Journal of the Iranian Chemical Society (2022) 19:4035–4092
https://doi.org/10.1007/s13738-022-02603-x

REVIEW

Multicomponent synthetic strategies and perspectives for synthesis of linked or fused coumarin heterocycles

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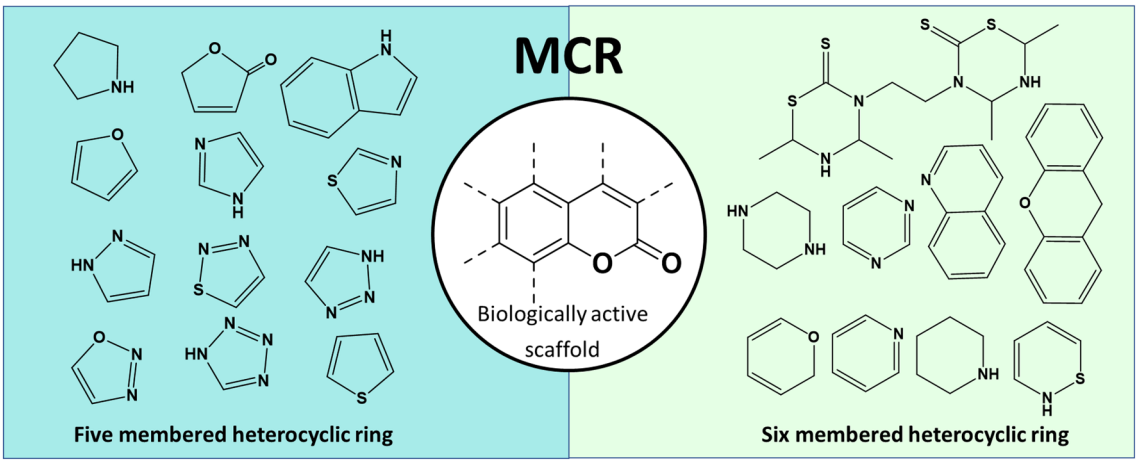
Received: 9 January 2022 / Accepted: 27 May 2022 / Published online: 21 June 2022

Abstract

Natural and synthetic hybrid molecules are an attractive scaffold for therapeutic agent development due to their dual/multiple modes of action, minimum or no side effects, favorable pharmacokinetics and other advantages. Coumarin-fused/linked heterocycles are important classes of natural products affording intriguing array of pharmacological activities, which make them ideal for building effective biological scaffolds for medicinal research. Given their promising medicinal applications, an extraordinarily large emphasis is placed on the design of efficient and greener synthetic procedures. Multicomponent reactions (MCRs) are an important tool to expedite the tailoring of a vast number of organic molecules. In recent years, MCRs have simplified access to diverse coumarin heterocycles through molecular hybridization. This review highlights the broad range of science that has arisen from the multicomponent synthesis of coumarin-fused/ linked templates bearing heterocycle ring/s either fused or linked to positions 3 or 4 of the pyran ring or the phenyl ring. The review facilitates a better understanding of the role of homogenous or heterogeneous catalyst, inert support and substituents, on the reaction parameters, stereo-/chemo-/regioselectivity of the product. The effect of catalyst functionalization on the number and types of catalytic sites (acidic or basic), stability of the catalyst and synergic catalysis are also discussed. The role of some selected catalysts in the reactions is depicted through reaction mechanisms, to further advance the understanding of the catalytic role. The reports between 2017 and 2022 are analyzed succinctly in this review. Some perspectives for the future, focusing on relevant synthetic strategies are also discussed.

Graphical abstract

Multicomponent strategies for synthesis of linked and fused coumarin heterocycles are explored



Sharda Pasricha and Kavita Mittal have contributed equally to this work.

Extended author information available on the last page of the article

Keywords Molecular hybridization · Green chemistry · Cascade reactions · Linked coumarin heterocycles · Fused coumarin heterocycles · Catalysis

Introduction

Multicomponent reactions (MCRs) constitute a class of convergent reactions wherein three or more reactants undergo one-pot cascade reaction to form a single product, incorporating significant portions of all the precursors. Molecular diversity in the product, high convergence efficiency, high atom economy and very little waste make it a sustainable and potent tool for optimizing non-green chemical processes and for synthesizing diverse bioactive molecules in the medicinal industries [1–13]. Multicomponent reactions have been reported for synthesis of several biologically important heterocycles [1–4].

Coumarins, benzopyran-2-ones, constitute a leading class of natural products with π-conjugated lactone moiety. Their structural diversity ranges from simple unsubstituted coumarins to polycyclic/polysubstituted linked/ fused coumarins. The existence of numerous vital features like lactone moiety fused to the planar aromatic nucleus, capability to employ non-covalent interactions (like electrostatic, hydrophobic, π-π interactions, Van der Waal forces, hydrogen bonds and organometallic linkages, etc.), strong ligand–protein interaction, and usually low toxicity characterize this exceptional pharmacophore. This intrinsic biological importance has attracted the momentous interest of organic and medicinal chemists in designing a plethora of novel bioactive compounds by incorporating the coumarin nucleus as the molecular scaffold [14–24].

Over the past decade, molecular hybridization has evolved as an innovative approach which conglomerates two or more pharmacophore units into one scaffold for the development of novel hybrid molecules. Due to hybridization of two or more pharmacophores into a single unit, these hybrids possess manifold biological activities, improved selectivity profiles, dual or multiple action modes and/or minimize side effects. These skeletal systems may be further tailored to display suitable bioavailability and pharmacokinetics [25]. These scaffolds have been reported for the treatment of multifactorial diseases like cancers, malaria, organophosphorous poisoning, metabolic disorders, inflammation and ischemia. Hybridization or joining of coumarins with diverse bioactive scaffolds such as chalcones, pyridines, quinolines, pyrazolines and triazoles produces potent hybrid molecules which exhibit anticancer, antimicrobial, vasorelaxant, antioxidant, antidepressant, anticoagulant agents or demonstrate monoamine oxidase-B (MAO-B) inhibitor, platelet anti-aggregating and anti-inflammatory activity [26]. Some of the recent examples [21] include neotanshinlactone, a furanocoumarin, which exhibited enhanced breast cancer activity in comparison with tamoxifen, SP500263, a coumarin piperidine hybrid exhibited potent antiestrogen activity against both estrogen α and β receptor. Similarly, Ensaculin, a coumarin piperazine hybrid, has been reported for treatment of dementia; flemichapparin C and coumestrol exhibit estrogenic, antioxidant, antihepatotoxic and antitumor activity (Fig. 1). Clearly, molecular hybridization is the key to design and construction of diverse coumarin heterocycle hybrids for treatment of a plethora of multifactorial diseases. Ideally, coumarin heterocycle hybrids can be obtained by either fusing or linking (with help of a linker) a heterocycle ring at either 3- & 4-position of α-pyrone ring or on the phenyl ring of coumarin (Fig. 2) [27]. Both these strategies are covered in this review.

Several reviews have been written in the past focusing on the synthesis of coumarins and coumarin-based molecules [28–31]. However, none of them have focused especially on synthesis of coumarin-linked or -fused heterocycles through benign multicomponent approach and this subject, to our mind, is pertinent enough to be given independent attention. The current review discusses all the literature reported for the multicomponent synthesis of structurally diverse coumarin-fused and coumarin-linked heterocycles, reported between 2017 and 2022. The

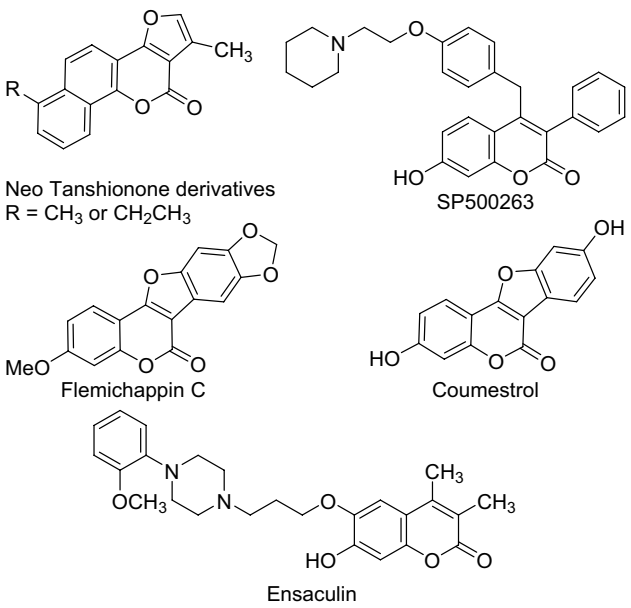


Fig. 1 Some recent examples of biologically active coumarin hybrids containing diverse heterocyclic moieties

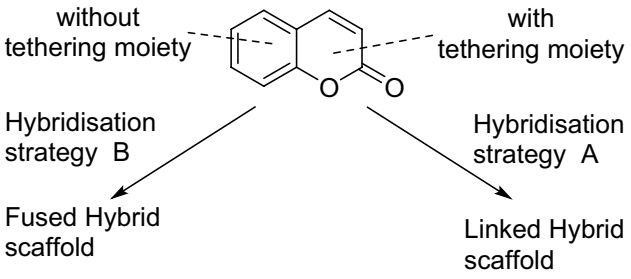


Fig. 2 Design strategies and types of coumarin hybrid scaffolds

literature in this paper is compiled into different sections based on the nature of heteroatom, number and ring size of the fused/linked heterocycle molecule/s attached to the coumarin nucleus.

The growing volume of publications in this field reflects its standing and importance. We trust that the current review will open doors to innovative avenues for organic and medicinal chemists to discover and synthesize potent and diverse leads for drug development.

Five-membered heterocycles with one heteroatom

Furans, dihydrofurans, furanones

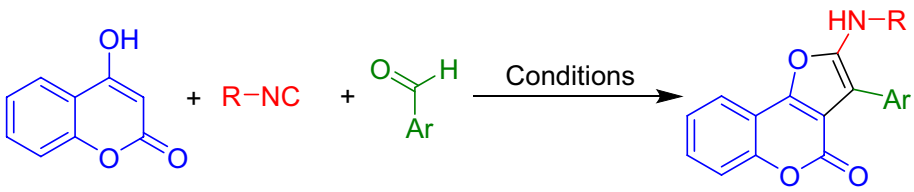
Furocoumarins are obtained by fusing furans with the lactone ring of the coumarin molecule. Three possible structural isomers of furocoumarin are furo[2,3-*c*]coumarin, furo[3,2-*c*]coumarin and furo[3,4-*c*]coumarin. Furocoumarin scaffold has gained the attention of organic chemists due to varied pharmaceutical and biological activities like antifungal, anticancer, antibacterial, immunotoxicity, anticholinesterase and antimicrobial activity [32]. Furanyl coumarins are yet another class of coumarins with extraordinary therapeutic activities like anticancer, antibacterial and anti-analgesic activity.

Chan and co-workers [33] synthesized a series of 2-cyclohexylamino-3-phenyl-4H-furo[3,2-c]chromen-4-ones **1** via one-pot multicomponent reaction of 4-hydroxycoumarin, aromatic aldehydes with and cyclohexyl isocyanide in benzene as solvent (Scheme 1a). The reaction tolerated all electron-rich, electron-deficient and halogen-substituted aldehydes. The pathway plausibly progressed through [4 + 1] cycloaddition followed by [1, 3]-hydride shift to produce the desired product in moderate to good yield.

Kerru et al. [34] synthesized furo[3,2-*c*]coumarins **1** via three-component, one-pot condensation reaction between the isocyanides, 4-hydroxycoumarin and aromatic aldehydes using zinc oxide tailored fluorapatite (ZnO/FAp) as a heterogeneous catalyst (Scheme 1b). Lewis acid–base pair formation due to tetrahedral coordination of Zn and O, the occurrence of numerous Lewis acidic sites due to collaboration between fluorapatite and zinc as well as tunable nature of the catalyst was reported for efficient catalysis. Authors highlighted that 4-methoxyphenyl isocyanide or ethyl isocyanoacetate or along with election-deficient and electron-rich aldehydes offered high conversions and fast reaction rate. The catalyst could be recycled five times with the marginal loss of activity.

Chang and co-workers [35] have reported an efficient synthesis of furo[3,2-*c*]coumarins **2a/2b** via multicomponent cascade reactions using $FeCl_3$ or $ZnCl_2$ as Lewis acid catalyst. A reaction of arylglyoxal monohydrates,

Scheme 1 Synthesis of furocoumarins



a

Ar = C_6H_5, 4-OHC_6H_4, 2-OHC_6H_4, 4-$OCH_3C_6H_4$, 4-ClC_6H_4, 4-FC_6H_4, 4-$NO_2C_6H_4$, 2-$NO_2C_6H_4$

R = cyclohexyl

Conditions: Benzene, 120 °C, 24 h, 8 examples, 71-92 %

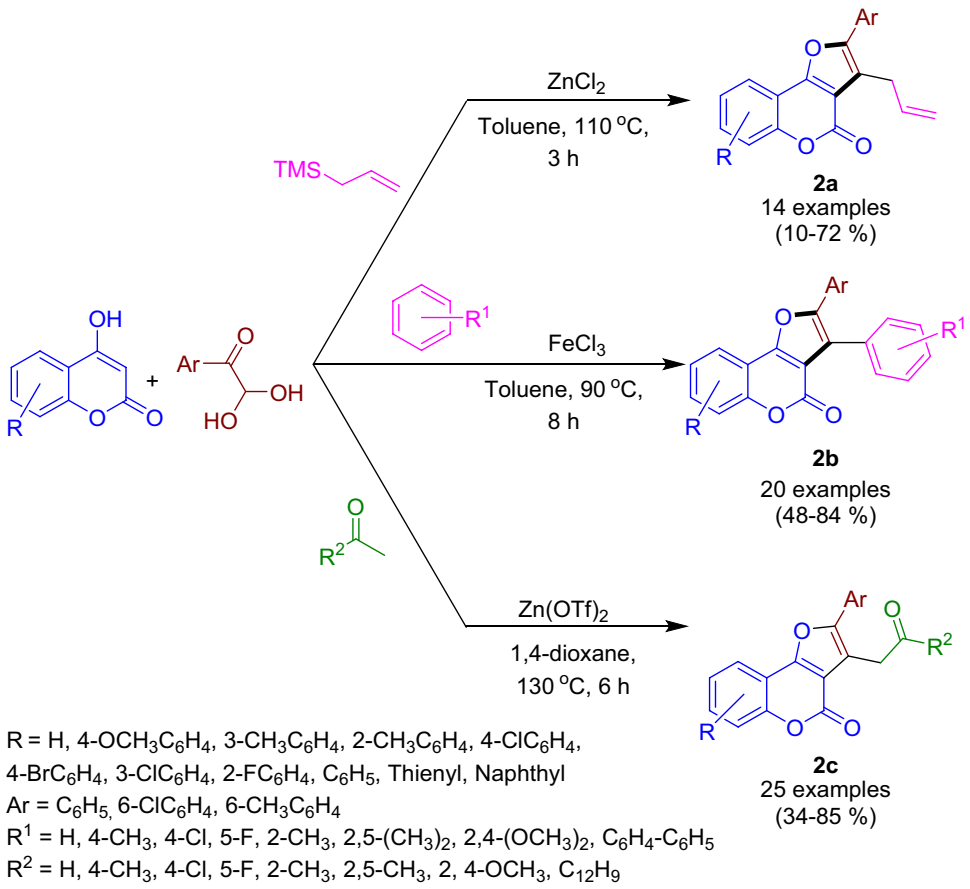
b

Ar = 4-$OCH_3C_6H_4$, 4-BrC_6H_4, 4-$SCH_3C_6H_4$, 3-$OCH_3C_6H_4$, 2,4,6-tri-$OCH_3C_6H_2$, 4-ClC_6H_4, 4-$C_2H_5C_6H_4$, 4-$N(CH_3)_2C_6H_3$, 3,4,5-tri-$OCH_3C_6H_2$, C_6H_5

R = CH_2-$COOC_2H_5$, 4-$OCH_3C_6H_4$

Conditions: ZnO/FAp, EtOH, r.t., 16-20 min., 10 examples, 94-98 %

Scheme 2 Synthesis of furo[3,2-*c*]coumarins

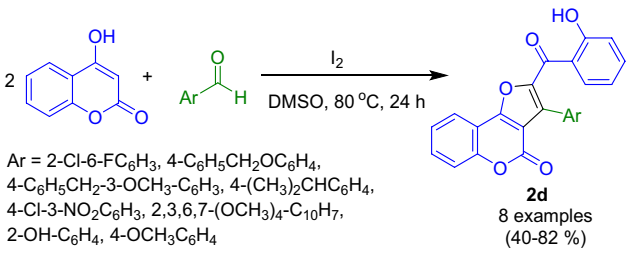


4-hydroxycoumarin and allyltrimethyl silane or substituted benzenes afforded the desired product/s **2a/2b** (Scheme 2), in the presence of toluene as solvent. The polar solvents THF and DMF were not effective in the reaction. 2-thienylglyoxal led to drop in yields due to decreased electrophilicity of the carbonyl group. Arylglyoxals bearing 4-Cl, 4-Br, 3-Cl or 2-F substituents also gave lower yields.

Later, Chen and co-workers [36] also synthesized furo[3,2-*c*]coumarins **2c** via one-pot, multicomponent tandem reaction of aromatic methyl ketones, 4-hydroxycoumarin and phenylglyoxal monohydrates using $Zn(OTf)_2$ as catalyst (Scheme 2). The reaction with diverse arylglyoxals, hydroxycoumarins and substituted methyl ketones gave the desired product in moderate to good yields. Electron-deficient arylglyoxals, however, gave lower yields of the desired product.

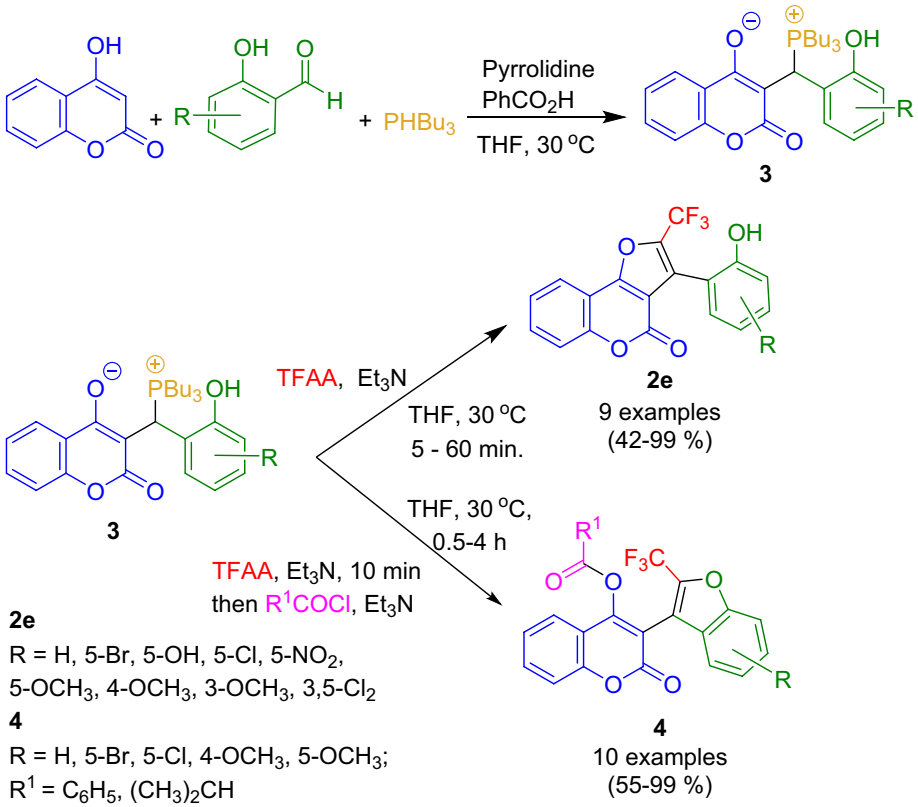
Fattah et al. [37] proposed a facile synthesis for functionalized furo[3,2-*c*]coumarins **2d** using pseudo-one-pot, three-component reaction of 2 equivalents of 4-hydroxycoumarin with aldehydes, using iodine in the presence of DMSO as solvent as well as oxidizing agent (Scheme 3).

Yang et al. [38] have proposed a one-pot, chemoselective procedure for the diversity-oriented synthesis of 3-benzofuranylchromenones **4** and furo[3,2-c]coumarins



Scheme 3 Synthesis of furo[3,2-*c*]coumarins using DMSO as oxidant

2e through intramolecular Wittig reaction of phosphorus zwitterions (prepared from 4-hydroxycoumarin and various 2-hydroxy benzaldehydes and PBu_3) with TFAA and benzoyl chloride and or 2 equivalents of TFAA in the presence of triethyl amine (Scheme 4). Authors hypothesized that chemoselective formation of furocoumarins **2e**, when TFAA is used as the sole acylating agents, was due to extended conjugation and extra stability in furocoumarin skeleton. Significantly, the obtained furocoumarin was devoid of trifluoroacetate ester owing to its lability toward hydrolysis. Further, it was noted that substrates with electron-withdrawing groups at the para



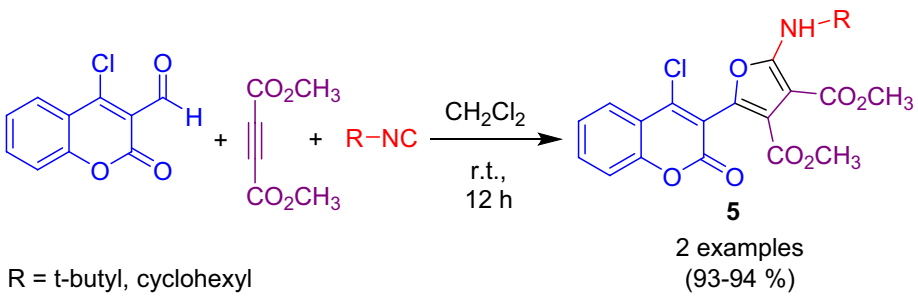
Scheme 4 Synthesis of 3-benzofuranylchromenones and furo[3,2-c]coumarins

position on the phenolic ring provide good yields of products in shorter reaction times. Further, it was proved that the selective acylation of phosphorus zwitterions with a more electrophilic acyl group (TFAA), in the presence of Et_3N, proceeded at the phenolic and not enolic site. Subsequent acylation with less electrophilic acyl halides could successfully reverse the direction of cyclization to afford benzofuranyl coumarins through chemoselective intramolecular Wittig reaction.

Mehdi and co-workers [39] have synthesized coumarin-linked furans **5** via a three-component reaction of dimethyl acetylene dicarboxylate, isocyanides and 4-chloro-coumarin-3-carbaldehyde, taking dichloromethane as solvent (Scheme 5). The product was found as efficient starting material for synthesis of 4H-chromeno[4,3-b]furo[2,3-d] pyridine-1-carboxylates.

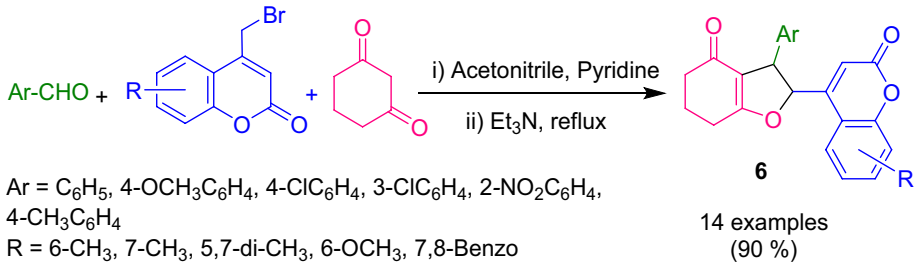
Madar et al. [40] established a multicomponent protocol for the synthesis of 2,3-dihydrofurocoumarin **6** via the reaction of various aromatic aldehydes, 4-bromomethyl coumarin and 1,3-cyclohexanedione, using pyridine as mild base (Scheme 6). The plausible mechanism for the synthesis is illustrated in Scheme 7. Authors hypothesized that pyridine facilitates addition by increasing the nucleophilicity of coumarin unit.

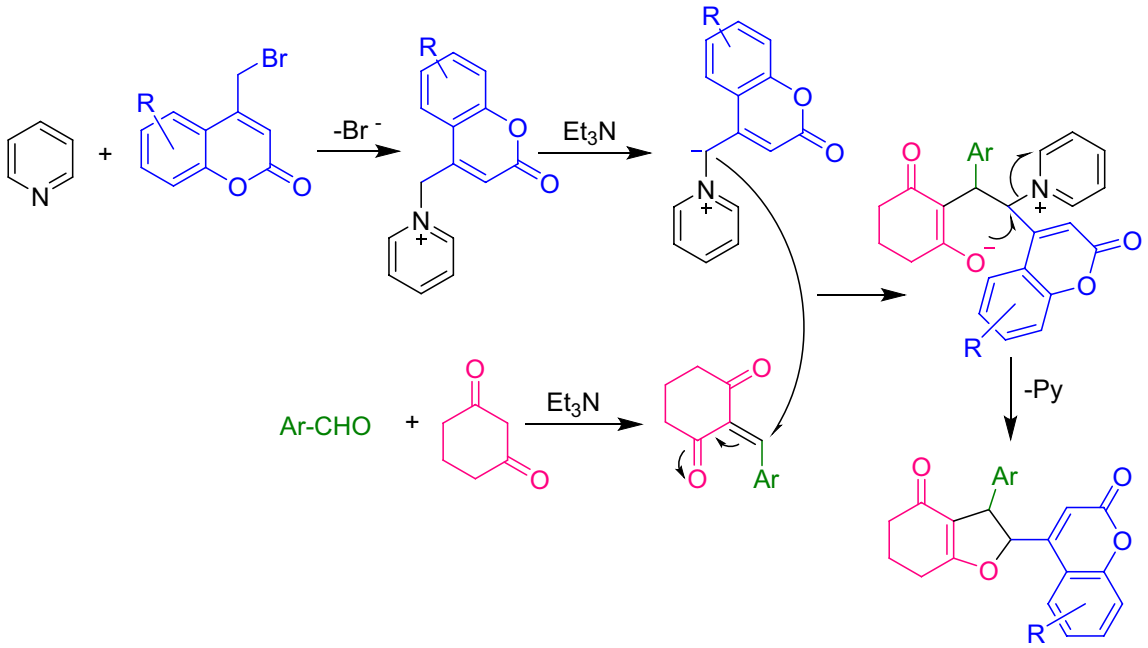
- Olyaei et al. [32] have explored a benign and simple synthesis of novel 2H-furo[3,2-*c*]chromene-2,4(3H)-diones **7** via three-component, one-pot reaction of glyoxalic acid**,** 4-hydroxycoumarin and aryl amines, using water as catalyst and solvent (Scheme 8). Authors proposed that water catalyzed the transformation by increasing the electrophilicity of the carbonyl group in glyoxalic acid,



Scheme 5 Synthesis of 3-furanyl-chromen-2-ones

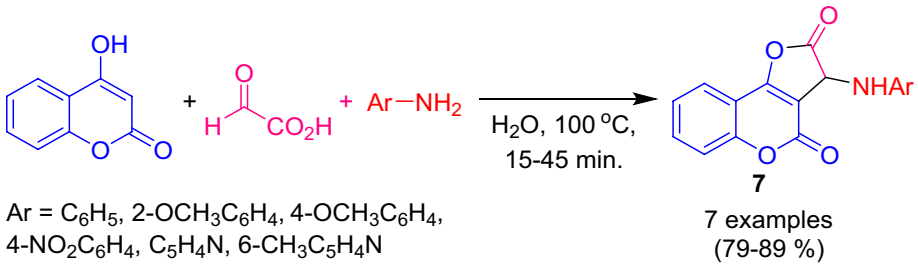
Scheme 6 Synthesis of 2,3-dihydrofurocoumarins





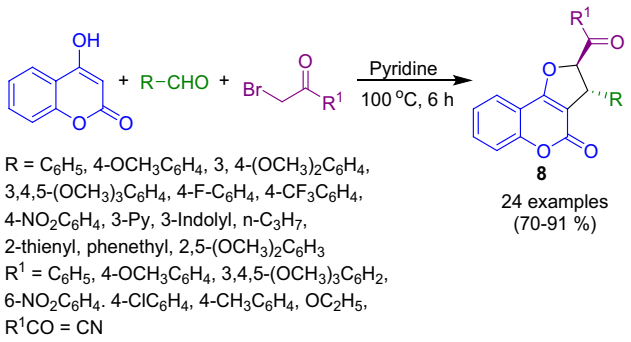
Scheme 7 Plausible mechanism for synthesis of 2,3-dihydrofurocoumarins

Scheme 8 Synthesis of 2H-furo[3,2-c]chromene-2,4(3H)-diones



via hydrogen bonding. Aryl and heteroaryl amines were well-tolerated, regardless of the electronic effect of the substituent groups. The reaction was fast and afforded good yields of the desired product.

Tangella et al. [41] developed a facile one-pot, multicomponent, diastereoselective synthesis of trans-2,3-dihydrofuro[3,2-*c*]coumarins **8** through the reaction of suitable aldehydes, α-bromocarbonyls and 4-hydroxycoumarin, in the presence of pyridine as solvent and catalyst (Scheme 9). This protocol proceeds through a plausible tandem reaction involving Knoevenagel condensation reaction, Michael addition followed by intramolecular S_N2 cyclization to afford **8**. Authors reported that the electron-rich aldehyde and α-bromocarbonyl compounds gave better yields of the desired products. The steric hindrance offered by the bulky substituents at C-2 (CN/ester/aryl) and C-3 (aryl) in the furan ring reportedly leads to selective generation of the trans isomer upon cyclization.



Scheme 9 Synthesis of trans-2,3-dihydrofuro[3,2-*c*]coumarins

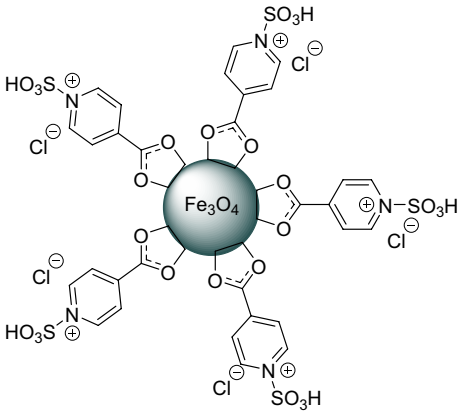


Fig. 3 SA-PCYA-Fe_3O_4 nanocatalyst

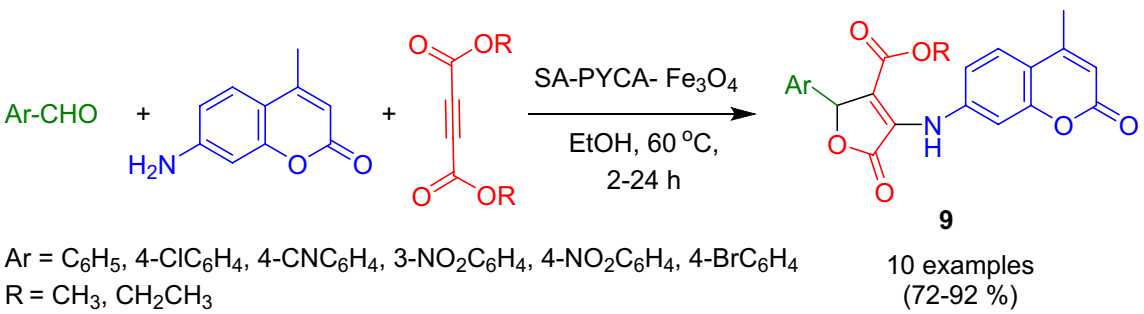
Asghari et al. [42] synthesized novel N-coumarin-2-furanones **9** through multicomponent reaction of arylaldehydes, 7-amino-4-methylcoumarin and dialkylacetylene dicarboxylate using sulfamic acid-pyridinium chloride-functionalized Fe_3O_4 nanoparticles (Fig. 3) as heterogeneous catalyst (SA-PYCA-Fe_3O_4) (Scheme 10). It was proposed that the Bronsted acid catalyst, SA-PYCA-Fe_3O_4, activated carbonyl group by protonation. Authors reported that aldehyde containing electron withdrawing groups lead to higher yields, due to increased electrophilicity of the carbonyl group. The catalyst was recycled ten times without substantial loss of catalytic activity.

Pyrrolidines, pyrroles

Pyrrole, a five-member nitrogen heterocycle, has gained substantial attention due to its broad range of pharmacological properties and abundance in biomolecules. Pyrrole nucleus is found in varied pharmacologically active compounds including antimicrobial, antifungal, antidepressants, anti-inflammatory, HMG-CoA reductase inhibitors, antitumor agents, etc. [43]. Coumarin-fused or -linked pyrroles are an important class of natural products with varied pharmacological activities including anticancer and human topoisomerase inhibitor potential.

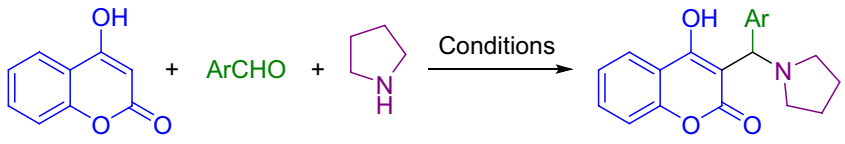
Ghafuri and co-workers [44] have established an effective procedure for the stereoselective synthesis of α-benzylamino coumarin pyrrolidines **10** through Mannich type reaction of pyrrolidine, aromatic aldehydes and 4-hydroxycoumarin, in the presence of nanomagnetic sulfated zirconia (Fe_3O_4@ZrO_2/SO_4^{2-}) as catalyst (Scheme 11a). Authors revealed that electron-deficient aromatic aldehydes require a shorter reaction time. The catalyst is magnetically recoverable and reused several times without any appreciable loss of catalytic activity.

In another report, Geetha et al. [45] designed microwave-assisted synthesis of α-benzylaminocoumarin-pyrrolidines **10,** utilizing sulfated titania (TiO_2−$SO4^{2-}$) as a hybrid solid acid catalyst (Scheme 11b). The plausible mechanism is shown in Scheme 12. Synergistic catalysis by Lewis and Bronsted acidic sites of the catalyst promoted the reaction. The Bronsted acidity of the titania catalyst was ascribed to the numerous –OH groups linked to Ti atom (existing and those generated on contact with water). The -I effect of Ti atom-attached SO_4^{2-} ions generated Lewis acid sites which further enhanced the acidic character of the catalyst. The catalyst could be recycled at least 5 times without any appreciable loss in catalytic activity. The reaction under microwave irradiation was faster, resulted in a clean product, afforded better yields and could be carried out in an aqueous medium.



Scheme 10 Synthesis of novel N-coumarin-2-furanones

Scheme 11 Synthesis of α-benzylamino coumarin pyrrolidines



a

Ar = C_6H_5,4-$OCH_3C_6H_4$, 4-ClC_6H_4, 4-$CH_3C_6H_4$, 4-$NO_2C_6H_4$, 3-$NO_2C_6H_4$, 3-OHC_6H_4, 2,4-$(Cl)_2C_6H_3$, 2-ClC_6H_4

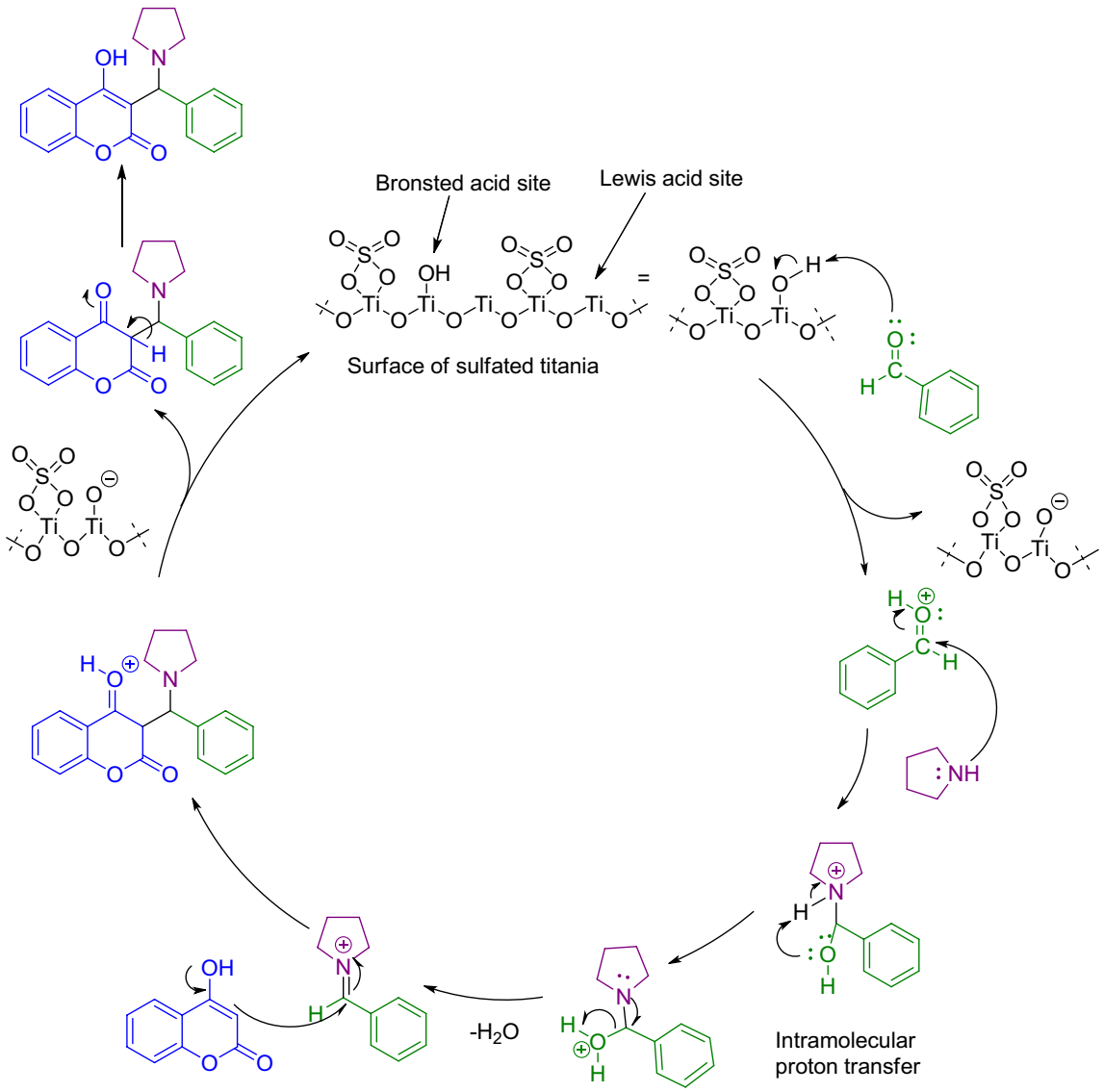
Conditions: Fe_3O_4@ZrO_2/SO_4^{2-}, CH_3CN, r.t., 5-30 min., 11 examples, 80-95 %

10

b

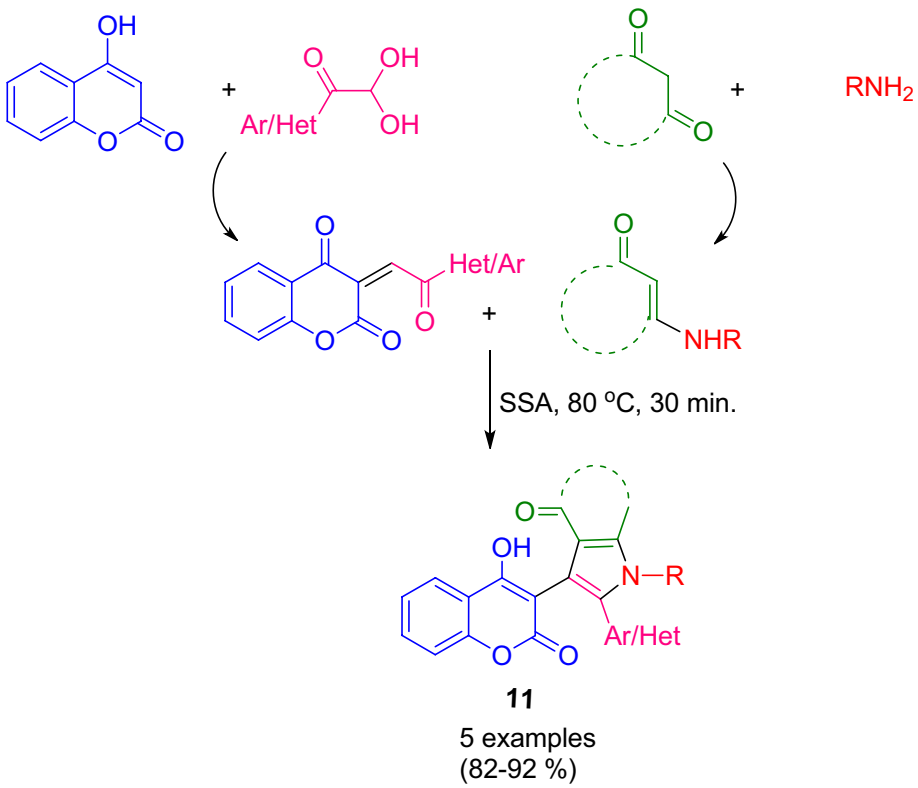
Ar = 2-tolylmethyl, 4-Pr^i-C_6H_4, 3-$NO_2C_6H_4$, 4-ClC_6H_4, 2,4-$(Cl)_2C_6H_3$

Conditions: TiO_2-SO_4^{2-}, H_2O, 100 °C, MW (4O W), 4-8 min., 5 examples, 89-94 %



Scheme 12 Plausible mechanism for synthesis of α-benzylamino coumarin pyrrolidines

Scheme 13 Synthesis of coumarin pyrroles



11

5 examples
(82-92 %)

Cyclic 1,3-diketone: 4-hydroxycoumarin, dimedone, 1,3-dioxycyclohexane,
Alicyclic 1,3-diketone: Acetylacetone and phenylacetylacetone,
Arylglyoxal monohydrates
R = 4-$CH_3C_6H_4$, C_6H_5, 4-$OCH_3C_6H_4$, thienyl

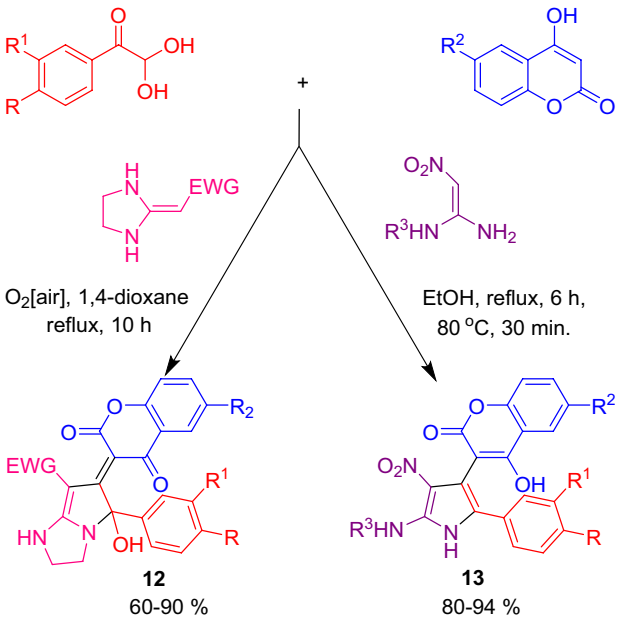
Kundu et al. [46] have proposed a microwave-assisted, solvent-free synthesis of coumarin-linked pyrroles **11** utilizing silica sulfuric acid (SiO_2−OSO_3H) as a heterogeneous acid catalyst. 4-hydroxycoumarin, arylglyoxal monohydrates, primary amine (aliphatic or aromatic) and acyclic or cyclic 1,3-diketone undergo one-pot, four-component condensation reaction to form the desired product **11** (Scheme 13).

Zi et al. [47] used an innovative method for the synthesis of two types of coumarin pyrroles viz. 2-amino-4-coumarinyl-5-arylpyrroles (ACAPs) **12** or 2-amino-4-coumarinyl-5-aryl-5-hydroxypyrroles (ACAHPs) **13**, through multicomponent cascade reaction and a metal-free catalyzed aerobic oxidation reaction, respectively. A reaction of 4-hydroxcoumarin, arylglyoxal monohydrates and alicyclic/cyclic 1,1-enediamines (EDAMs) yielded the desired product **12/13** (Scheme 14) in ethanol as solvent. The addition of Et_3N was found to complicate the reaction. In the presence of dioxane, cyclic EDAMs reportedly underwent aerobic oxidation to form 2-amino-4-coumarinyl-5-aryl-5-hydroxypyrroles **13**. The substituents on arylglyoxal monohydrate and 4-hydroxycoumarin had little effect on the yields. EDAMs with a longer chain were found to produce ACAPs with higher yields, whereas the six numbered EDAMs were more favorable to ACAHPs synthesis.

Yadav et al. [48] have reported synthesis of polysubstituted 2-amino-5-coumarinyl pyrroles **14** via a meglumine catalyzed four-component reaction of glyoxal monohydrate derivatives, primary amines, 4-hydroxy coumarins, and malononitrile in aqueous medium (Scheme 15a). The plausible mechanism for the reaction is depicted in Scheme 16. It was proposed that meglumine possibly catalyzes nucleophilic addition to malononitrile and intramolecular cyclization reaction by abstracting proton and activating the nucleophiles.

Shao et al. [49] also proposed a regioselective synthesis of functionalized 2-amino-5-coumarinyl pyrroles, on similar lines as Yadav et al. [48], in the presence of Et_3N as the catalyst/base (Scheme 15b). The meglumine catalyzed reaction was superior since it is faster, proceeds under mild conditions and employs water as solvent. Both Yadav et al. [48] and Shao et al. [49] have reported that the yield of product was low when the aromatic amine and malononitrile have electron-withdrawing groups.

In another report, Yang et al. [50] synthesized chromeno[4,3-*c*]pyrrol-4(1H)-ones **15** by catalyst-free,



R = R^1 = H, CH_3, F
R^2 = H, Br
R^3 = 4-OCH_3-$C_6H_4(CH_2)_2$, 4-$ClC_6H_4(CH_2)_2$, 4-CH_3-$C_6H_4(CH_2)_2$, $C_6H_4(CH_2)_2$, 4-CH_3-C_6H_5, 4-F-$C_6H_4(CH_2)_2$

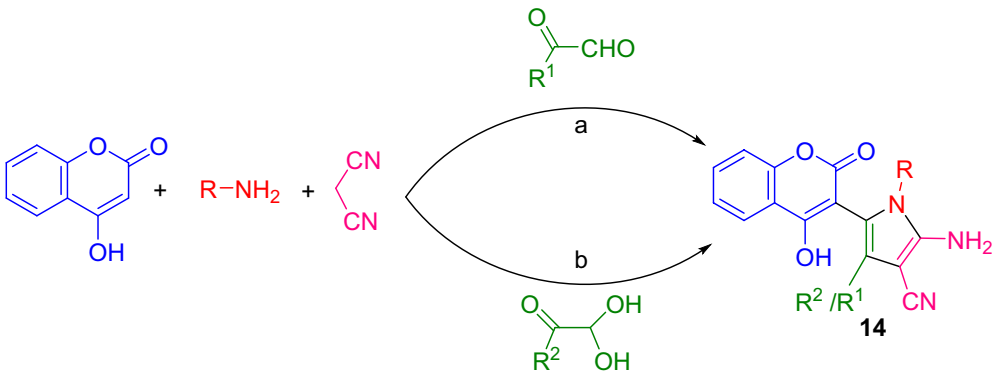
Scheme 14 Synthesis of 2-amino-4-coumarinyl-5-arylpyrroles

three-component tandem reaction of 4-aminocoumarins, arylglyoxal monohydrate and 1,3-dicarbonyl in the presence of ethanol as the solvent (Scheme 17). Authors reported that the electronic effect of the substituents on arylglyoxal monohydrates had little influence on the reaction efficiency. Significantly, halogen substituted aryl glyoxal was tolerated well and provided the possibility for further functionalization through cross-coupling reactions.

Mishra et al. [51] regioselectively synthesized coumarin-fused pyrroles **16** using multicomponent reaction of arylglyoxals, substituted 4-hydroxycoumarins and coumarin based primary amines like 7-amino-4-methylcoumarins, under metal-free conditions, and microwave irradiation using acetic acid as catalyst (Scheme 18). Authors explained the formation of 7,8-fused ring through higher nucleophilicity of C-8 (due to the presence of electron-donating oxygen of the pyrone ring in the neighborhood).

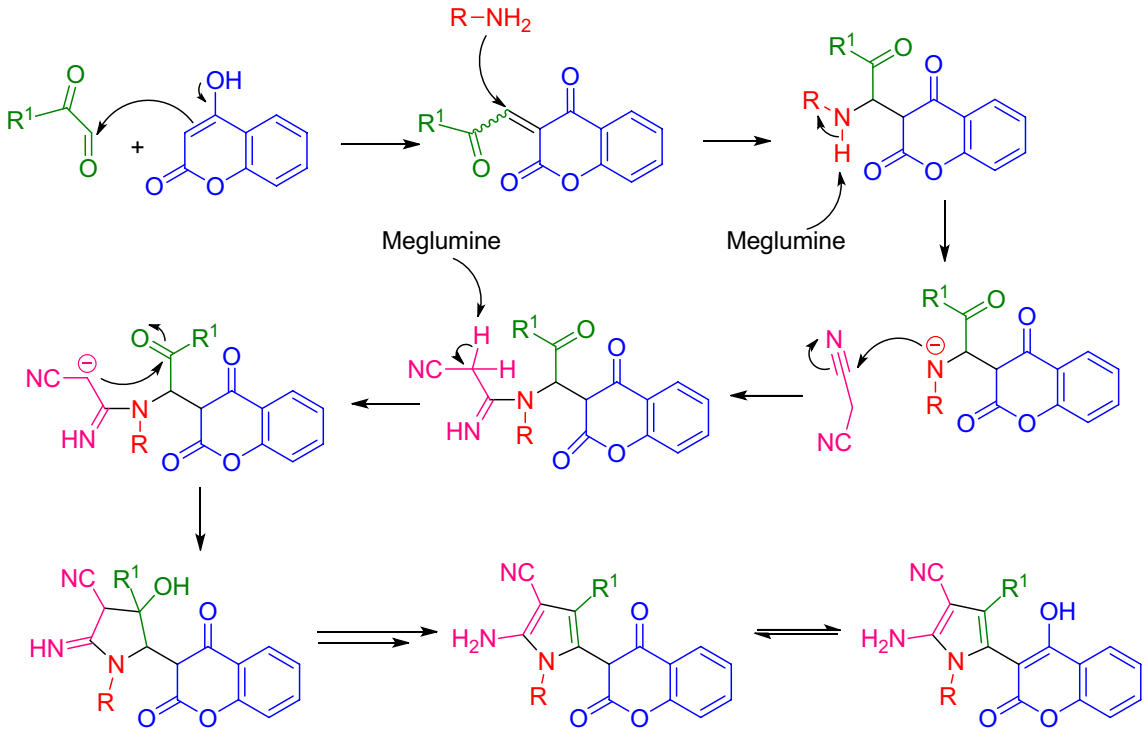
Das et al. [52] have produced a library of 6-(pyrrolyl)coumarins **17** via microwave-assisted three-component, one-pot reaction of β-nitrostyrenes, 6-aminocoumarin, and dialkylacetylene dicarboxylates, in the presence of indium(III) chloride as Lewis acid catalyst (Scheme 19). The plausible mechanism (Scheme 20) shows that the presence of strong EWG groups on the acetylene moiety is the key for nucleophilic reaction with amine and that nitrostyrenes having electron-donating groups (EDG) on the aromatic ring afforded better yields of the product.

Belal et al. [53] have demonstrated the synthesis of pyrrolo(2,3-*c*)coumarins **18** via a three-component, one-pot reaction of arylglyoxals, 4-hydroxycoumarin and 3-aminocoumarins, utilizing molecular iodine as homogeneous catalyst (Scheme 21). Significantly, the products were produced



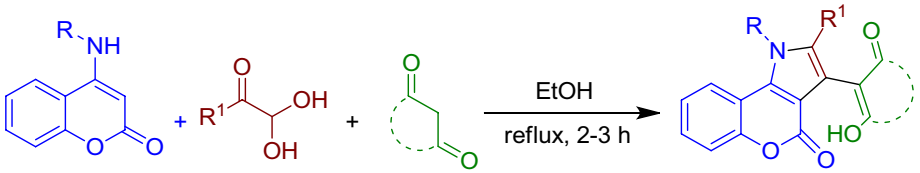
a
R = 4-ClC_6H_4, 4-$CH_3C_6H_4$, C_6H_5, $(CH_3)_3C$, 3-$OCH_3C_6H_4$
R^1 = $C_6H_5(CH_2)$, C_5H_{11}, $(CH_3)_2CHCH_2$, 4-$CH_3C_6H_4$, $C_6H_{11}CH_2$, C_6H_5, $C_6H_5(CH_2)_3$, 4-$COOHC_6H_4$, C_6H_{11}
Conditions: Meglumine, H_2O, 65 °C, 5 h, 17 examples, 49-90 %
b
R = $C_6H_5(CH_2)$, C_5H_{11}, Me_2CHCH_2,4-$CH_3C_6H_4$, $C_6H_{11}CH_2$, C_6H_5, $C_6H_5(CH_2)_3$, 4-$COOHC_6H_4$, C_6H_{11}, NHBOC-$(CH_2)_2$; R^2 = 4-ClC_6H_4, 4-$CH_3C_6H_4$, C_6H_5, $(CH_3)_3C$, 4-$OCH_3C_6H_4$, 4-$CF_3C_6H_4$, thienyl
Conditions: DCE, base, r.t., 8 h, 24 examples, 40-94 %

Scheme 15 Synthesis of 2-amino-5-coumarinyl pyrroles



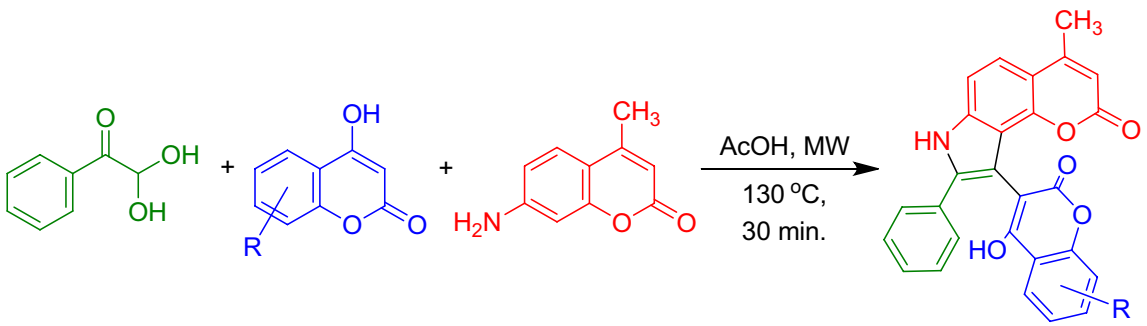
Scheme 16 Plausible mechanism for synthesis of 2-amino-5-coumarinyl pyrroles

Scheme 17 Synthesis of chromeno[4,3-*c*]pyrrol-4(1H)-ones



15
23 examples
(35-89 %)

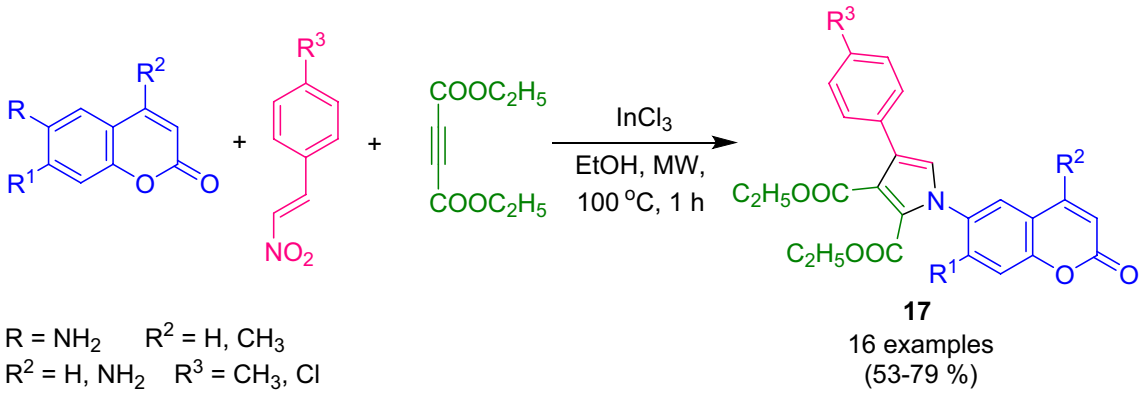
R = C_6H_5, H, $CH_3CH_2CH_2$, $OHCH_2CH_2$
R^1 = 4-ClC_6H_4, 2-ClC_6H_4, 4-FC_6H_4, 4-BrC_6H_4, 4-$NO_2C_6H_4$, C_6H_5, 4-CH_3-C_6H_4, 2-CH_3-C_6H_4, 4-OCH_3-C_6H_4, 3-OCH_3-C_6H_4, 4-OH-C_6H_4, thienyl, 5-benzo[*d*][1,3]dioxolyl, CH_3



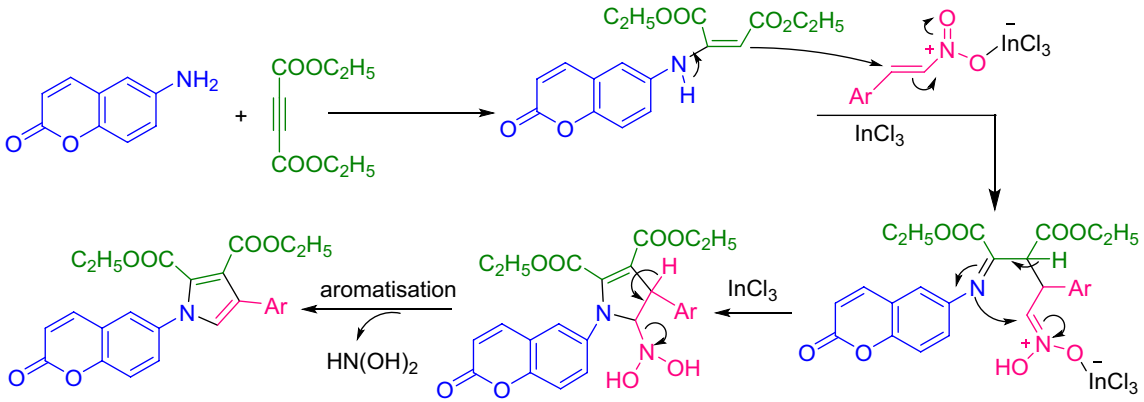
16
4 examples
(83-87 %)

R = 6-CH_3, 6-Br, 6-Cl, 7-CH_3

Scheme 18 Synthesis of coumarin-fused pyrroles

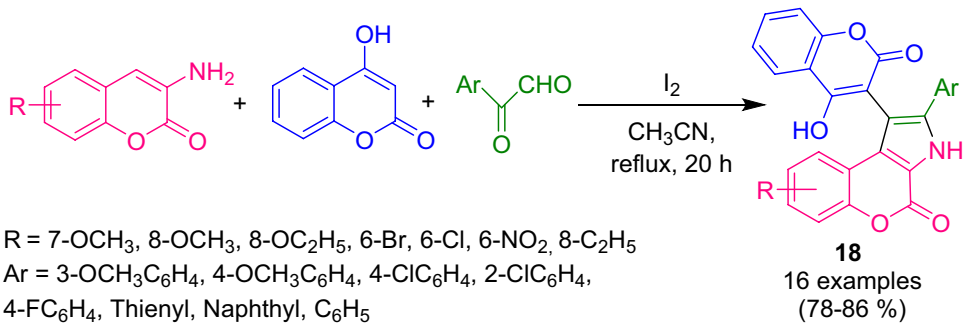


Scheme 19 Synthesis of 6-(pyrrolyl)coumarins



Scheme 20 Plausible mechanism for synthesis of 6-(pyrrolyl)coumarins

Scheme 21 Synthesis of pyrrolo(2,3-*c*)coumarins

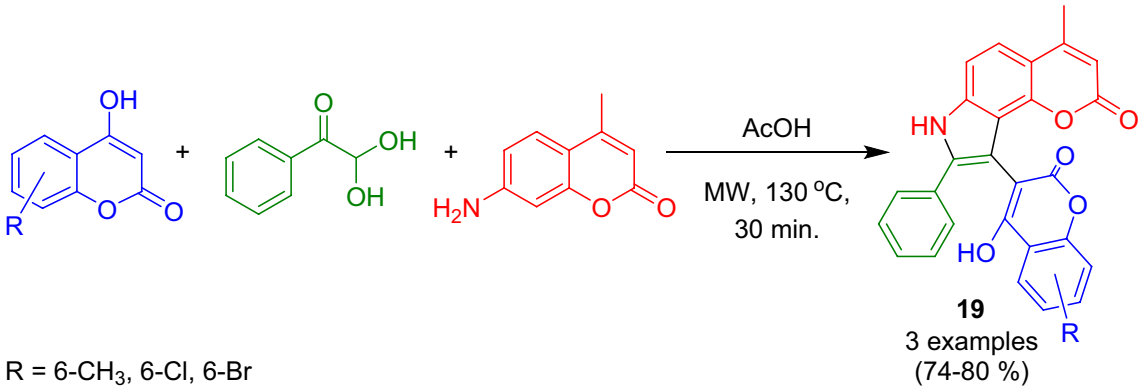


in good yields without the need for column chromatography. The reaction, however, involves the use of toxic organic solvent, is rather slow and gives moderate to good yields of the product.

Indoles

Indolyl coumarins are a group of potent heterocycles which have been reported for diverse biological activities like antiproliferative activity. Thus, the expansion of efficient protocols for building these compounds is of great value [54].

Mishra et al. [51] also synthesized regioselective indolyl coumarins **19** by the reaction of 4-hydroxycoumarins, aromatic primary amines like 7-amino-2-methylchromone and arylglyoxals (Scheme 22), in the presence of acetic acid as catalyst and solvent. Notably, C-8 behaved as the C-nucleophilic cyclization site. Interestingly, use of



Scheme 22 Synthesis of indolyl coumarins

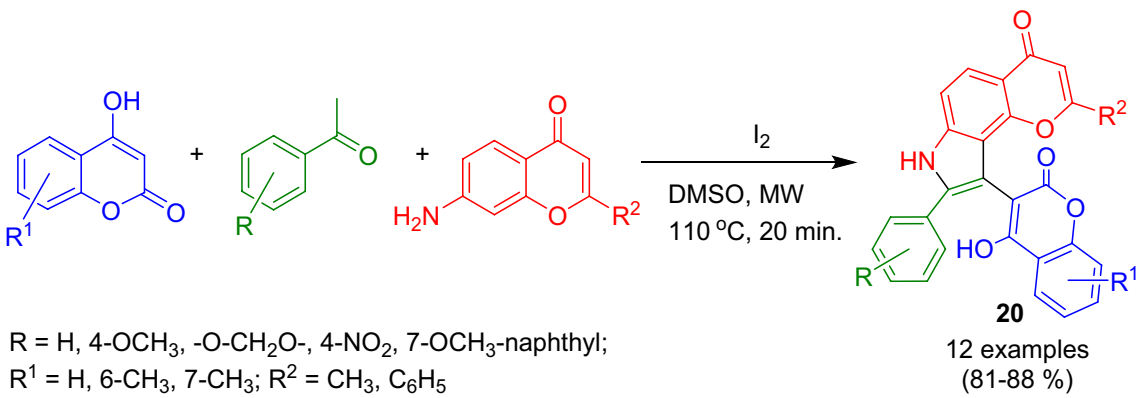
3,4-dimethoxyaniline and 3,4-ethylenedioxyaniline in place of 7-amino-2-methylchromone produced the indoles through C-6 of the aromatic ring. This alteration in regioselectivity of the two substrates was attributed to greater Vander Waal repulsions between both the substituents on the aromatic ring and with the electrophile (aryl glyoxals). The authors also prepared indolyl-coumarins **20** by oxidative cyclization of acetophenone with 4-hydroxycoumarins and primary aromatic amines like 7-amino-2-methylchromone in the presence of iodine/DMSO as catalyst/oxidant (Scheme 23). The plausible mechanism of the reaction is shown in Scheme 24. The reaction proceeded by *in-situ* generation of arylglyoxal by C(sp^3)–H oxidation of acetophenone. Authors reported that the *in-situ* methodology was not appropriate for the heterocyclic methyl ketones.

Thiophenes

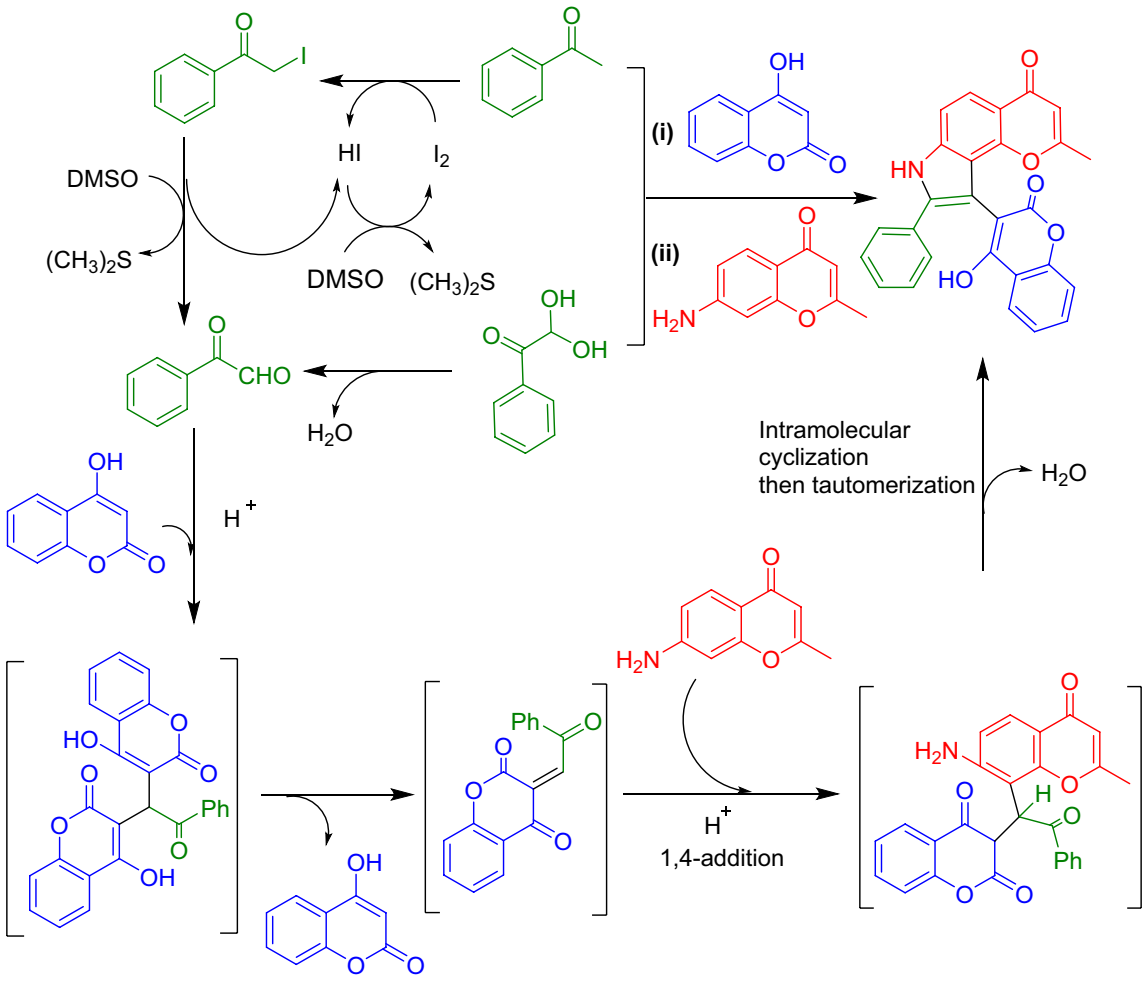
Thiophene moieties have been extensively studied in the field of medicine, fungicides and dyes [55]. Molecular hybridization with coumarin scaffold may further enhance the potency/selectivity of the thiophene moiety.

Yahaya et al. [56] synthesized 4-coumarin-3-yl-thiophenes **21** via Gewald reaction of 3-acetyl coumarin, malononitrile and elemental sulfur (S_8), under microwave irradiation, using a mixture of Et_2NH and ethanol as solvent (Scheme 25). Author proved that MWI protocols for the reaction were more efficient (yield: 90–100%) than the thermal method (yield: 80–98%) and led to greater purity and enhanced yields of the desired compounds.

Aydıner et al. [57] reported a solvent-free synthesis of a series of 3-coumarin-3-yl-5-(2-thienyl)-2,6-dicyanoanilines **22** via one-pot, three-component reaction of 2-(1-(7-(diethylamino)-2-oxo-2H-chromen-3-yl)ethylidene)malononitrile, thiophene-2-carboxaldehyde and malononitrile, under microwave irradiation (Scheme 26), using piperidine as catalyst. A plausible mechanism for the reaction is depicted in Scheme 27. MW irradiation led to shorter reaction time, higher yields, pure products and reduced cost.

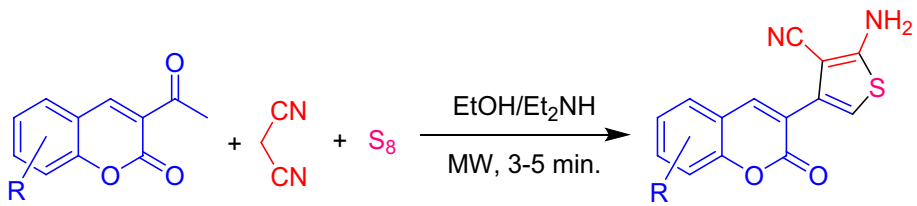


Scheme 23 Synthesis of indolyl coumarins



Scheme 24 Plausible mechanism for synthesis of indolyl coumarins

Scheme 25 Synthesis of 4-coumarin-3-yl thiophenes



R = 6-Br, 6-Cl, 6-OH, 7-$(C_2H_5)_2NH$, 7-OCH_3, 7-OH, 8-OCH_3, 8-OC_2H_5

21
9 examples
(85-90 %)

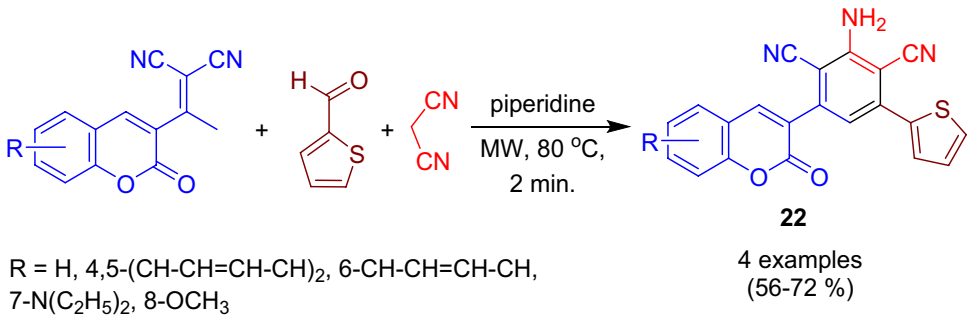
Five-membered ring with two heteroatoms

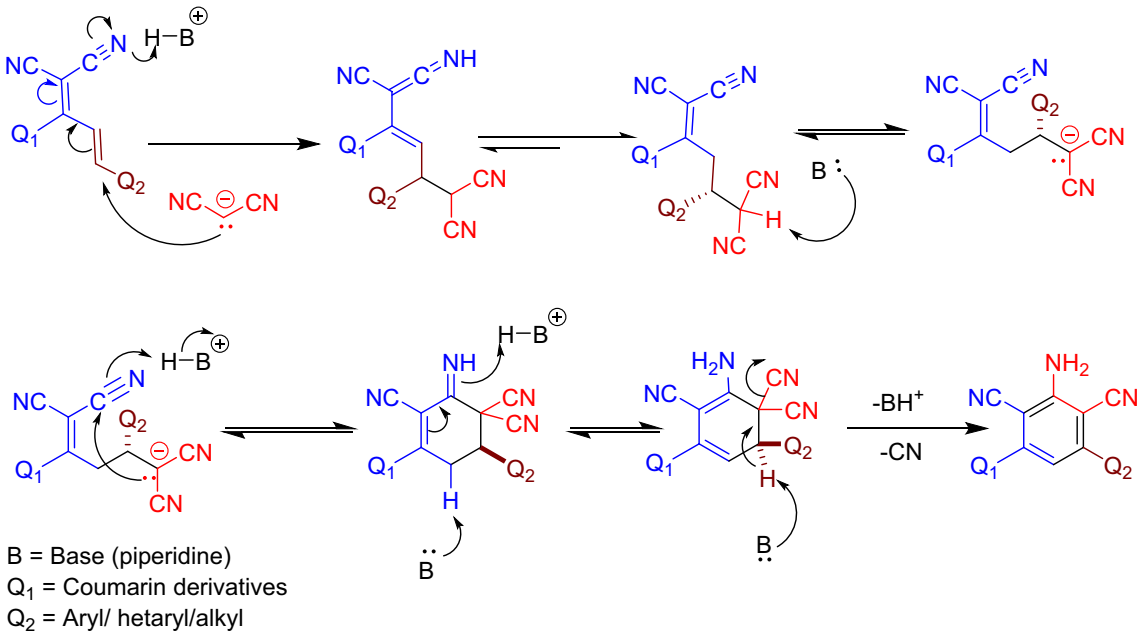
Pyrazoles

Coumarin and pyrazole scaffolds are found in many natural and synthetic drug molecules. Pyrazolocoumarins comprising of both pyrazole and coumarin scaffolds exhibit antibacterial, antifungal and anticancer activities [58]. Newer synthetic strategies for coumarin-fused or -linked pyrazoles may open doors to novel biologically active molecules.

Many research groups explored the synthesis of benzyl pyrazolylcoumarins using a variety of catalysts and solvent systems, like Shaikh et al. [59] synthesized benzyl pyrazolylcoumarins **23** via MWCNT/Silica aerogel catalyzed one-pot, multicomponent condensation of phenylhydrazine, ethylacetoacetate, 4-hydroxycoumarin and aromatic aldehyde,

Scheme 26 Synthesis of 3-coumarin-3-yl-5-(2-thienyl)-2,6-dicyanoanilines





Scheme 27 Plausible mechanism for synthesis of 3-coumarin-3-yl-5-(2-thienyl)-2,6-dicyanoanilines

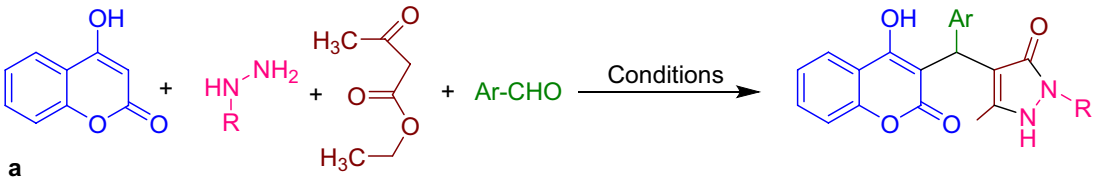
in the presence of acetonitrile as the solvent (Scheme 28a). Authors reported that the catalytic activity of MWCNT/Silica aerogel probably was due to hydrophobic nature arising from the surface methyl groups as well as high silicon content. The active sites on MWCNT/Silica aerogel were reportedly generated by dehydroxylation of the isolated surface hydroxyl groups or the strained siloxane bridge.

Jelali and co-workers [60] have proposed synthesis of a series of benzyl pyrazolylcoumarin **23** using Bmim[triflate] as a green solvent and glacial acetic acid as the catalyst (Scheme 28b). The reaction proceeded at high temperature (210 °C) but required a shorter reaction time and gave moderate to good yields. Authors reported that the nature of the functionalities on the aromatic aldehydes did not affect the reaction parameters significantly.

Similarly, Siddiqui and co-workers [61] explored the reusable Chitosan-GO NPs (CS-GO) as a hybrid catalyst for synthesizing benzyl pyrazolylcoumarins **23,** using ethanol as solvent (Scheme 28c). Although the reaction took longer time but gave good yields of the desired product and further the easy separation of the catalyst simplified the protocol. The authors reported that the functional groups (carboxyl, epoxide or hydroxy, etc.) bestow appropriate acidity, oxidizing ability and high tenability to the catalyst toward polar reagents and organic substrates.

Another library of benzyl pyrazolylcoumarin **23** was developed by Kamble et al. [62] taking niobium pentachloride-$AgClO_4$ as a Lewis acid catalyst and ethanol as the solvent (Scheme 28d). The reaction provided excellent yields of the product, many electron-rich and electron-deficient aldehydes were well endured. The reaction was faster than that proposed by Siddiqui and co-workers [61] and was energy efficient as it could be carried out at room temperature.

Later on, Siddiqui et al. [63] improvised their previous report and used human urine carbon (HUC) as a nanocatalyst for the same protocol to synthesize benzyl



23

a

R = C_6H_5; Ar = C_6H_5

Conditions: MW CNT/Silica, aerogel, acetonitrile, r.t. , 40 min., 1 example, 60 %

b

R = H, C_6H_5

Ar = C_6H_5, 4-$CH_3C_6H_4$, 4-$NO_2C_6H_4$, 4-$N(CH_3)_2C_6H_4$, 3-BrC_6H_4, 3-$OCH_3C_6H_4$, 3-OHC_6H_4

Conditions: Gla. HOAc, Bmim[triflate], 210 °C, 30 min., 14 examples, 60-95 %

c

R = C_6H_5; Ar = C_6H_5, 4-$CH_3C_6H_4$, 4-$NO_2C_6H_4$, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 3-BrC_6H_4, 3-$NO_2C_6H_4$, 2-$NO_2C_6H_4$, 2-ClC_6H_4

Conditions: Chitosan-GO NPs (CS-GO), EtOH, 50 °C, 3-10 h, 10 examples, 86-93 %

d

R = C_6H_5; Ar = 4-$NO_2C_6H_4$, 3-OHC_6H_4, thienyl, 3,4-$(OCH_3)_2C_6H_3$, 4-$CH_3C_6H_4$, 4-ClC_6H_4, 3-$NO_2C_6H_4$, 4-FC_6H_4, 4-OHC_6H_4, 4-$OCH_3C_6H_4$

Conditions: Niobium pentachloride- $AgClO_4$, EtOH, r.t., 30-60 min., 10 examples, 80-93 %

e

R = C_6H_5; Ar = 4-$NO_2C_6H_4$, 4-$CH_3OC_6H_4$, 4-ClC_6H_4, 4-BrC_6H_4, 3-$CH_3OC_6H_4$, 3-BrC_6H_4, 3,5-$(OCH_3)_2C_6H_3$

Conditions: Human urine carbon (HUC), EtOH/H_2O, 50 °C, 1-3 h, 7 examples, 85-97 %

f

R = 2,4-$(NO_2)_2C_6H_3$; Ar = C_6H_5, 2-$CH_3C_6H_4$, 2-$OCH_3C_6H_4$, 3-OHC_6H_4, 3-BrC_6H_4, 4-$CH_3C_6H_4$, 4-tBuC_6H_4, 4-ClC_6H_4, 4-CNC_6H_4, 4-$NO_2C_6H_4$, 3-C_2H_5O-4-OHC_6H_3

Conditions: Fe_3O_4@SiO_2@MCM-41-IL/ WO_4^{2-}, EtOH/H_2O, 70 °C, 25-45 min., 11 examples, 95-100 %

g

R = H, C_6H_5; Ar = 2-NO_2-5-OHC_6H_3, 4-$NO_2C_6H_4$, 4-FC_6H_4, 4-OHC_6H_4, 3-$NO_2C_6H_4$, 4-Br-2-OHC_6H_3, 2,4-$(Cl)_2C_6H_3$, 4-ClC_6H_4

Conditions: Amberlite IR-120, H_2O, reflux, 25-80 min., 12 examples, 57-91 %

h

R = H, C_6H_5; Ar = 2-OHC_6H_4, 4-$N(CH_3)_2C_6H_4$, 4-$OCH_3C_6H_4$, n-Pr, 4-$NO_2C_6H_4$, 3-OHC_6H_4, thienyl, 3,4-$(OCH_3)_2C_6H_3$, 4-$CH_3C_6H_4$, 4-ClC_6H_4, 4-BrC_6H_4, 2-OMe-1-Naphthyl

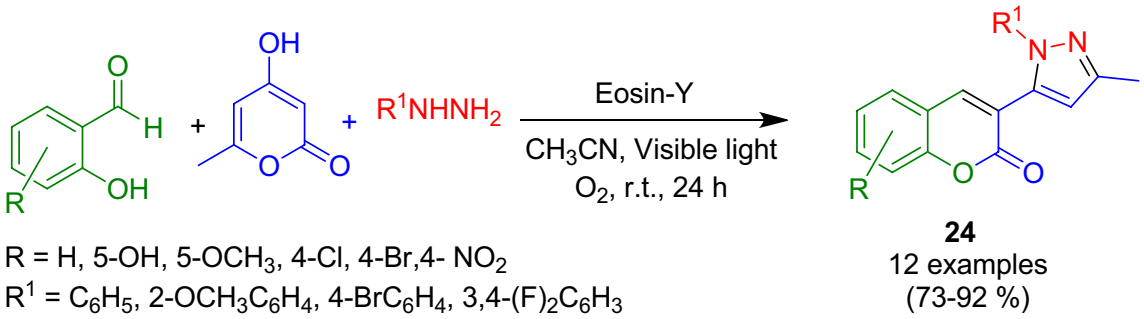
Conditions: Taurine, H_2O, 70 °C, 20-30 min., 18 examples, 80-94 %

Scheme 28 Synthetic routes for benzyl pyrazolylcoumarins

pyrazolylcoumarins **23** employing EtOH/H_2O as a greener solvent (Scheme 28e). The use of HUC nanocatalyst and different conditions drove the reaction at a much faster rate (1–3 h) than their previous report. Authors have also reported that electron-deficient aromatic aldehydes react faster and give higher yields of the target compounds.

In another report, Mofatehnia et al. [64] designed a novel magnetic yolk-shell nanocatalyst, Fe_3O_4@SiO_2@MCM-41 immobilized with ionic liquid/WO_4^{2-} to prepare benzylpyrazolyl coumarins **23** in excellent yields using EtOH/H_2O as solvent (Scheme 28f). Authors explained that synergistic acid–base catalysis was responsible for the higher yields and shorter reaction time. The reusable catalyst proved to be efficient for at least five successive runs. Notably, the electronic effects of the substituents on aromatic aldehyde did not significantly affect the reaction parameters.

Amberlite IR-120 in combination with water has been proved as a greener catalyst by Katariya et al. [65], for the synthesis of a series of benzyl pyrazolylcoumarins **23** on similar lines (Scheme 28 g). The authors reported that water (polar protic solvent) works best in the reaction. It was found that the electronic effects of substituted aldehydes did not affect the reaction parameters.



Scheme 29 Synthesis of 3-pyrazol-3-yl-coumarins

Chate et al. [66] reported by far the best synthetic route for synthesizing a diverse library of benzylpyrazolyl coumarins **23** employing the same protocol with 2-aminoethanesulfonic acid (taurine) as a bifunctional catalyst, and water as the solvent (Scheme 28 h). It was proposed that the ammonium ion of catalyst activated the carbonyl group by protonation and sulfonate ion increased the nucleophilicity of the amine through hydrogen bonding or inductive effect. The catalyst could be reused a minimum of three times with little loss of activity. Protic solvents were reportedly superior for the reaction since they stabilized the intermediate carbocation through dipole–dipole interactions and also reduced the reactivity of the nucleophile through electrostatic interactions.

To synthesize pyrazolyl coumarins **24**, Sharma et al. [67] carried out a one-pot, visible light catalyzed protocol using salicylaldehydes, 4-hydroxy-6-methyl-2H-pyran-2-one and phenylhydrazines, taking Eosin Y as photoredox catalyst (Scheme 29). Authors concluded that organic dye and visible light are mandatory components for the reaction. The plausible mechanism for photoredox reaction is depicted in Scheme 30, which shows that the radical reaction leads to the opening of pyran ring. Authors reported that arylhydrazines containing electron releasing group lead to an efficient reaction.

A different strategy was used by Chate et al. [68] for the aqueous phase construction of biologically active coumarin-linked pyrazolines **25** by a multicomponent reaction. The authors used ethyl acetoacetate in place of pyran, salicylaldehyde, hydrazine hydrate and aromatic aldehydes, engaging β-cyclodextrin as a supramolecular catalyst (Scheme 31). The reaction is well tolerated with aldehydes having electron-withdrawing, electron-donating groups as well as halogens. It was delineated that the formation of guest–host complexes, where the substrates are accommodated inside the lipophilic cavity of the catalyst, via non-covalent interactions, helps to solubilize the reactants in water and enhances the effectiveness of the catalyst.

Kovvuri and co-workers [69] have reported another catalyst-free, one-pot synthesis of pyrazole-aniline linked coumarins **26** by reaction of anilines, 4-hydroxycoumarin and pyrazole aldehydes (Scheme 32). Authors reported that electron-rich anilines produced lower yields in comparison with electron-deficient analogues.

Imidazoles

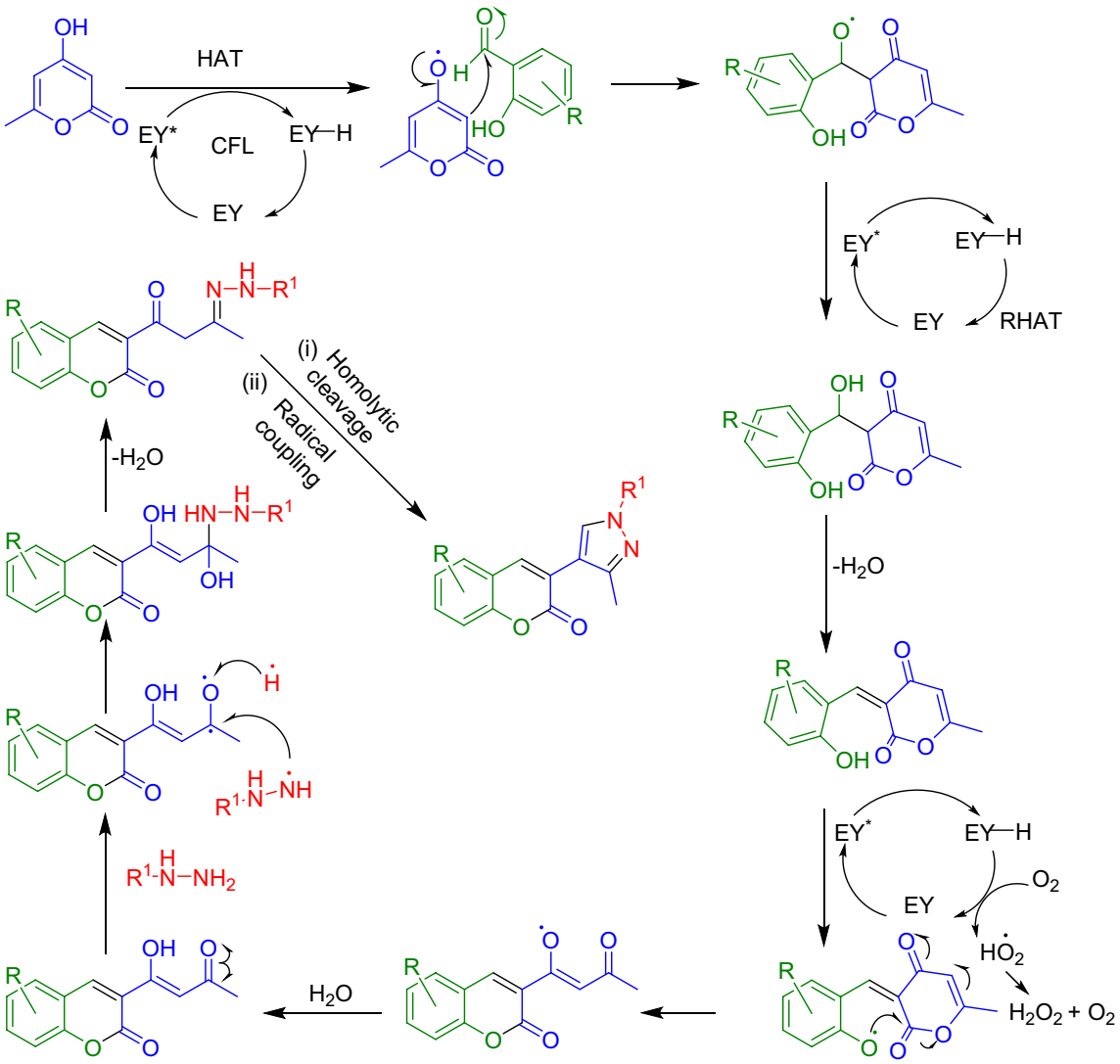
Being an integral part of important biomolecules like histidine, Vitamin B12, histamine and DNA bases, imidazole and its derivatives gained immense interest as they also exhibit diverse biological activities, like anticancer, antimicrobial, anti-inflammatory and analgesic activity [70]. Hybridization of biologically potent coumarin and imidazole scaffold in one molecule may result in a new series of bioactive molecules.

A novel synthetic protocol for coumarin imidazole hybrids **27** was proposed by Holiyachi and co-workers [70] via three-component, one-pot reaction of 4-formylcoumarin, ammonium acetate and benzil, in the presence of acetic acid as solvent and catalyst (Scheme 33). Sulfonamides are well known for their biological importance [16]. The authors synthesized coumarin imidazole sulfonamides **28** in excellent yields via reaction of **27** with p-toluenesulfonyl chloride in the presence of triethylamine (TEA) as a catalyst.

In another methodology, imidazole-linked coumarins **29** were synthesized by Bayat and co-workers [71] via one-pot, four-component reaction of salicylaldehydes, 1,1-bis(methylsulfanyl)-2-nitroethene, alkyl diamines, and ethyl/methyl cyanoacetate (Scheme 34)**.** Authors reported that the electron donor group on aromatic aldehyde and 1,2-diamino ethane gave slightly higher yields of the product as compared to other derivatives.

Thiazoles

Coumarins and thiazoles are both biologically potent pharmacophores. Hybrids of these two moieties have



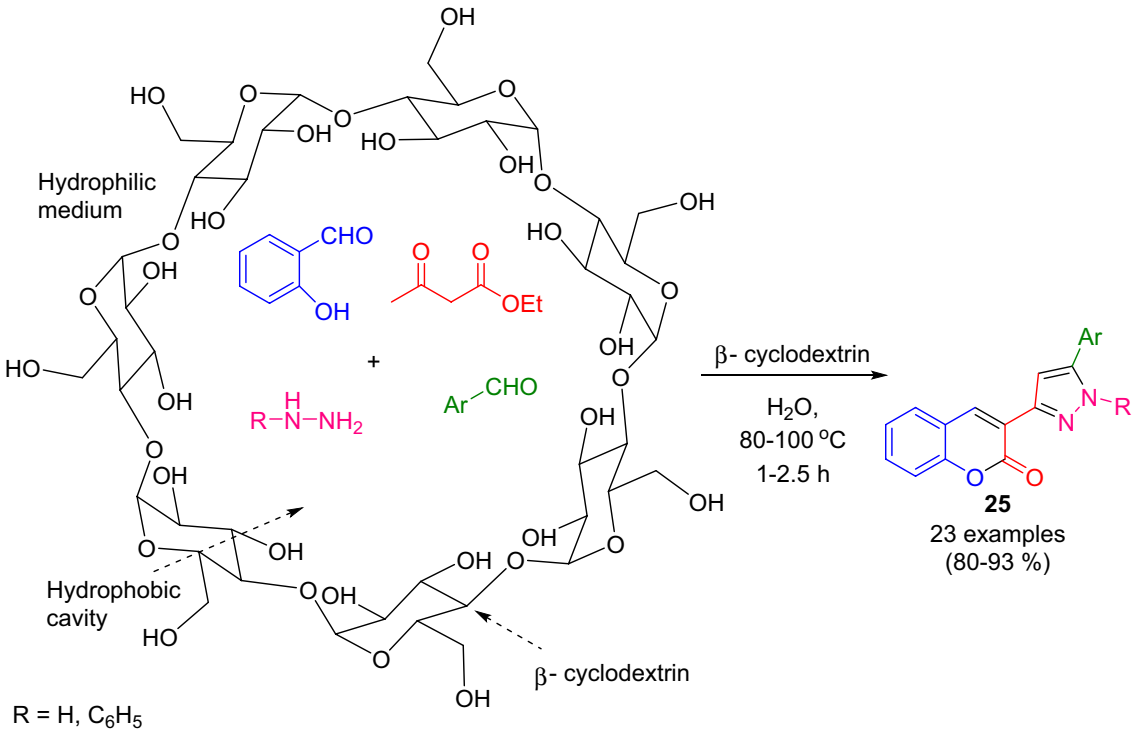
Scheme 30 Plausible mechanism for synthesis of 3-pyrazol-3-yl-coumarins

demonstrated significant antibacterial, antifungal, antidiabetic, antiviral, anti-inflammatory and anticancer activities [72].

Mamidala and co-workers [73] have synthesized a library of coumarin thiazoles **30a/30b** by the microwave irradiation of thiocarbohydrazide with aldehydes and 3-(2-bromoacetyl)coumarins (Scheme 35), using acetic acid as the catalyst. The reaction was fast and gave high yields of the product. The pathway possibly proceeds via condensation of 2 equivalents of aldehydes with one equivalent of thiocarbohydrazide to form bis-thiocarbohydrazone, which undergoes the S_N2-type attack on the 3-(2-bromoacetyl) coumarin followed by dehydrative cyclization to form the desired compound.

Yang et al. [72] prepared another library of novel coumarin thiazoles, bearing trifluoromethyl group **31,** through a solvent-free, one-pot, Hantzch reaction of 3-(trifluoroacetyl) coumarin with thiosemicarbazide and 2-bromoacetophenone (Scheme 36). Authors reported that coumarin and thiosemicarbazides bearing electron-withdrawing substituents were unfavorable for the reaction. The nature of substituents on 2-bromoacetophenone however did not affect the cyclization of thiazole.

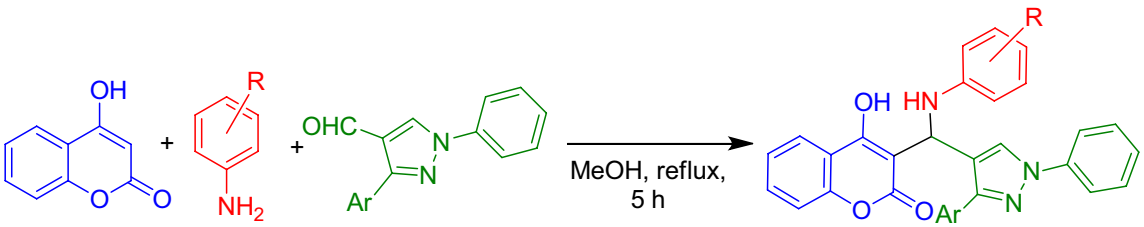
Kumar et al. [74] demonstrated the use of a green Lewis acid catalyst, montmorillonite (MMT) K10 clay, in an aqueous phase, three-component synthesis of donor(D)–acceptor(A) type hydrazinylthiazolyl coumarins (HTCs), via a reaction of thiosemicarbazides, various aromatic aldehydes/ketones, and 3-(2-bromoacetyl)-2H-chromen-2-one (Scheme 37)**.** The authors reported that the reaction progressed well in polar protic solvents. The catalyst could be reused 7 times. The method was found to



R = H, C_6H_5

Ar = C_6H_5, 3,4-$(OCH_3)_2C_6H_3$, 3,4,5-$(OCH_3)_3C_6H_2$, 4-$OCH_3C_6H_4$, 2-OCH_3-Naphthaldehyde, 4-OHC_6H_4, 3-$OCH_3C_6H_4$, 4-$CH_3C_6H_4$, 4-ClC_6H_4, 2,6-$(Cl)_2C_6H_3$, 2-Thiophenealdehyde, Valeraldehyde, Butyraldehyde, N,N-$(CH_3)_2C_6H_4$, 3-BrC_6H_4, 4-FC_6H_4, 3-$CH_3C_6H_4$

Scheme 31 Synthesis of pyrazolyl coumarins



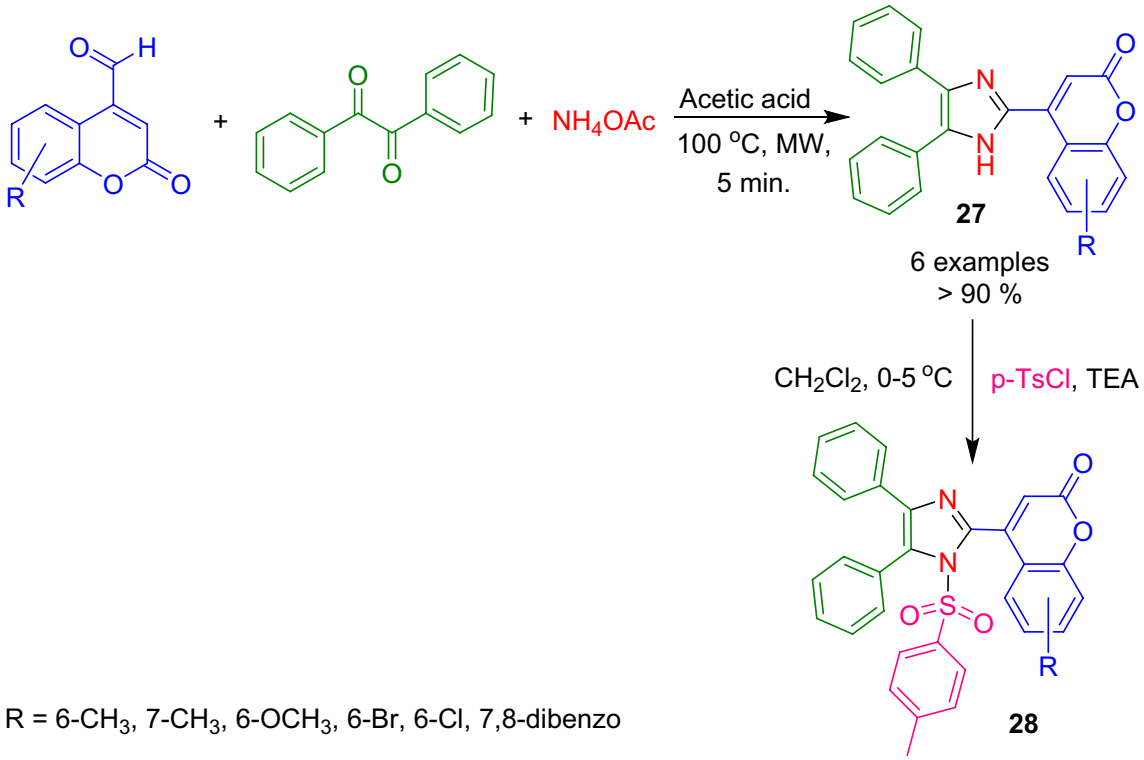
R = 4-CH_3 4-CH_3O, 3-CH_3O, 4-Cl; Ar = C_6H_5, 4-ClC_6H_4, 4-$NO_2C_6H_4$, 4-$CH_3OC_6H_4$, 4-$Cl_2C_6H_3$, 2-Naphthyl

Scheme 32 Synthesis of aniline substituted pyrazolylcoumarins

be suitable for mono- or disubstituted aldehydes/ketones/hetero aromatic aldehydes/ketones having electron-deficient and electron-rich groups.

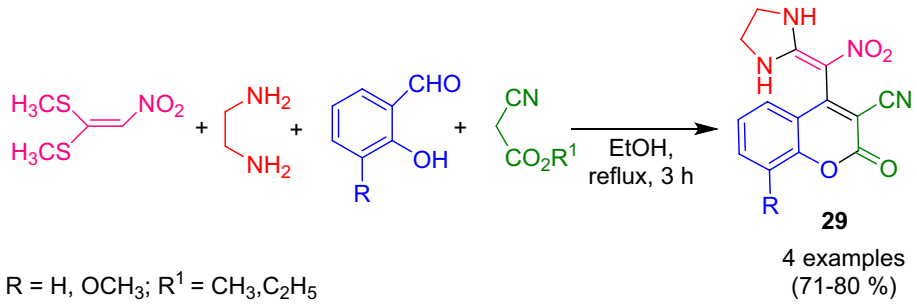
Bensalah et al. [75] carried out a three-component, one-pot synthesis of 3-thiazolyl-4-hydroxycoumarins **33** by condensing arylaldehydes, 3-acetyl-4-hydroxycoumarin, ammonium acetate and thiourea (Scheme 38), in the presence of dimethyl carbonate (DMC) as solvent and ammonium acetate as a mild Bronsted acid catalyst. Authors reported that the nonpolar and high boiling solvents lead to lower yields and higher reaction time. The presence of ammonium acetate and solvent polarity reportedly plays an important role in the success of the reaction. The reaction very well tolerated both the electron-rich and electron-deficient aromatic aldehydes.

Kavitha et al. [76] have reported a reaction of ethyl-4-chloroacetoacetate and arylthiourea with salicylaldehyde in ethanol, using L-proline as a catalyst, for the synthesis of 3-thiazol-5-yl-coumarins **34** (Scheme 39). The



Scheme 33 Synthesis of coumarin imidazoles

Scheme 34 Synthesis of coumarin imidazoles

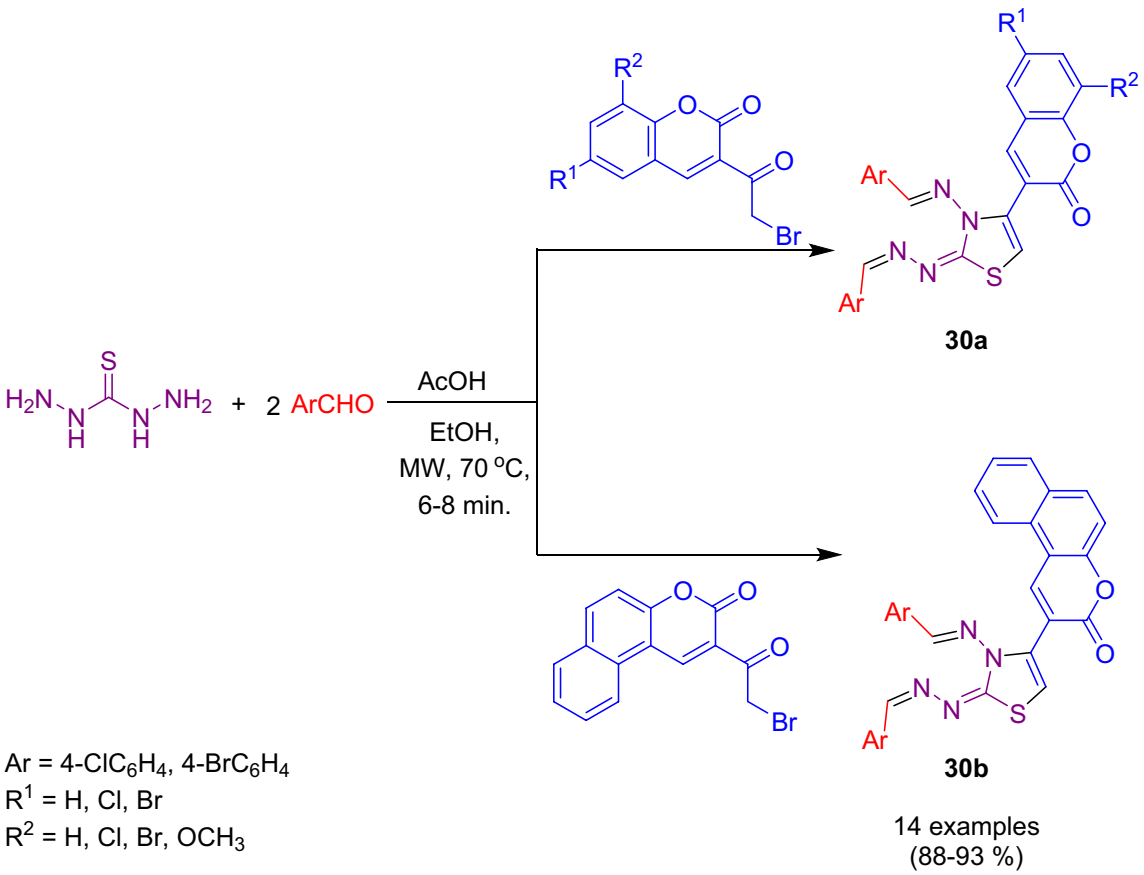


reaction tolerated various substituents on the aromatic ring of arylthiourea to form target compounds in good yields.

Pavurala et al. [77] have carried out the synthesis of a library of bis(phenylimino dihydrothiazolyl-2-H-chromene) **35** derivatives via one-pot, three-component approach involving 3-(2-bromoacetyl)-2H-chromen-2-ones, phenylisothiocyanates and *p*-phenylenediamine, in the presence of DMF as catalyst/solvent (Scheme 40).

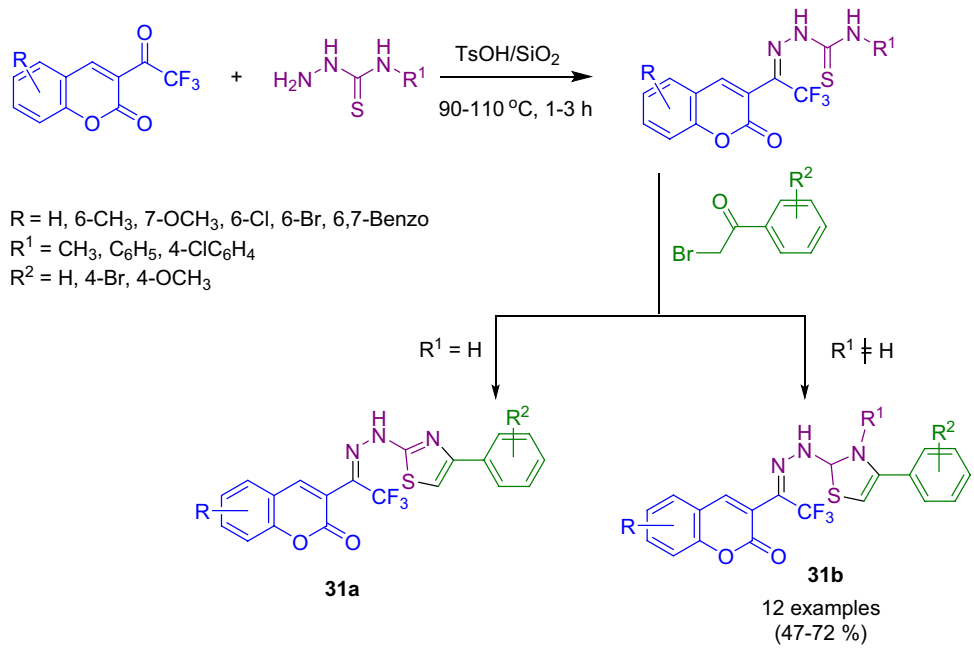
M. D. Obushak and co-workers [78] have developed an efficient, three-component approach for the synthesis of 3-hydroxy-4-(4-[2-{*N*′-[4-(dimethylamino)benzylidene] hydrazino}thiazol-4-yl]phenyl)-2*H*-chromen-2-one **36a** and 3-hydroxy-4-{4-[3-(4-chlorophenyl)-2-[(4-chlorophenyl) imino]-2,3-dihydrothiazol-4-yl]phenyl}-2*H*-chromen-2-one **36b** via reaction of pre-synthesized bromoacetyl chromenone with either aromatic aldehyde and thiosemicarbazide or aryl isothiocyanate and an aromatic amine (Scheme 41), using anhydrous ethanol as solvent.

Vaarla and co-workers [79] carried out a three-component, one-pot, synthesis of alkyl 4-oxo-coumarinyl ethylidene hydrazono-thiazolidin-5-ylidene acetates **37** via reaction of thiosemicarbazide with various substituted dialkyl acetylenedicarboxylates and 3-acetylcoumarins, using acetic acid as solvent (Scheme 42).

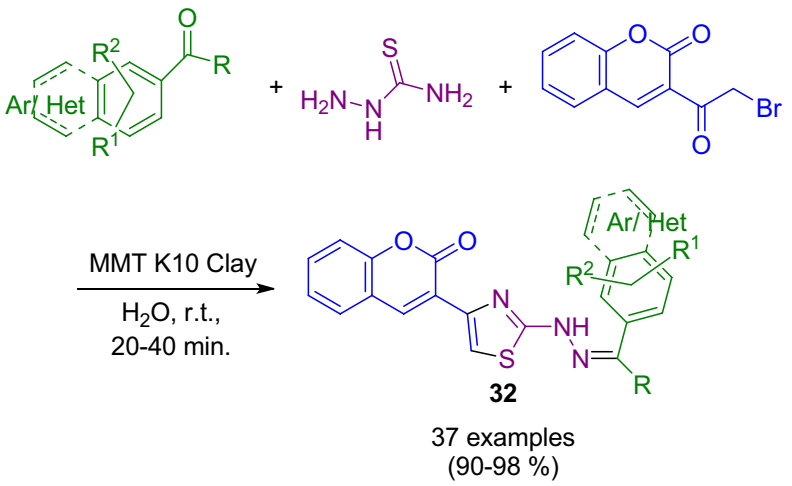


Scheme 35 Synthesis of coumarin thiazoles

Scheme 36 Synthesis of 2-(coumarin-3-yl)trifluoroethylidene thiazoles



Scheme 37 Synthesis of hydrazinylthiazolyl coumarins

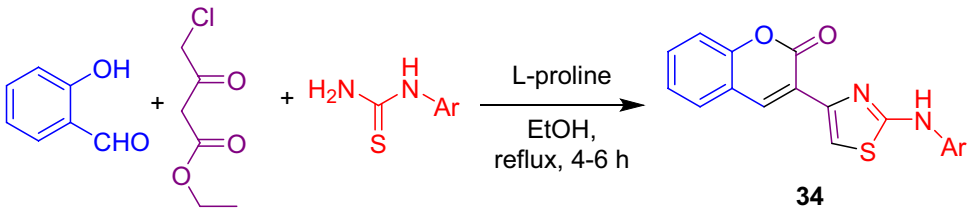


R = H, CH_3, C_6H_5; R^1 = CH_3, OCH_3, OH, OC_6H_5, NH_2, NO_2, CN, Br, F, Br, Cl; R^2 = H, Cl, Br, OCH_3, OH,

Scheme 38 Synthesis of 3-thiazolyl-4-hydroxycoumarins

Ar = C_6H_5, 4-$NO_2C_6H_4$, 3-OHC_6H_4, 4-$OCH_3C_6H_4$, 4-$CH_3C_6H_4$, 4-C_6H_5CHO

Scheme 39 Synthesis of 3-thiazol-5-ylcoumarins



Five-membered rings with three heteroatoms

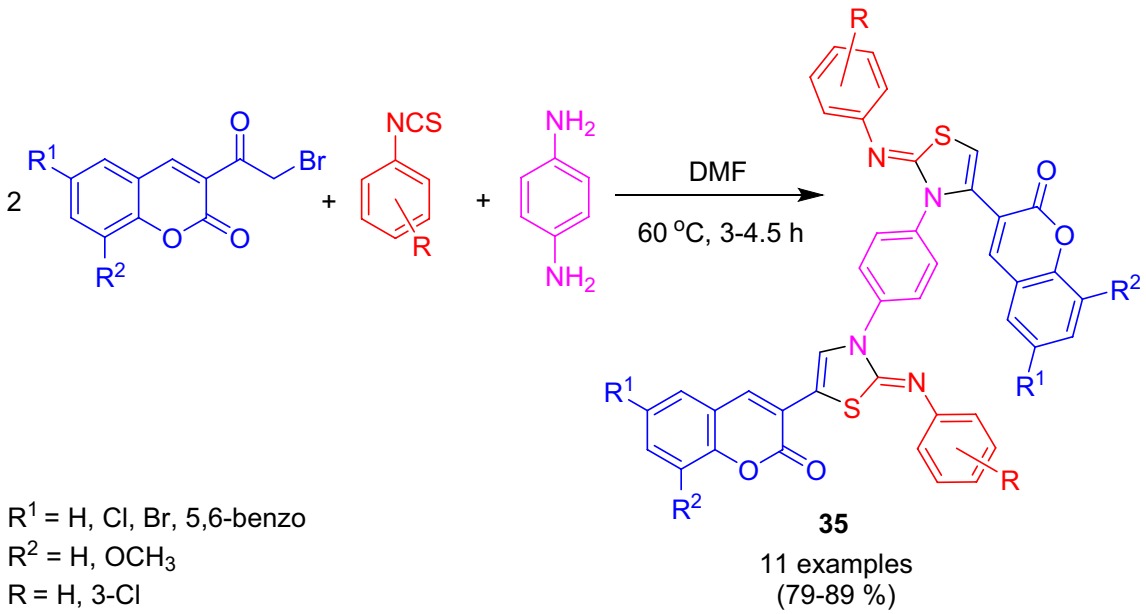
Oxadiazoles

Coumarin and oxadiazole scaffolds occur universally in a varied array of natural compounds and are treasured for their diverse and valuable pharmacological activities [80]. Oxadiazole and its derivatives are used in the treatment of multiple diseases like cancer, inflammation, diabetes and obesity [81]. A combination of oxadiazole unit with coumarin scaffold may further advance the reactivity and selectivity of the potent molecule.

Kazmi and co-workers [81] have developed three series of diamine bridged bis-coumarinyl-1,3,4-oxadiazoles **38** by one-pot, multicomponent reaction of coumarinyl oxadiazoles, aryl aldehydes and diamines, in the presence of ethanol as solvent (Scheme 43). It was reported that the reaction was diversity oriented and could tolerate both electron-rich and electron-poor aromatic aldehydes.

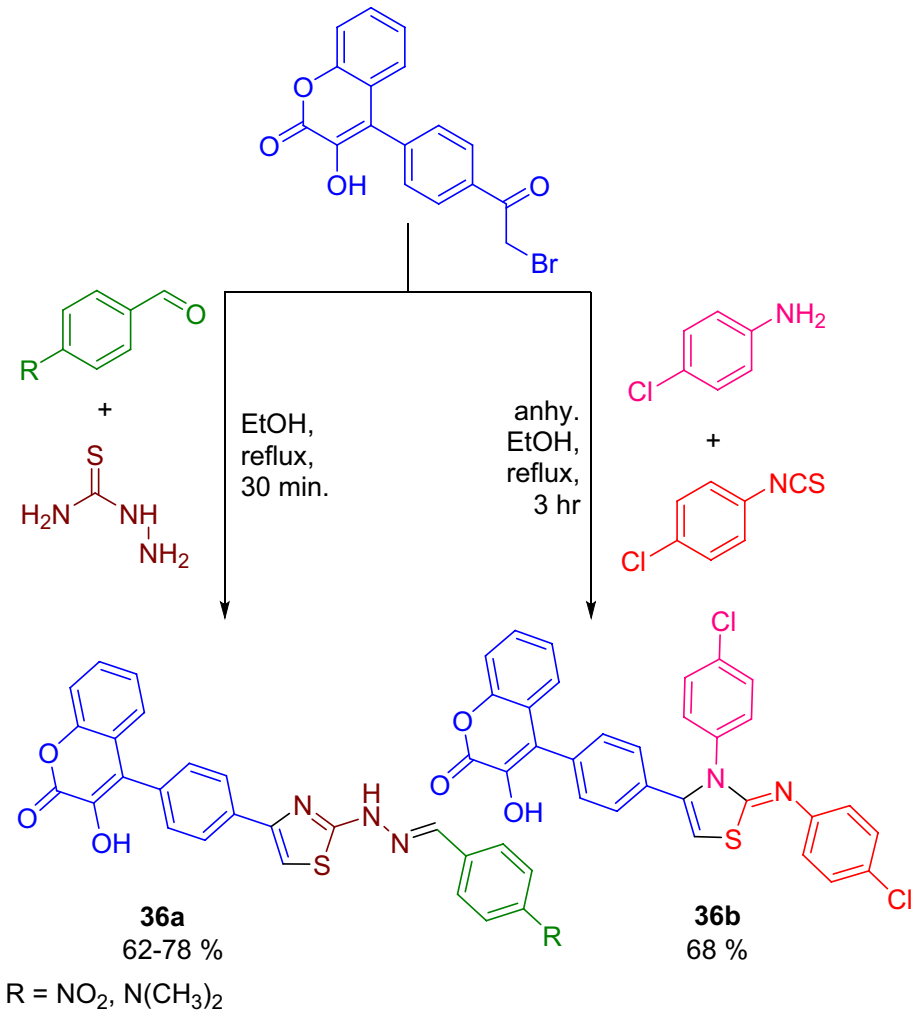
Thiadiazoles

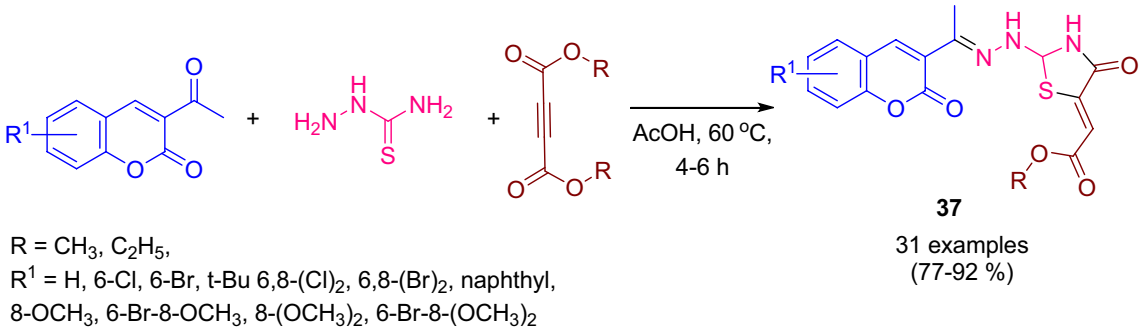
1,3,4-thiadiazoles are vital group compounds exhibiting a plethora of biological activities like antiviral, antimicrobial, antimycobacterial, anticonvulsant, antidepressant, anticancer



Scheme 40 Synthesis of bis(phenylimino dihydrothiazolyl-2-H-chromene) derivatives

Scheme 41 Synthesis of thiazolylcoumarins

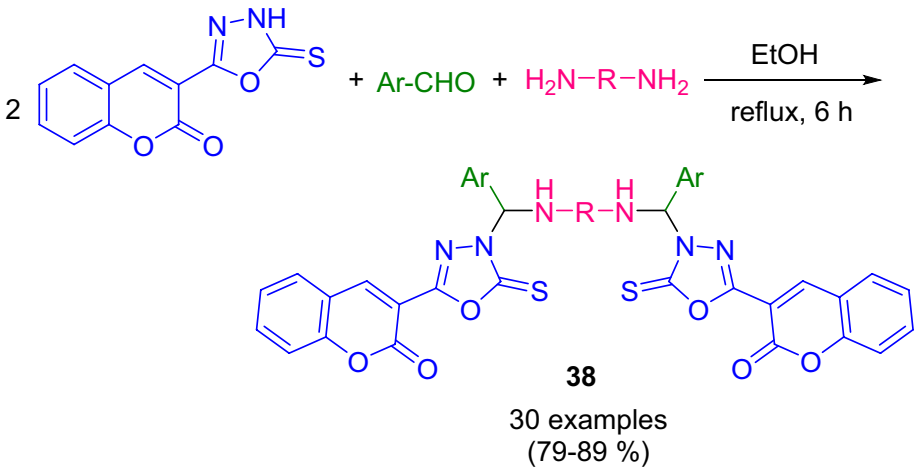




R = CH_3, C_2H_5,
R^1 = H, 6-Cl, 6-Br, t-Bu 6,8-$(Cl)_2$, 6,8-$(Br)_2$, naphthyl,
8-OCH_3, 6-Br-8-OCH_3, 8-$(OCH_3)_2$, 6-Br-8-$(OCH_3)_2$

Scheme 42 Synthesis of coumarin thiazoles

Scheme 43 Synthesis of diamine bridged bis-coumarinyl-1,3,4-oxadiazoles



Ar = 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 4-$NO_2C_6H_4$, 3-ClC_6H_4,
3-BrC_6H_4, 4-$CH_3C_6H_4$, 2,4-$(Cl)_2C_6H_3$, 4-$N(CH_3)_2C_6H_4$, 3-$OCH_3C_6H_4$.
R = C_6H_5, C_6H_5-C_6H_5, C_6H_5-O-C_6H_5

and antixiolytic activities. They are important intermediates in the commercial synthesis of useful like furidiazine, megazol and acetazolamide [82, 83]. A combination of coumarin and thiadiazole in the same molecule may further advance their biological potential.

Shahcheragh and co-workers [83] described a three-component, one-pot synthesis of new coumarinyl-1,3,4-thiadiazoles **39/40** using a Meldrum's acid or barbituric acid based ketene-S,S-acetal, 3-acetyl-coumarin and thiocarbohydrazides in the presence of a deep eutectic solvent, choline chloride-urea (Scheme 44). Authors reported that electron-deficient aromatic aldehydes produced higher yields than electron-rich counterparts.

Triazoles

1,2,3-triazoles and 1,2,4-triazoles occupy a central place in medicinal chemistry research courtesy of their diverse biological activities, some of them even find use in clinical practice. Hybridization of this scaffold with equipotent coumarin core may lead to novel candidates with a wider spectrum, greater efficiency and a manifold mechanism of action [84].

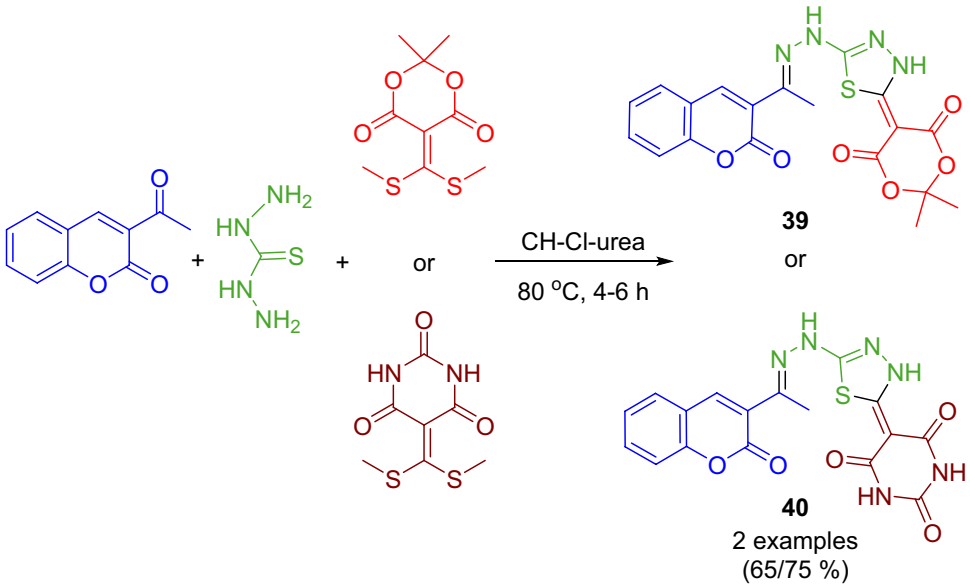
Hrishikesh and co-workers [85] have proposed a regioselective three-component, one-pot azide-alkyne click reaction to synthesize bis-coumarinyl triazoles **41** using coumarin propargyl ethers, halocoumarins and sodium azide, in the presence of copper(I) catalyst (Scheme 45).

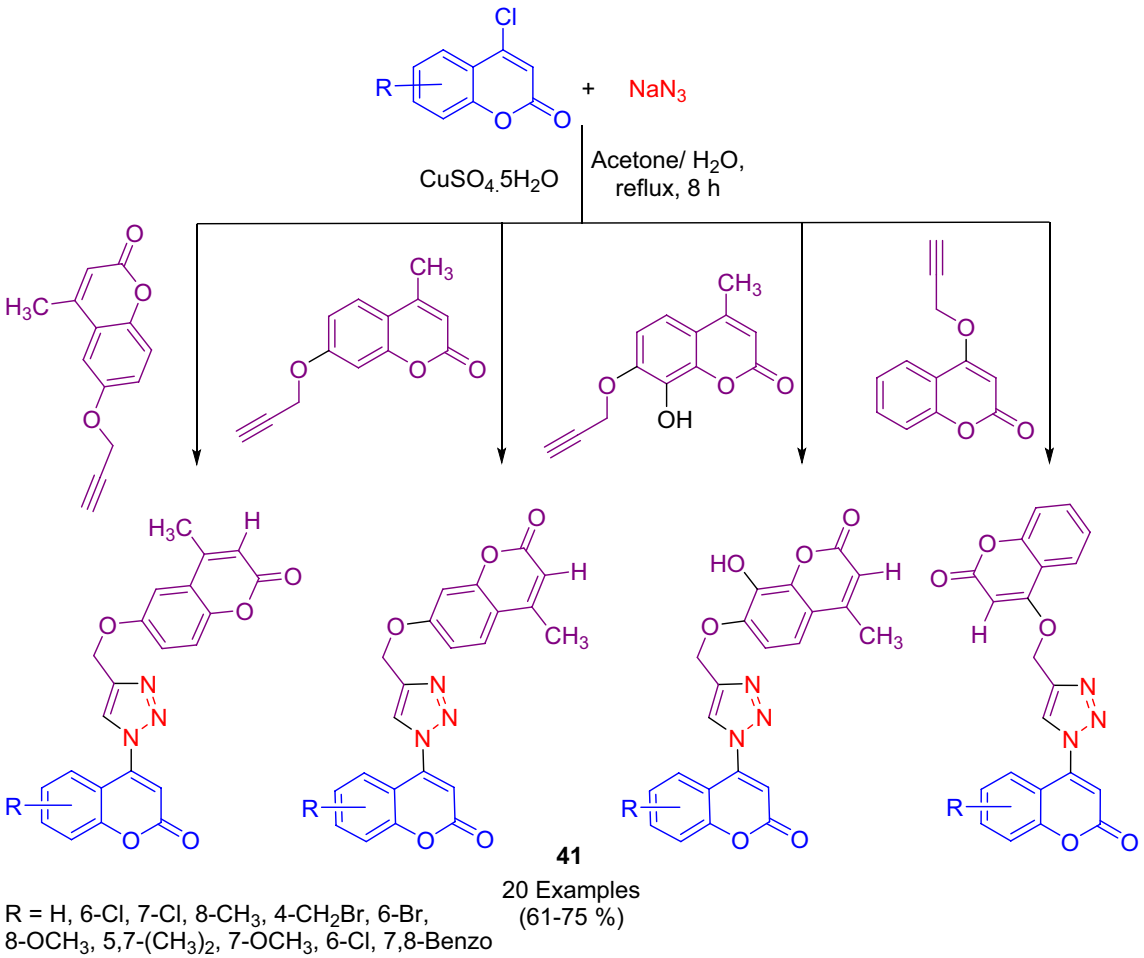
Five-membered ring with four heteroatoms

Tetrazoles

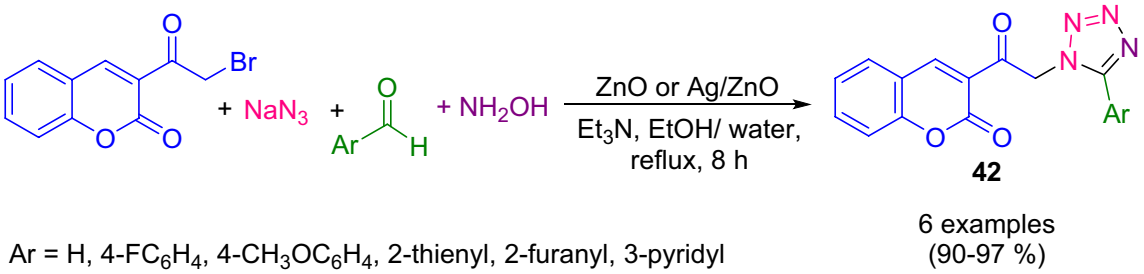
Tetrazoles, the non-metabolized bioisosteres of carboxylic acids and *cis*-amides possess varied chemotherapeutic properties, including antibacterial and antifungal activities. Hybridization of tetrazole with coumarin pharmacophore is

Scheme 44 Synthesis of coumarinyl-1,3,4-thiadiazoles





Scheme 45 Synthesis of bis-coumarinyl triazoles



Scheme 46 Synthesis of tetrazole coumarins

expected to enhance the biological potential of the resulting scaffold and also overcome drug resistance [86].

To synthesize 1,5-disubstituted tetrazole-coumarin hybrids **42,** Attia and co-workers [87] reported a facile, one-pot, strategy taking aldehyde, sodium azide, 3-bromoacetyl coumarin and hydroxylamine, in the presence of triethyl amine, and Ag-doped ZnO nanocomposites (NCs) as photocatalysts (Scheme 46). The authors explained that the incident light provides energy to push the catalyzed reaction, Ag NPs help in the absorbance of the light and subsequently, the holes of ZnO and the electrons move to the conduction band and participate in acceleration of [3 + 2] cycloaddition. It was further reported that Ag/ZnO nanocatalyst could be reused at least seven times.

Six-membered ring with one heteroatom

Pyrans and dihydropyrans

Pyranocoumarins have been reported for various biological activities including antibacterial, insecticidal, antifungal, anti-inflammatory, anticancer, anti-HIV and antioxidant activities [88], so this moiety occupies a key position in the class of oxygen-containing heterocyclic compounds and a large number of biochemists gained interest in exploring this scaffold.

Synthetic routes for 2-amino-3-cyanopyrano[3,2-*c*]chromenes **43** via the reaction of aryl aldehydes, 4-hydroxy coumarin and malononitrile in alcoholic, aqueous-alcoholic (H_2O:EtOH), or aqueous medium or solvent-free conditions using homogenous or heterogeneous catalysts or nanocatalysts have been proposed by several groups. A brief account is presented below.

Sarkate and co-workers [89] reported the synthesis of pyrano[3,2-*c*]chromene-3-carbonitrile using DMAP as a homogenous catalyst and ethanol as a green solvent (Scheme 47a). The reaction was fast, proceeded under mild conditions and gave moderate yields of the desired product.

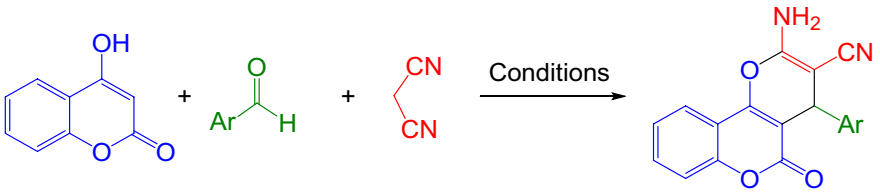
Sharghi and co-workers [90] used nanostructured 7-hydroxy-4-methyl-8-coumarinylglycine-Co complex [Co(MCG)$(H_2O)_3$] as a hybrid catalyst for synthesizing 2-amino-3-cyanopyrano chromenes **43** (Scheme 47b). The authors reported that the catalyst could be reused at least five times.

Azarifar and co-workers [91] exploited novel urea-functionalized silica-modified titanomagnetite ($Fe_{3-x}Ti_xO_4$@SiO_2@urea) nanoparticles as efficient basic catalyst for synthesizing 2-amino-3-cyanopyrano[3,2-*c*]chromenes **43** on similar lines, using ethanol/water (4:1) as solvent (Scheme 47c). The use of heterogeneous catalyst led to reduction in reaction time. It has been shown that the existence of Ti^{+4} ions in the nanoparticles skeleton led to an increase in the surface hydroxyl group count as well as the catalytic group (urea) loading on the surface of the nanoparticles. $Fe_{3-x}Ti_xO_4$ MNPs were prevented from oxidation or aggregation by introducing a coating of silica on their external surface. It was reported that the electron-deficient aldehydes reacted swiftly as compared to their electron-rich counterparts. The catalyst could be reused for at least five fresh runs.

Pourshojaei and co-workers [92] employed molybdenum oxide nanoparticles (MoO_3 NPs) as a catalyst for the synthesis of 2-amino-3-cyanopyrano[3,2-*c*]chromenes **43** (Scheme 47d) in an aqueous-alcoholic medium. Authors hypothesized that the Lewis acid character of Mo and hydrogen bonding to the oxygen atom of the MoO_3 is responsible for pushing the reaction and reducing the reaction time further. The catalyst can be recycled for six successive runs.

Another improved tandem method for the synthesis of 2-amino-3-cyano-pyrano[3,2-*c*]chromenes **43** using water/ethanol (1:1) as solvent and poly(4-vinylpyridine) [P_4VPy] as the catalyst (Scheme 47e), was proposed by Nasirmahale and co-workers [93]. It was found that the reaction was much faster than all the previous reports in the same solvent system and had much wider applicability. The authors have also reported the reusability of catalyst at least five times.

Abbasabadi and co-workers [94] explored the use of novel magnetite immobilized 1-naphthalenesulfonic acid-tailored graphene oxide (Fe_3O_4@GO–Naphthalene-SO_3H), as a catalyst for the synthesis of 2-amino-3-cyano-pyrano[3,2-c]chromenes **43** (Scheme 47f). The reaction was energy



43

a

Ar = C_6H_5, 4-OHC_6H_4, 4-BrC_6H_4, 2-ClC_6H_4, 2-$NO_2C_6H_4$, 4-$CH_3C_6H_4$, 2,4-$(Cl)_2C_6H_3$

Conditions: DMAP, EtOH, reflux, 15-30 min., 9 examples, 79-86 %

b

Ar = 4-$NO_2C_6H_4$, 4-$OCH_3C_6H_4$, 2,6-$Cl_2C_6H_3$

Conditions: [Co(MCG)$(H_2O)_3$], EtOH/water, reflux, 1-2 h, 3 examples, 78-91 %

c

Ar = C_6H_5, 4-$CH_3C_6H_4$, 2-BrC_6H_4, 2-$OCH_3C_6H_4$, 4-ClC_6H_4, 4-OHC_6H_4, 4-$NO_2C_6H_4$, 4-BrC_6H_4, 2,4-$(Cl)_2C_6H_3$, 2-ClC_6H_4, 3-$NO_2C_6H_4$, 3-Pyridyl

Conditions: Fe_3-xTixO_4@SiO_2@urea, EtOH/water (4:1), reflux, 15-80 min., 10 examples, 86-98 %

d

Ar = C_6H_5, 4-OHC_6H_4, 4-$NO_2C_6H_4$, 3-ClC_6H_4, 3-OHC_6H_4, 4-BrC_6H_4, 2-ClC_6H_4, 4-ClC_6H_4, 2-(morpholinoethoxyphenyl2-(piperidin-1-yl)ethoxy)phenyl, 3-(morpholinopropoxy)phenyl, 4-(bromobenzyl)oxy)phenyl, 4-(chlorobenzyl)oxy)phenyl, 3-(chlorobenzyl)oxy)phenyl

Conditions: MoO_3 NPs , EtOH/Water, 80 °C, 30-50 min., 15 examples, 87-95 %

e

Ar = C_6H_5, 4-CNC_6H_4, 4-OHC_6H_4, 4-$OCH_3C_6H_4$, 4-$CH_3C_6H_4$, 4-BrC_6H_4, 4-ClC_6H_4, 4-FC_6H_4, 4-$NO_2C_6H_4$, 3-$NO_2C_6H_4$, 3-ClC_6H_4, 2-ClC_6H_4, 2-$OCH_3C_6H_4$, Isatinyl, 4-$CHOC_6H_4$, 3-$CHOC_6H_4$, $C_6H_5CH_2CH_2$, $C_6H_5CH(CH_3)$, 5-F-isatinyl

Conditions: P_4VPy, EtOH-Water, 70 °C, 5-25 min., 19 examples, 90-95 %

f

Ar = C_6H_5, 4-$CH_3C_6H_4$, 4-ClC_6H_4, 4-OHC_6H_4, 3,4-$(OCH_3)_2C_6H_3$, 3-ClC_6H_4, $(CH_3)_2CHC_6H_4$, 4-$CH_3OC_6H_4$, 4-BrC_6H_4, 2-ClC_6H_4, 3-$OCH_3C_6H_4$, 4-OHC_6H_4, 3-BrC_6H_4

Conditions: Fe_3O_4@GO-Naphthalene-SO_3H, water, r.t., 2-10 min., 19 examples, 90-98 %

g

Ar = C_6H_5, 4-$CH_3C_6H_4$, 4-ClC_6H_4, 4-OHC_6H_4, 3,4-$(OCH_3)_2C_6H_4$, 3-ClC_6H_4-$(CH_3)_2CHC_6H_4$, 4-$CH_3OC_6H_4$, 4-BrC_6H_4, 2-ClC_6H_4, 3-$OCH_3C_6H_4$, 4-OHC_6H_4, 3-BrC_6H_4

Conditions: Fe_3O_4@SiO_2@imidazol-bisFe[HCO_3], solvent-free, 100 °C, 13-34 min., 12 examples, 80-94 %

h

Ar = C_6H_5, 4-OHC_6H_4, 4-$OCH_3C_6H_4$, 4-$CH_3C_6H_4$, 4-$N(CH_3)_2C_6H_4$, 4-ClC_6H_4, 4-FC_6H_4, 4-$NO_2C_6H_4$, 3-$NO_2C_6H_4$, 3-$OCH_3C_6H_4$, 2-ClC_6H_4, 2-$OCH_3C_6H_4$, 2-$CH_3C_6H_4$, 3,4-$(OCH_3)_2C_6H_3$, 4-OH-3-$CH_3OC_6H_3$,

Conditions: SCM NPs@BPy-SO_3H, solvent-free, 80 °C, 15-35 min., 15 examples, 92-97 %

i

Ar = C_6H_5, 4-OHC_6H_4, 4-$OCH_3C_6H_4$, 4-$CH_3C_6H_4$, 4-BrC_6H_4, 2-ClC_6H_4, 2,4-$(Cl)_2C_6H_3$, 2-$NO_2C_6H_4$

Conditions: Fe_3O_4@SiO_2@CPTES@Cu(II) Schiff base, solvent-free, 80 °C, 10-15 min., 8 examples, 89-98 %

j

Ar= C_6H_5, 4-$CH_3OC_6H_4$, 4-FC_6H_4, 4-Indole carbaldehyde, 3-$CH_3C_6H_4$

Conditions: $CoFe_2(C_4H_4O_6)_3.6H_2O$, water, MW, 2 min., 5 examples, 87- 93 %

Scheme 47 Synthesis of 2-amino-3-cyanopyrano[3,2-*c*]chromenes

efficient (proceeded at room temperature) and used water as a green solvent. It was reported that the catalyst could be reused for at least six fresh runs without noticeable loss of the catalytic activity.

Magnetically recoverable bis-ferrocene-tailored ionic liquid immobilized on silica grafted magnetite (Fe_3O_4@SiO_2@imidazol-bisFc[HCO_3]), as a new hybrid catalyst has been used by Mofrad and co-workers [95] for the synthesis 2-amino-3-cyano-pyrano[3,2-c]coumarins **43** under solvent-free conditions (Scheme 47 g). The plausible mechanism of the reaction is depicted in Scheme 48. The authors proposed that synergic catalysis via several acidic and basic sites on the catalyst surface helped to promote the reaction. It was further reported that electron-deficient aldehydes lead to faster reactions and higher yields. Further, it was reported that the catalyst could be reused for six consecutive reaction cycles.

Another useful synthesis of 2-amino-3-cyano-pyrano[3,2-c]chromen-5(4H)-ones **43** using sulfonated 2,2′-bipyridyl ketone (BPy)-Schiff base complex grafted on magnetic silica NPs (SCMNPs@BPy-SO_3H), as a hybrid reusable catalyst, has been developed by Chen and co-workers [96], under solvent-free conditions (Scheme 47 h). The authors reported that the catalyst pushes the reaction through increased electrophilicity of the carbonyl group as well as nucleophilicity of coumarin via hydrogen bonding.

Recently, Ebrahimiasl and co-workers [97] used a novel, Schiff base Cu(II) complex tailored on Fe_3O_4@SiO_2 nanoparticles(Fe_3O_4@SiO_2@CPTES@Cu(II) Schiff base complex) for the regioselective synthesis of 2-amino-3-cyano-pyrano[3,2-*c*]chromene **43** under solvent-free conditions (Scheme 47i). The reaction could be completed in a very short time and produced high yields of the product. Authors have reported that the nanocatalyst can be reused for six runs.

Similarly, Walle and co-workers [98] proposed aqueous phase, three-component, one-pot, strategy for synthesizing a library of 2-amino-5-oxo-4,5-dihydropyrano[3,2-c] chromene-3-carbonitriles **43** (Scheme 47 j) using cobalt doped iron (III) tartrate as a heterogeneous catalyst.

Darweesh and co-workers [99] proposed a synthesis of Bis-pyranocoumarins **44** via a pseudo-five-component reaction of one mole of 2,2′-(ethane-1,2-diylbis(oxy))dibenzaldehyde and four moles of 4-hydroxycoumarin, utilizing catalytic amounts of p-toluenesulfonic acid (Scheme 49). The authors showed that the position and length of the spacer group in the bis-aldehydes play a significant role in characterizing the nature of the final product.

Tanuraghaj and co-workers [100] have recently designed a novel one-pot reaction between 5,7-dihydroxy-4-methylcoumarin, aromatic aldehydes and dialkylacetylene dicarboxylate to form a library of pyrano[2,3-*h*] coumarins **45,** using sodium carbonate as catalyst (Scheme 50a). The reaction plausibly involves Michael-type addition, followed by nucleophilic addition and intramolecular dehydrative cyclization to produce the target compounds. The same research group [101] reported another synthesis of pyrano[2,3-*h*]coumarins **45** using sodium carbonate functionalized silica coated-iron oxide nanoparticles (Fe_3O_4@SiO_2@$(CH_2)_3OCO_2Na$) as heterogeneous catalyst (Scheme 50b). The authors reported that the heterogeneous catalyst afforded better yield in shorter reaction time. The nanocatalyst could be easily recovered by using an external magnet and reused ten times without a notable change in the catalytic activity.

Adil Omar and co-workers [102] developed a novel synthesis for fluorescent coumarin-4H-pyran conjugates **46** through a multicomponent reaction of malononitrile, various coumarin β-ketoesters and aldehydes, in aqueous media using cetyltrimethylammonium chloride (CTAC) (Fig. 4) as a catalyst (Scheme 51). It was proposed that CTAC merely acts as a weak base by abstraction of a proton from coumarin β-ketoester and malononitrile to help Knoevenagel condensation and Michael addition respectively.

Santos and co-workers [103] have designed synthesis of pyrano[3,2-*c*]coumarin **47** via a multicomponent reaction of aryl or aliphatic aldehydes, 4-hydroxycoumarin and 1,3-cyclohexanedione, using niobium pentachloride as Lewis acid catalyst and DCE/CH_3CN (1:1) as solvent (Scheme 52a).

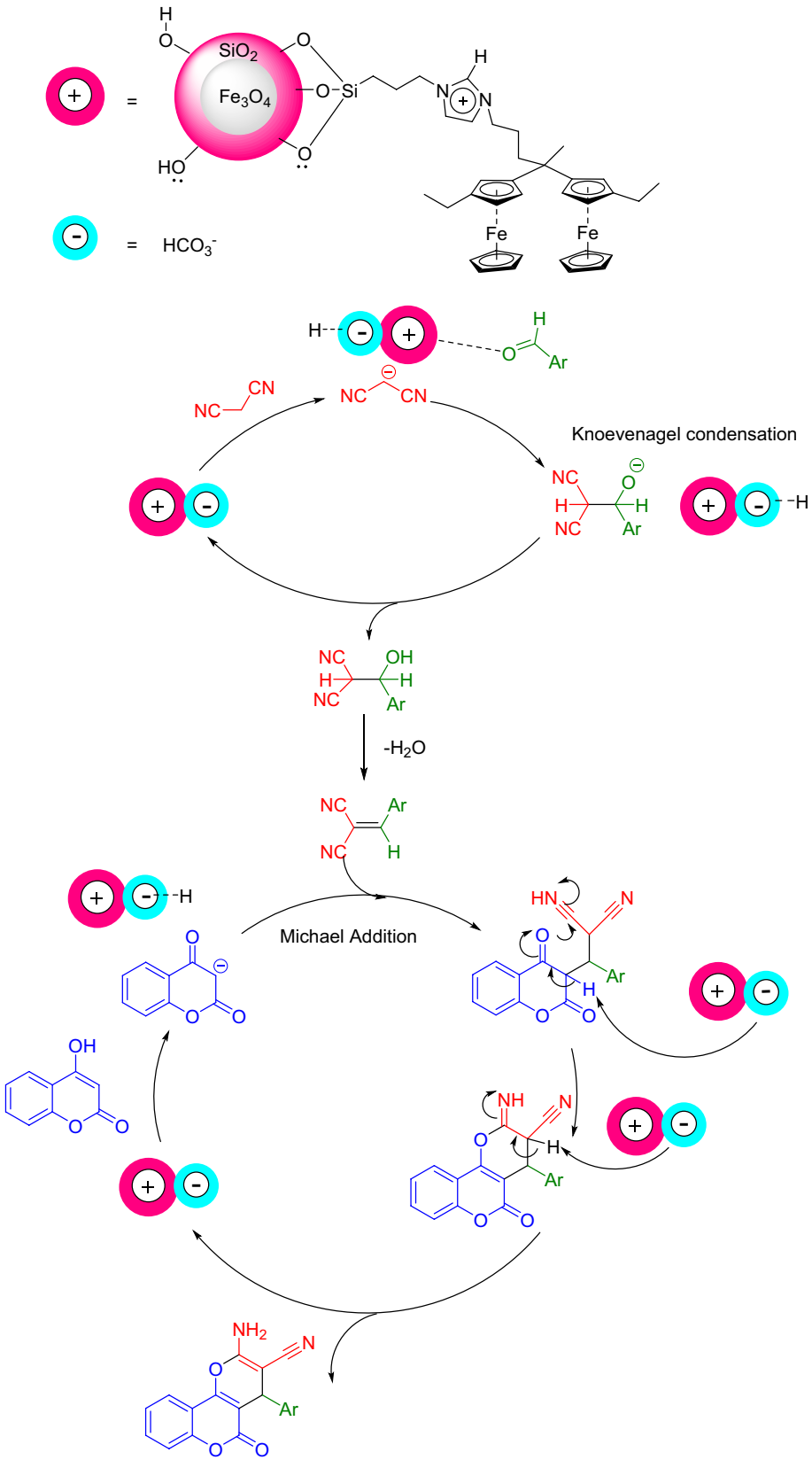
Similarly, Kamali and co-workers [104] synthesized **47** under milder conditions taking $SnCl_2.2H_2O$ as a Lewis acid catalyst and ethanol as the green solvent (Scheme 52b). Both pathways plausibly proceed via tandem reactions involving Knoevenagel condensation, Michael addition and cyclodehydration to produce the final product.

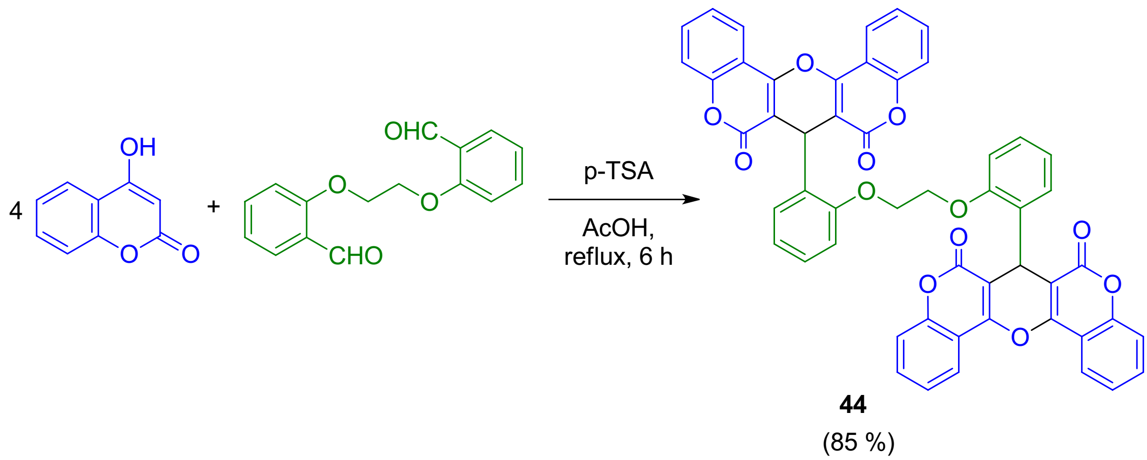
Fused pyrano biscoumarin analogs, are also interesting heterocyclic scaffolds, being useful for building a varied library of drug-like molecules, which find use in the pharmaceutical industry [105].

Narasashetty and co-workers [105] have established a facile synthesis of fused pyrano biscoumarins **48** via condensation of four equivalent of 4-hydroxycoumarin and one equivalent of 1,2-diphenylethane-1,2-diols, in the presence of acetonitrile as a solvent and lead tetraacetate as the oxidizing agent (Scheme 53). Authors reported that lead tetraacetate oxidized 1,2-diol into benzaldehyde releasing acetic acid, which catalyzes the reaction by promoting condensation reaction between 4-hydroxycoumarin and benzaldehyde as well as dehydrative cyclization in the final step to form the target compounds, **48**.

Kumar and co-workers [106] have proposed an efficient synthesis of biscoumarin-fused pyrans **49**, via one-pot, multicomponent reaction of malononitrile and various hydroxycoumarins and formylcoumarins in the presence of triethylamine as the catalyst. For example, a reaction of

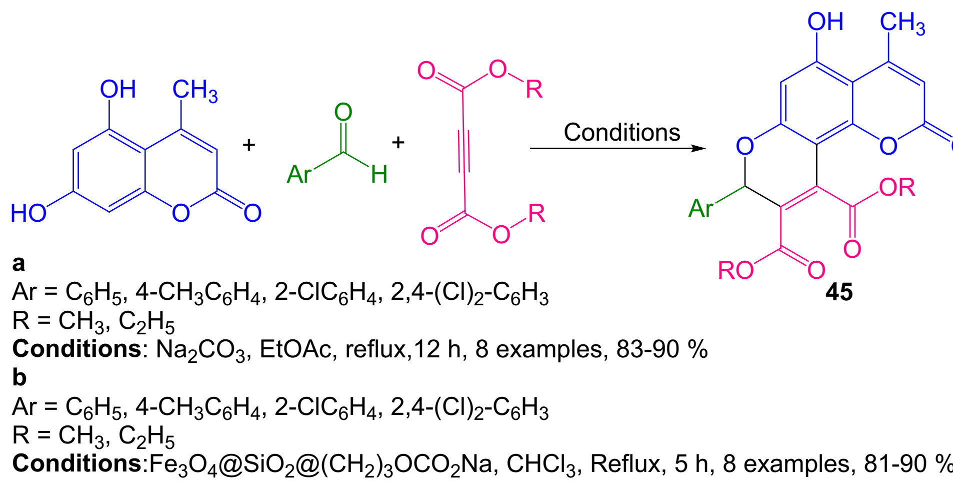
Scheme 48 Plausible mechanism for synthesis of 2-amino-3-cyanopyrano[3,2-*c*]coumarins





Scheme 49 Synthesis of Bis-pyranocoumarins

Scheme 50 Synthesis of pyrano[2,3-*h*]coumarins



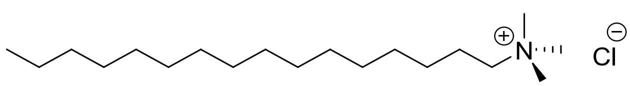
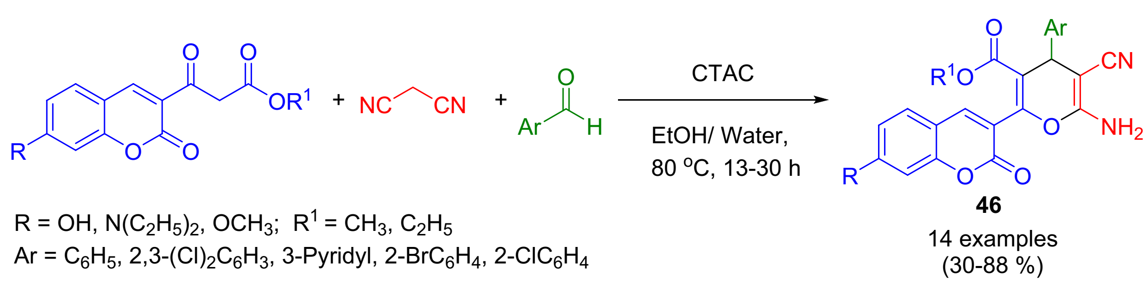


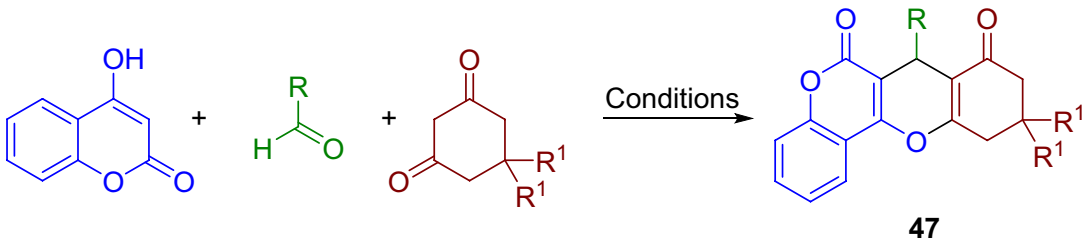
Fig. 4 Cetyltrimethylammonium chloride (CTAC)

malononitrile, 4-hydroxycoumarin and 6-formyl coumarin under the reaction conditions afforded **49** (Scheme 54).

Sammem and co-workers [107] have proposed one-pot, multicomponent tandem reactions of aldehyde grafted to phthalimide moiety, malononitrile, and 4-hydroxycoumarin,



Scheme 51 Synthesis of coumarin-4H-pyran conjugates



a

R = C_6H_5, 4-$CH_3C_6H_4$, 2-BrC_6H_4, 2-$OCH_3C_6H_4$, 4-$COOHC_6H_4$, 4-$CH_3OC_6H_4$, 4-$NO_2C_6H_4$, 4-BrC_6H_4, 4-PhenylC_6H_4, 4-OH-3-$OCH_3C_6H_3$, 2-Thienyl, 4-$(CH_3)_2NC_6H_4$, CH_3, CH_2=CH

R^1 = H

Conditions: $NbCl_5$, DCE/CH_3CN, reflux, 2 h, 14 examples, 53-74 %

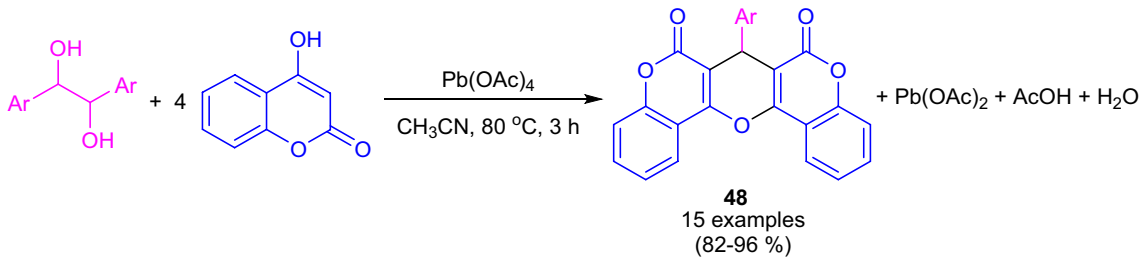
b

R = 4-$NO_2C_6H_5$, 2,4-$(Cl)_2C_6H_3$, 3-BrC_6H_4, 4-$N(CH_3)_2C_6H_4$

R^1 = CH_3

Conditions: $SnCl_2.2H_2O$, EtOH, 60 °C, 3 h, 4 examples, 51-87 %

Scheme 52 Synthesis of pyrano[3,2-*c*]coumarin



Ar = C_6H_5, 4-ClC_6H_4, 4-BrC_6H_4,4-FC_6H_4, 4-$CH_3C_6H_4$, 4-OHC_6H_4, 3-ClC_6H_4, 3-$C_2H_5OC_6H_4$, 3-BrC_6H_4, 3-Br-4-$CH_3OC_6H_3$, 3-Br-4-FC_6H_3, 3-Cl-4-FC_6H_3, 3,4-$(CH_3O)_2C_6H_3$, 2-Cl-6-FC_6H_3

Scheme 53 Synthesis of bis-coumarin-fused pyrans

in the presence of DABCO as the catalyst, to form phthalimide-pyrano[3,2-*c*]chromenes **50** (Scheme 55).

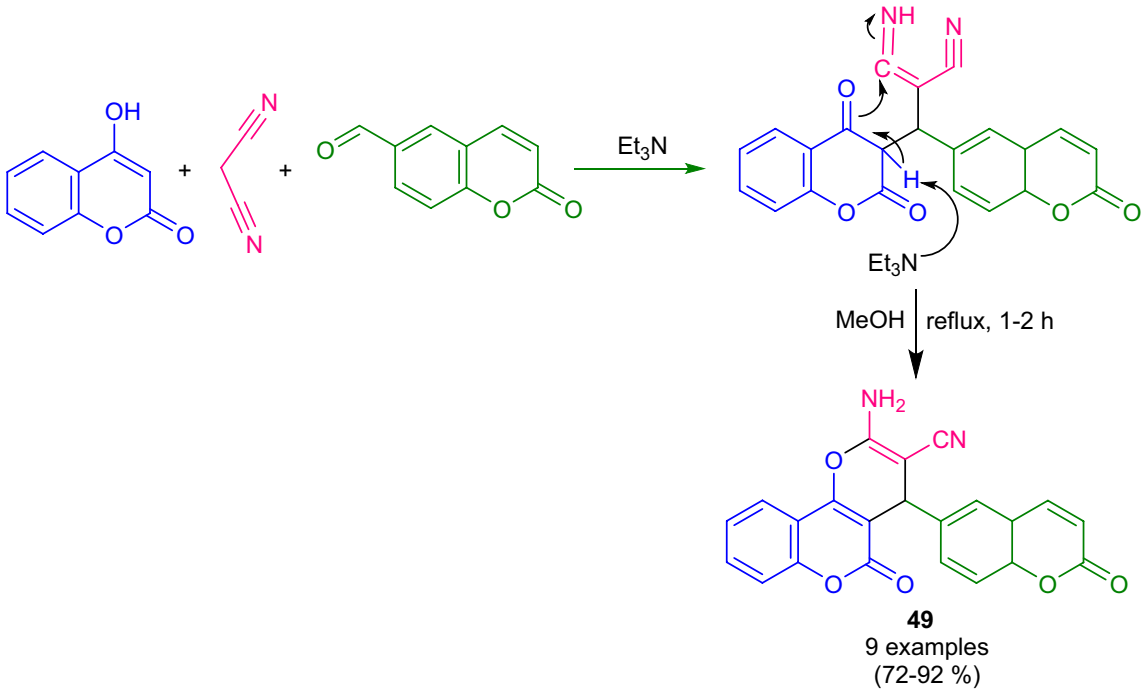
Pyridines, dihydropyridines, piperidines

Coumarin-fused pyridine, dihydropyridines and piperidines possess a variety of biological activities like anti-fungal, antibacterial, antidiabetic, anti-inflammatory, anticancer, calcium antagonist, monoaminoxidase, acetylcholine esterase inhibitor properties, besides being fluorescence active [108].

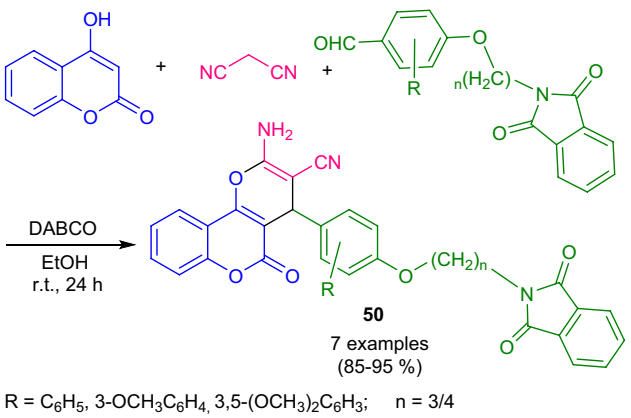
Bodke and co-workers [109] have utilized Chichibabin reaction for synthesizing 2,6-bis(1-coumarin-2-yl)-4-(4-substituted phenyl)pyridines **51** through one-pot, three-component reaction of aromatic aldehydes, 5-bromo-3-acetylcoumarin or 3-acetyl coumarin, and ammonium acetate, in the presence of glacial acetic acid as catalyst (Scheme 56).

Slimani and co-workers [110] have carried out a three-component, one-pot, cyclocondensation of 3-acetyl-4-hydroxycoumarin with ethyl cyanoacetate and aryl aldehydes, in the presence of dimethyl carbonate as solvent and ammonium acetate as the catalyst to produce biologically active 4-aryl-1,2-dihydro-6-(4-hydroxy-2-oxo-2H-chromen-3-yl)-2-oxopyridin-3-carbonitriles **52** (Scheme 57). Ammonium acetate acts as a base and also as the nitrogen source in the reaction. It was reported that the electron donor groups on aromatic aldehydes augmented the reactivity and produced higher yields.

Khajuria et al. [111] synthesized linked coumarin pyridones **53** via one-pot, three-component reaction between ethyl-2-nitroacetate, (E)-3-(3-arylacryloyl)-2H-chromen-2-ones and ammonium acetate (Scheme 58). Ammonium acetate serves both purposes of a base and ammonia source in the reaction.

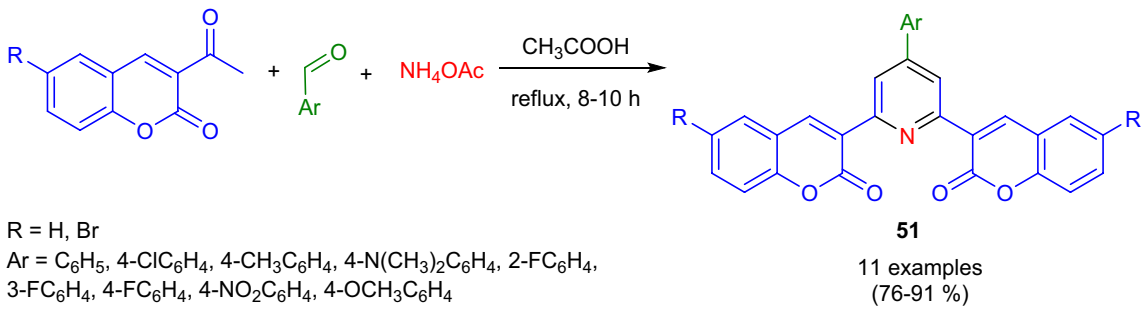


Scheme 54 Synthesis of pyrano bis-coumarins

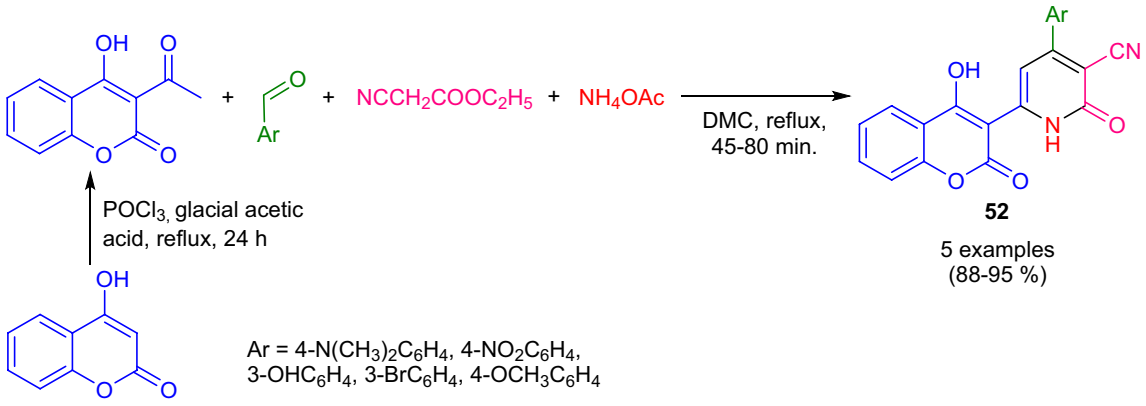


Scheme 55 Synthesis of phthalimide-pyrano[3,2-c]chromenes

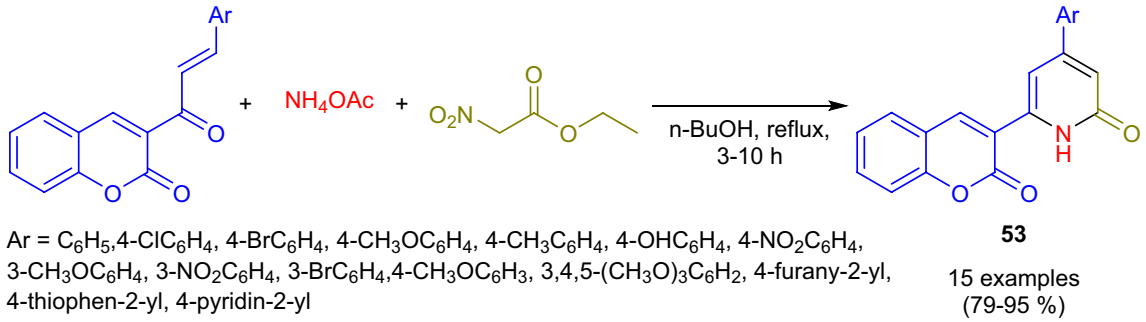
Mnasri and co-workers [112] have recently developed a simple and green procedure synthesizing 2-amino-6-(4-hydroxy-2-oxo-chromen-3-yl)-4-(aryl) nicotine nitriles **54** via one-pot, four-component reaction of 3-acetyl-4-hydroxycoumarin, aromatic aldehyde, malononitrile, with ammonium acetate**,** in the presence of Bmim triflate as solvent and ammonium acetate as the catalyst (Scheme 59). Authors reported that organic solvents such as THF, dichloromethane lead to lower yields and longer reaction time. Even though few examples have been discussed by the authors, it can be seen that the reaction is useful for aldehydes having both electron-donating or electron-withdrawing groups as well as halogens. The reaction leads to moderate to good yields of the desired product.



Scheme 56 Synthesis of 2,6-bis(1-coumarin-2-yl)-4-(4-substituted phenyl)pyridines

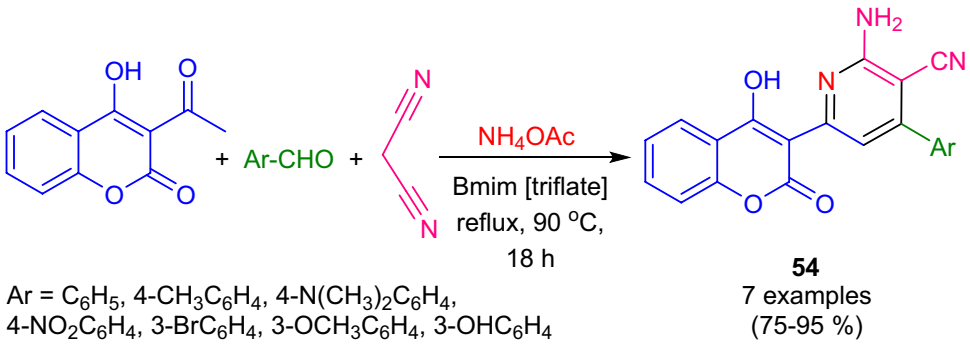


Scheme 57 Synthesis of coumarin pyridines



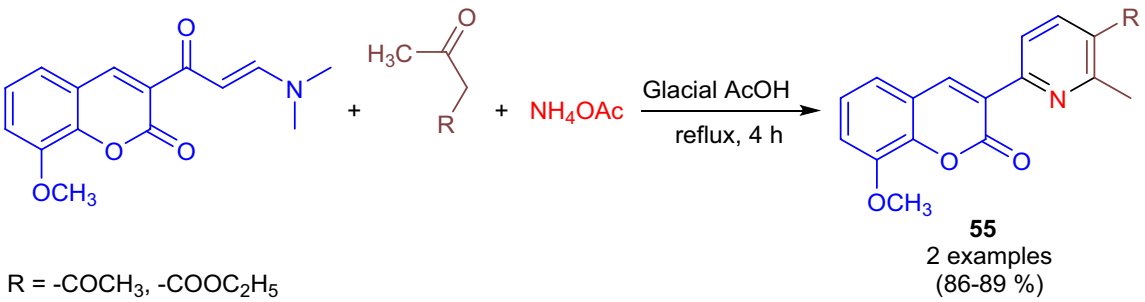
Scheme 58 Synthesis of coumarin pyridones

Scheme 59 Synthesis of linked coumarin pyridines

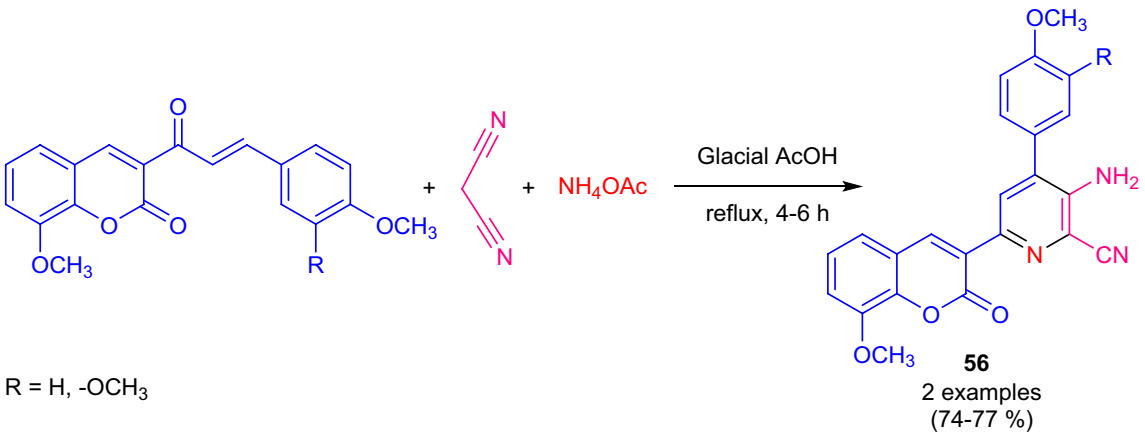


Elshemy and co-workers [113] have developed three-component, one-pot synthesis of biologically active coumarin pyridines **55/56** either from the reaction of 3-(3-(dimethylamino)acryloyl)-8-methoxy-2H-chromen-2-one, acetylacetone /ethyl acetoacetate and ammonium acetate or reaction of ammonium acetate, malononitrile and chalcone, in the presence of glacial acetic acid as catalyst, respectively (Scheme 60, 61).

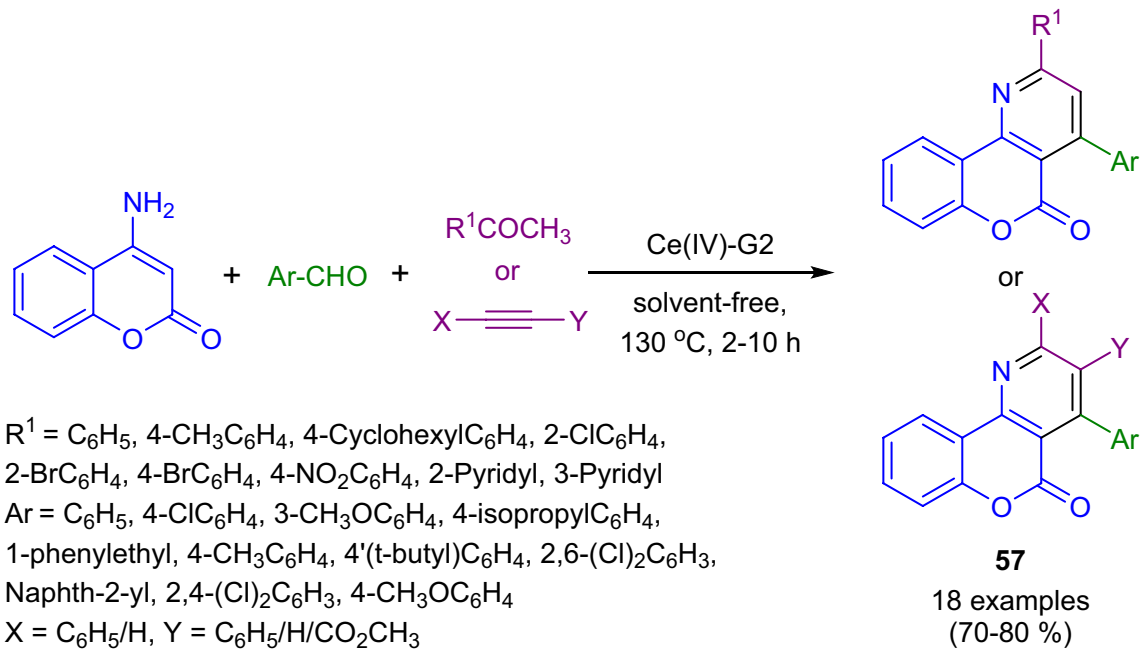
Kachouei and co-workers [114] have proposed a one-pot, three-component solvent-free synthesis of fused pyrido[3,2-*c*]coumarins **57** from aromatic aldehydes, 4-aminocoumarin and aryl/alkyl methyl ketones or phenyl acetylenes or methyl propiolate (Scheme 62), in the presence of catalytic amount of Ce(IV) grafted on Halloysite nanotube (HNT, $Al_2Si_2O_5(OH)_42H_2O$) functionalized dendrimer [Ce(IV)–G2 catalyst](Fig. 5). The authors reported that the reaction with internal and terminal alkynes proceeded with high regioselectivity. The plausible mechanism, shown in Scheme 63, was proved experimentally by performing the same reaction under argon atmosphere, where the yields of



Scheme 60 Synthesis of coumarin pyridines



Scheme 61 Synthesis of coumarin pyridines



Scheme 62 Synthesis of pyrido[3,2-*c*]coumarins

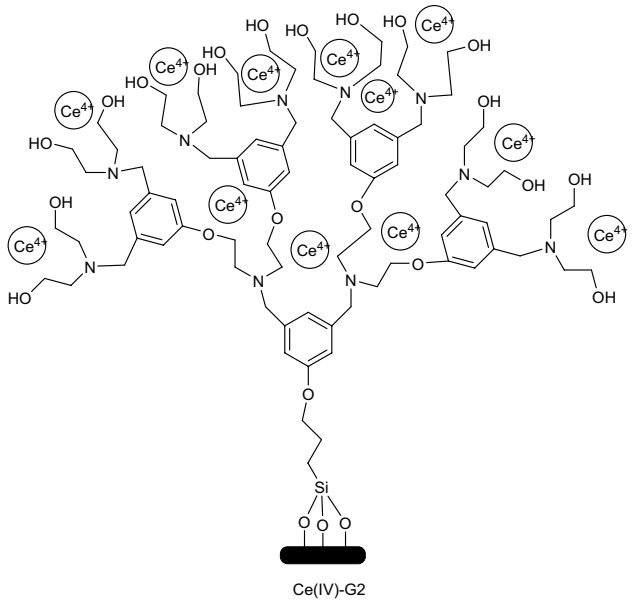


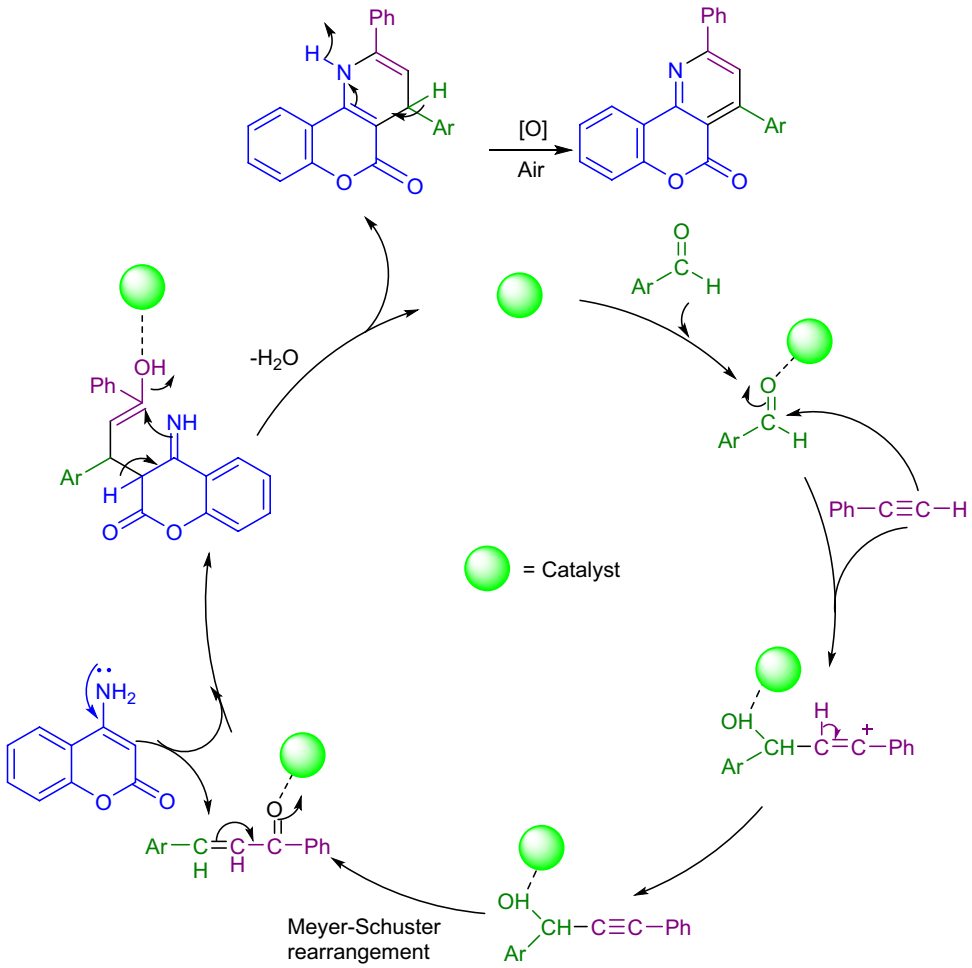
Fig. 5 Ce(IV)–G2 catalyst

the product were considerably reduced. This confirmed that no ABO is coming into play during the final oxidation reaction to produce **57**. The electronic effects of the substituents attached to aldehyde or aromatic ketone did not influence the reaction parameters. The dendrimers reportedly play a fundamental role in stabilizing Ce(IV) ions, which behave as Lewis acid in the reaction. The catalyst could be reused five consecutive times.

Olyaei and co-workers [115] have demonstrated an effective synthesis of benzyl heteroarylamino coumarins, 3-(aryl(pyridin-2-ylamino)methyl)-2H-chromen-2-ones **58**, via three-component, one-pot reaction of aromatic aldehydes, 4-hydroxycoumarin, and 2-aminopyridines, utilizing formic acid as the catalyst (Scheme 64). The electron-deficient aromatic aldehydes reacted faster. Among the various heteroaryl amines, the reaction advanced efficiently and gave the highest yields in the case of 2-aminopyridines.

Olyaei et al. [116] also synthesized novel coumarin enamines, (Z/E)-3-[(pyridin-2-ylamino)methylidene]chromane-2,4-diones **59**, via a three-component, one-pot, solvent-free condensation reaction of triethyl orthoformate,

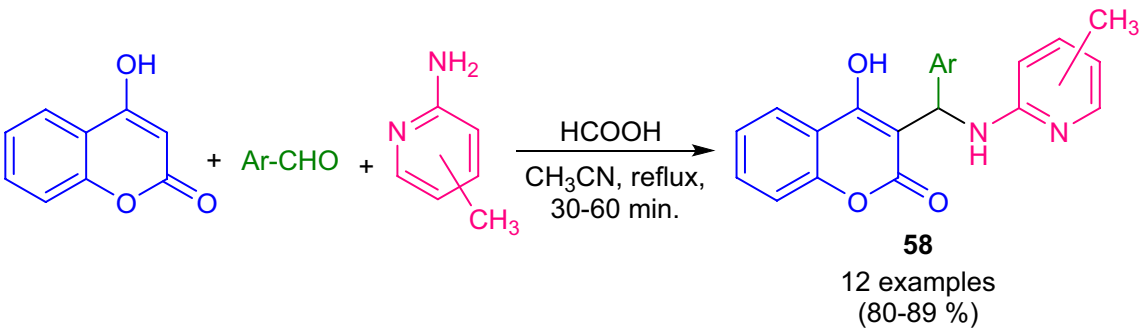
Scheme 63 Plausible mechanism for synthesis of pyrido[3,2-*c*]coumarins



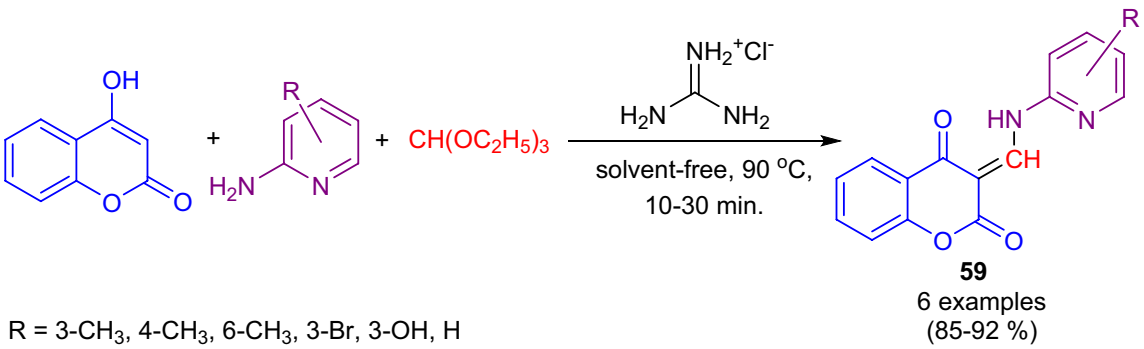
4-hydroxycoumarin, and 2-aminopyridines, utilizing guanidinium chloride as the catalyst (Scheme 65). The electronic effects of the substituents on the heterocyclic ring did not affect the reaction parameters significantly. ^{1}H-NMR spectra directed that E-ketoenamines were the major product. Authors hypothesized that the E-isomer is formed preferentially due to its additional stability enthused via a robust chelate-type intramolecular hydrogen bonding with the oxygen atom of the C(4) = O group.

Aydıner and co-workers [57] have also developed fluorescent coumarin comprising 3,5-disubstituted-2,6-dicyanoanilines **60** through microwave irradiated, three-component, one-pot, the solvent-free reaction of formyl pyridines, 2-(1-(7-(diethylamino)-2-oxo-2H-chromen-3-yl)ethylidene malononitrile and malononitrile, utilizing piperidine as the catalyst (Scheme 66). The reaction was fast and energy-efficient but had limited application as only a few aldehydes could be used and the product was obtained in moderate to poor yields.

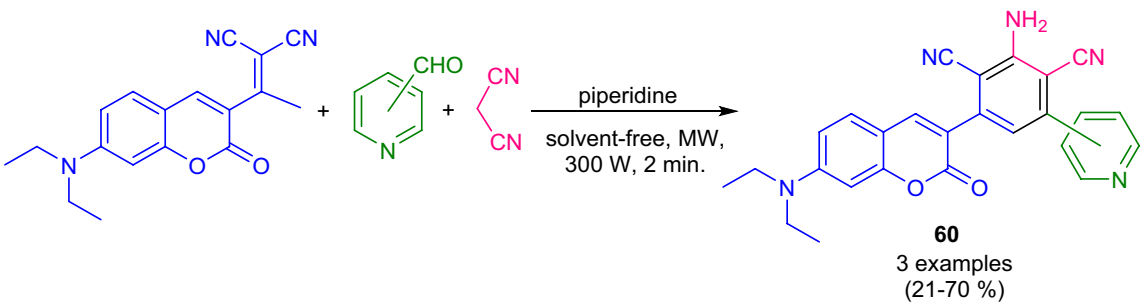
Saffarian and co-workers [117] designed nanomagnetic Fe_3O_4@SiO_2@$(CH_2)_3$-urea-quinoline sulfonic acid chloride, as a novel catalyst and explored its use for the solvent-free synthesis of coumarin-fused 1,4-dihydropyridines (DHPs) **61**, via a one-pot, three-component tandem



Scheme 64 Synthesis of 3-(aryl(pyridin-2-ylamino)methyl)-2H-chromen-2-ones



Scheme 65 Synthesis of (Z/E)-3-[(pyridin-2-yl-amino)methylidene]chromane-2,4-diones

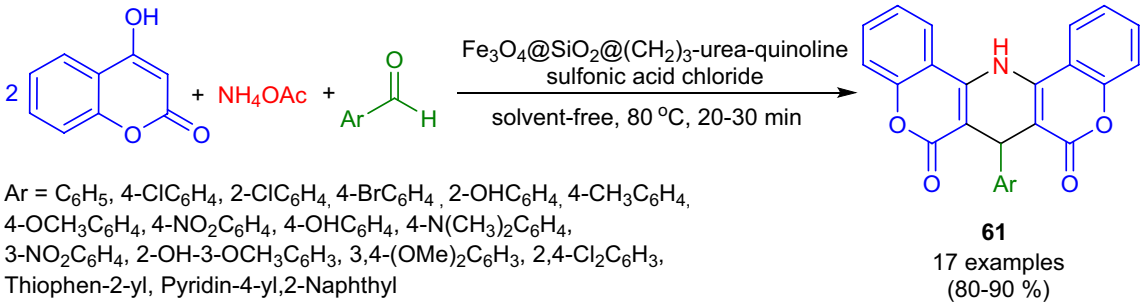


Scheme 66 Synthesis of coumarin containing 3,5-disubstituted- 2,6-dicyanoanilines

reaction of 4-hydroxycoumarin, ammonium acetate and aromatic aldehydes (Scheme 67). The authors reported a dual role for the catalyst since it has both H-bond donor–acceptor and acidic sites. The catalyst is magnetically recoverable and could be reused over five continuous runs. The authors also confirmed that in contrast to their prediction, no "anomeric based oxidation" (ABO) was involved during the reaction.

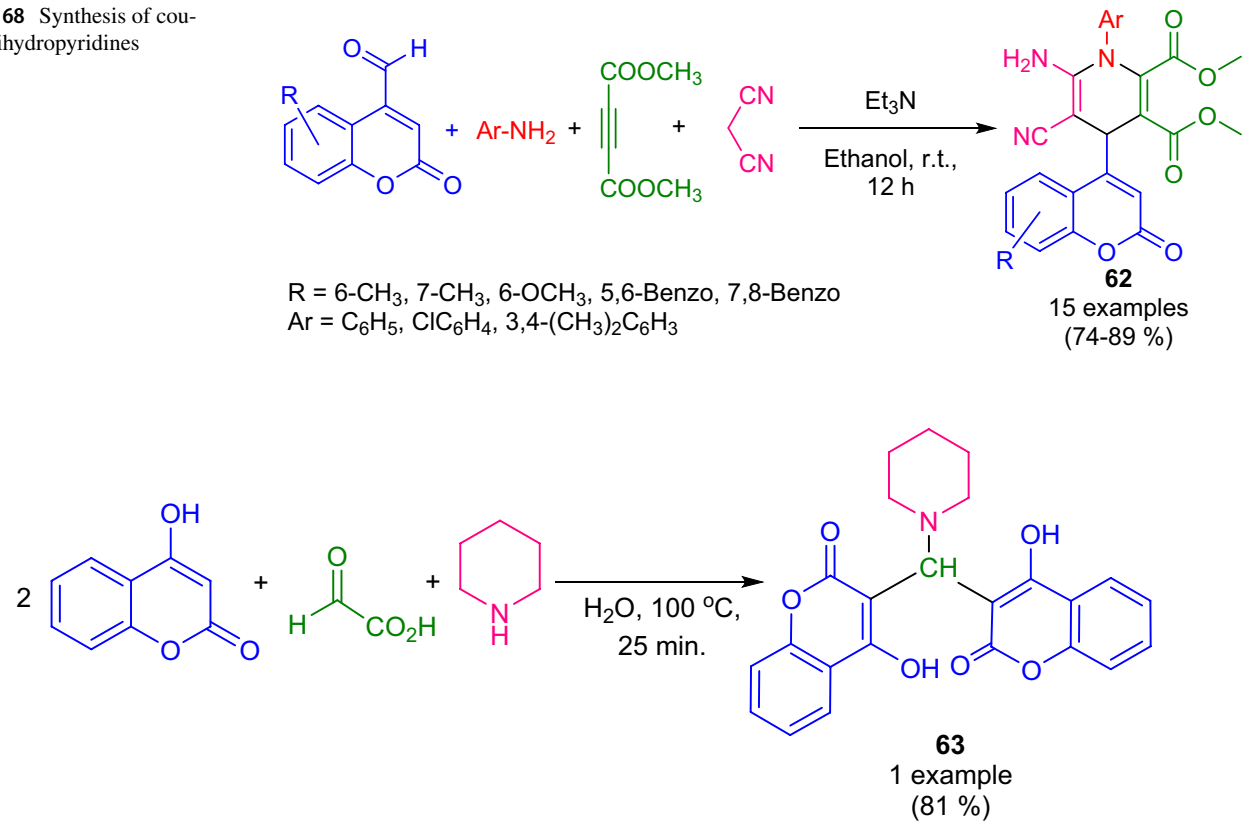
Madar and co-workers [118] have carried out the synthesis of linked coumarin-1,4-dihydropyridine **62** via four-component tandem reactions, using 6-methyl-4-formylcoumarin, malononitrile, substituted anilines and dimethyl acetylene dicarboxylate, in the presence of catalytic amount of triethylamine (Scheme 68). The multicomponent cascade reactions proceed via Aza-Michael addition, Knoevenagel condensation, Michael addition followed by intramolecular cyclization and tautomerization to form the target compounds, **62**.

Olyaei et al. [119] also synthesized 3,3′-((piperidino) methylene)bis(4-hydroxycoumarin) **63** from a three-component, one-pot reaction of glyoxalic acid monohydrate**,** 4-hydroxycoumarin and piperidine (Scheme 69).



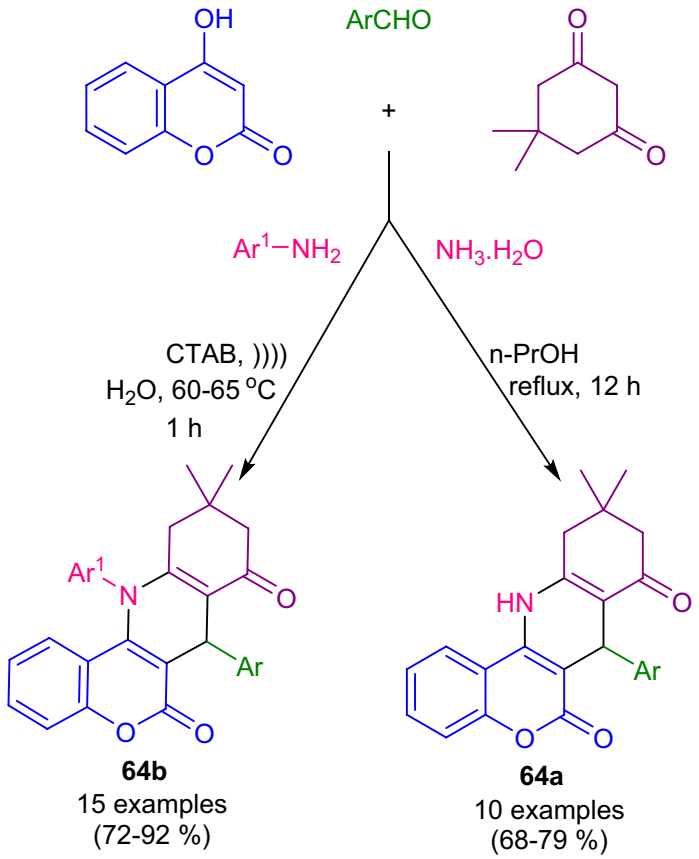
Scheme 67 Synthesis of fused bis-coumarin dihydropyridines

Scheme 68 Synthesis of coumarin dihydropyridines



Scheme 69 Synthesis of 3,3'-((piperidino)methylene)bis(4-hydroxycoumarin)

Scheme 70 Synthesis of chromeno quinolinediones



a

Ar = C_6H_5, 3-HOC_6H_4, 2-$CH_3OC_6H_4$, 4-$CH_3OC_6H_4$, 3,4,5-$(CH_3)_3OC_6H_2$, 4-$CH_3C_6H_4$, 4-FC_6H_4, 2-ClC_6H_4, 2-$NO_2C_6H_4$, 3-$NO_2C_6H_4$

b

Ar = C_6H_5, 4-$CH_3C_6H_4$, 4-$OCH_3C_6H_4$, 4-$N(CH_3)_2C_6H_4$, 4-ClC_6H_4, 2-OHC_6H_4, 3-OHC_6H_4, 4-OHC_6H_4, 3,4,5-$(OCH_3)_3C_6H_2$, Indolyl, Thienyl, 4-BrC_6H_4

Ar^1 = C_6H_5, 4-$CH_3C_6H_4$, 4-ClC_6H_4

Quinolines

Chromenoquinolines belong to an important class of nitrogen heterocycles, which exhibit promising biological activities such as anticancer, anti-inflammatory, progesterone and 5-HT receptor antagonist and glucocorticoid modulator activity [120].

Alireza Foroumadi and co-workers [121] have developed a four-component, catalyst-free synthesis of 10,11-dihydro-10,10-dimethyl-7-substituted-7H-chromeno[4,3-*b*]quinoline-6,8(9H,12H)-diones **64a** using 4-hydroxycoumarin, dimedone, ammonium hydroxide and various aromatic aldehydes (Scheme 70a), utilizing n-propanol as the solvent. NH_4OH acts both as a base and source of nitrogen in the reaction. Employing ammonium acetate in place of ammonium hydroxide, as a nitrogen source, produced a lower yield of the desired product.

Recently, Bhosle and co-workers [122] demonstrated the use of micellar CTAB as a catalyst for the same protocol and explored aromatic amines in place of ammonium hydroxide (Scheme 70b). The ultrasound irradiated synthesis of 7-(aryl)-10,10-dimethyl-12-(aryl)-9,10,11,12-tetrahydro-6H-chromeno[4,3-*b*]quinoline-6,8(7H)-dione derivatives **64b** was proved to be quite fast and catalytic efficiency of CTAB was found to be maximum at CMC. The electrostatic and hydrophobic interactions of the surfactant micelles with the reactants reportedly change the reaction rate. Amines solubilize in micellar cavities while 4-hydroxycoumarin, dimedone, and aldehydes solubilize in the hydrophobic interface of the micelles. The increased localized concentration of the reactants in the micellar cavity plausibly accelerates the reaction, according to authors. Under ultrasound conditions, acoustic cavitation generates energetic bubbles that absorb energy

from ultrasound radiations. These bubbles then collapse to generate a high concentration of high-energy particles, due to high temperature and pressure changes and facilitate intermolecular reactions. Aromatic aldehydes, with both electron-withdrawing/ electron-donating groups, furnish excellent yields of target compounds.

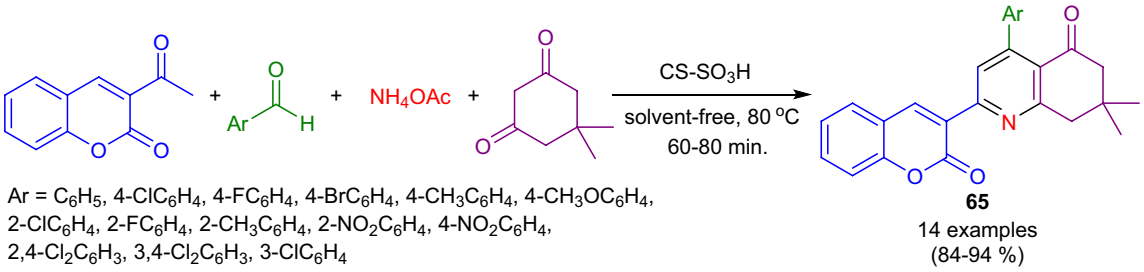
Another type of chromeno quinolinone derivatives was synthesized efficiently by Mansoor and co-workers [123] employing Chitosan sulfonic acid (CS–SO_3H) as a green recyclable catalyst, under solvent-free conditions. This one-pot protocol utilizes aromatic aldehydes, dimedone, 3-acetylcoumarin, ammonium acetate for the synthesizing 7,7-dimethyl-2-(2-oxo-2*H*-chromen-3-yl)-4-aryl-7,8-dihydroquinolin-5(6*H*)-one **65** (Scheme 71). The authors hypothesized that the multiple SO_3H groups in the catalyst stabilize the intermediates and push the reaction. Aldehydes bearing electron-withdrawing group were found to be more reactive, moreover, the steric effect led to lower yields in all ortho-substituted aldehydes irrespective of the electronic effect.

Taheri and co-workers [124] have developed a simple preparation for biologically linked quinoline-coumarin derivatives **66** using a four-component Ugi reaction of cyclohexyl isocyanide, aromatic amines coumarin-3-carboxylic acid and 2-chloroquinoline-3-carbaldehydes, (Scheme 72).

Xanthenes

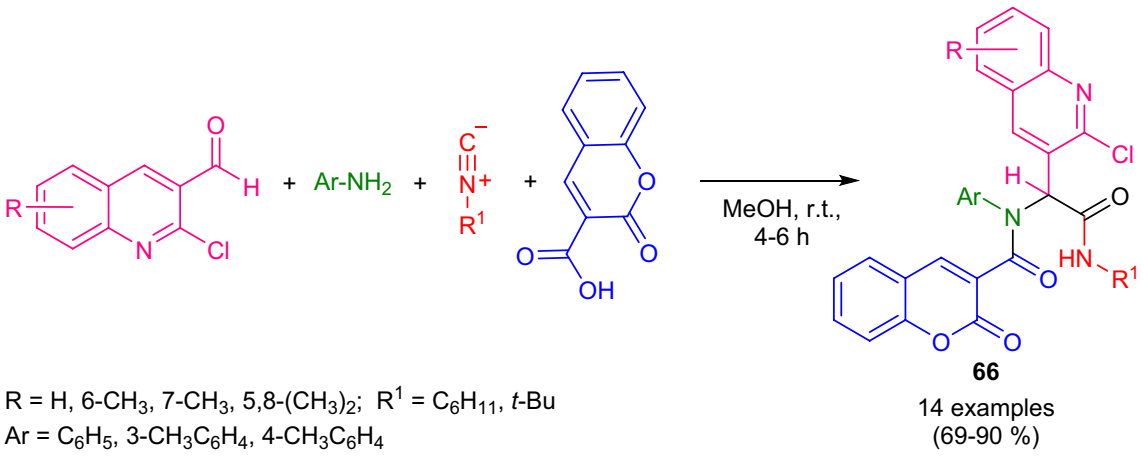
Xanthenes are another important class of heterocycles that demonstrate promising synthetic and biological applications. Xanthenes, particularly benzoxanthenes and xanthenediones, constitute potent scaffolds in pharmaceutical chemistry given their plentiful applications in biological systems. They compose biodegradable agrochemicals and are also used as dyes, pH-sensitive fluorescent materials [125, 126].

A solvent-free, one-pot multicomponent synthesis of coumarinyl xanthenes **67** or benzoxanthene coumarins **68** was reported by Madar and co-workers [126] via reaction of 4-formylcoumarin and two equivalents of 1,3-cyclohexanedione or α-naphthol in the presence of concentrated HCl as a catalyst. The use of acetic acid or silica-supported tungstic acid (STA) in place of HCl gave poor yields of the desired product (Scheme 73). The reaction had limited application, used corrosive HCl as the catalyst, could be used only for aldehydes with electron-donating groups, involved high reaction times and gave moderate yields of the product.



Ar = C_6H_5, 4-ClC_6H_4, 4-FC_6H_4, 4-BrC_6H_4, 4-$CH_3C_6H_4$, 4-$CH_3OC_6H_4$, 2-ClC_6H_4, 2-FC_6H_4, 2-$CH_3C_6H_4$, 2-$NO_2C_6H_4$, 4-$NO_2C_6H_4$, 2,4-$Cl_2C_6H_3$, 3,4-$Cl_2C_6H_3$, 3-ClC_6H_4

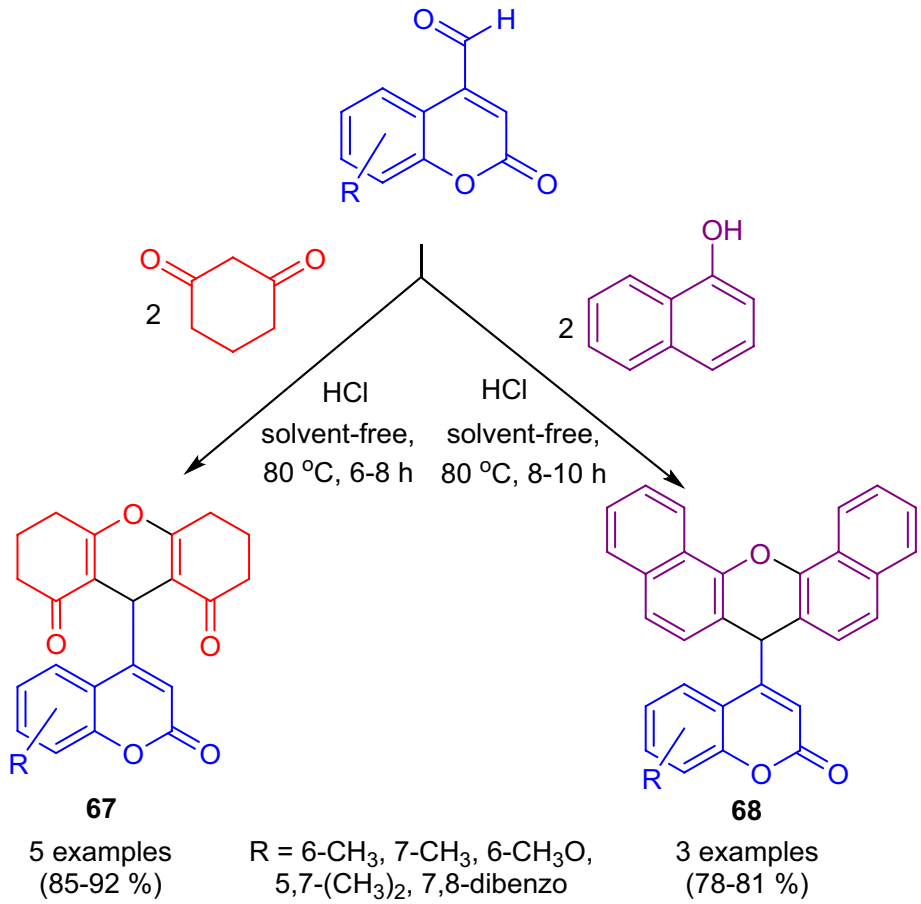
Scheme 71 Synthesis of chromeno quinolinone



R = H, 6-CH_3, 7-CH_3, 5,8-$(CH_3)_2$; R^1 = C_6H_{11}, *t*-Bu
Ar = C_6H_5, 3-$CH_3C_6H_4$, 4-$CH_3C_6H_4$

Scheme 72 Synthesis of coumarin quinolines

Scheme 73 Synthesis of coumarinyl xanthenes



67

5 examples
(85-92 %)

R = 6-CH_3, 7-CH_3, 6-CH_3O,
5,7-$(CH_3)_2$, 7,8-dibenzo

68

3 examples
(78-81 %)

Six-membered rings with two heteroatoms

Piperazines

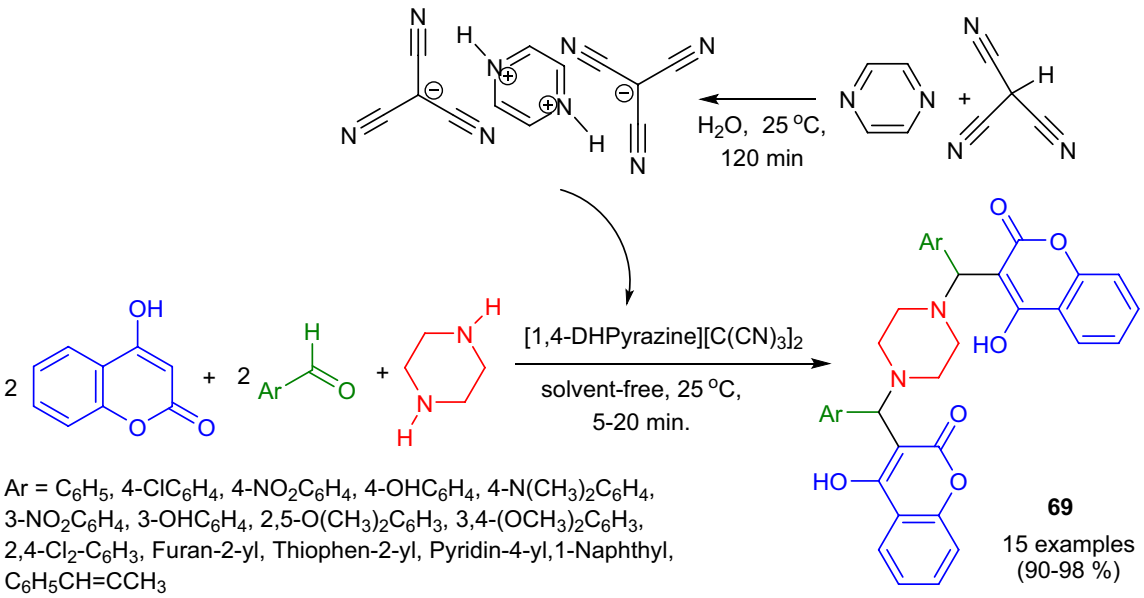
Baghery and co-workers [127] reported a solvent-free synthesis of piperazine containing bis(4-hydroxy-2Hchromen-2-one) **69** derivatives via a Mannich type multicomponent reaction of piperazine, aromatic aldehydes and 4-hydroxycoumarin, utilizing pyrazine-1,4-diium tricyanomethanide {[1,4-DHPyrazine] $[C(CN)_3]_2$} as a novel nanomolten salt (NMS)-based catalyst, at room temperature (Scheme 74). The reaction required lower catalyst loading, shorter reaction time and gave higher yields of the product. Electron-rich aldehydes gave lower yields as compared to electron-deficient counterparts. Notably, hetero-aromatic aldehydes required a longer reaction time than aryl aldehydes and decreased the yield of the products. The NMS catalyst could be reused up to six times.

Pyrimidines and pyrimidones

Natural and synthetic coumarins along with the pyrimidine moiety have attracted the immense focus of pharmacologists for demonstrating myriad therapeutic potentials like antimicrobial [128], antitumor, and found to slow down the progression of Alzheimer's disease (AD) by inhibiting acetylcholinesterase (AChE).

A highly effective three-component reaction using an equimolar amount of 4-hydroxycoumarin, 1,3-dimethyl-6-aminouracil, and diverse aromatic aldehydes, under ultrasonication, has been reported by Ghanashyam and co-workers [129], for synthesizing coumarin uracil hybrids, 6-amino-5-((4-hydroxy-2-oxo-2H-chromen-3-yl)(phenyl) methyl)-1,3-dimethylpyrimidine-2,4(1H,3H)-dione derivatives **70a**, using DABCO as catalyst (Scheme 75 a), under ultrasonication. Authors revealed that other catalysts like DBU, DBN, 4-DMAP and Amberlyst A21 resulted in a lower yield of the product comparatively. Aryl and heteroaryl aldehydes were well-tolerated in the reaction, regardless of the electronic nature of the substituents.

Basumatary and co-workers also [130] also reported the synthesis of asymmetric coumarin uracil hybrids **70a** through a similar reaction, utilizing L-proline derived secondary aminothiourea as a multifunctional organocatalyst and water as green solvent (Scheme 75b). The authors proposed that the presence of hydroxyl group at 4-position in coumarin is important. A plausible mechanism, depicted in Scheme 76, showed that thiourea triggered the H-bond



Scheme 74 Synthesis of piperazine based bis(4-hydroxy-2H-chromen-2-ones)

activation of the aldehyde and catalyzed the synthesis of iminium salt thereby increasing the electrophilicity of the C–C bond and facilitating the reaction at a much faster rate.

Brahmachari and co-workers [131] described an ultrasound-promoted, metal-free synthesis of coumarin uracil molecular hybrids, 6-amino-5-((4-hydroxy-2-oxo-2H-chromen-3-yl)(aryl)methyl)pyrimidine-2,4(1H,3H)-diones **70b**, via a similar reaction, using 6-aminouracils/6-amino-2-thiouracil (Scheme 75c), in the presence of sulfamic acid as a green catalyst and aqueous ethanol as the solvent. The proposed methodology was found to be highly advantageous due to its ambient conditions, good selectivity, excellent yields, cost-effectiveness, 93.98% and 96.39% atom-efficiency and atom-economy, respectively.

Parthiban et al. [132] demonstrated another synthesis of functionalized chromeno-pyrimidine-2,5-dione/thione compounds **71** via a three-component, one-pot cyclo-condensation reaction of 4-hydroxycoumarin, urea /thiourea and various substituted aldehydes in the presence of tannic acid as a green catalyst (Scheme 77a). Tannic acid plausibly acts as an H-bond donor because of its several hydroxyl groups and helps in the polarization of the carbonyl group (C=O) of aldehydes. A 1:1 mixture of EtOH: H_2O proved to be the best green solvent under refluxing conditions.

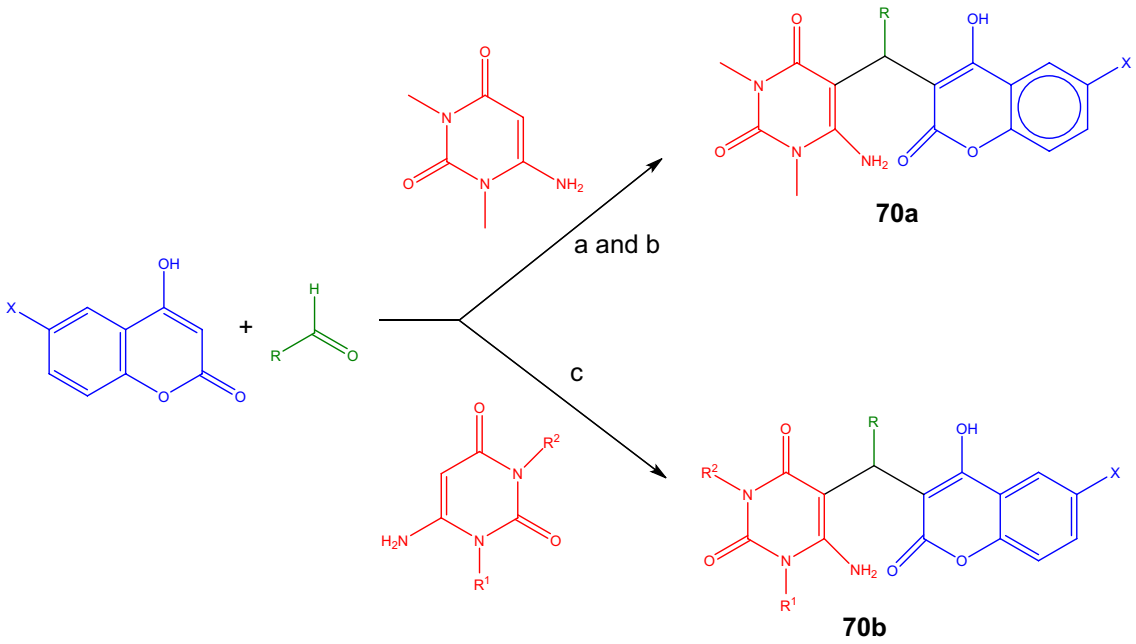
In another report, Sahu and co-workers [133] used microwave irradiation for the same protocol to synthesize coumarin-fused pyrimidines enantioselectively (Scheme 77b). The later reaction proceeded under milder conditions affording the desired product with more than 98% ee. Synergistic acid–base catalysis of bifunctional L-proline plausibly helps in the formation of C–N and C–C bonds. Water has been reported as the best solvent with asymmetric induction in the reaction.

A pseudo-four-component reaction has been reported by Jiang-Sheng Li and co-workers [134] for the synthesis of coumarin-fused pyrimidines **72,** using 2 mol of various aromatic aldehydes, 4-aminocoumarins and ammonium iodide (Scheme 78). The presence of molecular oxygen and chlorobenzene was essential for the reaction.

Lv and co-workers [135] also synthesized coumarin-fused pyrimidine **73** through a four-component, one-pot reaction of ethyl cyanoacetate, salicylaldehyde, 3-hydroxybenzaldehyde and ammonium acetate (Scheme 79).

Thiazines

Santhosh Penta and his research group [136] reported a synthesis of new (4-hydroxy-2-thioxo-3,4-dihydro-2*H*-[1,3]thiazin-6-yl)-chromen-2-one derivatives **74** via a three-component reaction of substituted primary amines, 3-chloro-3-(2-oxo-2*H*-chromen-3-yl)acrylaldehyde and carbon disulfide, utilizing triethylamine as catalyst and acetonitrile as solvent (Scheme 80). The reaction provided the desired product in good yields. Authors have shown that trials with aliphatic amines resulted in lower yields than aryl alkyl amines. It was also revealed that in this one-pot synthesis, selective heterocyclization took place as different heteroatom bonds like two C–N and C–S were formed simultaneously, without the formation of any other products.



a

R = C_6H_5, 2-$NO_2C_6H_4$, 3-$NO_2C_6H_4$, 4-$NO_2C_6H_4$, 4-FC_6H_4, 2-ClC_6H_4, 4-ClC_6H_4, 2-BrC_6H_4, 4-BrC_6H_4, 4-CNC_6H_4, 2-$OCH_3C_6H_4$, 4-$OCH_3C_6H_4$, 4-Cl-3-$NO_2C_6H_3$, 3-Cl-4-$OCH_3C_6H_3$, pyridin-3-yl, -$COOC_2H_5$, piperonyl

X = H

Conditions: DABCO, EtOH,))))), r.t., 1.5 h, 17 examples, 51- 93 %

b

R = C_6H_5, *o*-$NO_2C_6H_5$,- *m*-$NO_2C_6H_5$, *p*-$NO_2C_6H_5$, *o*-ClC_6H_5, *p*-ClC_6H_5, *p*-FC_6H_5, *o*-BrC_6H_5, *p*-BrC_6H_5, *p*-CNC_6H_5, *o*-$OCH_3C_6H_5$, *p*-$OCH_3C_6H_5$, *p*-$CH_3C_6H_5$, butanal

X = H, Cl, Br

Conditions: 2-(3-Phenylthioureido)ethyl prolinamide, water, reflux, 15-30 min., 21 examples, 81-98 %

c

R = C_6H_5, 3-BrC_6H_4, 4-FC_6H_4, 4-CNC_6H_4, 4-$CF_3C_6H_4$, 3-$CH_3C_6H_4$, 4-$CH_3C_6H_4$, 4-$OCH_3C_6H_4$, 4-$CHOC_6H_4$, 3-OHC_6H_4, 4-$OCH_3C_6H_4$, 4-OHC_6H_4, 3-$OCH_3C_6H_4$, 2,5-$(OCH_3)_2C_6H_3$, 3,4-$(OCH_3)_2C_6H_3$, 3,4-$(OCH_2O)C_6H_3$, 3,4,5-$(OCH_3)_3C_6H_2$, 4-$CHOC_6H_5$

R^1, R^2 = H, CH_3

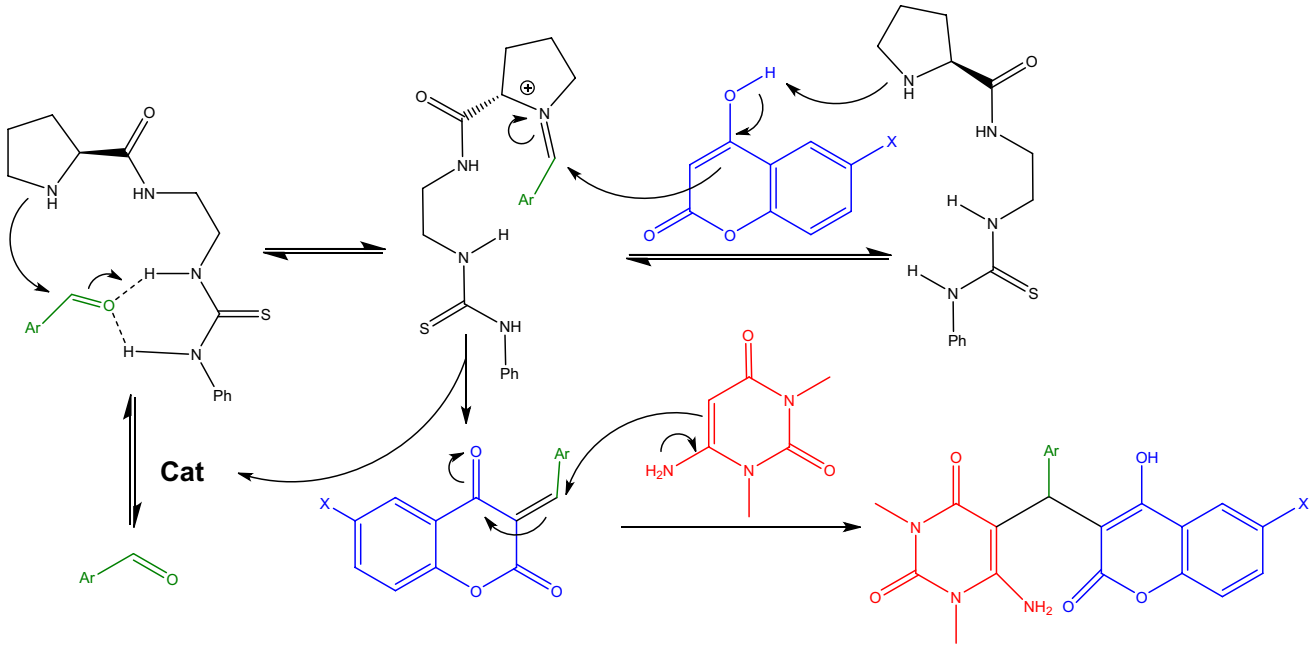
X = H

Conditions: Sulfamic acid, EtOH:H_2O (1:1),))))), ambient temp., 20 examples, 10-30 min.

Scheme 75 Synthesis of coumarin pyrimidines

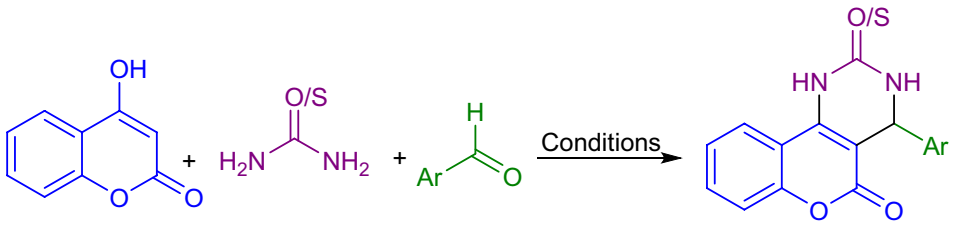
Pyrano pyridines

Sayahi and co-workers [137] have reported an aqueous phase methodology for synthesizing 10-methyl-7-aryl-7,12-dihydro-6H,8H-chromeno[4,3-b]pyrano[3,4-e] pyridine-6,8-diones **75** via four-component reaction of 6-methyl-2H-pyran-2,4(3H)-dione, 4-hydroxycoumarin, ammonium acetate and aromatic aldehydes, using L-proline as the catalyst (Scheme 81). The reaction proved to be diversity oriented since the electronic nature of the aldehyde did not affect the reaction parameters significantly. Compared to other reported catalytic systems, L-proline gave the highest yields of the desired product in the shortest reaction time. The efficiency of proline was attributed to its significant acidity. Notably, the reaction could be scaled up to an industrial level with good yields of the desired product.



Scheme 76 Plausible mechanism for the synthesis of coumarin pyrimidines

Scheme 77 Synthesis of functionalized chromeno-pyrimidine-2,5-dione/thione



71

a

Ar = C_6H_5, 2-$NO_2C_6H_4$, 2-OHC_6H_4, 3-$NO_2C_6H_4$, 2-ClC_6H_4, 4-ClC_6H_4, 4-OHC_6H_4, 4-BrC_6H_4, 4-$OCH_3C_6H_4$, 4-$CH_3C_6H_4$, furan, thiophene

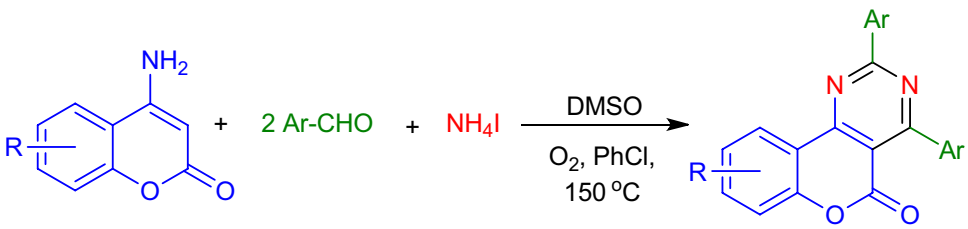
Conditions: Tannic acid, 1:1 (EtOH:H_2O), reflux, 45-90 min., 13 examples, 80-95 %

b

Ar = C_6H_5, 2-OHC_6H_4, 2-ClC_6H_4, 4-ClC_6H_4, 4-$N(CH_3)_2C_6H_4$, 4-BrC_6H_4, 2-$OCH_3C_6H_4$, 4-$OCH_3C_6H_4$, 4-$CH_3C_6H_4$, furan, thiophene

Conditions: L-Proline, water, 70 °C, 45-90 min., 20 examples, 80-95 %

Scheme 78 Synthesis of coumarin-fused pyrimidines



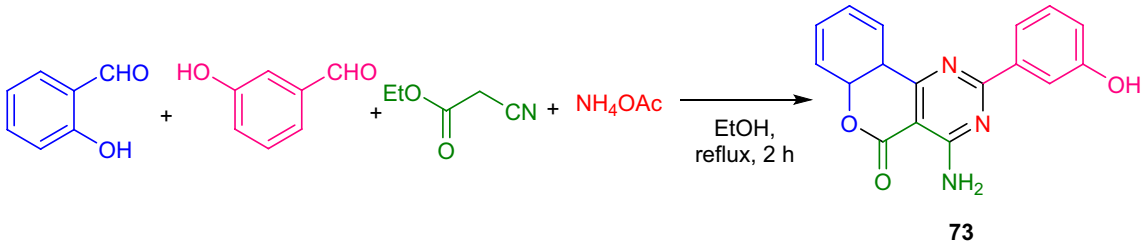
Ar = C_6H_5, 2-$CH_3C_6H_4$, 4-$CH_3C_6H_4$, 3,4-$(CH_3)_2C_6H_3$, 4-ClC_6H_4, 2-BrC_6H_4, 3-BrC_6H_4, 4-BrC_6H_4, 4-$CF_3C_6H_4$, 2-$NO_2C_6H_4$, 2,4-$Cl_2C_6H_3$

R = H, Cl

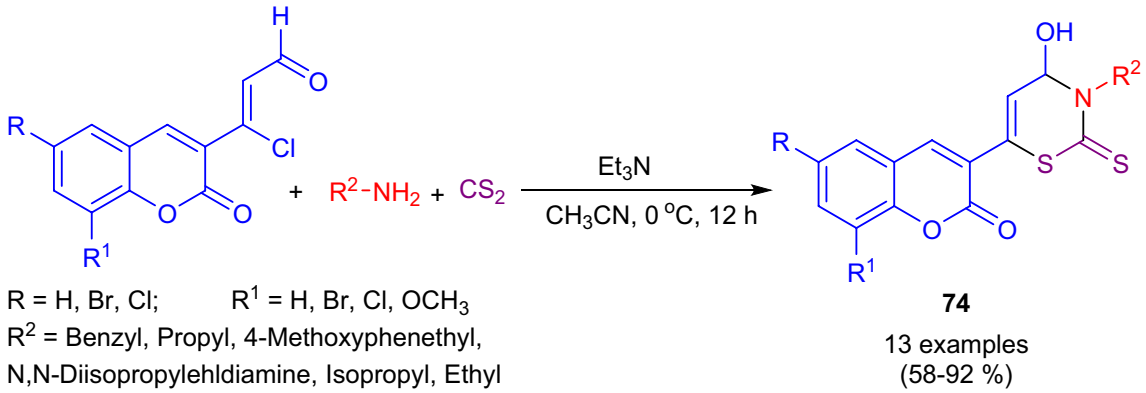
72

12 examples

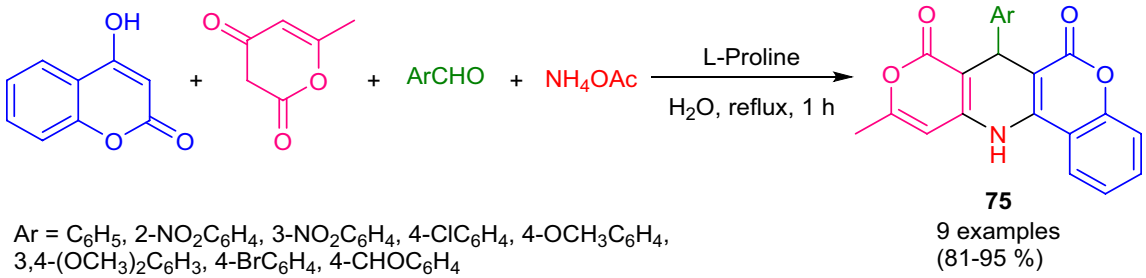
(51-95 %)



Scheme 79 Synthesis of coumarin-fused pyrimidine



Scheme 80 Synthesis of coumarin-1,3-thiazine-2-thiones



Scheme 81 Synthesis of coumarin pyrano pyridines

Six-membered rings with three or more heteroatoms

Thiadiazines

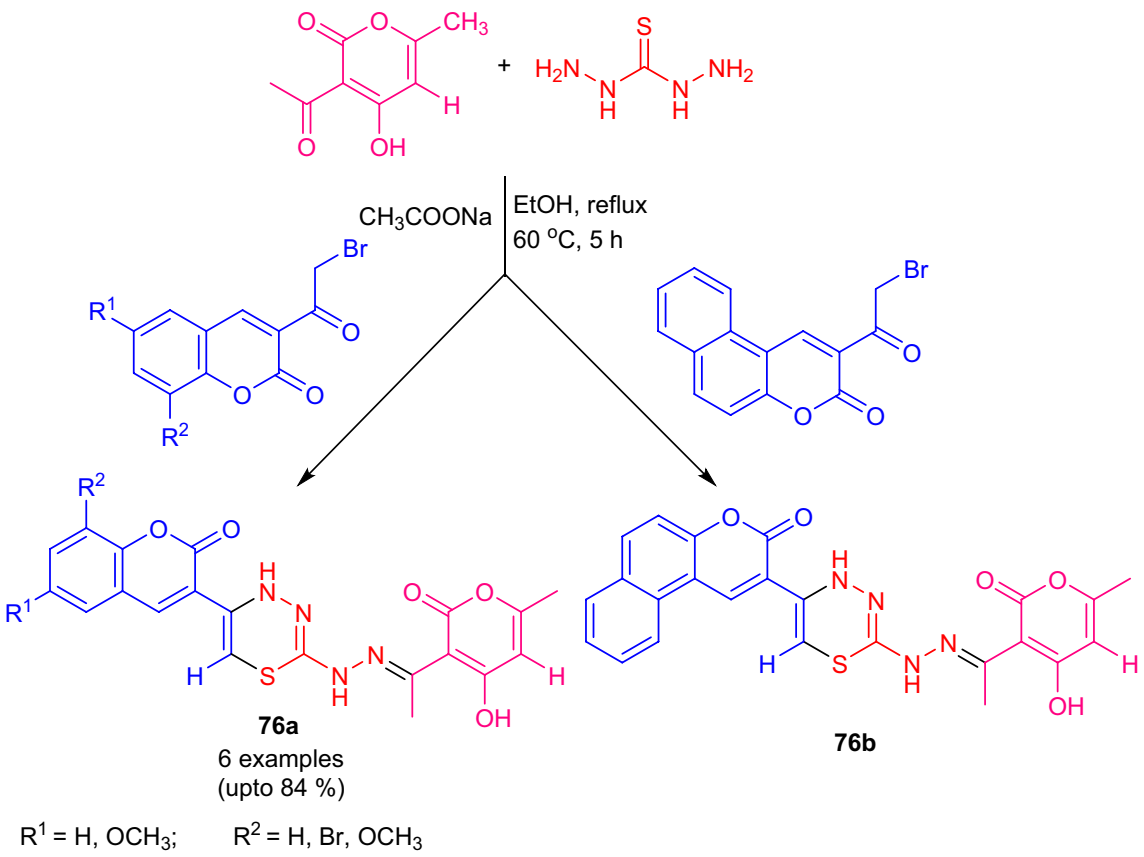
Thiadiazines and their derivatives evident diversified activities like anticancer, antifungal and inhibitory activities [138]. Coumarins are also been proved as the pharmaceutically important compounds due to their diversified properties. These two templates collectively magnitude the interest of the biochemists.

Vedula and co-workers [139] synthesized 3-(2-(2-(1-(4-hydroxy- 6-methyl-2-oxo-2*H*-pyran-3-yl) ethylidene)hydrazinyl)-4*H*-1,3,4-thiadiazin-5-yl)-2*H*-chromen-2-one derivatives **76a/76b** using catalytic amount of NaOAc. The multicomponent reaction occurs between the equimolar ratio of thiocarbohydrazide, dehydroacetic acid along with unsubstituted and substituted 3-(2-bromoacetyl)coumarins in ethanol as solvent (Scheme 82).

Other rings

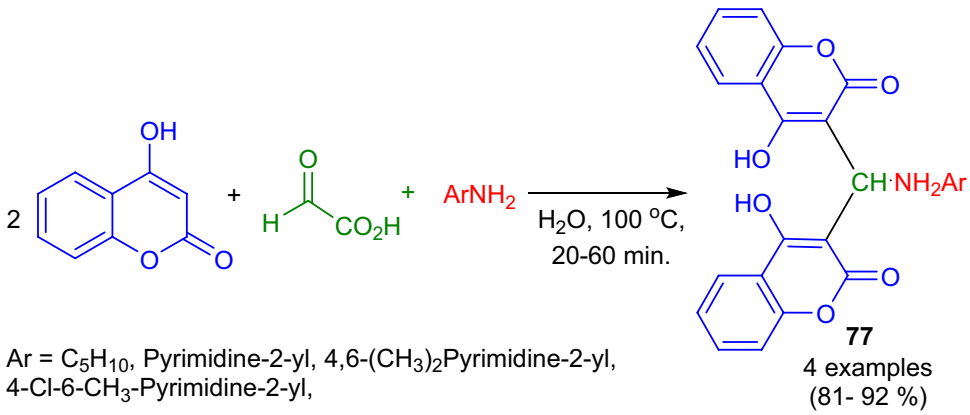
Bis-coumarins

Bis-coumarin derivatives are a potent group of compounds showing several pharmacological and biological activities



Scheme 82 Synthesis of coumarin-1,3,4-thiadiazines

Scheme 83 Synthesis of 3,3'-((arylamino)methylene) bis(4-hydroxycoumarin)



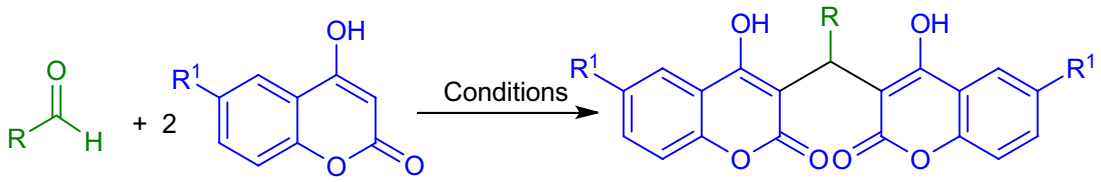
like anticoagulant, anti-thrombosis, antiseptic and urease inhibitory activity [119].

Olyaei et al. [119] also synthesized 3,3′-((arylamino) methylene)bis(4-hydroxycoumarins) **77** via three-component, one-pot reaction of glyoxalic acid monohydrate**,** 4-hydroxycoumarin, and arylamines (Scheme 83).

Several groups have reported the synthesis of bis-coumarinyl arylmethanes **78** via pseudo-multicomponent reaction of aromatic aldehydes with two molecules of 4-hydroxycoumarins, in the presence of homogenous or heterogeneous catalysts, using ethanol or aqueous ethanol or water as a solvent or under solvent-free conditions (Scheme 84a–h). A brief account is presented below.

Recently, bis-coumarins **78** were prepared by Regal and co-workers [140] in the presence of piperidine as homogenous catalyst and ethanol as solvent (Scheme 84a). The reaction gave moderate yields and could be used only for activated electron-rich aromatic aldehydes.

Siddiqui et al. [63] used human urine carbon (HUC) as the catalyst for the same reaction in the presence of EtOH/



a

R = 4-$CH_3OC_6H_4$, 3,4-$OCH_2OC_6H_3$; $R^1 = CH_3$

Conditions: Piperidine, EtOH, reflux, 3 h, 2 examples, 57-63 %

b

R = 4-$CH_3OC_6H_4$, 4-$CH_3C_6H_4$, 4-ClC_6H_4, 3-$CH_3OC_6H_4$, 3,4-$(OCH_3)_2C_6H_3$

R^1 = H

Conditions: HUC, EtOH/H_2O, 50 °C, 1-2.5 h, 5 examples, 85-97 %

c

R = C_6H_5, 4-$CH_3OC_6H_4$, 4-$CH_3C_6H_4$, 4-ClC_6H_4, 4-$NO_2C_6H_4$, 4-$CHOC_6H_4$, 3-$NO_2C_6H_4$, 3-$NO_2C_6H_4$, 4-ClC_6H_4, 3-OH-4-$OCH_3C_6H_3$, 3-CH_3O-4-OHC_6H_3, 3-$CHOC_6H_4$, 2-$OCH_3C_6H_4$, 2-ClC_6H_4, 2,4-$Cl_2C_6H_3$

R^1 = H

Conditions: Fe_3O_4@SiO_2@Ni-Zn-Fe LDH, Water, reflux, 1-40 min., 15 examples, 87-95 %

d

R = C_6H_5, 4-CNC_6H_4, 4-$OCH_3C_6H_4$, 4-BrC_6H_4, 4-ClC_6H_4, 4-$NO_2C_6H_4$, 3-$NO_2C_6H_4$, 3-ClC_6H_4, 3-$OCH_3C_6H_4$, 2-$OCH_3C_6H_4$, 2-ClC_6H_4, 2-$NO_2C_6H_4$, Isatinyl, Cinnamyl, 4-$SCH_3C_6H_4$

R^1 = H

Conditions: P_4VPy, Water, 90 °C, 5-10 min., 14 examples, 91-96 %

e

R = C_6H_5, 4-CNC_6H_4, 4-ClC_6H_4, 4-$NO_2C_6H_4$, 2-$NO_2C_6H_4$, Cinnamyl, pyridyl, 3-indolyl

R^1 = H

Conditions: TrBr, solvent-free, 70 °C, 10-40 min., 8 examples, 76-94 %

f

R = C_6H_5, 4-CNC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 4-$NO_2C_6H_4$, 4-$CH_3C_6H_4$, 4-$CH_3OC_6H_4$, 2-$NO_2C_6H_4$, 2-ClC_6H_4, 3-$NO_2C_6H_4$, 1-ethylbenzyl, Pyridyl, Thienyl

R^1 = H

Conditions: SBDBSAC, solvent-free, 70 °C,10-18 min., 13 examples, 85-95 %

g

R = C_6H_5, 4-CN-C_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 4-$NO_2C_6H_4$, 4-$CH_3C_6H_4$, 4-FC_6H_4, 4-$CH_3OC_6H_4$, 2-$NO_2C_6H_4$, 2-Cl-C_6H_4 ,3-$NO_2C_6H_4$, 1-ethylbenzyl, Pyridine-4-yl,Thiophene-2-yl, 3,4-$(OCH_3)_2C_6H_3$, 2,5-$(OCH_3)_2C_6H_3$, 2,6-$(Cl)_2C_6H_3$, 4-$OCHOC_6H_4$

R^1 = H

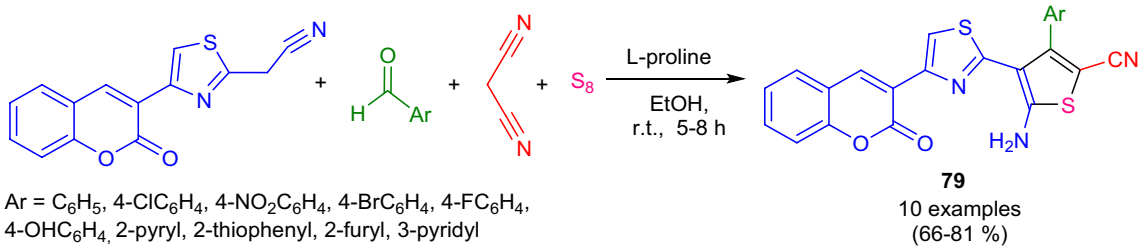
Conditions: APVPB, solvent-free, 70 °C,10-20 min., 17 examples, 82-94 %

h

R = 2,3-$(OCH_3)_2C_6H_3$, 2-FC_6H_4, 2-Br,4-OCH_3-C_6H_3, 2,5-$(OCH_3)_2C_6H_3$, 4-BrC_6H_4, 2,3-$(OH)_2C_6H_3$, 2,3,4-$(OH)_3$-C_6H_2, 2,3-$(CH_3)_2C_6H_3$, 2-OH,5-ClC_6H_3, 2,4-$(OH)_2$-C_6H_3, 2-OH-5-ClC_6H_3, 3,5-$(Cl)_2C_6H_3$; R^1 = H, Cl, F

Conditions: TEAB, water, reflux, 2 h, 44 examples, 77-87 %

Scheme 84 Synthesis of bis-coumarins



Scheme 85 Synthesis of coumarin thiazole thiophenes

H_2O solvent (Scheme 84b). The reaction was faster and involved mild conditions. The presence of an electron-donating group led to good yields of the desired product.

Gilanizadeh and co-workers [141] reported aqueous phase synthesis using Nano Ni–Zn–Fe hydrotalcite grafted on silica-layered magnetite (Fe_3O_4@SiO_2@Ni–Zn–Fe LDH) as catalyst (Scheme 84c). The catalyst plausibly promotes Knoevenagel condensation reaction by activating the aldehyde and triggering the nucleophilic attack of 4-hydroxycoumarin on the activated carbonyl group of the aldehyde.

Nasirmahale and co-workers [93] used P_4VPy as a catalyst in an aqueous medium reaction (Scheme 84d). Both reactions (Scheme 84c and d) were much faster, gave excellent yield and had much wider applicability since aldehydes having both electron-withdrawing, electron-donating groups, as well as halogens, were well tolerated.

Solvent-free reactions are an efficient tool for carrying out organic transformations as they avoid the use of harmful organic solvents. Their use is in line with the green chemistry principles and often leads to significantly faster reactions, higher product yields and easy workup. Some of these reactions have been reported to enhance the regioselectivity and stereoselectivity of reactions [142–146]. A brief account of solvent-free synthesis of bis-coumarinyl arylmethanes **78** is presented below.

Zolfigol et al. [147] used trityl bromide as a homogenous organocatalyst or nanomagnetic [Fe_3O_4@SiO_2@$(CH_2)_3$−$ImSO_3H$]Cl as a heterogeneous, acidic catalyst, under solvent-free conditions, for the synthesis of bis-coumarinyl arylmethanes **78** (Scheme 84e). Heterogeneous catalyst was found to be superior as it required a shorter reaction time and gave better yields. Significantly, the reaction was found to be diversity oriented since, aromatic aldehydes containing electron-releasing, electron-withdrawing groups, halogens as well as hetero-aromatic compounds were well-tolerated in the reaction. The catalyst could be reportedly recycled for 7 successive runs without noticeable loss of activity.

Zolfigol et al. [148] also used nanostructured silica-grafted 1,4-diazabicyclo[2.2.2]octane-sulfonic acid chloride (SBDBSAC) as a heterogeneous catalyst for the same reaction (Scheme 84f). SBDBSAC could be recycled for 4 successive recycle runs. Aromatic aldehydes containing electron-pulling, electron-releasing groups as well as halogen were well tolerated, indicating wide reaction applicability.

Noroozizadeh and co-workers [149] demonstrated the use of acetic acid-immobilized poly(4-vinylpyridinium)bromide (APVPB) as a heterogeneous biocatalyst for the same reaction (Scheme 84 g). The reaction had diverse applicability as aryl aldehydes comprising of electron-pulling, electron-releasing groups, as well as halogens gave excellent yields of the product. The catalyst could be recycled 5 times.

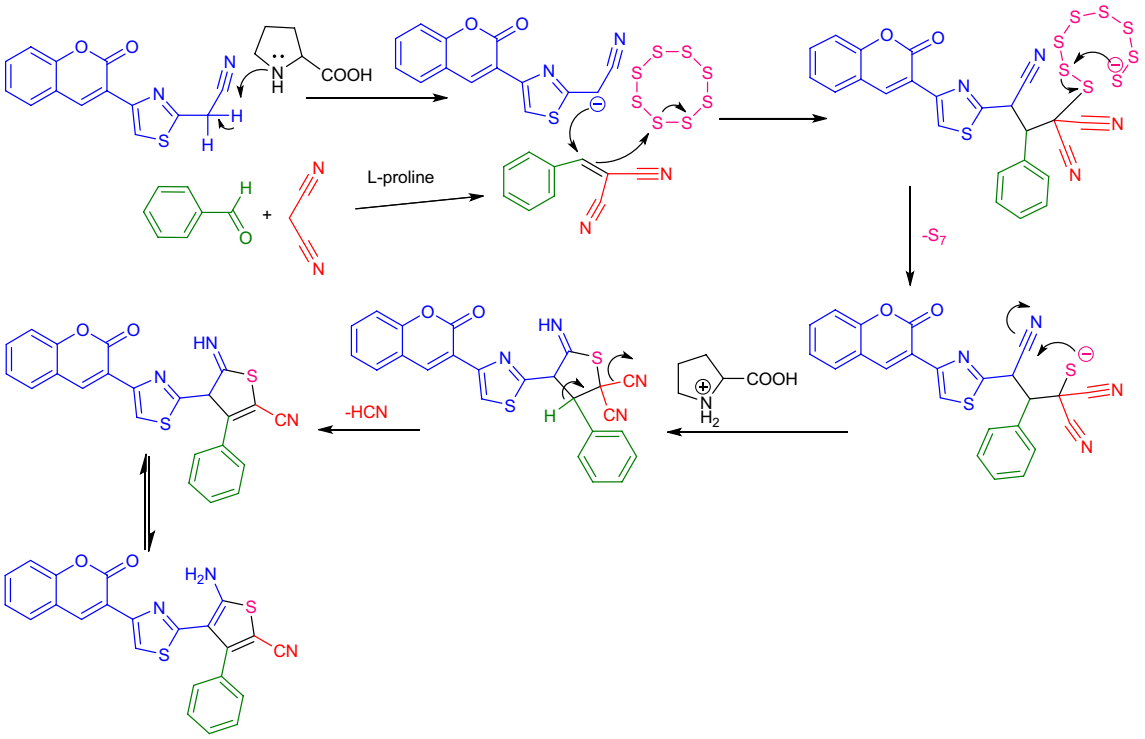
Salar and co-workers [150] used tetraethyl ammonium bromide (TEAB) as the catalyst for the reaction. The desired product was obtained in moderate to good yields, using water as a green solvent (Scheme 84 h). The reaction showed wide applicability as aldehydes and coumarins containing both electron-donating groups, as well as halogens gave excellent yields of the product.

Thiazolyl thiophene

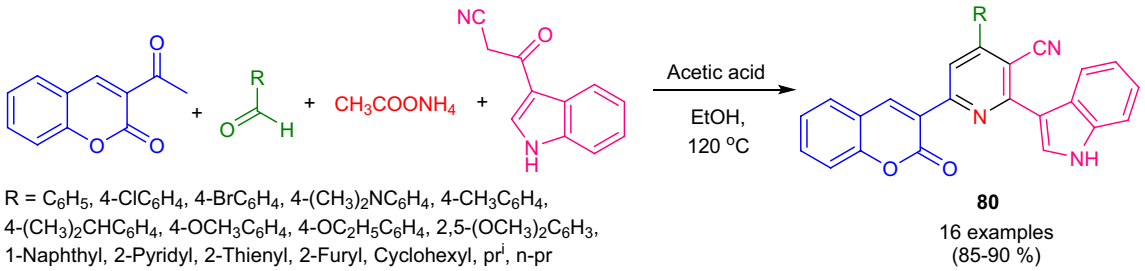
Kavitha and co-workers [151] have outlined an efficient, multicomponent Gewald reaction for synthesizing coumarin thiazole-thiophene hybrid **79,** via a reaction between malononitrile, 2-[4-(2-oxo-2*H*-chromen-3-yl)thiazol-2-yl]acetonitrile, different aromatic aldehydes and molecular sulfur, in the presence of catalytic amounts of *L*-proline (Scheme 85). A plausible mechanism for the transformation is depicted in Scheme 86.

Indolyl pyridines

Yeon Tae Jeong and co-workers [152] have reported a four-component, one-pot method for the synthesis of coumarin indole pyridine hybrids **80**, containing pyridine-carbonitriles moiety, by reacting aldehydes, 3-acetyl-2*H*-chromenones, 3-(1*H*-indol-3-yl)-3-oxopropanenitrile and ammonium acetate, utilizing acetic acid as catalyst and ethanol as the solvent (Scheme 87). The aldehydes bearing both electron-releasing and electron-pulling substituents worked well in the reaction.



Scheme 86 Plausible mechanism of the synthesis of coumarin thiazole thiophenes



R = C_6H_5, 4-ClC_6H_4, 4-BrC_6H_4, 4-$(CH_3)_2NC_6H_4$, 4-$CH_3C_6H_4$, 4-$(CH_3)_2CHC_6H_4$, 4-$OCH_3C_6H_4$, 4-$OC_2H_5C_6H_4$, 2,5-$(OCH_3)_2C_6H_3$, 1-Naphthyl, 2-Pyridyl, 2-Thienyl, 2-Furyl, Cyclohexyl, pr^i, n-pr

Scheme 87 Synthesis of coumarin indole pyridines

Pyrazolyl pyridines

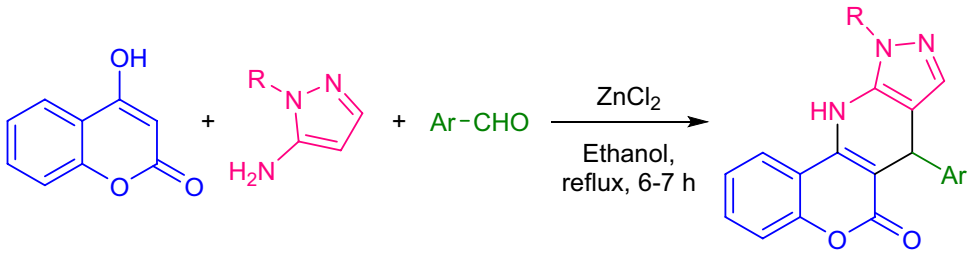
Shiva Shankar and co-workers [153] have proposed a multicomponent, one-pot protocol to synthesize a library of diversified coumarin pyrazole-pyridine hybrids **81** through a reaction of 4-hydroxycoumarin, 1-alkyl-5-amino-pyrazoles and various benzaldehydes, utilizing $ZnCl_2$ as a Lewis acid catalyst and ethanol as a solvent (Scheme 88). The authors have explored the electronic effect of the substituents on aryl aldehyde and did not find substantial difference except 4-NO_2 group, which resulted in the poor yield of the product.

Wei Lin and co-workers [154] demonstrated a concise and efficient three-component, one-pot, microwave irradiated Domino reaction to synthesize coumarin-fused pyrazolo[3,4-*b*]pyridines **82** utilizing silica sulfuric acid (SSA) as heterogeneous acid catalyst, via a reaction of 2-butyryl-3H-benzo[f]chromen-3-one and 3-alkyl/aryl-1- phenyl-1H-pyrazol-5-amine, and alkyl alcohol (Scheme 89a)/aryl alcohol (Scheme 89b)**.**

Pyrido pyrimidones

In order to synthesize hybrid coumarin pyridine pyrimidinediones **83**, Hosein Sayahi and co-workers [155] reported a three-component, one-pot reaction of thiobarbituric acid (TBA), 4-aminocoumarin and various aromatic aldehydes (Scheme 90) using PSSA-MGO as acidic catalyst and ethanol–water as the solvent. The reaction afforded high yields of the product, under mild conditions with the recovery of the fully stable catalyst many times. The authors reported that the electronic nature of the functionalities on aromatic

Scheme 88 Synthesis of coumarin pyrazole pyridines



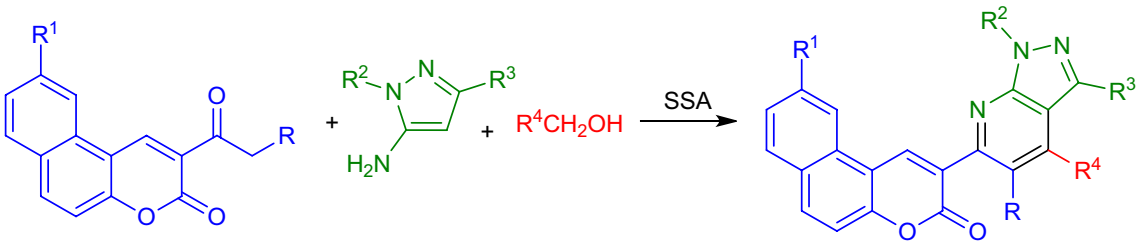
Ar = C_6H_5, 4-BrC_6H_4, 2-OHC_6H_4, 4-$OCH_3C_6H_4$, 2,3-$(OCH_3)_2C_6H_3$, 3,4,5-$(CH_3)_3C_6H_2$, 4-ClC_6H_4, 4-$NO_2C_6H_4$

R = CH_3, C_2H_5

81

8 examples

(81-96 %)



82

a

R = C_2H_5 R^1 = H, OCH_3 R^2 = C_6H_5, CH_3 R^3 = C_6H_5, CH_3

R^4 = CH_3, C_2H_5, C_3H_7

Conditions: MW, 140 °C, EG, 45 min., 6 examples, 64-84 %

b

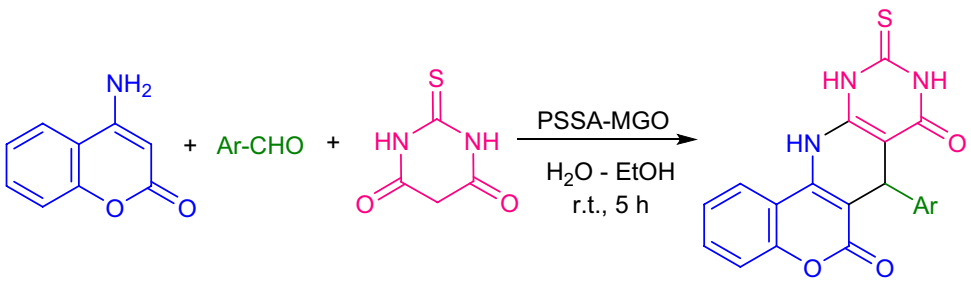
R = C_2H_5, CH_3, H R^1 = H, OCH_3 R^2 = C_6H_5, CH_3 R^3 = C_6H_5, CH_3

R^4 = C_6H_5, 4-$CH_3C_6H_4$, 4-$OCH_3C_6H_4$, 3-$OCH_3C_6H_4$, 4-BrC_6H_4, Pyridine-4-yl, Furan-2-yl

Conditions: MW, 140 °C, EG, 45 min., 23 examples, 45-77 %

Scheme 89 Synthesis of coumarin-fused pyrazolo[3,4-*b*]pyridines

Scheme 90 Synthesis of chromeno pyrido pyrimidinediones



Ar = C_6H_5, 2-ClC_6H_4, 2-$NO_2C_6H_4$, 3-ClC_6H_4, 3-$OCH_3C_6H_4$, 4-ClC_6H_4, 4-CNC_6H_4, 2,4-$Cl_2C_6H_3$, 2-OHC_6H_4, 4-BrC_6H_4, 4-FC_6H_4, 4-$NO_2C_6H_4$, 3-$NO_2C_6H_4$

83

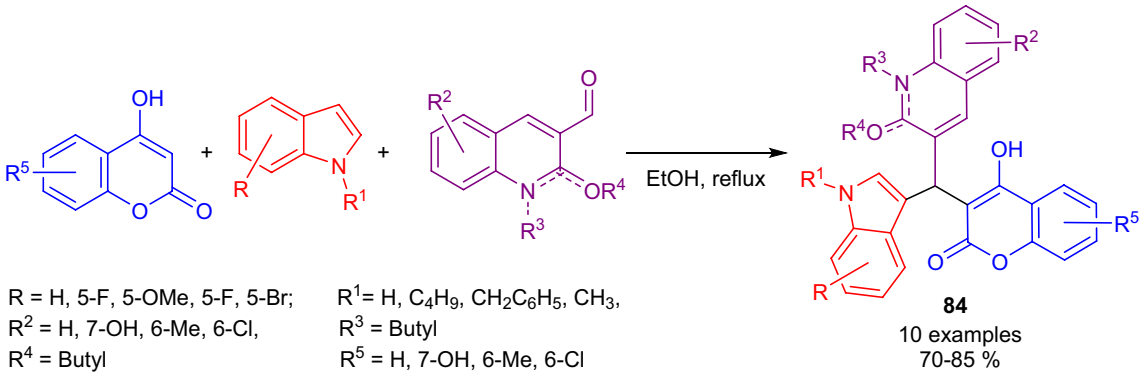
13 examples

(82-95 %)

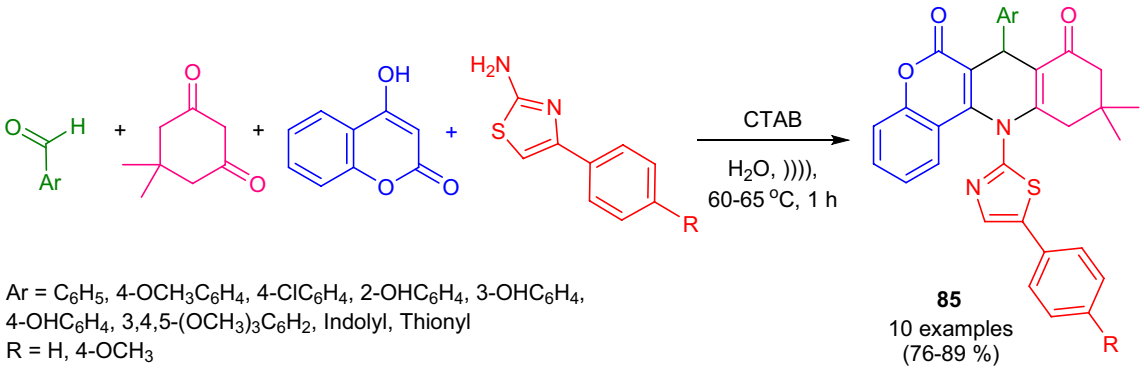
aldehyde did not affect the reaction parameters but aliphatic and heterocyclic analogues failed to furnish the products.

Indolyl quinolines

Laali and co-workers[156] synthesized an array of massive tris(heteroaryl)methanes **84** via Yonemitsu-based three-component, one-pot reaction of diversely substituted indoles (Ar_1), coumarins (Ar_2) and fluorene aldehydes (Ar_3CHO), in 1:1:1 ratio, to afford tris(heteroaryl)methanes $(Ar_1Ar_2Ar_3)CH$ along with $(Ar_1Ar_1Ar_2)CH$ triads (Scheme 91).



Scheme 91 Synthesis of tris(heteroaryl)methanes with indole, quinoline and coumarin units



Scheme 92 Synthesis of thiazolyl chromeno[4,3-*b*]quinolones

Thiazolyl quinolones

Bhosle and co-workers [122] extended their previous report to synthesize thiazolyl chromeno [4,3-*b*]quinolones **85** in good to excellent yields, using 2-aminothiazoles, aromatic aldehydes, dimedone and 4-hydroxycoumarin (Scheme 92), under ultrasound irradiation.

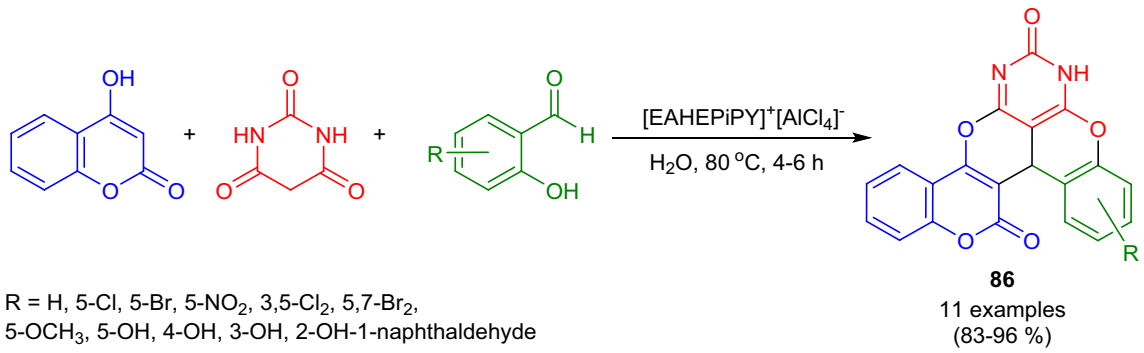
Pyrano pyrimidones

The previously reported literature has cited that chromene and chromenyl barbiturates demonstrated excellent antitubercular activities [157]. In this respect, an ionic liquid, 1-(ethylacetoacetate)-1-(2-hydroxyethyl)piperidinium tetrachloroaluminate $[EAHEPiPY]^+$ $[AlCl_4]^-$ was utilized by Pore and group [158] to synthesize bioactive novel dichromeno pyrano pyrimidinones **86** via a three-component, one-pot condensation of salicylaldehydes, 4-hydroxycoumarin and barbituric acid (Scheme 93). The authors reported that the enhancement of the rate of reaction is shown due to the active involvement of OH group of task-specific ionic liquid throughout the reaction. The results indicated that a variety of substituents worked well.

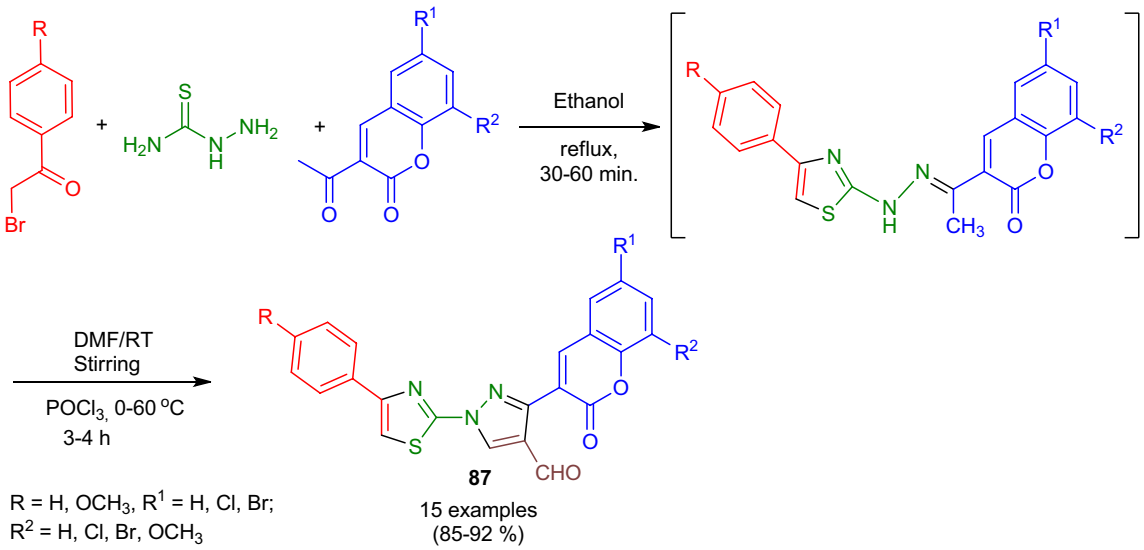
Thiazolyl pyrazoles

Due to the pharmaceutical importance of coumarin, thiazole and pyrazole scaffolds, chemists are trying to design the synthesis of new compounds by incorporating these three moieties. This combination may produce more effective, less toxic and more selective molecules.

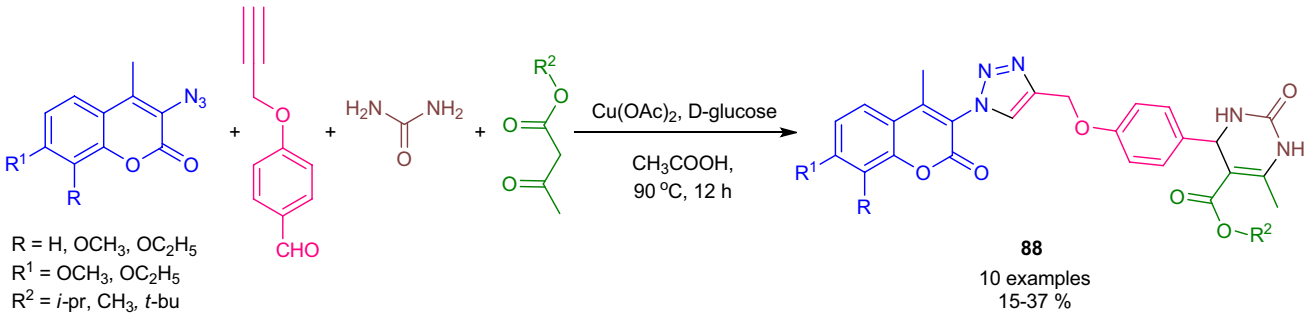
Vedula and group [159] proposed one-pot synthesis of a family of coumarin based thiazolyl pyrazole carbaldehydes through a reaction of substituted phenacyl bromides, thiosemicarbazide, substituted 3-acetylcoumarins and Vilsmeier–Haack reagent**.** Refluxing the mixture in ethanol, followed by stirring for 3–4 h in the presence of DMF/ $POCl_3$ gave the desired product (Scheme 94).



Scheme 93 Synthesis of novel dichromeno pyrano pyrimidinones



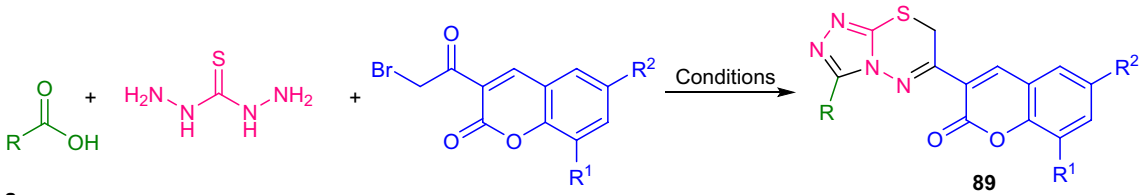
Scheme 94 Synthesis of coumarin thiazolyl pyrazole carbaldehydes



Scheme 95 Synthesis of coumarin triazole dihydropyrimidinones

Triazolyl dihydropyrimidines

A one-pot, multicomponent protocol has been reported as the best way for the synthesis of coumarin-linked triazolyl-dihydropyrimidinones (DHPM) **88** by Singh and coworkers [160]. The authors explored many ways including Biginelli reaction to obtain the desired product but the reaction proceeded with four-components; 3-azido coumarin, urea, propargyloxy benzaldehyde, and β-ketoesters taking copper acetate and *D*-glucose as a catalyst and acetic acid as solvent (Scheme 95).



a

R = CH_3, CH_3CH_2, CF_3; R^1 = H, OCH_3, OCH_3CH_2, Cl, Br; R^2 = H, Cl, Br

Conditions: Solvent-free, 75-80 °C, 4-5 h,10 examples, 82-91 %

b

R = 2-methylisoindoline-1,3-dione; R^1 = H, Cl, Br; R^2 = H, Cl, Br, OCH_3, OCH_2CH_3

Conditions: Solvent-free, 150-160 °C, fuse, 25-30 min.,10 examples, 78-92 %

Scheme 96 Synthesis of triazole thiadiazine coumarins

Triazolyl thiadiazines

Vaarla and co-workers [161] have reported a facile, solvent-free, one-pot, tandem approach to synthesize triazole thiadiazine coumarin hybrids **89** by the reaction of aromatic/aliphatic/heterocyclic carboxylic acids, substituted 3-(2-bromoacetyl)coumarins and thiocarbohydrazide (Scheme 96a).

Vaarla and co-workers [161] also reported one-pot synthesis of coumarin indole-triazole-thiadiazine hybrids, coumarinyl-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazin-3-yl)methyl) isoindoline-1,3-diones **89**, via the reaction of 2-(1,3- dioxoisoindolin-2-yl)acetic acid, with thiosemicarbazide followed by the condensation with various 3-(2-bromoacetyl) coumarins (Scheme 96b).

Thiadiazolo quinazolinones

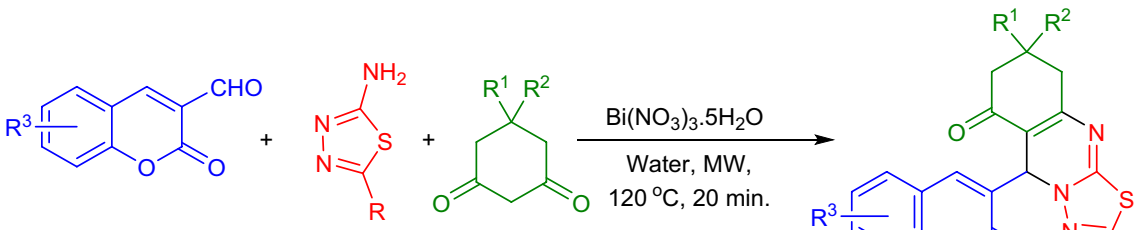
Thiadiazolo quinazolinones are important bioactive compounds that possess anticancer, antibacterial, anti-inflammatory and antifungal activities.

Sharma and co-workers [162] have prepared a library of novel 5-(2-oxo-2H-chromen-3-yl)-2-phenyl-8,9-dihydro-5H-[1,3,4]thiadiazolo[2,3-*b*]quinazolin-6(7H)-one derivatives **90** (Scheme 97) through aqueous phase reaction of substituted 5-phenyl-1,3,4-thiadiazol-2-amine, 2-oxo-2H-chromene-3-carbaldehyde and 1,3-cyclohexanedione derivatives, in the presence of $Bi(NO_3)_3.5H_2O$ as catalyst. The authors proposed that $Bi(NO_3)_3.5H_2O$ is decomposed into HNO_3 and $Bi(OH)_3$ during the reaction. The HNO_3 and $Bi(OH)_3$ plausibly catalyze the reaction through Bronsted/Lewis acid chemistry.

Spiroindoline pyrans

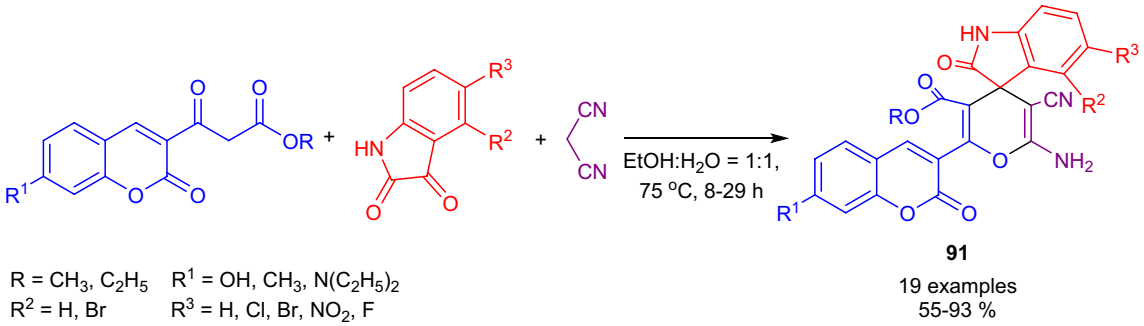
Ablajan and co-workers [163] developed a green, catalyst-free, multi-component reaction for the designing fluorescent coumarin spiro[indoline-3,4′-pyran] conjugates **91** taking various coumarin beta-ketoesters, 4-bromoisatin and malononitrile, in aqueous ethanol as the solvent (Scheme 98).

Another synthetic approach for novel spirooxindoles with fused pyrano[3,2-*c*]chromenes **92** was reported by Mazahar Farooqui and co-workers [164] using one-pot, multi-component reaction of 4-hydroxycoumarin, active methylene compounds and substituted isatin in the presence of γ-valerolactone as a bio-based green solvent (Scheme 99). Substituted isatin having both electron-pulling and

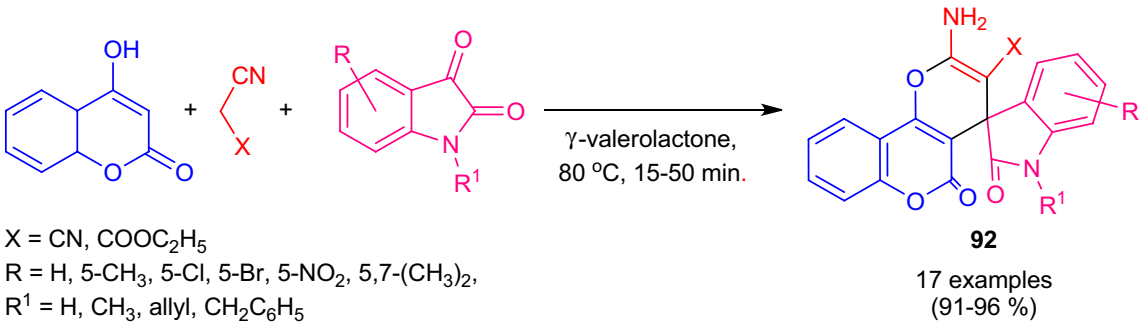


R = C_6H_5, 4-ClC_6H_4, 4-CNC_6H_4, 4-$NO_2C_6H_4$, cinnamyl.
R^1 R^2 = H, CH_3
R^3 = H, 7-CH_3, 7-Cl

Scheme 97 Synthesis of coumarin thiadiazoloquinazolines



Scheme 98 Synthesis of coumarin spiro[indoline-3,4'-pyran] conjugates



Scheme 99 Synthesis of spirooxindoline with fused pyrano[3,2-*c*]chromenes

electron-releasing groups worked in the reaction without the formation of any other side product. Furthermore, it was reported that the nitrogen substituted isatin moieties gave the desired products in excellent yield.

Spirooxindolyl Dihydropyridyl pyrazoles /isoxazoles

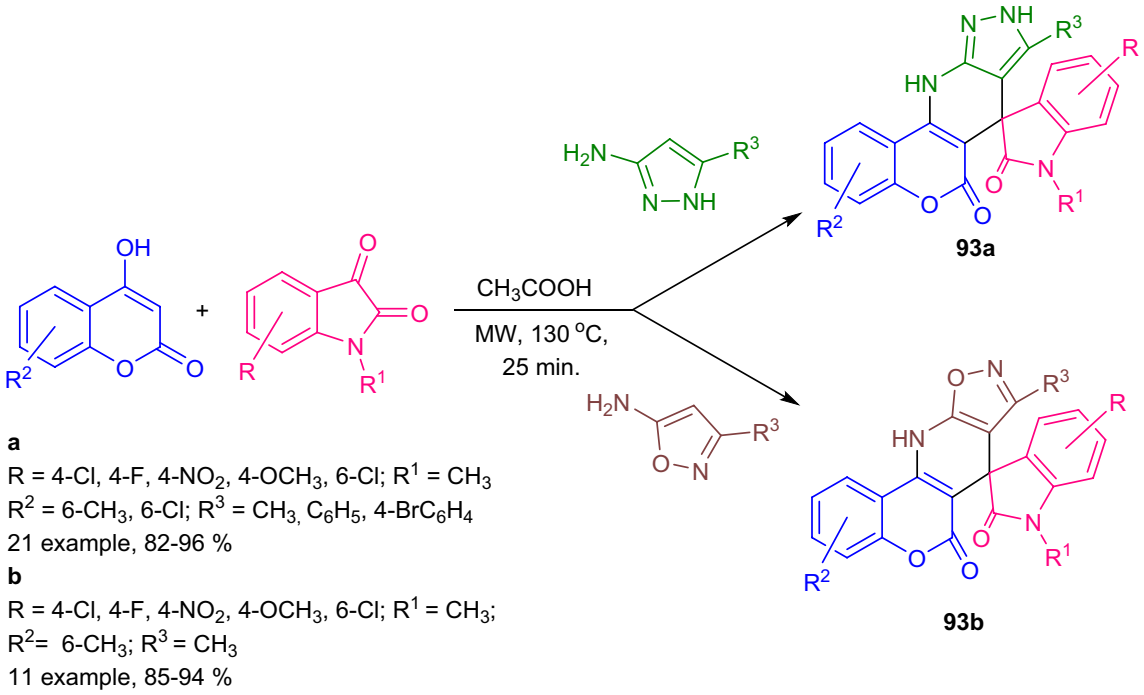
Synthesis of fused spirooxindoles with a tetracyclic coumarin dihydropyridine-pyrazole /isoxazole scaffold **93a/93b** was reported by Lokman H. Choudhury and co-workers [165] via multicomponent reaction (Scheme 100), employing isatin, substituted 4-hydroxycoumarins and aminopyrazoles or aminoisoxazole, under microwave irradiations, utilizing acetic acid as the solvent and catalyst.

Bispyrazolyl thiazoles

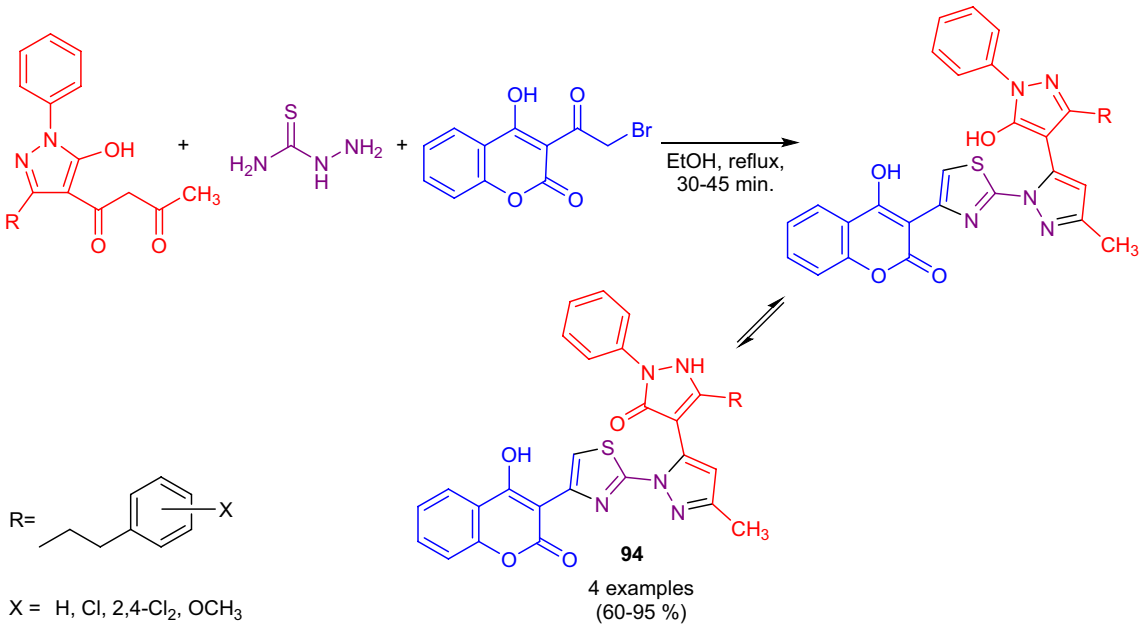
Rachedi and co-workers [166] explored a three-component Hantzsch–thiazole reaction to synthesize bispyrazole-thiazole-2*H*-chromen-2-ones **94** in one-pot, multicomponent reaction of coumarin, thiosemicarbazide and diketophenylpyrazoles, in the presence of ethanol as solvent (Scheme 101). The desired products with high purity and excellent yield were obtained in a short reaction time.

Conclusion

This article reviews recent trends for the construction of fused or linked coumarin hybrids using multicomponent synthetic techniques. The article demonstrates that curiosity in developing newer synthetic routes for coumarins fused or linked hybrids has been gaining attention over the last few decades, reflecting the status in this field for both chemical and pharmaceutical research. The present review emphasizes innovative multicomponent synthetic techniques for a diverse array of biologically active coumarin hybrids. We believe that the data communicated through this review will not only acquaint the chemists with current discoveries in synthetic routes of coumarin heterocycles but will also inspire them to explore this potent scaffold for more backbone functionalization and screening, as numerous linked and fused coumarin heterocycles with diverse chemical and biological properties are conceivable. Future prospects in this field include finding newer, simple, low cost and benign synthetic routes for molecules with increased structural complexity but decreased number of synthetic steps. Further, fueling SAR and molecular mechanism studies of these newer molecules will lead to the development of more potent drug candidates.



Scheme 100 Synthesis of spirooxindoles fused coumarin dihydropyridine pyrazoles/ isoxazoles



Scheme 101 Synthesis of bispyrazole-thiazole-2*H*-chromen-2-ones

Acknowledgements The authors gratefully acknowledge the Principal, Sri Venkateswara College and Principal, Acharya Narendra Dev College, University of Delhi, India for the library resources and technical support provided.

Declarations

Conflict of interest The authors have no relevant financial or non-financial interests to disclose.

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