared to standard drugs.



Scheme 26. Synthetic strategy for coumarin derivatives using ionic liquid.

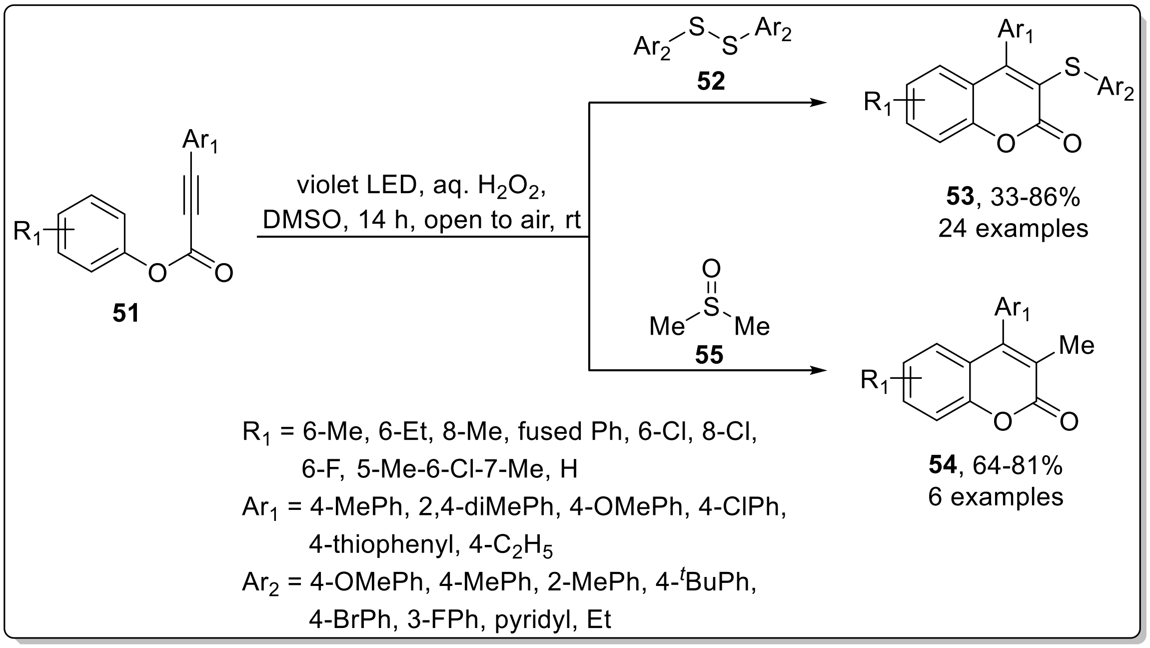
An efficient and facile methodology for synthesis of coumarin via Pechmann condensation have been introduced by Ling and co-workers in 2020 (Scheme 27).[69] For this novel synthesis, 3-ethyl-1-(butane sulfonic acid) imidazolium hydrogen sulfate ([EBsImH][HSO_4]) **50** was employed for the synthesis of substituted coumarins from substituted phenols **9** and ethyl acetoacetate **10**. The acidic ionic liquid catalyst [EBsImH][HSO_4] **50** was a reusable catalyst showing good yield (85%) after 4 runs. It can be recovered by ethyl acetate/water extraction of product mixture. Ling *et al*. also performed this reaction in microfluidic flow setup while flow parameters and reactant molar amounts were optimized in the present study.



Scheme 27. Synthetic pathway for substituted coumarins in the presence of [EBsImH][HSO_4].

2.5. Photocatalytic synthesis of coumarin.

With the profound interest of organic chemists in green chemistry, photocatalysis has garnered their attention significantly in this domain owing to its water purification, self-cleaning and air purifying applications.[70] Natarajan *et al.* in 2024, employed a photocatalyst and solvent-free methodology for the synthesis of substituted coumarins i.e., 3-sulfenylcoumarins **53** or 3-methylcoumarins **54**. The reaction between aryl alkynoate esters **51** and diaryl sulfides **52** or DMSO **55** irradiated with violet LED in the presence of hydrogen peroxide for 14 h furnished 33-86% of products comprising of 30 examples (Scheme 28).[71] The mechanism involved synthesis of hydroxyl radical via irradiation of light followed by methyl radical generation from DMSO. The methyl radical reacts with diaryl sulfides producing a reactive intermediate which further reacts with aryl alkynoate ester **51**. The final step involved sulfonylation-cyclization, which leads to coumarin synthesis. The developed protocol supports green chemistry because of non-toxic H_2O_2 and DMSO under room temperature conditions providing high yields of products with simple work-up procedure.



Scheme 28. Photocatalytic synthesis of coumarin.

3. Conclusion and Future Outlook

In this review, we have summarized the recent methodological developments for the synthesis of coumarin nucleus by recruiting diverse catalytic systems i.e., Bronsted acids, natural acids, nanoparticles, ionic liquids and visible light involving synthetic strategies. In addition, various base-catalyzed synthetic approaches for coumarins syntheses with high substrate scope have been reported. Advantages of these reaction conditions include minimization of side products, fast reaction rate, eco-friendliness, minimum use of organic solvent, energy efficient, recyclable and reusable nature of catalysts alongwith inexpensive and facile experimental procedures. This article is endeavoring to discover further directions in the preparation of more potent oxygen containing heterocyclic compounds. We also anticipate that the synthetic protocols illustrated in this paper will also encourage the organic chemists to make strides regarding the development of more efficient and facile synthetic pathways to synthesize coumarin frameworks and many more biologically active coumarin-based molecules for the betterment of humanity.

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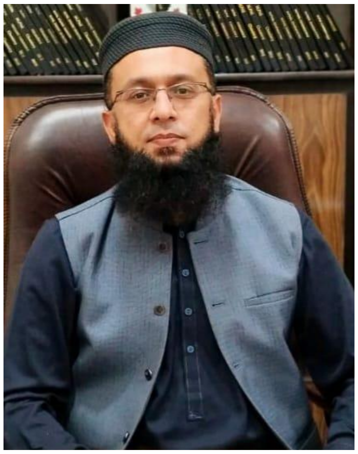
Aqsa Mushtaq is a PhD scholar, pursuing her research work from medicinal chemistry research lab (MCRL) under the mentorship of Prof. Dr. Ameer Fawad Zahoor in chemistry department of Government College University, Faisalabad. Earlier, she received her M.Phil and BS degree from the same institute. She was awarded a gold medal in BS(HONS.) chemistry. Her research focuses on the applications of cross-coupling reactions in the synthesis of heterocycles.



Prof. Dr. Ameer Fawad Zahoor is a tenured Professor in the Department of Chemistry at Government College University, Faisalabad. He successfully defended his PhD thesis from Saarland University, Germany in 2011. He received gold medal and academic roll of honour in BSc (Hons.) from GC University Lahore, Pakistan. He has participated in the 56th Meeting of Nobel Laureates with young scientists/scholars. His current research domain focuses on the organic synthesis and development of diverse heterocycles by using novel as well as facile methodological approaches, underscoring the potential medicinal and therapeutic applications of desired heterocyclic scaffolds.

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