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Coumarin heterocyclic derivatives: chemical synthesis and biological activity

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This review highlights the broad range of science that has arisen from the synthesis of coumarin-linked and fused heterocycles derivatives. Specific topics include synthesis and biological activity.

1 Introduction

Coumarins, of natural and synthetic origin, constitute a large family of heterocyclic compounds with a benzo-α-pyrone moiety. Coumarins are widely distributed in plants; e.g., coumarin, which is the most representative molecule, was initially found in tonka bean (*Dipteryx odorata* Wild), and it has been extensively studied both in biochemical and pharmaceutical fields.[1] Dicoumarol, was discovered in mouldy, wet, sweet-clover hayand, and is a naturally occurring anticoagulant.[2] Osthole, which recently has taken considerable attention because of its broad spectrum of pharmacologic activities,[3] was found in *Cnidium monnieri* whilst scoparone, with potential pharmacological properties including immunosuppression and vasorelaxation,[4] was found in *Artemisia scoparia* (Figure 1).[1a]

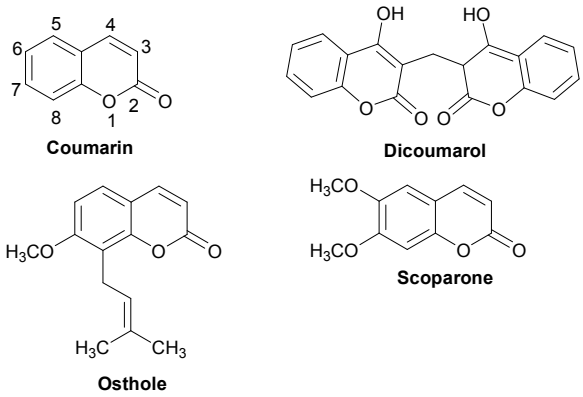


Figure 1. Examples of biologically active compounds bearing a coumarin motif.

Over the past decades, coumarins have attracted strong scientific interest stemming from their broad spectrum of pharmacological activities acting as antidepressants,[5] antimicrobials,[6] anti-oxidants,[7] anti-inflammatory activities,[8] antinociceptives,[9] anti-tumor activities,[1a] antiasthmatics,[10] antivirals (including anti-HIV)[11] and anti-coagulants.[12] A beneficial effect of warfarin in cancer patients leading to prolonged survival was demonstrated by Zacharski and colleagues.[13] These derivatives have also been shown to be novel lipid lowering agents that possess moderate triglyceride lowering activity.[14] Some reviews have recently summarized many important medicinal properties of coumarins and its derivatives.[15] Coumarins show optical properties, including: an extended spectral response, high quantum yields and superior photostability. Optical applications of these compounds, such as laser dyes, nonlinear optical chromophores, fluorescent whiteners, fluorescent probes, polymers, optical recording and solar energy collectors, have been widely investigated.[16] Moreover, the compounds containing this heterocyclic motif are widely found as additives in food, in

cosmetic products, as pharmaceutical agents[17] and luminescent materials.[18]

Compounds with two or more heterocycles play a vital role in natural and synthetic bioactive compounds.[19] Within this context, many examples of biologically active coumarins containing heterocycles have been cited in the literature. The incorporation of another heterocyclic moiety either as a substituent group or as a fused component into coumarin alters the properties of the parental material, and the resulting compounds may generally exhibit promising or even unprecedented properties. For example, neo-tanshinlactone, a minor component isolated from an ethanolic extract of *Salvia miltiorrhiza*, was 10-fold more potent and 20-fold more selective against breast cancer cells than tamoxifen.[20] SP500263, a coumarin derivative with a piperidin-ethoxy-benzyl side-chain at C-4, bound with high affinity to both estrogen receptor α and β, and functioned as a potent anti-estrogen in *in vitro* and *in vivo* models of breast cancer.[21] Ensaculin, a coumarin with a piperazine moiety, was identified as a compound with a unique profile of pharmacodynamic effects on the central nervous system and it has been tagged as a potential support in the treatment of dementia (Figure 2).[22]

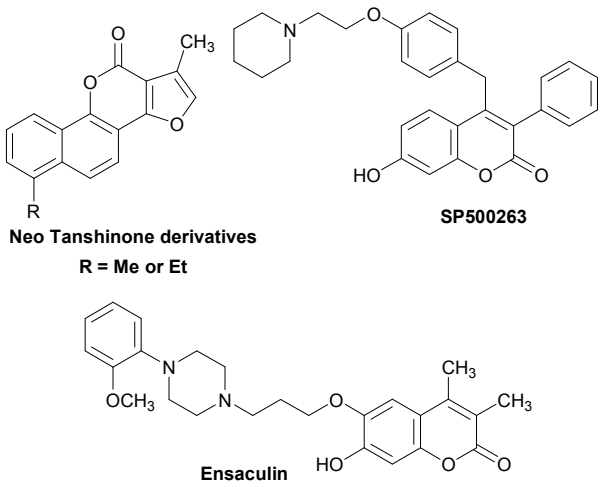


Figure 2. Some coumarin derivatives containing heterocyclic moieties.

The possibility of wide range biological and physical properties makes coumarins an interesting synthetic target. As a consequence, developing straightforward and flexible synthetic methods toward functionalized coumarins has attracted much attention from organic chemists. Perhaps because of this, great efforts have been focused on developing new methodologies to increase the structural complexity while decreasing the number of synthetic steps to facilitate the construction of new coumarin derivatives.[23]

Therefore, bearing in mind that coumarins have recently gained increasing importance due to their technological potential in many industries, their synthesis and applications have been recently reviewed.[1a, 7-8, 12, 15-16, 24] In this review, we intend to present an overview of the most significant advances described in the latest literature concerning biologically active coumarins containing heterocycles either as substituent groups or as a fused component, although we excluded Lamellarin alkaloids because several reviews have been recently published.[25] To facilitate the location of the corresponding synthetic applications, we organized this review according to the size and type of heterocycle. Even though several reviews covering the chemistry and biological aspects of coumarins have been published to date, none of them has focused specifically on coumarins containing heterocycles, and we consider this topic to be relevant enough to be treated independently.

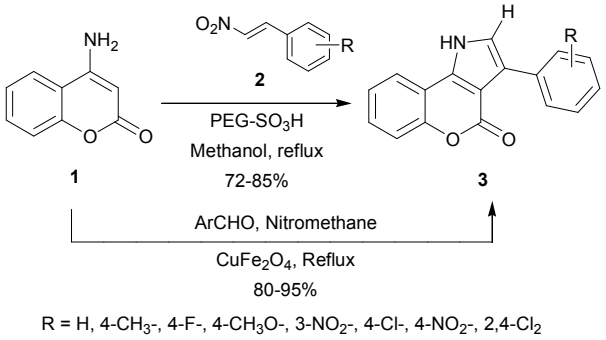
2 Synthesis of coumarin-linked and coumarin-fused heterocycles

2.1 5-Membered rings with one heteroatom

2.1.1 Pyrroles, Indoles and Isoindoles

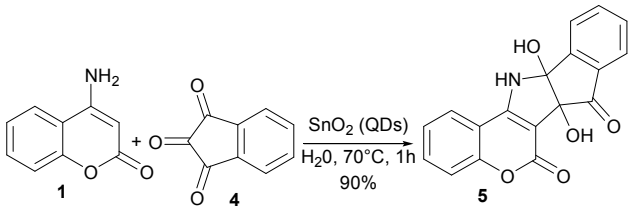
Among the numerous heteroaromatic compounds, the pyrrole ring has shown a large number of applications and is present in many natural products. To date, many synthetic methods have been developed for the construction of pyrroles, including the classical Knorr reaction, the Hantzsch reaction, Buchwald–Hartwig coupling and the Paal–Knorr condensation reaction, and new methodologies, such as transition-metal-catalyzed cyclizations, cycloaddition reactions and multicomponent reactions, are also used.[26]

A two-component coupling reaction of 4-aminocoumarin **1** and α,β-unsaturated nitroalkenes **2**, has been developed by Das and co-workers toward the formation of coumarin-fused pyrrole system **3**. In the presence of PEG-6000, a polyethylene glycol-supported catalyst,[27] it has been observed that the reaction leads to functionalized tricyclic system **3** (Scheme 1).[28] The efficient one-pot syntheses were accomplished using $CuFe_2O_4$ as catalyst instead of PEG-6000, involving three components: 4-aminocoumarin **1**, nitromethane **2** and aldehydes (Scheme 1).[29] Although both methods are attractive protocols, they have the inconvenience that in all derivatives prepared, the C-2 positions are always unsubstituted.



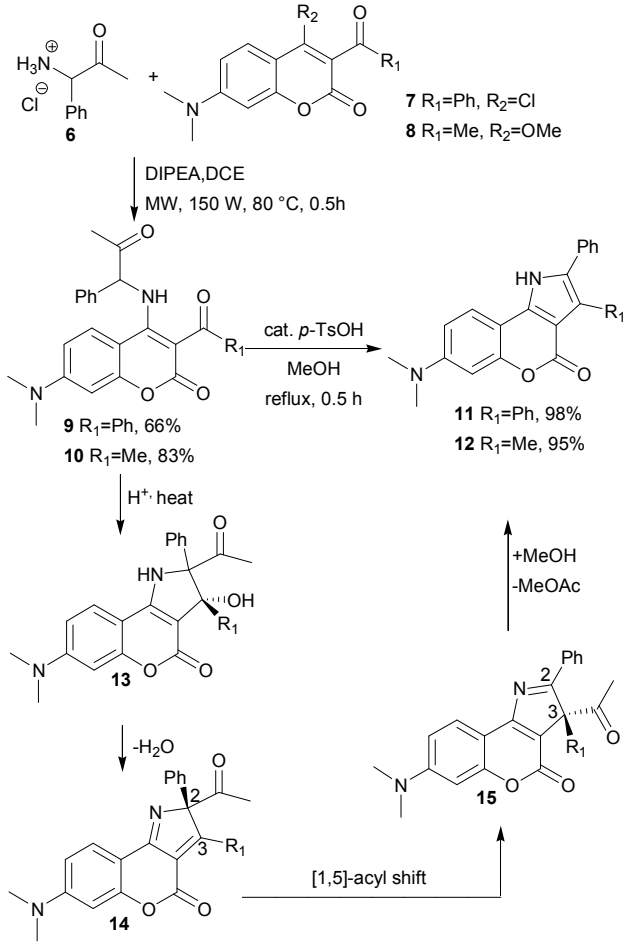
Scheme 1. Synthesis of a pyrrole core containing a coumarin system.

Recently, the same research group developed the synthesis of fused dihydroxy indeno[1,2-*b*]pyrrole and acenaphtho[1,2-*b*]pyrrole core via a one-pot approach in aqueous medium catalysed by tin oxide (SnO_2) quantum dot, using 1,2-diketo compound and 4-aminocoumarin **1** (Scheme 2).[30] Quantum dots are nano-materials which show unique electrical and catalytic properties because of their ultra-fine grain size. Unfortunately the relative stereochemistry could not be established.



Scheme 2. Synthesis of a pyrrole core containing a coumarin system.

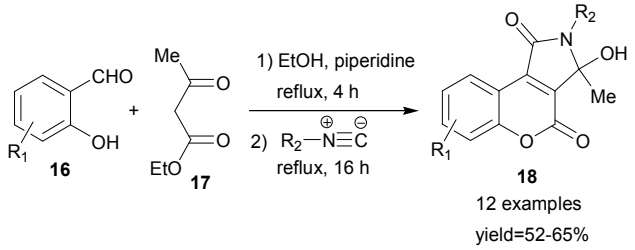
In 2013, Lin and Yang described a two steps synthesis starting from the microwave-promoted coupling of 1-amino-1-phenylpropan-2-one **6** with 3-acylcoumarins **7**-**8**, which provides access to 1,2,3,5-tetrasubstituted pyrroles **11**-**12** (Scheme 3).[31] Although only two pyrrolocoumarin derivatives were prepared by this method, they include C_2 substituents other than hydrogen.



Scheme 3. Preparation of pyrrolocoumarins **11** and **12**.

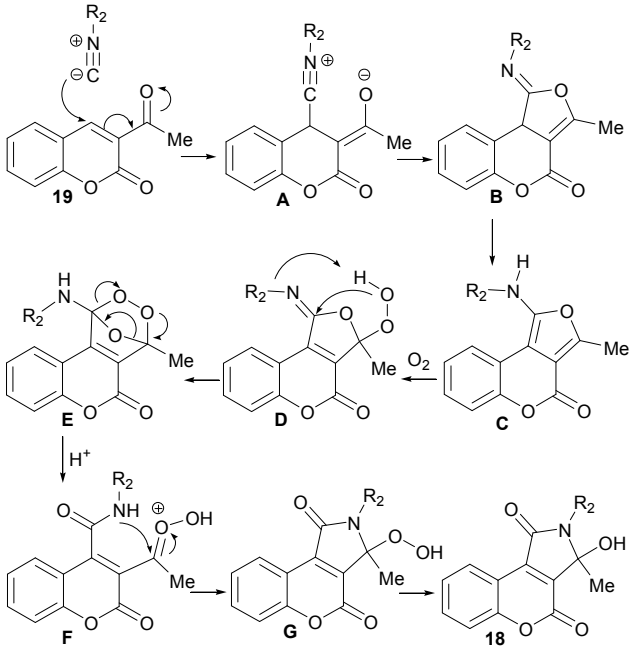
Regarding the mechanism of this transformation, the authors propose that a [1,5]-acyl migration from the C-2 to the C-3 position of **14**, followed by a final methanolysis of **15**, with loss of methyl acetate, are needed to obtain the target compounds. This mechanism was strongly supported during the reaction by the isolation and characterization of the rearranged intermediate **15** (R_1=CH_3).

A three-component reaction between 2-hydroxybenzaldehydes **16**, ethyl acetoacetate **17** and an isonitrile was found to afford 5-hydroxy-3-pyrrolin-2-one moieties fused to a coumarin system **18** in moderate yields (Scheme 4).[32] The strategy is based on the known participation method of the *in situ* generated quinone methides, obtained from 4-hydroxycoumarins and aldehydes, in a [4+1] cycloaddition reaction with isocyanides.[33]



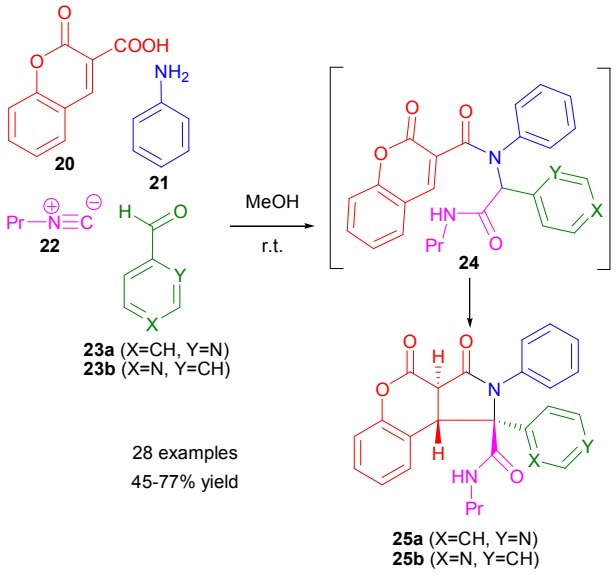
Scheme 4. One-pot synthesis of **18**.

The mechanism proposed for this transformation is summarized in Scheme 5 and assumes an addition of the isonitrile to the *in situ* generated 3-acetyl-2H-chromen-2-one intermediates **19** to give a 2-aminofuran ring **C**, which cannot be isolated. This reaction is followed by a fast oxidation by triplet oxygen at C-5 to afford hydroperoxide **D**, which is in equilibrium with an ozonide **E**. Double fragmentation occurs on both bridged five-member rings, giving rise to the carboxyamide function, the precursor of the final lactam. This proposal is based on a similar mechanism previously reported.[34]



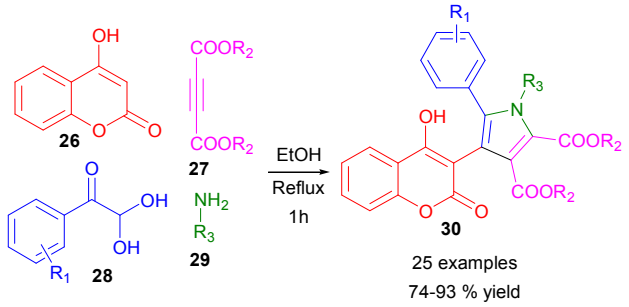
Scheme 5. Proposed mechanism for the formation of **18**.

The use of a sequential four-component Ugi reaction and intramolecular Michael addition between coumarin-3-carboxylic acid **20**, anilines **21**, isonitriles **22** and pyridine-based aryl aldehydes **23** affords diverse chromeno[3,4-c]pyrrole-3,4-diones **25** in good yield (Scheme 6).[35] However, when these aldehydes were replaced with 2- and 4-nitrophenyl aldehyde, no reaction was obtained under various reaction conditions.



Scheme 6. Synthesis of chromeno[3,4-c]pyrrole-3,4-diones **25** by an Ugi reaction.

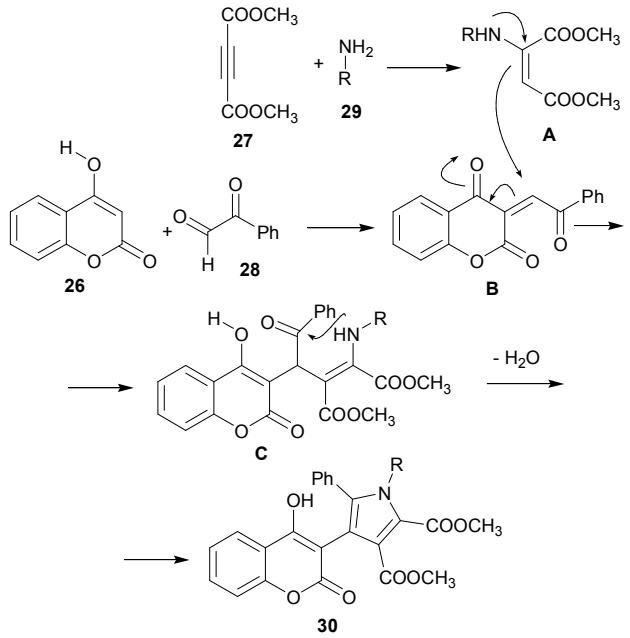
The tricyclic pentasubstituted pyrrolyl coumarin derivatives **30** has been constructed by Shi and co-workers through a four-component reaction between 4-hydroxycoumarin **26**, acetylenedicarboxylates **27**, arylglyoxal monohydrate **28** and amines **29** under catalyst-free conditions (Scheme 7).[36] This method is especially attractive because it followed the GAP chemistry process, which avoids traditional chromatography and recrystallization purification methods.[37]



Scheme 7. The synthesis of 3-pyrrolyl coumarin derivatives **30** via four-component reaction.

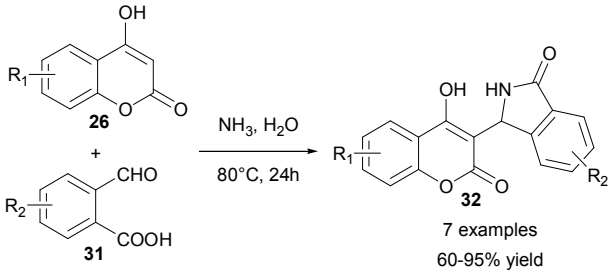
The mechanism proposed by the authors to explain the isolation of pyrrole-fused coumarin **30**, in accordance with reports from the literature,[38] involves the initial Knoevenagel condensation of 4-hydroxycoumarin **26** with phenylglyoxal **28** to give intermediate B. Incorporation of enamine A by a Michael addition provides intermediate C, which then undergoes intramolecular cyclization and dehydration to form the desired product (Scheme 8).

Isoindolinone frameworks have attracted much attention from the scientific community since they represent the core unit of an increasing number of compounds with extensive use in therapeutic activities. Consequently, much effort has been devoted to the development of new methods for their synthesis.[38] The incorporation of coumarins, as a "privileged scaffold", into isoindolinones, may potentially provide a novel class of drug candidates, with unusual biological activities. As a result, some efficient and straightforward methods for the synthesis of this type of compounds have been developed.[39]



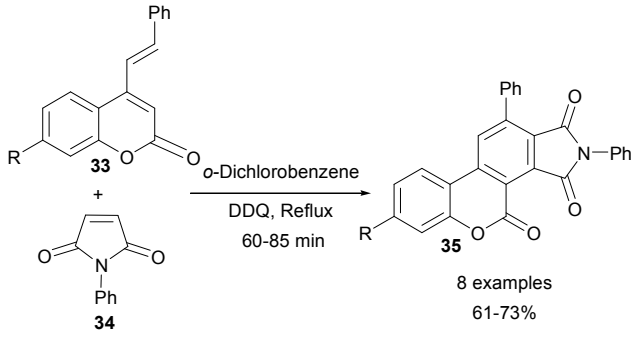
Scheme 8. Proposed mechanism for the formation of compound **30**.

Recently, Sun and Lin has developed a three-component reaction under catalyst-free conditions of 3-coumarinyl-substituted isoindolinones **32** (Scheme 9).[40] This process has been carried out in gram-scale although.



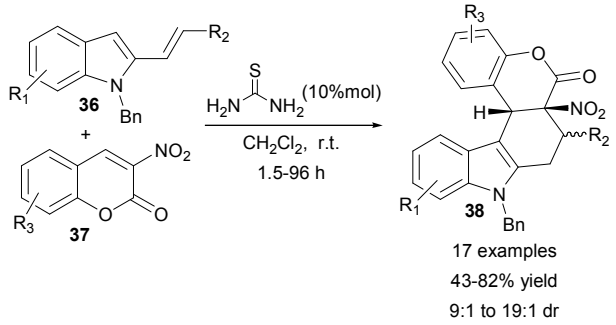
Scheme 9. Synthesis of 3-(4-hydroxy)coumarinyl-substituted isoindolinones **32** in ammonia.

A one pot Diels–Alder/dehydrogenation process has been developed by Sanap and Samant in 2013 toward the formation of tretracyclic ring systems **35** (Scheme 10).[41] In the presence of DDQ as oxidant, it has been observed that the reaction between 4-styrylcoumarins **33** and *N*-phenylmaleimide **34**, leads to functionalized tricyclic architectures like **35**.



Scheme 10. Diels-Alder reaction of 4-styrylcoumains **33** and N-phenylmaleimide **34** in *O*-dichlorobenzene.

When 2-vinylindoles **36** are used as dienophile in the Diels-Alder reaction with 3-nitrocoumarins **37**, coumarin-fused tetrahydrocarbazoles **38** were obtained in a highly diastereoselective form (Scheme 10).[42] The strategy requires a simple thiourea as catalyst. A plausible transition state is proposed by the authors to explain the observed stereocontrol involved an endo-selective Diels-Alder cycloaddition.



Scheme 11. Diels-Alder reaction of 2-vinyl-1*H*-indole **36** with 3-nitrocoumarin **37**.

Recently an efficient palladium-catalyzed domino C–N coupling/hydroamination reaction of coumarin derivatives **39** and amines **29** has been developed by Langer.[43] Thus, the reaction of 3-bromo-4-ethynyl-coumarin derivatives **39** with amines **29**, performed by using $Pd(OAc)_2$, Cs_2CO_3 and SPhos as the ligand, efficiently delivers chromeno[3,4-*b*]pyrrol-4(3*H*)-ones **40**. Aliphatic amines were successfully employed.

Scheme 12. Synthesis of pyrrolocoumarins **40**.

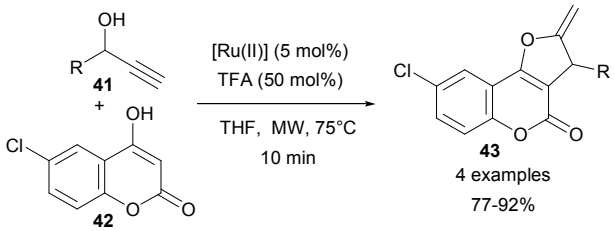
2.1.2 Furans, Benzofurans and Thiophenes

An important class of heterocyclic fused coumarin derivatives, furocoumarins, also have attracted considerable attention due to their properties.[44] Consequently, much effort has been directed towards the synthesis of this type of compounds. In this review, we focus on furocumarins, in which the furan ring is fused to the lactone moiety. Three structural isomers of these molecules are possible: furo[2,3-*c*], furo[3,2-*c*] and furo[3,4-*c*] coumarins.

2.1.2.1 Furo[3,2-c]coumarin or furo[2,3-c]coumarin.

The cycloisomerization of acetylenic compounds containing pendant oxygen functionalities offers a straightforward and atom-economical access to 2-substituted fused furans.[45] These transformations are powerful ways to generate furo[3,2-*c*]chromen-2-ones from relatively simple starting materials.

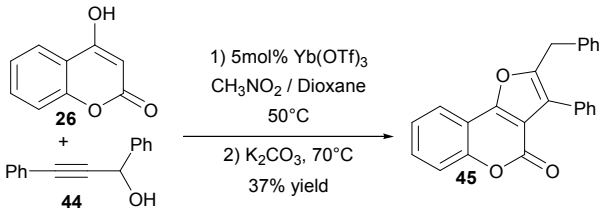
As a recent contribution to this field reactions, a synthetic approach to 2-methylene-2,3-dihydrofuro[3,2-*c*]chromen-2-ones **43** by Cadierno and co-workers is reported.[46] The key coupling reaction between secondary propargylic alcohols **41** and 6-chloro-4-hydroxycoumarin **42**, carried out with a catalytic system consisting of ruthenium(II) and trifluoroacetic acid, delivers the desired products intermediate in good yield. The process, which happens in a one-pot manner, involves an initial trifluoroacetic acid-promoted propargylic substitution of the alkynol by the 1,3-dicarbonyl compound and the subsequent cycloisomerization of the resulting γ-keto alkyne catalysed by the ruthenium(II) complex.



Scheme 13. Synthesis of 2-methylene-2,3-dihydrofuro[3,2-c]chromen-2-one (**43**) from propargylic alcohols (**41**) and 6-chloro-4-hydroxycoumarin (**42**).

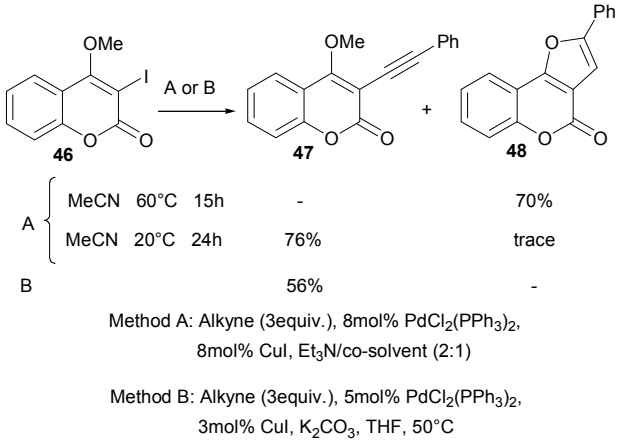
Brønsted acid catalysed propargylations of several organic substrates, including 1,3-dicarbonyl compounds, with alkynols have been reported.[47] In most cases, only 5 mol% of the acid catalyst is required to promote the propargylation process efficiently. In the case of Cadierno and co-workers, they had to use larger quantities of acid (50% mol) in order to avoid the Meyer–Schuster isomerisation of the propargylic alcohol catalysed by ruthenium complex.[48]

These methodologies present the problem that the alkyl-substituted propargylic alcohols are ineffective substrates therein. Zhou and co-workers avoided this problem using $Yb(OTf)_3$ as a Lewis acid.[49] The strategy involves a one-pot $Yb(OTf)_3$ propargylation-cycloisomerization sequence of 4-hydroxycoumarins **26** with the propargylic alcohol **44** for the construction of multi-substituted furocoumarins furochromen-2-one skeletons **45** (Scheme 14).



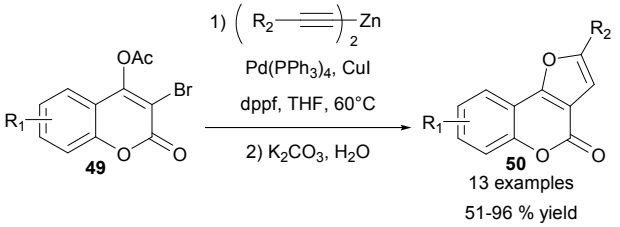
Scheme 14. Synthesis of 2-benzyl-3-phenyl-4*H*-furo[3,2-*c*]chromen-4-one **45** catalysed by $Yb(OTf)_3$.

While extensive work has been devoted to the cyclization of arylalkynol derivatives, investigations into the potential utility of arylalkynyl ethers as furan precursors are scarce.[50] The initial dealkylation steps can be achieved by Et_3N-induced SN2 as demonstrated by Monteiro and Balme, who described the synthesis of 2-substituted furan-fused coumarin **48** from 3-iodo-4-methoxycoumarin **46** by means of an *in situ* sequential Sonogashira-acetylide coupling, demethylation step induced by Et_3N, followed by an intramolecular attack of the enolate onto the cuprohalide π-complex of triple bond. (Scheme 15). [51] When the reaction is carried out in MeCN at 60°C, the furocoumarin system **48** was obtained directly.



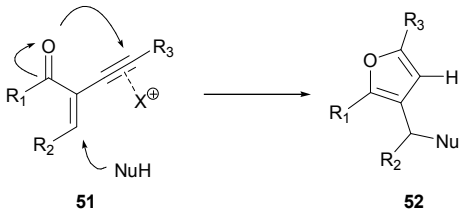
Scheme 15. One-Pot Synthesis of furocoumarin **48** by an Et_3N-induced demethylation process.

This method represents an efficient entry to furo[3,2-*c*]coumarins. Most of previous methods obtained mixtures of isomeric furo[3,2-*c*]coumarins and furo[3,2-*b*]chromones.[52]
More recently, Xu has described the elaboration of furocoumarins **50** by a similar palladium/copper-catalyzed coupling/cyclization reaction cascade from the 3-bromo-4-acetoxycoumarins **49** with *in situ* prepared dialkynylzincs (Scheme 16).[53] Aromatic as well as aliphatic alkynes could be employed in the reaction, although protection of the hydroxyl group at C-4 with acetyl group is necessary.



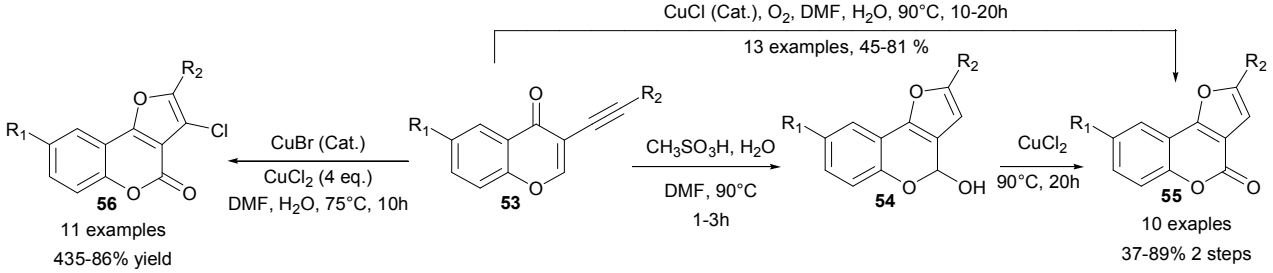
Scheme 16. Synthesis of diverse substituted furocoumarins **50**.

The 2-(1-alkynyl)-2-alken-1-ones **51**, have three special functional groups, and can be considered as privileged starting materials for the preparation of highly substituted furans by transition metal-catalyzed (Au, Pt, Cu)[54] or electrophilic cyclization (Scheme 17).[55]



Scheme 17. Synthesis of highly substituted furans **52** from 2-(1-alkynyl)-2-alken-1-ones **51**.

Based on this previous work, Cheng and Hu reported a regioselective synthesis of furo[3,2-*c*]coumarins **55** by a consecutive addition/cyclization/oxidation process from substituted 3-alkynyl-4*H*-chromen-4-one **53.** The strategy features the CH_3SO_3H-catalyzed construction of furan ring, followed by oxidation of **54** with $CuCl_2$ (Scheme 18)[56]
When the reaction was carried out in the presence of catalytic amount of CuCl as Lewis acid and atmospheric oxygen as oxidant, a cascade addition/cyclization/oxidation process provided the 2-substituted 4*H*-furo[3,2-*c*]coumarin **55**, while the presence of 10% CuBr and $CuCl_2$ excess as the oxidant afforded the 3-chloro derivative **56** (Scheme 18).[57]
In recent years, much effort has been devoted to the development of oxidative intramolecular C–O bond-forming cyclization reactions, although the applicable substrate scope in most cases remains limited to arenes, such as *O*-arylphenols. [58]
The Hong group developed a C–H bond functionalization, with an intramolecular C–O cyclization of 4-(2-hydroxyphenyl)-coumarins **57**, in the presence of 1-2 equivalents of $Cu(OAc)_2$ and a catalytic amount of $Zn(OTf)_2$, which afforded the corresponding 6*H*-benzofuro[2,3-*c*]coumarins **58** (Scheme 19).[59]
The formation of these products can be explained by the coordination of Cu(II) species with the phenolic hydroxyl group. Once a complex is generated, the electrophilic metalation at the C3-position of the chromone on Cu(II) may proceed. The electrophilic metalation of coumarins at the C3 is favourable due to the nucleophilic 3-position.[60]



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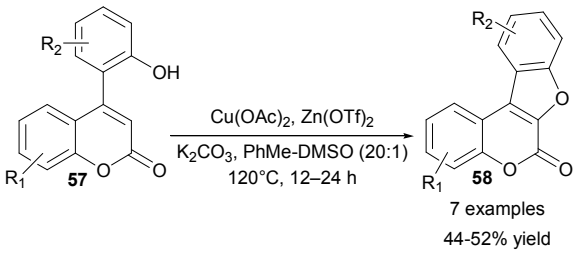
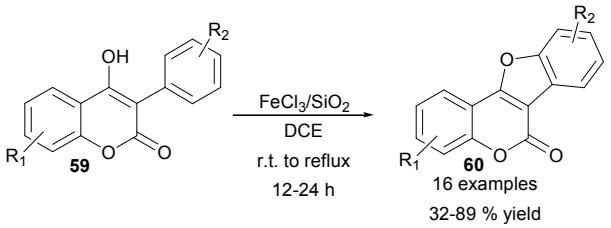
Scheme 18. Catalyzed cascade reaction of 3-alkynyl-4-chromone **53** to furocoumarins.



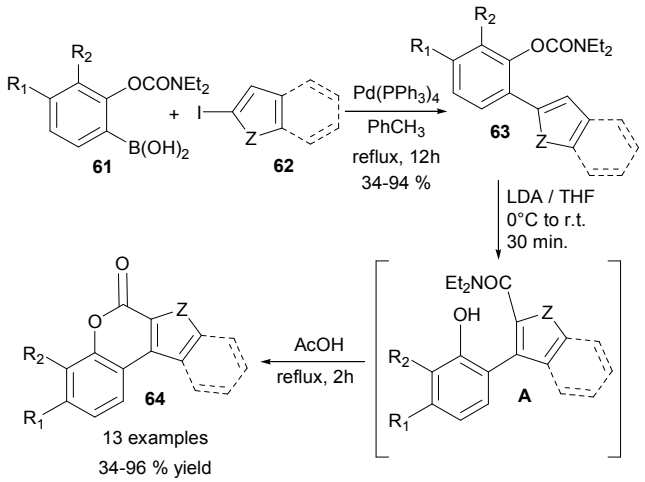
Scheme 19. C–H functionalization/C–O cyclization of coumarins.

A closely related reaction that allows the preparation of isomeric 6*H*-benzofuro[3,2-*c*]coumarin **60** was developed by Du and Zhao,[61] following a similar procedure but starting from 4-hydroxy-3-phenyl-coumarins **59** and using a combination of $FeCl_3$ and SiO_2 as catalyst (Scheme 20).[62]



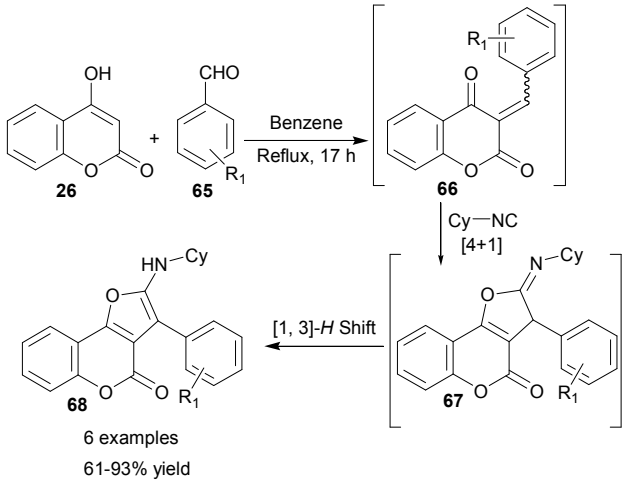
Scheme 20. Synthesis of coumestans **60** via intramolecular heterocyclization reaction mediated by $FeCl_3/SiO_2$.

The combination of directed *ortho*-metallation and transition metal-catalysed cross-coupling has evolved into a common strategy in synthesis.[63] Using this strategy, the synthesis of coumestans and thio coumestans has been reported.[64] The synthesis of **64** started from *O*-carbamoyl *ortho*-boronic acids **61** by Suzuki–Miyaura cross coupling with available heterocyclic iodides **62**. The resulting heterobiaryls **63** was transformed into coumestan derivatives **64** by a base induced carbamoyl migration to afford intermediate amides (A) which, upon acid-catalyzed cyclization, would afford the benzopyranones with heterocyclic annelation **64** (Scheme 21).

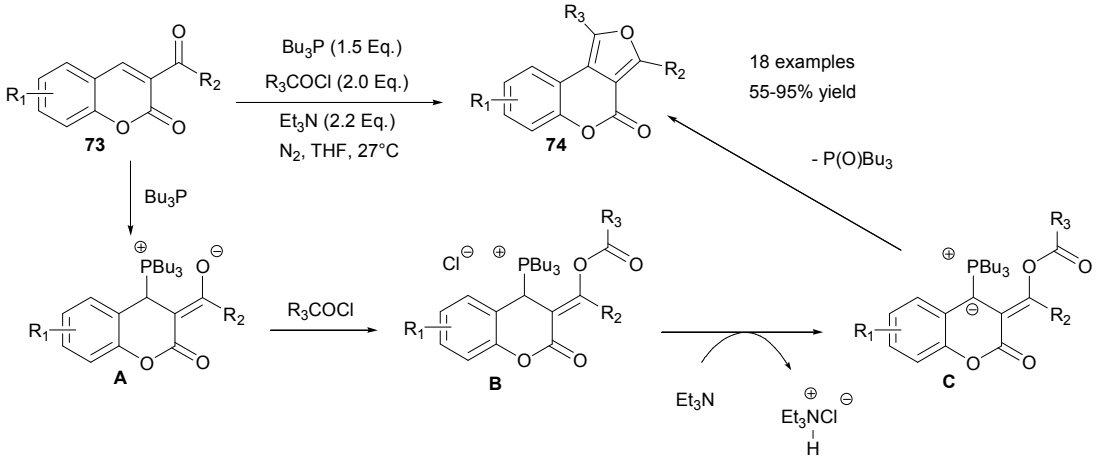


Scheme 21. Synthesis of coumestan derivatives **64**.

The synthesis of furocoumarins **68** has been accomplished by Nair employing an intermolecular [4+1] cycloaddition of quinone methide **66** with cyclohexyl isocyanide as the key step. [65] The reaction conditions are compatible with a variety of functional groups of the benzaldehydes, although the other two components are restricted to 4-hydroxycoumarin **26** and cyclohexyl isocyanide. First, a condensation of 4-hydroxycoumarin **26** with benzaldehydes **65** provides quinone methide **66**, which is then converted into dihydrofuran derivative **67** by an intermolecular [4+1] cycloaddition with the isocyanide. Finally, a [1,3]-*H* shift provide the furocoumarin **68** as the end product (Scheme 22).



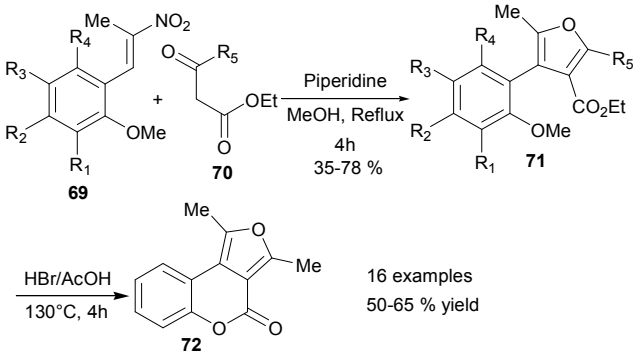
Scheme 22. Reaction of 4-hydroxycoumarin (**26**) and benzaldehydes (**65**) with cyclohexyl isocyanide.



Scheme 24. Preparation of highly functionalized furocoumarins (**74**) from acyl chloride and coumarins (**73**).

2.1.2.2 Furo[3,4-c]coumarins

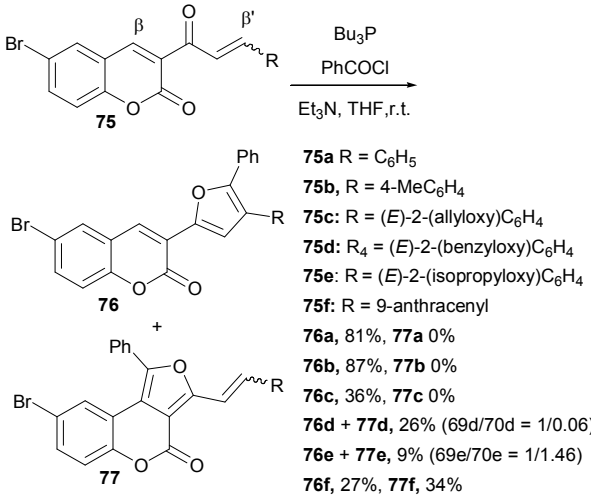
In 2006, Brahmbhatt described a furo[3,4-*c*]coumarin **72** synthesis via a demethylation–cyclization of 3-aryl-4-ethoxycarbonyl furans **71** process (Scheme 23). The starting material **69** was prepared from β-methyl-β-nitrostyrenes through Nef reactions. Their application has been limited due to tolerance difficulties to a broad range of functional groups, which is a result of high temperatures and harsh reaction conditions. In addition, the preparation of 3-aryl-4-ethoxycarbonyl furans **71** from substituted benzaldehydes via β-methyl-β-nitrostyrenes is laborious and low yielding.[66]



Scheme 23. Synthesis of furo[3,4-*c*]coumarins **72**.

Enones can serve as strong acceptors of phosphines and can be smoothly converted into furans via phosphorus ylides as intermediates.[67] On this basis, a new synthesis of highly functionalized furo[3,4-*c*]coumarins **74** was developed, based on the treatment of coumarins **73** with acyl chlorides and *n*-tributylphosphine in the presence of triethylamine (Scheme 24).[68] A plausible mechanism starts with an initial Michael addition of the phosphine onto the conjugated double bond that affords the dipolar intermediate A, which is then acylated with an acid chloride, leading to the formation of B. Deprotonation of B by Et_3N and an intramolecular Wittig reaction, affords the observed product.

Lin and coworkers explored the scope of this method.[68] When a coumarin-chalcone hybrid reacted with Bu_3P, the steric effect played a key role in the determination of the regiochemistry of the Michael addition, and Bu_3P selectively attacked the less hindered chalcone carbon leading to the formation of 3-(2-furyl)-coumarins **76**. When R became bulkier, the addition of Bu_3P took place less selectively and two regioisomers **76** and **77** were obtained. (Scheme 25).

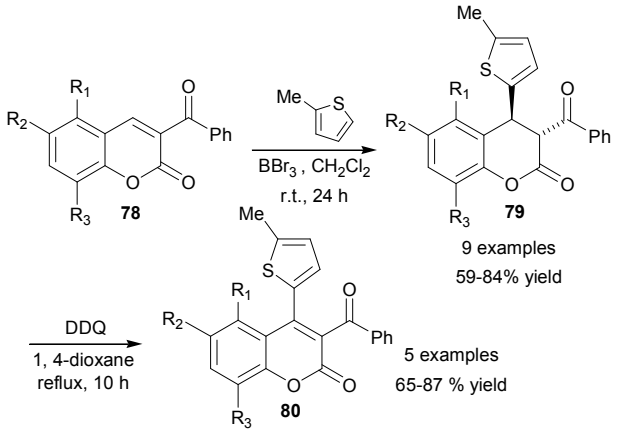


Scheme 25. Regioselective preparation of highly functionalized furyl coumarin derivatives **76** and/or **77**.

Although the electron-deficient character of coumarins, bearing an acceptor substituent at C-3, make these excellent acceptors in Michael type addition at C-4, only a few examples of reactions of coumarins with aromatic or heteroaromatic *C*-nucleophiles have been reported.[69,70]

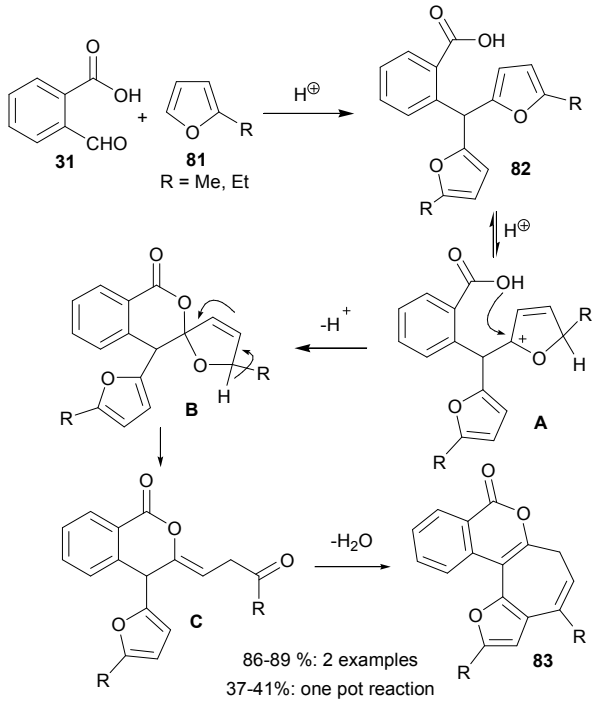
Recently, Irgashev and co-workers have reported the development of a synthesis of 3-benzoyl-4-(thien-2-yl)coumarins **80**, which involve the addition of thiophenes at C-4 of 3-benzoylcoumarins **78** under BBr_3 catalysis, followed by oxidation of the intermediate with DDQ (Scheme 26).[71] The addition of

thiophenes to coumarins **78** proceeds in a highly diastereoselective manner and leads to the formation of the thermodynamically controlled 3,4-*trans*-substituted product **79**.



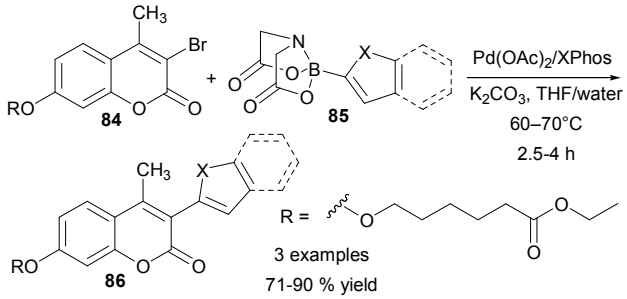
Scheme 26. The synthesis of 3,4-dihydrocoumarins (**79**) and its oxidation with DDQ.

It is a well-known fact that *O*-substituted benzylfurans in acidic media undergo the recyclization reaction of furan ring to form new heterocycles. [72, 73] Thus, the group of Butin has described a two-step approach to the synthesis of a novel tetracyclic isocoumarin derivatives **83**. [74] As shown in Scheme 27, the reaction starts with the formation of a bis-furylmethanes **82**, which reacts with a methanolic HCl solution, leading the isochromones **83** in good yields (86-89%). They also reported the one-pot version of the same process where the requisite bis-furylmethanes was prepared *in situ*, althought the reaction resulted in a lower yield than the reaction performed in two-steps (Scheme 27). The proposed mechanism begins with the protonation of one of two furan rings of **82**, followed by the intramolecular attack of the hydroxy group of 2-carboxyphenyl residue on the furanyl cation A. The intermediate spiro compound B then transforms isochromenone C, which undergoes intramolecular cyclization of the carbonyl group to the 3-position of the furyl moiety affording the tetracyclic isochromones **83** (Scheme 27). This result is consistent with those obtained previously by the same research group, as intramolecular cyclization of *N*-benzyl-2-bis(5-methyl-2-furyl)-methylbenzamide[73b] and 2-hydroxyarylbis(5-methyl-2-furyl)methanes.[75]



Scheme 27. Synthesis of tetracyclic isochromone derivatives (**83**).

The synthesis of 3-aryl-substituted coumarins **86** with enhanced fluorogenic properties, has been reported by Chan and co-workers.[76] The 3-aryl substituents are installed via a Suzuki–Miyaura cross-coupling reaction between a 7-alkoxy-3-bromo-4-methylcoumarin **84** and various heteroaryl MIDA boronate **85** in the presence of a palladium catalyst (Scheme 28).



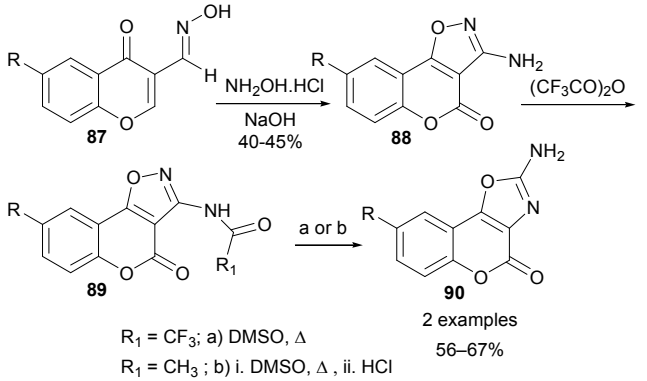
Scheme 28. Synthesis of fluorescent 7-alkoxy-3-aryl-4-methylcoumarin derivatives (**86**).

2.2 5-Membered rings with two heteroatoms

2.2.1 Oxazoles, Isoxazoles and Thiazoles

In recent years, studies on structural elucidation of biologically significant natural products have frequently incorporated novel oxazole and thiazole ring systems within complex molecular architectures.[77] The synthesis of this fundamental structural building block has received significant attention and a wide variety of approaches are available to the synthetic practitioner. One of the key synthetic challenges is a mild and selective oxazole formation in the presence of other sensitive functional groups.[78]

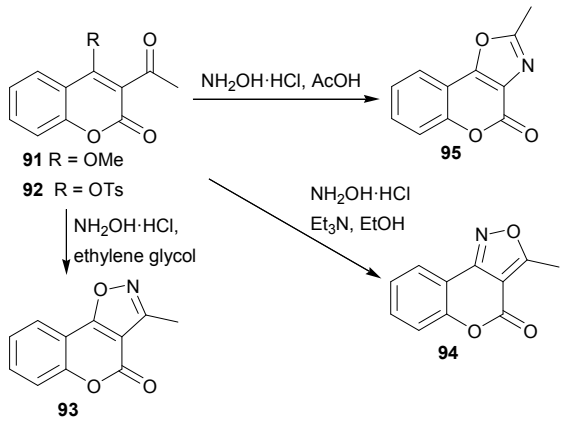
The chemistry of 3-substituted chromones has been developed since the Vilsmeier–Haack method was proposed for the synthesis of 3-formylchromones,[79] 3-cyanochromones[80] and 3-acetylcoumarin.[81] These molecules have been used as building block in the synthesis of numerous coumarin-heterocyclic derivatives.



Scheme 29. Rearrangement of 3-aminoisoxazolo[4,5-*c*]coumarins **89** mediated by carboxylic acid anhydrides.

The oximation of 3-formylchromone **87** in alkaline medium produced 3-aminoisoxazolo[4,5-*c*]coumarin **88** in moderate yields, which easily reacted with an excess of trifluoroacetic anhydride affording trifluoroacetyl derivatives **89** which rearranged into isomeric compounds 2-amino-oxazolo[4,5-*c*]coumarins **90** in DMSO at 90 °C (Scheme 29)[82]. When acetic anhydride was used as acylation reagent, a posterior hydrolysis step was necessary to obtain the deacetylated oxazole **90** (Scheme 26).[83]

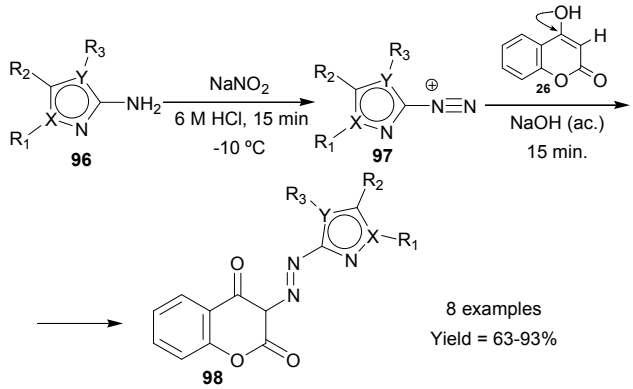
This ring isomerization is a well-documented reaction under thermal conditions (at 230°C under nitrogen atmosphere).[84] In this case, the ability of isoxazoles to rearrange into oxazoles under lower temperature is presumably due to the favourable combination of 4-carbonyl and 3-acylamino groups in the isoxazole ring, which increases the acidity of the amidic proton.[85]



Scheme 30. Synthesis of coumarin-isoxazol derivatives.

Latypov and coworkers independently synthesized chromeno[3,4-*d*]isoxazol **93**, chromeno[4,3-*c*]isoxazol **94** and chromeno[3,4-*d*][1,3]oxazol **95**, through the reaction of the bis-nucleophile hydroxylamine with the appropriate 3-acetyl derivatives **91-92** as described in Scheme 30.[86]

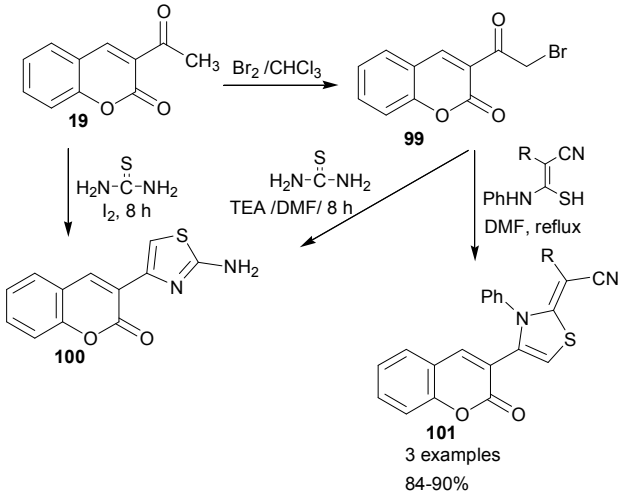
In order to synthesize novel hydrazinylidene-chroman derivatives **98**, Huwiler and co-workers used the fact that electrophiles are attacking the coumarin core at position 3.[87] The strategy involves the coupling of five member heterocyclic diazonium salts **97** with 4-hydroxycoumarin **26** under basic conditions (Scheme 31).[88]



Scheme 31. Synthesis of hydrazinylidene-chroman-2,4-diones **98**.

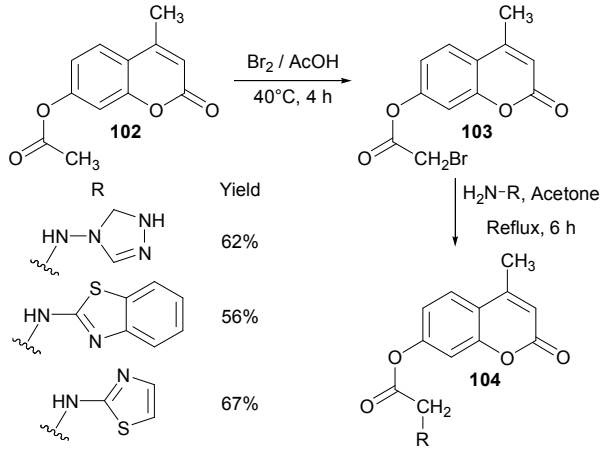
The Hantzsch thiazole synthesis, in its traditional form, is based on the reaction between a α-haloketone and thiourea or thioamides.[89]

A two steps protocol starting from 3-acetylcoumarin **19** provides access to 3-(2-aminothiazol)-coumarin derivatives **100**, via bromination of the starting material. The same product was obtained in one step by the condensation reaction between acetophenone **19** and thiourea in the presence of iodine, but unfortunately no yields were reported (Scheme 32).[90] Furthermore, condensation of acetylbromide **99** with the appropriate thiocarbamoyl derivatives in DMF at reflux produced the corresponding thiazole derivatives **101** in high yields.



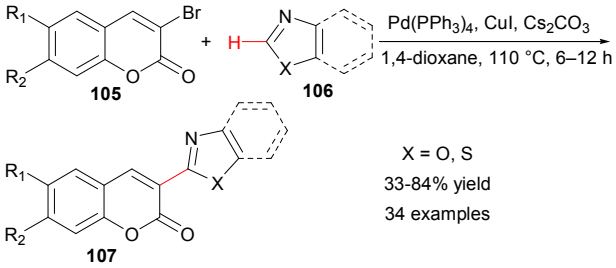
Scheme 32. Synthesis of thiazol-coumarin derivatives.

The coupling of α-bromoacetate and different heterocyclic amines may also be used as the basis for a thiazole-coumarin derivative synthesis. As shown in Scheme 33, a simple example of this strategy consists of the nucleophilic substitution of bromine of bromoacetate **103** for different heterocyclic amines.[91] In this case, bromine in acetic acid was employed in the bromination reaction to selectively obtain halogenation in the acetyl group.



Scheme 33. Synthesis of coumarin derivatives **104**.

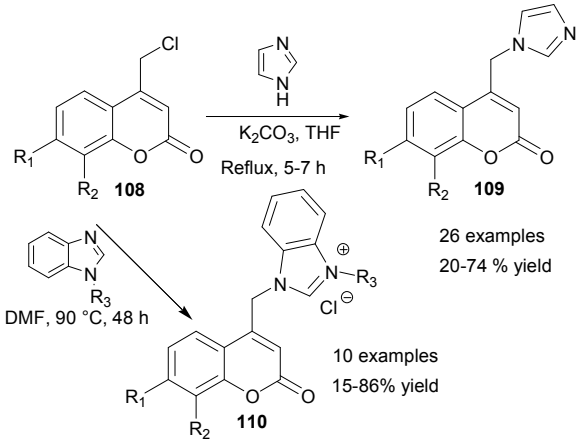
Following a similar sequence to the one used in the synthesis of 3-aryl-substituted coumarins **86**,[76] the synthesis of various 3-thiazol, 3-benzothiazol and 3-benzoxazol-coumarin scaffolds has been achieved by Hong and co-workers. [92] The 3-bromocoumarins **105** is converted into 3-heteroaryl coumarins **107** via a palladium-catalyzed C–H functionalization reaction (Scheme 34).



Scheme 34. Pd-catalyzed direct cross-coupling of various coumarins with heteroarenes.

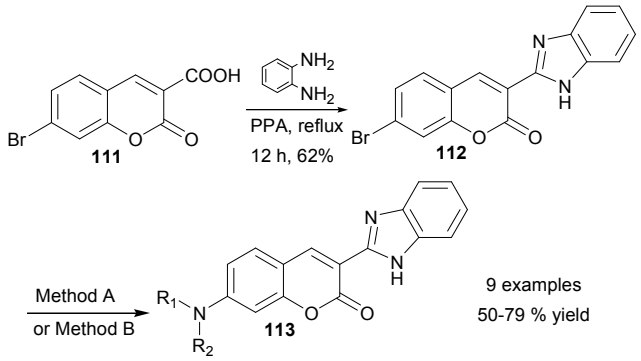
2.2.2 Imidazoles, Benzimidazoles and Pyrazoles

4-Methyl-3,7-substituted coumarins have played an important role in the discovery of novel molecules of interest.[93] Key to this synthesis is the functionalization of methyl groups, typically as 4-halogenated or 4-oxygenated methyl moiety.[94] An example of this approach is the *N*-alkylation of imidazole[95] and benzimidazole[96] with halogenated 4-methylcoumarin **108** (Scheme 35).



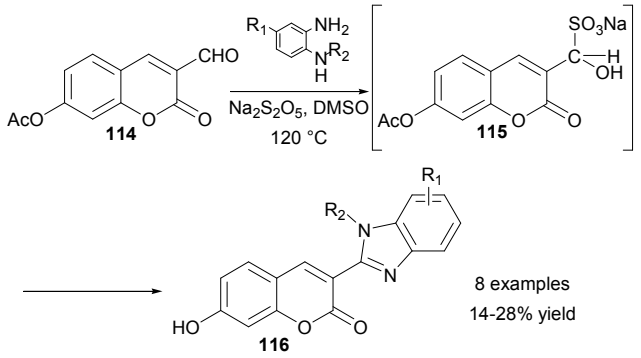
Scheme 35. Synthesis of imidazolyl derivatives of coumarins.

Paul and coworkers described a method for the synthesis of 3-benzoimidazol-coumarin derivatives **113** in moderate to good yields (Scheme 36).[97] The synthetic strategy was based in a two-step procedure involving a condensation of *O*-phenylenediamine with carboxylic acid **111**, followed by the substitution of bromide with different amines.



Scheme 36. Synthesis of 3-(1*H*-benzo[*d*]imidazol-2-yl)-2*H*-chromen-2-one analogs **113**.

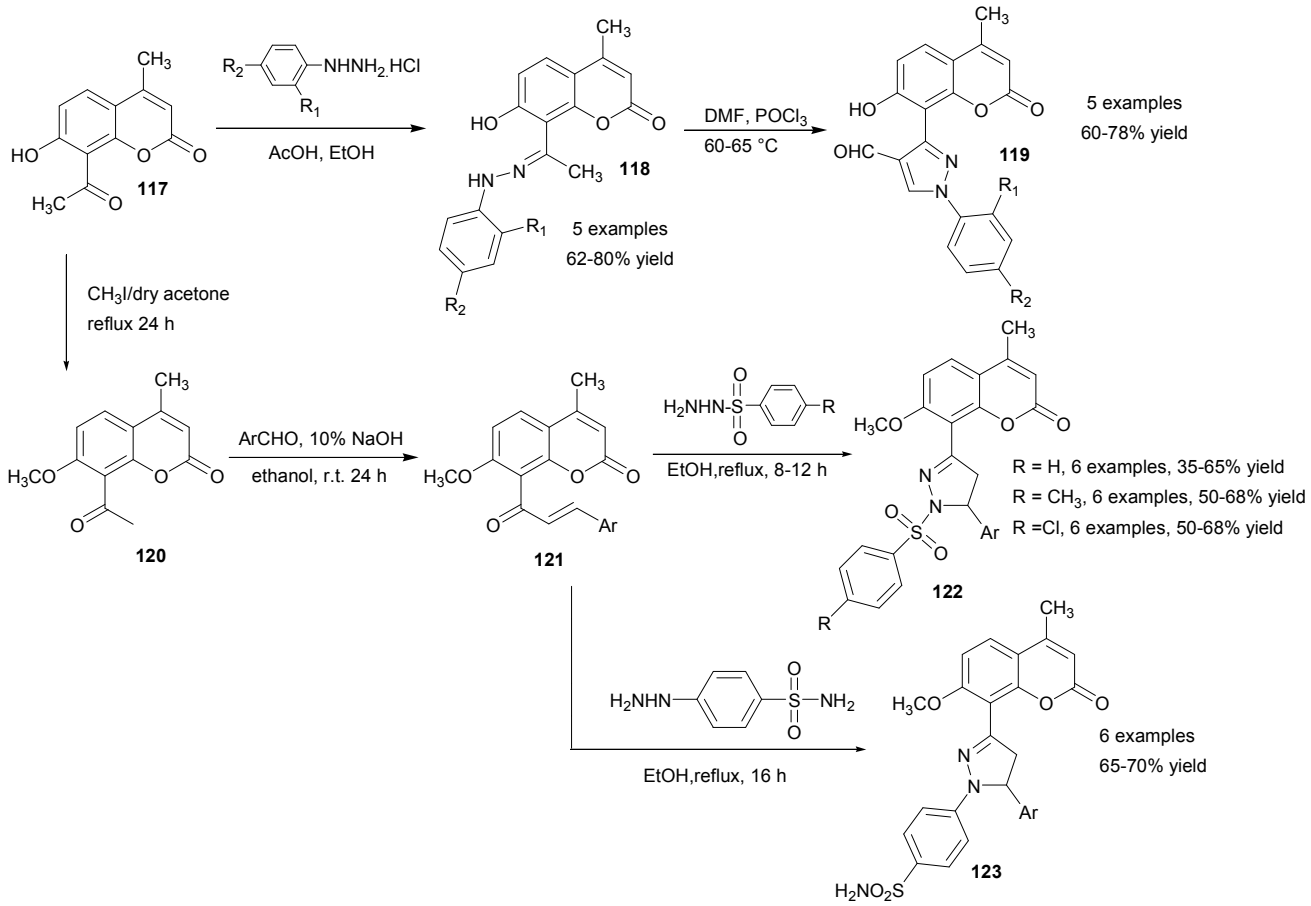
Inspired by recent work by Yoon on the efficient synthesis of 1,2-disubstituted benzimidazoles,[98] Romieu and co-workers described a concise synthetic route to functionalized 3-heteroarylcoumarins **116**, whose key step is a condensation between 7-acetoxy-3-formylcoumarin **114** and *ortho*-phenylenediamine derivatives in presence of sodium metabisulfite ($Na_2S_2O_5$) (Scheme 37).[99] As suggested by others authors,[100] this additive may favor the *in situ* formation of the more reactive bisulfite adduct **115**. This approach proved particularly effective for introducing different hydrophilic groups, leading coumarins that were both water-soluble and strongly fluorescent under physiological conditions.



Scheme 37. Synthesis of water-soluble 3-(2-benzimidazolyl)-7-hydroxycoumarin dyes.

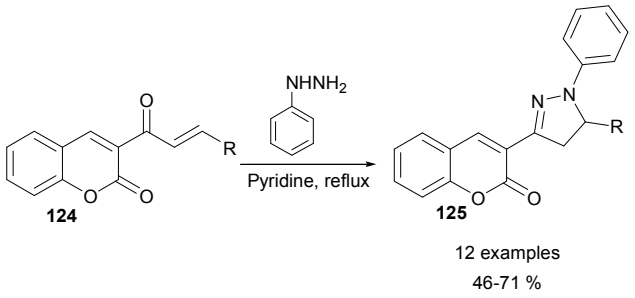
The application of the Vilsmeier-Haack reagent for the formylation of a variety of both aromatic and heteroaromatic substrates is well documented.[101] A notable example of these reactions is the synthesis of 4-formylpyrazoles from the double formylation of hydrazones.[102] Based in this work, the treatment of 8-acetyl-4-methyl-7-hydroxy coumarin **117**[103] with phenylhydrazines followed by Vilsmeier-Haack reagent yielded formyl-pyrazoles bearing coumarin moiety **123**,[104] while its aldol condensation with different benzaldehydes followed by

treatment with phenylsulfonyl hydrazines yielded the corresponding 4,5-dihydro-pyrazole derivatives **122** and **123** (Scheme 38).[105]



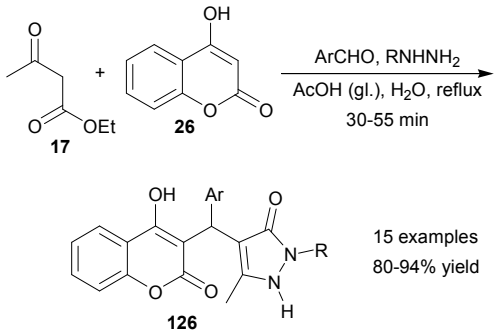
Scheme 38. Synthesis of coumarine-pyrazoline hybrids.

Maddi and co-workers applied a similar method to generate a series of 5-(substituted)aryl-3-(3-coumarinyl)-1-phenyl-2-pyrazolines **125** in good yields, by reacting various substituted coumarin chalcone hybrid **124** with phenylhydrazine in the presence of hot pyridine (Scheme 39).[106]



Scheme 39. Synthesis of 5-(substituted)aryl-3-(3-coumarinyl)-1-phenyl-2-pyrazolines **125**.

Recently, a four-component reaction leading to substituted benzylpyrazolyl coumarin derivatives **126** has been reported from 4-hydroxycoumarin **26**, ethyl acetoacetate **17**, hydrazine and aromatic aldehydes (Scheme 40).[107] Fifteen examples were prepared in very good yield when the reaction mixture was refluxed in 10% mol glacial acetic acid in aqueous medium.



Scheme 40. Green synthesis of benzylpyrazolyl coumarins **126**.

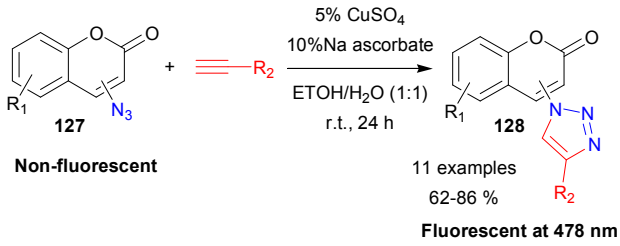
2.3 5-Membered rings with three heteroatoms

2.3.1 Triazoles

Click Chemistry is a term introduced by Sharpless to describe a set of nearly perfect ‘‘spring-loaded’’ chemical reactions.[108] The azide–alkyne cycloaddition can be considered as a typical ‘‘click’’ reaction, in which a 1,2,3-triazole, compounds of special interest in medicinal chemistry,[109] is formed in the presence of copper[110] or ruthenium,[111] allowing very high yields and good regioselectivity.[112]

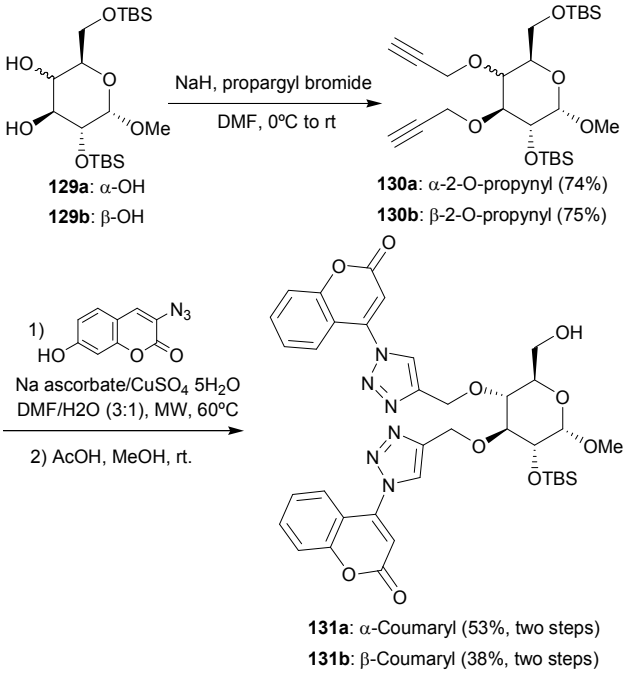
Fluorogenic chemistry has recently received considerable interest in numerous biochemical studies. Some recent efforts have been focused on the design of fluorogenic azide–alkyne cycloaddition reactions.[113]

Azidocoumarin shows only minor fluorescence due to a quenching effect from the electron-rich azide functional group, but upon formation of the 1,2,3-triazole ring, this quenching effect is suppressed, and the intensity of the fluorescence increases. This effect was demonstrated by Wang and co-workers,[114] who described a copper(I)-catalyzed 1,3-dipolar cycloaddition reaction of 3-azidocoumarins **127** and terminal alkynes to afford 1,2,3-triazole products **128** (Scheme 41). The Cu(I) species was generated *in situ* by the combination of 5%mol $CuSO_4.5H_2O$ and 10%mol of sodium ascorbate, a mild reductant.[115]



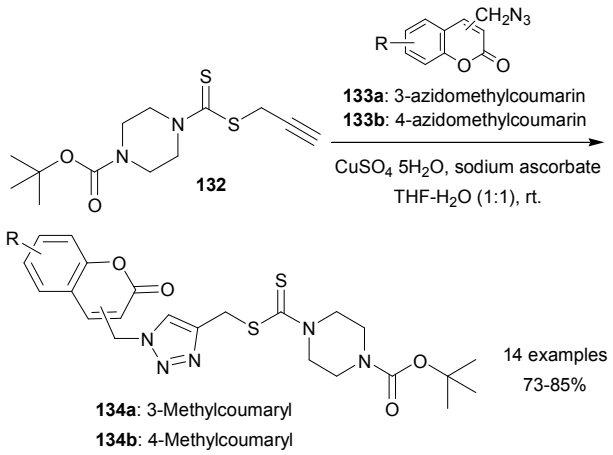
Scheme 41. Synthesis of Triazolylcoumarins **128**.

This methodology was used to prepare 3,4-bis-triazolocoumarine sugar conjugates **131**.[116] The microwave-assisted dual click reaction between 3-azidocoumarin and the dipropargyl gluco- **130a** and galactoside **130b** afforded the bis-triazolyl gluco- **131a** and galactoside **131b** in moderate yields, due probably to the excessive spatial hindrance of the bulky mono-triazolocoumarin formed on the neighboring C3- or C4-position of the sugar template (Scheme 42).



Scheme 42. Synthesis of 3,4-bis-triazolocoumarine sugar conjugates via flourogenic dual click chemistry.

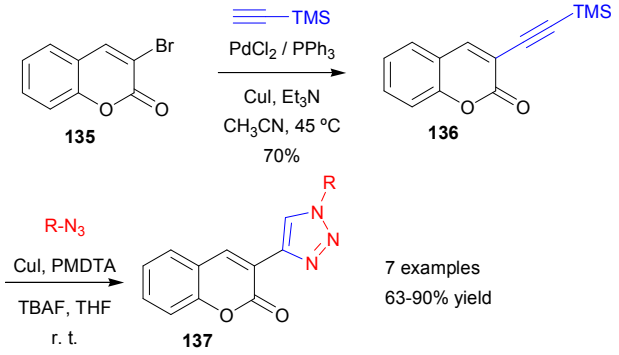
Liu and coworkers also applied this protocol to 3- and 4-azidomethylcoumarin **133a-b**, obtaining coumarin–1,2,3-triazole–dithiocarbamate hybrids **134a-b** in moderate to good yields (Scheme 43).[117]



Scheme 43. Synthesis of the coumarin-1,2,3-triazole-dithiocarbamate hybrids **134**.

A modification of this strategy is based on the introduction of a terminal alkyne in the coumarin ring. Stefani and co-workers reported the synthesis of 3-(1,2,3-triazolyl) coumarin derivatives **137** by means of a two-step procedure involving a palladium-catalyzed Sonogashira cross-coupling reaction followed by a 1,3-dipolar cycloaddition.

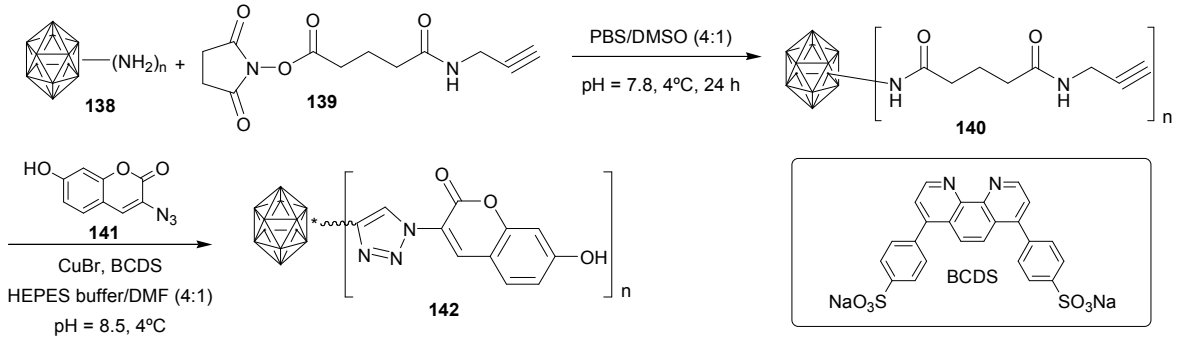
Thus, 3-bromocoumarin **135** is subjected to a Sonogashira reaction with terminal to provide 3-(trimethylsilylethynyl) coumarin **136** in 70% overall yield. This compound is further treated with various organic azides via CuI-promoted reaction in the presence of PMDTA as ligand (Scheme 44).[118] In general, the alkyl azides gave lower yields, whilst the electron-rich and neutral aryl azides gave high yields of the 1,2,3-triazoles.



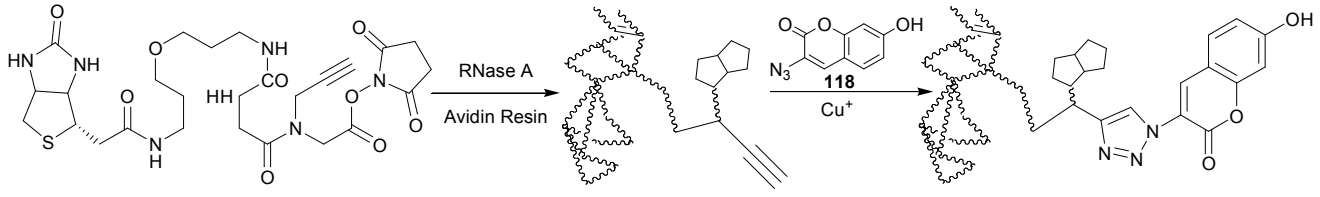
Scheme 44. Synthesis of 3-(1,2,3-triazolyl) coumarins **137** from 3-alkynylcoumarins **136** and organic azides.

Bioconjugation has emerged as a fast-growing technology that impacts almost every discipline of life science. Nowadays, a variety of different bioconjugation techniques are known for the purpose of in vitro studies, but many of them are limited in terms of their chemoselectivity and their application to chemical biology.[119] Common linkages for site-specific bioconjugation to label proteins rely on cysteine or lysine residues.[120] Newer methods target non-natural functional groups, including triazole products via Cu(I)-catalyzed 1,3-

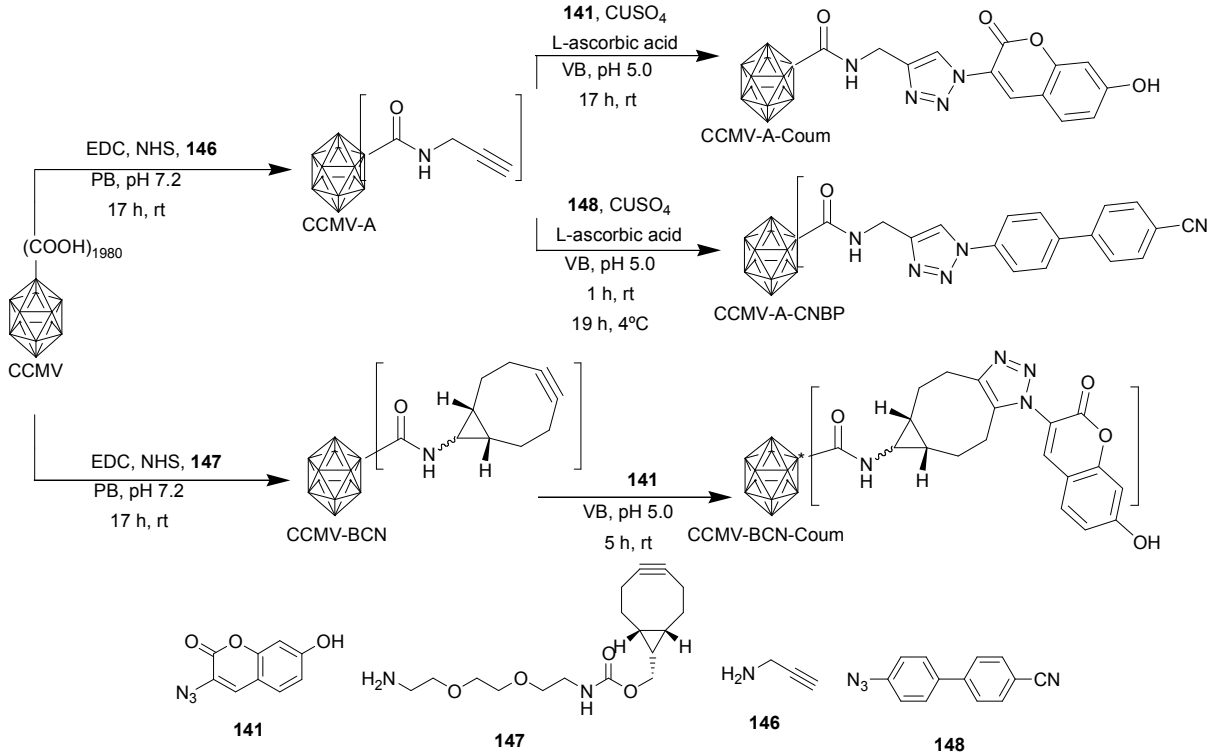
dipolar cycloaddition of azides and alkynes under mild conditions.[121] In this aspect, some authors have chosen coumarin as the profluorophore as it is small in size, biocompatible, and easy to manipulate synthetically.



Scheme 45. Chemoselective derivatization of apo-HSF **138** by click reaction.



Scheme 46. Formation of the click product coumarin-(K1)RNase A **145**.



Scheme 47. Functionalization of CCMV with alkynes and posterior click chemistry. CCMV: cowpea, chlorotic mottle virus; EDC: N-ethyl-N'-(3-dimethylaminopropyl)carbomide; NHS: *N*-hydroxysuccinimide; PB: phosphate buffer; VB: virus buffer.

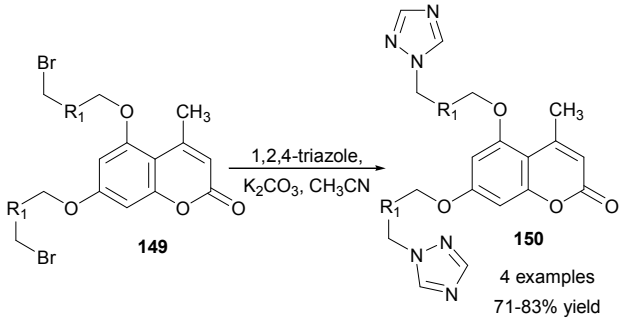
Substitutions at the 3- and 7-positions of coumarin dyes are known to have a strong impact on their fluorescence properties.[122] Wang and co-workers used these results to propose an interesting approach to the chemoselective derivatization of horse spleen apoferritin (apo-HSF) **138** by click chemistry by means of a two-step procedure (Scheme

45).[123] Thus, the lysine residues of apo-HSF **138** are subjected to a acylation of with *N*-hydroxysuccinimidyl ester (NHS) reagents **139**, and a post-functionalization of the alkyne derivatized apoferritin **140** by a Cu(I) mediated azide–alkyne 1,3-dipolar cycloaddition with 3-azido-7-hydroxycoumarin **141**. In this case, the authors used an alternative protocol developed by Finn and coworkers, in which a Cu(I) source and a bathophenanthroline ligand (BCDS) was used, [124] to avoid aggregation or denaturation of Apoferritin by introducing the reducing reagents.

In 2012, Weil and co-workers described the site-selective modification of the protein ribonuclease A (RNase A) (Scheme 46) using the same catalytic system.[125]

A closely related reaction that allows the modification of the outer protein shell of cowpea chlorotic mottle virus (CCMV) with linear and strained alkyne groups was developed by the Katsonis group, following the same strategy but using an amidation of exposed carboxyl residues to introduce alkyne groups instead of acylation of lysine residues (Scheme 47).[126]

The *N*-alkylation of imidazole offers an efficient alternative to the use of 1,3-dipolar cycloaddition route. Shi and Zhou Yu reported a facile synthesis of bis-triazoles derivatives from *N*-alkylation of intermediate coumarin bromides **149** with 1,2,4-triazole (Scheme 48). [127]

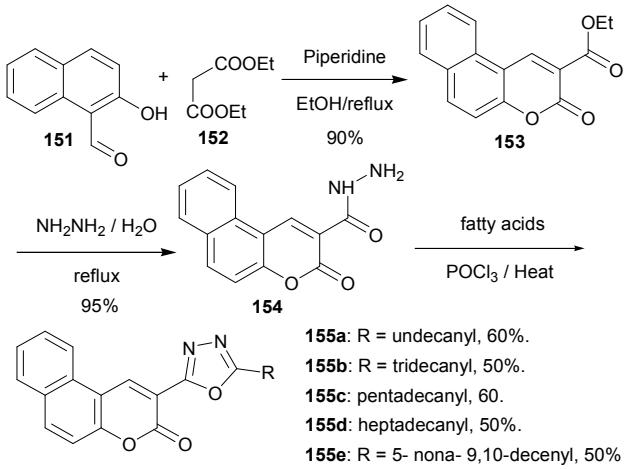


Scheme 48. Synthesis of coumarin-based 1,2,4-triazole derivatives **150**.

2.3.2. Oxadiazoles and Thiadiazoles

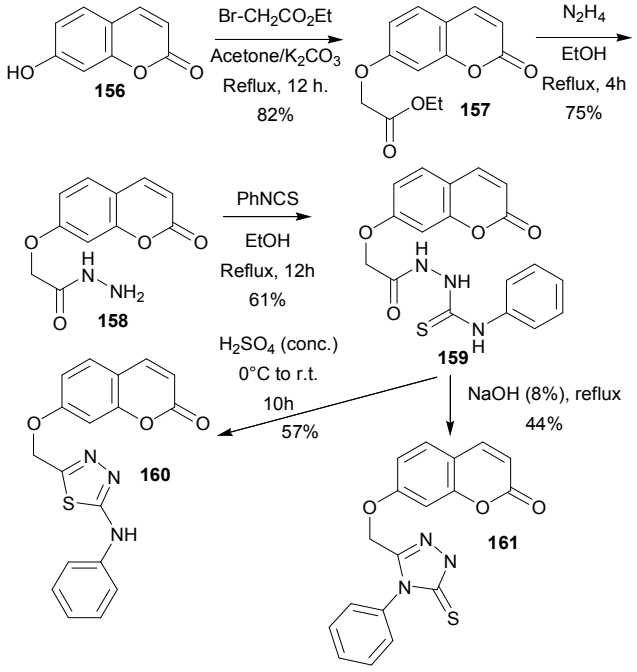
Oxa and thiadiazole are prevalent and important five-membered heterocyclic systems, particularly 1,3,4-oxadiazol and 1,3,4-thiadiazol.[128]

One of the popular methods for the synthesis of 1,3,4-oxadiazoles involves the cyclization of diacylhydrazines. Thus, the treatment of benzocoumarin-3-ethyl carboxylate **153** with hydrazine followed by direct cyclization with various fatty acids in the presence of $POCl_3$ afforded new benzocoumarin-3-oxadiazoles **155a-e** (Scheme 49). [129]



Scheme 49. Synthesis of long-chained 2-(5-alkyl-1,3,4-oxadiazol-2-yl)-3*H*-benzo[*f*]chromen-3-ones (**155**).

Al-Amiery and co-workers used 7-hydroxycoumarin (umbelliferone) **156** as starting material, which in four steps was converted into the corresponding thiadiazol **160** or triazole **161** derivatives (Scheme 50).[130] Thus, the ethyl acetate derivative **157** was converted to the corresponding phenyl thiosemicarbazide **158** by addition of phenyl isothiocyanate. The cyclization of the compound **159** by sulphuric acid yielded compound thiadiazol **160**, while reaction with sodium hydroxide produced compound triazole **161**. Unfortunately, the authors only used phenyl isothiocyanate in this protocol.

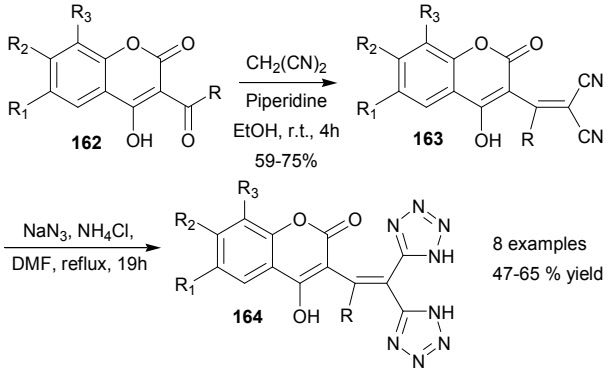


Scheme 50. Synthesis of umbelliferone derivatives.

2.4 5-Membered ring with four heteroatoms

2.4.1. Tetrazoles

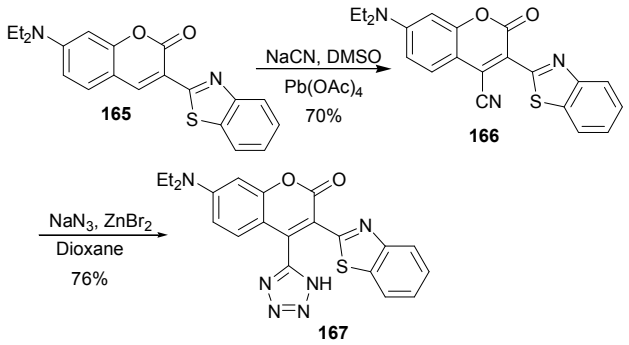
The 1*H*- and 2*H*-tetrazoles are regarded as isosteric replacements of carboxylic acids with improved properties in drug metabolism and pharmacokinetics.[131] Therefore, a number of methods have been reported for the preparation of tetrazoles.[132] The most direct method to form tetrazoles is via the formal [2+3] cycloaddition of azides and nitriles; however, there is continued debate as to the mechanism of the reaction.[133] Mulwad and co-workers reported the use of the combination of sodium azide/ammonium salt in the synthesis of bistetrazoles **164** in moderate yields (Scheme 51).[134] The synthesis begins with the condensation of **162** with malononitrile to afford the corresponding bis-nitrile **163**. Subsequent cycloaddition in the presence of azide form bistetrazole **164**.



Scheme 51. Synthesis of New 1,1-di-tetrazole derivatives **164**.

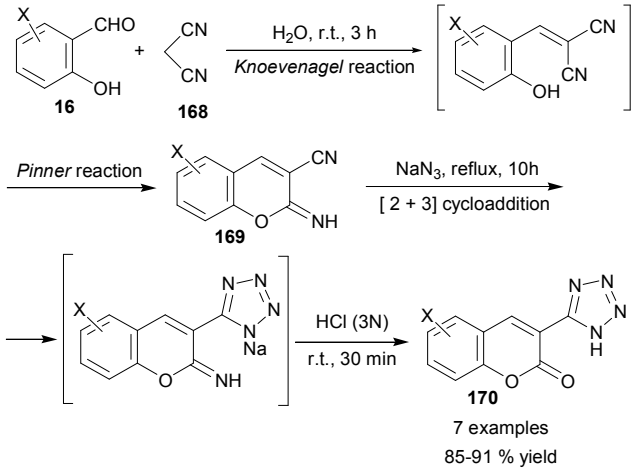
Sharpless and co-workers described the preparation of 5-substituted 1*H*-tetrazoles with excellent yields using a zinc salt and sodium azide.[135]

Wang, Moss and co-workers, have been using this approach to prepare 3-benzothiazol-4-(1*H*-tetrazol)-coumarin derivatives (**167**) in 76% (Scheme 52).[136]



Scheme 52. Synthesis of 3-Benzothiazol-4-(1H-tetrazol)-coumarin derivatives **167**.

A domino Knoevenagel condensation, Pinner reaction and 1,3-dipolar cycloaddition, between substituted salicylaldehydes **16**, malononitrile **168** and sodium azide, provided an efficient entry into 3-(1*H*-tetrazol-5-yl)coumarins **170** (Scheme 53). This transformation was carried out in water and catalyst-free conditions.[137]

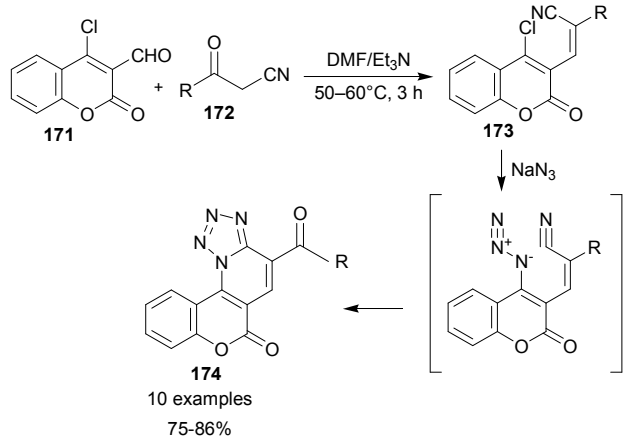


Scheme 53. Synthesis of 3-(1*H*-Tetrazol-5-yl)-2*H*-1-benzopyran-2-one (**170**).

The three-component reaction starting from 4-chloro-3-formylcoumarins **171**, alkyl/aryl acetonitriles **172** and sodium azide in the presence of catalytic amounts of triethylamine, led to tetrazole fused pyrido[2,3-*c*]coumarin derivatives **174** (Scheme 54).[138]

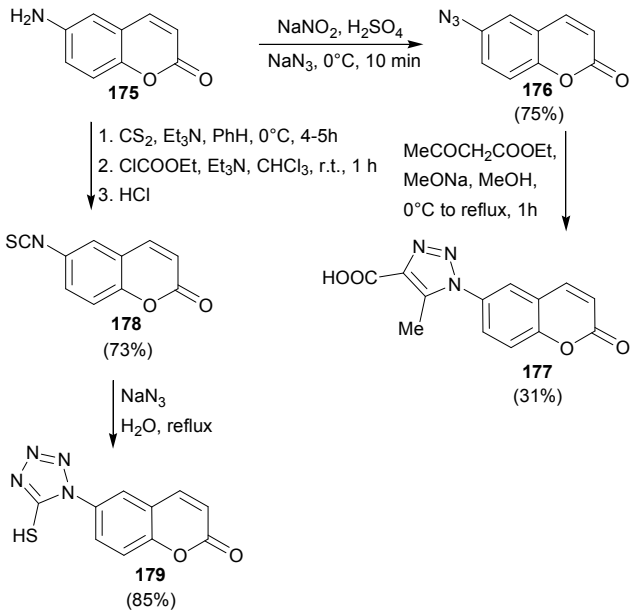
Although the attack of cyanide-stabilized carbanions on azide functions leading to 1,2,3-triazole is a well-established conversion in organic synthesis, only the tetrazole fused coumarin derivative was obtained exclusively by this method.[139]

Even though various tetrazole derivatives have long been studied, synthetic methodologies and physical or chemical properties of 1-substituted tetrazole-5-thiones, one class of tetrazole derivatives, have been relatively less explored.[140]



Scheme 54. Synthesis of tetrazolo[4',5':1,6]pyridido[2,3-*c*]coumarine derivatives **174**.

Pokhodylo and Obushak described an interesting diversity-oriented general protocol for the synthesis of 1,2,3-triazole and tetrazole coumarins derivatives. Azide **176** reacted with ethyl acetoacetate to give 1*H*-1,2,3-triazole-4-carboxylic acid **177**. Apparently, under the reaction conditions, the partial opening of the chromene ring occurred in competing reactions, so triazole was isolated in a moderate yield. When the initial reagent 6-aminocoumarin **175** was converted to the corresponding isothiocyanate **178**, which reacted with sodium azide, tetrazole **179** was obtained in 85% yield (Scheme 55).[141]



Scheme 55. Synthesis of triazole-coumarin **177** and tetrazol-coumarin **179** derivatives.

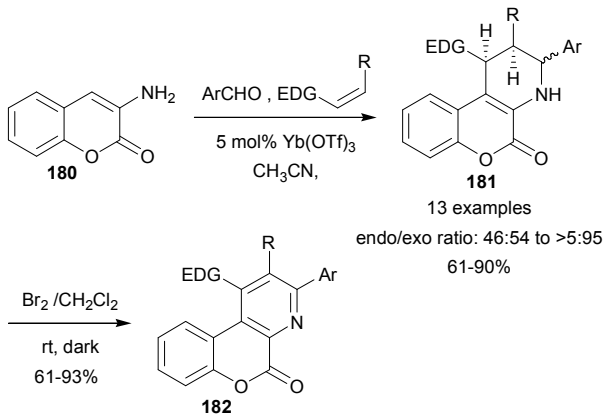
2.5 6-Membered ring with one heteroatom

2.5.1. Pyridines, Quinolines and Isoquinolines

The pyridine ring is a fundamental building block of nature and in the chemical industry. As a result, numerous methodologies have been developed to synthesize pyridine compounds.[142]

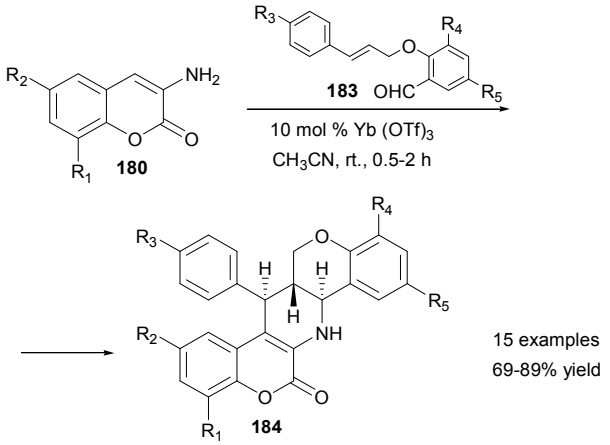
The Povarov reaction was originally reported in 1963 as a one-pot reaction of arylaldimines with electron-rich olefins, in particular, ethyl vinyl ether or ethyl vinyl sulfide in presence of BF_3/OEt_2, to obtain 2,4-disubstituted tetrahydroquinolines which were further oxidized to the corresponding quinolines.[143] The mechanism proposed is a concerted, formal [4+2]-type inverse electron-demand aza-Diels-Alder reaction. However, theoretical calculations show that the reaction can proceed through both concerted and stepwise pathways depending on the nature of the solvent and dienophiles used.[144]

In 2008, Bodwell and coworkers described a three-component Povarov reaction, which involves *in situ* formation of the 2-azadiene component, derived from the condensation of 3-aminocoumarins **180** and aromatic aldehydes, with various electron-rich alkenes in the presence of $Yb(OTf)_3$ to give 1,2,3,4-tetrahydropyrido[2,3-*c*]coumarins **181**, which were converted into the corresponding pyrido[2,3-*c*]coumarins **182** upon treatment with Br_2 or nitrous gases (Scheme 56).[145] Though the yields were generally good, the diastereoselectivity was variable, and did not appear to follow any clear trend. The mechanism suggested by the authors to explain this reaction, in contrast to the Povarov reactions of aniline derived 2-azadienes, was a concerted, yet asynchronous, mechanism. The difference in mechanism may be a consequence of the considerably weaker aromatic character of the 2-pyrone unit in coumarin-derived azadienes compared to that in the benzene ring of aniline-derived azadienes.



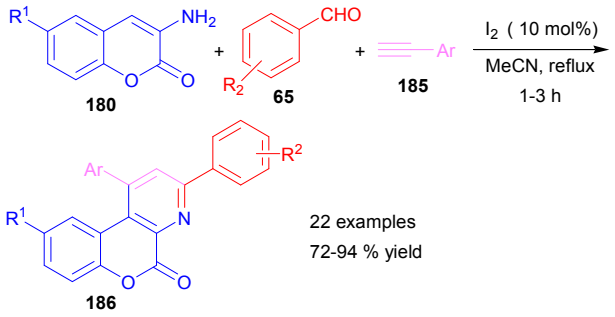
Scheme 56. The Povarov reaction involving 3-aminocoumarin **180**.

In a more recent work, this same research group reported an intramolecular Povarov reaction using 3-aminocoumarins **180** and *O*-cinnamylsalicylaldehydes bearing a pendant dienophile **183**, to synthesize a series of pentacyclic heterocycles **184** with high yields and endo/exo selectivity (Scheme 57).[146] The fused [6,6] ring system was obtained in good yields (69–89%) with a *trans*, *trans* relative stereochemistry, while the fused [6,5] ring systems was obtained in 49% yield, with the same stereochemistry in most cases. The use of an 2-(propargyloxy)benzaldehyde dienophile for the intramolecular inverse electron demand Diels–Alder reaction, yielded the aromatized pyrido[2,3-*c*] coumarins product in 47% yield after 9 days of reflux.[146]



Scheme 57. Povarov reaction of 3-aminocoumarin **180** and enals **183**.

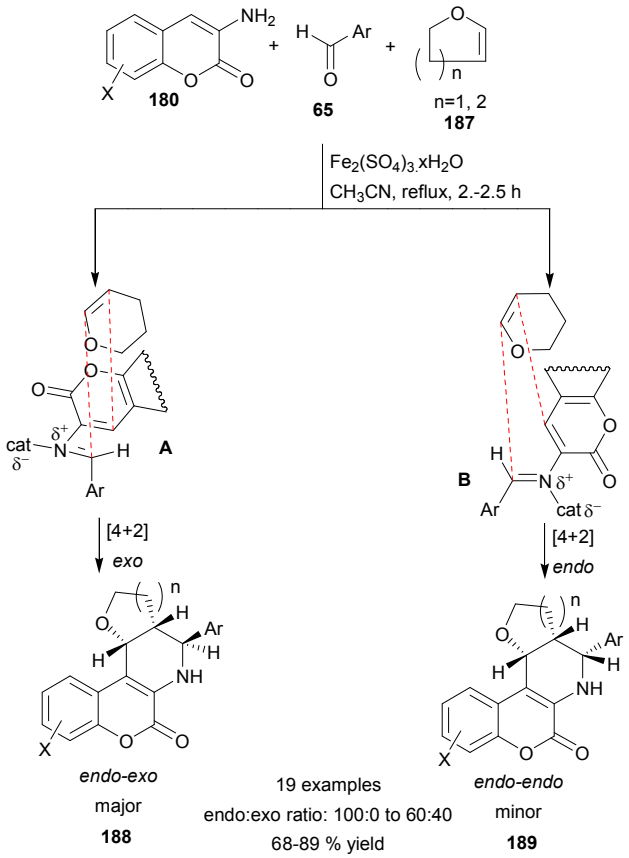
A related protocol, involving a three-component reaction starting from 3-aminocoumarins **180**, aromatic aldehydes **65** and alkynes **185**, was developed by Khan and co-workers and found to be complementary to the previous one in that it provides the oxidized product directly. The process yielded a variety of substituted pyrido[2,3-*c*] coumarin derivatives **186**, in the presence of 10% mol molecular iodine in acetonitrile under reflux conditions through one-pot Povarov reactions (Scheme 58).[147]



180 65 185 186

Scheme 58. One-pot synthesis of pyrido[2,3-*c*]coumarin derivatives (**186**).

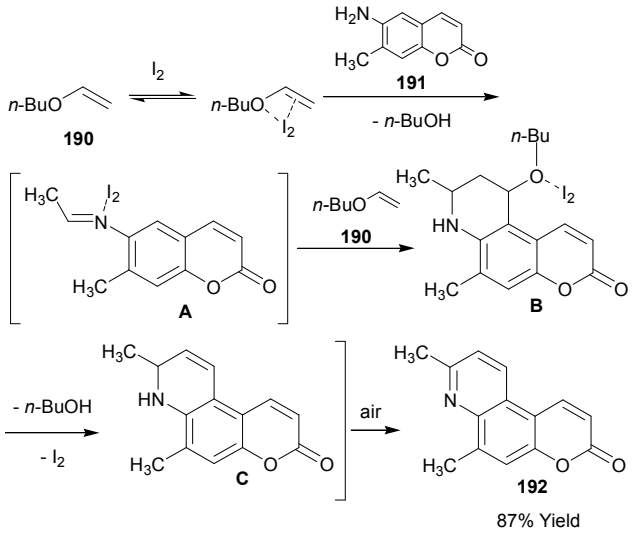
When the alkyne group **185** was replaced with cyclic enol ethers **187** and the reaction was carried out in the presence of 10% mol of hydrated ferric sulphate, tetrahydropyrido[2,3-*c*]coumarin derivatives **188**-**189** was obtained (Scheme 59).[148] The mechanism proposed to explain this transformation starts with the condensation reaction between aromatic aldehyde **65** and 3-aminocoumarin **180**, generating *in situ* the intermediate *N*-arylimines, which undergo a cycloaddition reaction with the electron-rich dienophiles in the presence of hydrated ferric sulfate. In this case, the authors found that the dienophile approaches the diene only from its *endo*-face. The major product obtained was *endo–exo* **188** due to steric repulsion between the aryl ring and tetrahydropyranyl ring.



180 65 187 A B 188 189

Scheme 59. One-pot synthesis of tetrahydropyrido[2,3-*c*]coumarins derivatives.

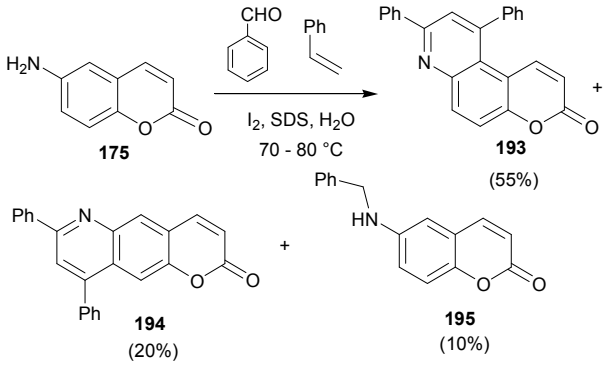
In 2013, Litinas and coworkers described the synthesis of 2-methyl substituted [5,6] or [7,8]-fused pyridocoumarins from three-component reaction of 6- or 7-aminocoumarins with two equivalents of *n*-butyl vinyl ether, catalysed by iodine.[149] The mechanism suggested by the authors is summarized in Scheme 60. Iodine catalyzes the reaction of ether **190** with aminocoumarin **191** to generate the imine A as well as the aza-Diels–Alder reaction of this imine with a second equivalent of ether **190** to form the intermediate B. Elimination of *n*-BuOH, followed by air oxidation leads the fused pyridocoumarin **192**.



190 191 A B C 192

Scheme 60. Synthesis of fused pyridocoumarins **192**.

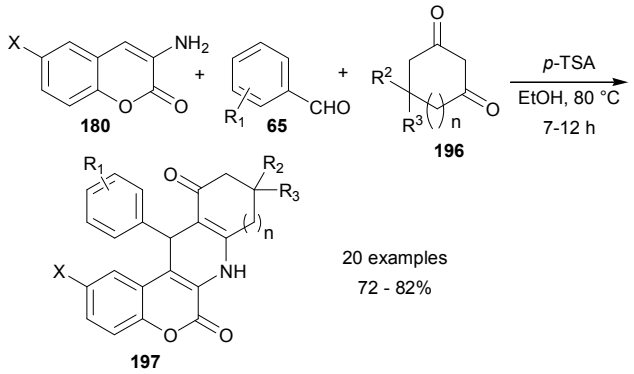
A similar three-component transformation, followed by oxidative aromatization under autotandem iodine catalysis in aqueous micellar conditions (in the presence of sodium dodecyl sulfate, SDS) provides a mixture of Schiff's base reduction product **195**, implying an internal hydrogen transfer process, together with mixture of the regioisomers **193** and **194** (Scheme 61).[150] The catalytic activity of iodine was presumably linked to its activation by SDS,[151] and its catalytic influence could be due to the electrophilic activation of the carbonyl.[152]



175 193 194 195

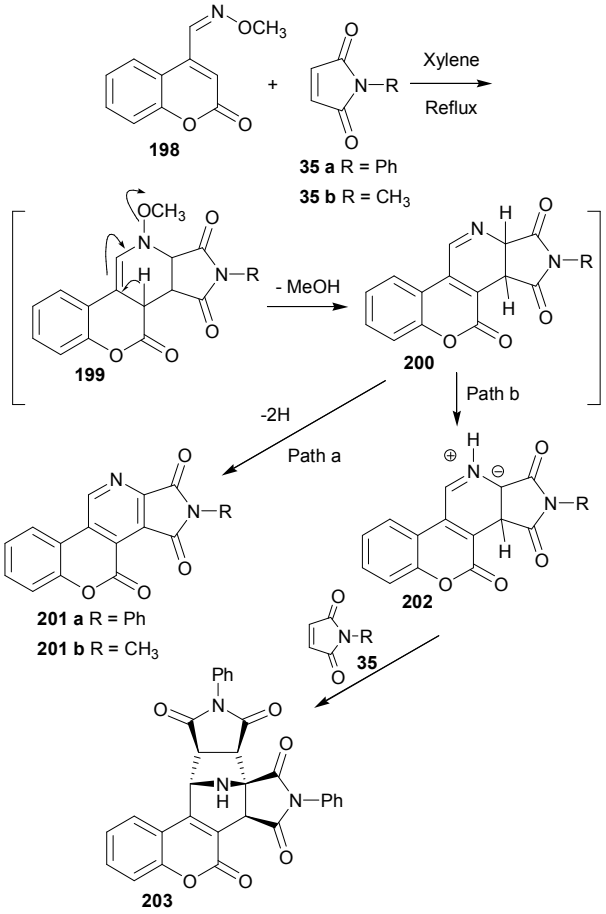
Scheme 61. Iodine-catalysed three-component reaction of 6-aminocoumarin **175**, benzaldehyde and styrene.

When the rich dienophiles was changed by cyclic 1,3-diketones (**196**), the chromeno[3,4-*b*]quinoline derivatives **197** were obtained (Scheme 62).[153] The proposed mechanism is initiated by the condensation reaction between aromatic aldehyde **65** with dimedone **196** to give Knoevenagel product, which reacts with 3-aminocoumarin **180** by a Michael addition, followed by intra-molecular ring closure reaction and dehydration to give the desired product **197**.



Scheme 62. One-pot three-component condensation reaction for the synthesis of chromeno[3,4-*b*]quinoline derivatives **197**.

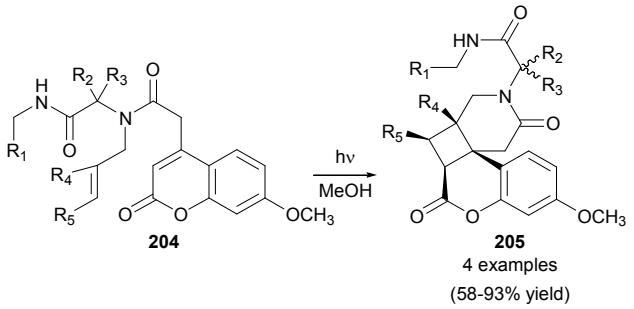
The condensation of *O*-methyl-4-coumarincarbaldehyde oxime **198** with maleimide **35** in a catalyst-free system afforded the corresponding coumarin[4,3-*c*]pyridines **201a** (38%) and **201b** (46%) (Scheme 63).[154] When the reaction was performed in the presence of 3 equiv of maleimide **35a**, the bis-cycloadduct **203** (24%) was formed along with **201a** (50%). In the proposed mechanism, elimination of methanol from the initially formed cycloadduct **199**, yields the unstable intermediate **200**, which by air oxidation (path a) gives the fully aromatized derivative **201**. However, the thermally induced 1,2-prototropic rearrangement leads to the formation of ylide **202** (path b), which in the presence of excess dienophile undergoes a subsequent 1,3-dipolar cycloaddition reaction to afford the tetracyclic derivative **203**.



Scheme 63. Hetero Diels-Alder reactions of *O*-methyl-4-coumarincarbaldehyde oxime **198** with maleimides **35**.

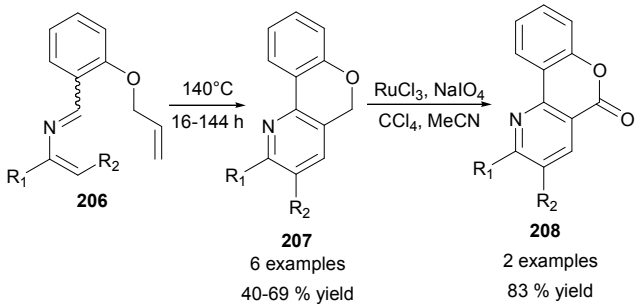
The intramolecular [2+2] Enone-olefin photocycloadditions proceed with high regioselectivity and diastereoselectivity when the double bonds are connected with 2-4 atom tethers providing in most cases a single diastereomer via a 1,4 biradical intermediate.[155]

Akritopoulou-Zanze reported in 2007 the first combination of an Ugi multicomponent reaction with a [2+2] enone-olefin photochemical transformations to access highly complex azabicyclo-[4.2.0]octan-4-one derivatives in moderate to good yields and high or complete diastereoselectivity (Scheme 64).[156]



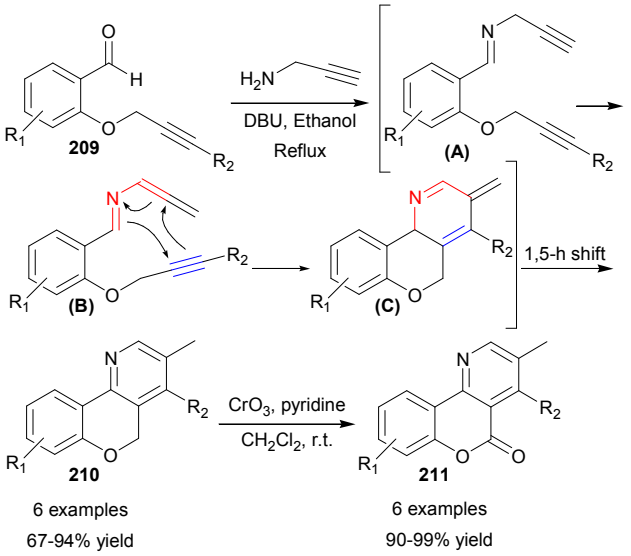
Scheme 64. [2+2] Ene-Enone photocycloadditions of Ugi adducts in MeOH.

Palacios and co-workers reported the synthesis of a variety of tricyclic and tetracyclic condensed chromenopyridines using an aza-Wittig reaction of *N*-vinylic phosphazenes with functionalized aldehydes, and a subsequent oxidation (Scheme 65).[157]



Scheme 65. Synthesis of aza coumarin **208** via Intramolecular Diels-Alder cycloadditions of 2-Azadienes **206**.

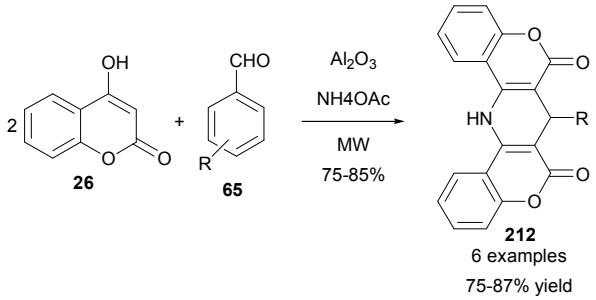
More recently, a new methodology for the synthesis of the chromenopyridine scaffold **211** was demonstrated using 2-(prop-2-yn-1-yloxy)benzaldehyde **209** with DBU catalyst to generate novel fused-tricyclic heterocycles **210**, which was oxidized with CrO_3 in pyridine to yield the desired product (Scheme 66).[158] The proposed mechanism started with the formation of the imine (A). The terminal alkyne connected to the imine group can undergo base-catalyzed isomerization to form an allene structure (B).[159] Then, the intramolecular [2 + 4] heterocycloaddition reaction between the alkyne and the diene system afforded, after a 1,5-H shift, the tricyclic product **210**.



Scheme 66. Synthesis of Chromenopyridinone **211**.

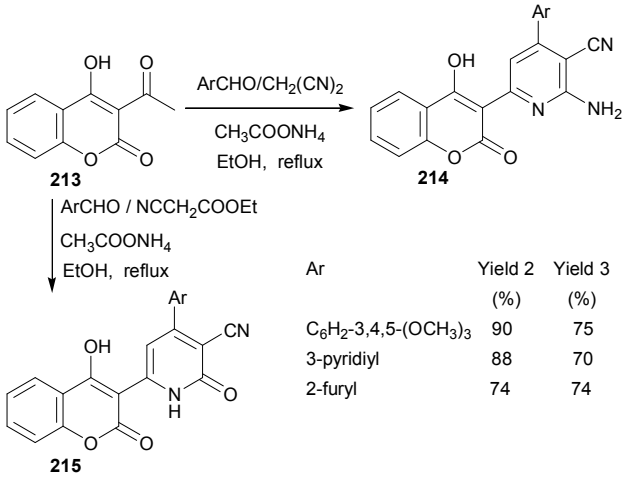
The Hantzsch synthesis remains the most widely used protocol to access to 1,4-dihydropyridine differently substituted in position 4.[160]

A single example of a four-component bis-coumarin fused 1,4-dyhydropyride **212** synthesis from aromatic or heteroaromatic aldehydes **65** in acidic alumina under microwave irradiation has been described (Scheme 67).[161] However, this protocol was performed in a domestic microwave oven, characterized by a non-homogeneous distribution of the electromagnetic waves, and could show some reproducibility problems.



Scheme 67. Synthesis of bis(benzopyrano)fused dihydropyridines **212**.

A one-pot, four-component reaction between 3-acetylcoumarin **213**, aromatic aldehydes, malononitrile and ammonium acetate under microwave irradiation provided an efficient entry into 3-(2'-amino-3'-cyano-4'-arylpyrid-6'-yl)coumarins **214**. On the other hand, when the reactions were carried out in the presence of ethylcyanoacetate instead of malononitrile, 4-aryl-1, 2-dihydro-6-(3-acetyl-4-hydroxycoumarin-3-yl)-2-pyridin-3-carbonitriles (**215**) were obtained (Scheme 68).[162]

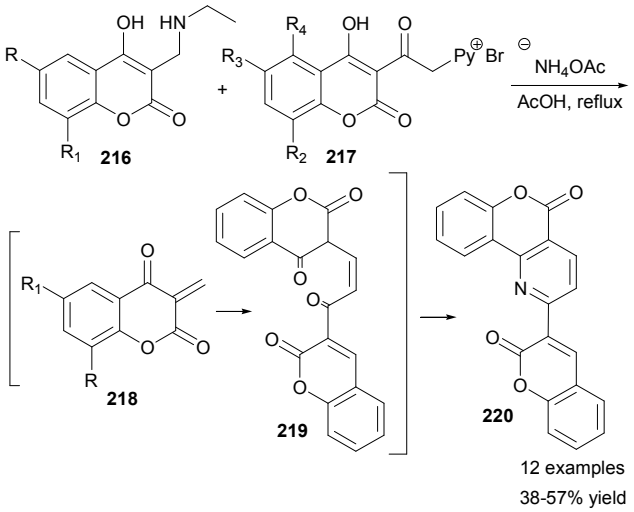


Ar	Yield 2 (%)	Yield 3 (%)
C_6H_2-3,4,5-$(OCH_3)_3$	90	75
3-pyridiyl	88	70
2-furyl	74	74

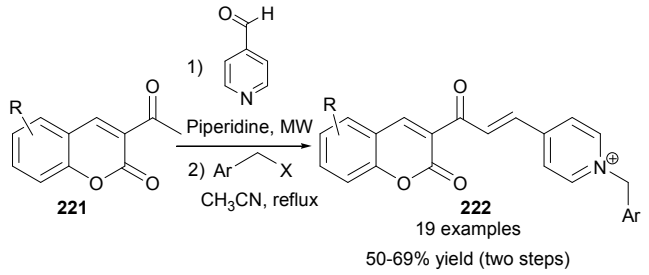
Scheme 68. Synthesis of 4-hydroxycoumarin-pyridine derivatives **214**-**215**.

In 2013 Brahmbhatt and co-workers reported the synthesis of a molecule which incorporate both pyridyl-substituted and pyrido-fused 2*H*-chromen-2-ones.[163] They developed a one-pot, three component reaction of precursor 3-[(ethylamino)methyl]-4-hydroxy coumarins **216** and pyridinium salts **217** in the presence of ammonium acetate, yielding 2-(2-oxo-2*H*-chromen-3-yl)-5*H*-chromeno[4,3-*b*]-pyridin-5-ones **220** in moderate to good yields (Scheme 69). The reaction pathways involved the decomposition of the starting Mannich base to form a coumarin methide **218**, which reacts with salt **217** in the presence of ammonium acetate, to obtain a 1,5-dicarbonyl intermediate **219** that finally gets converted into the expected product by Krohnke's reaction.

A novel series of coumarin derivatives linked to benzyl pyridinium group were synthesized by Shafiee and co-workers.[164] The 3-acetylcomarin derivatives **221** were transformed into the coumarin chalcone hybrid (only in *E*-configuration), which were transformed in compounds **222** through its reaction with proper benzyl bromide or chloride derivatives (Scheme 70).

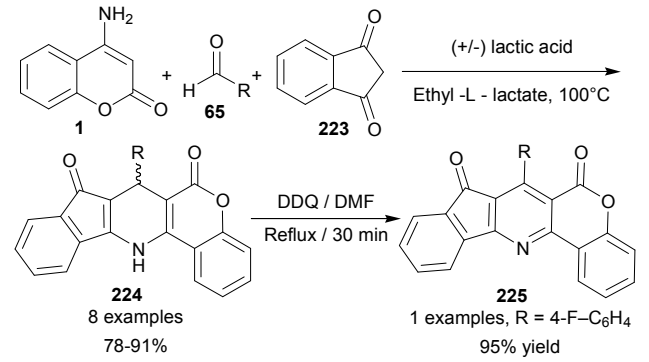


Scheme 69. Synthesis of 2-(2-oxo-2*H*-chromen-3-yl)-5*H*-chromeno[4,3-*b*]pyridin-5-ones **220**.



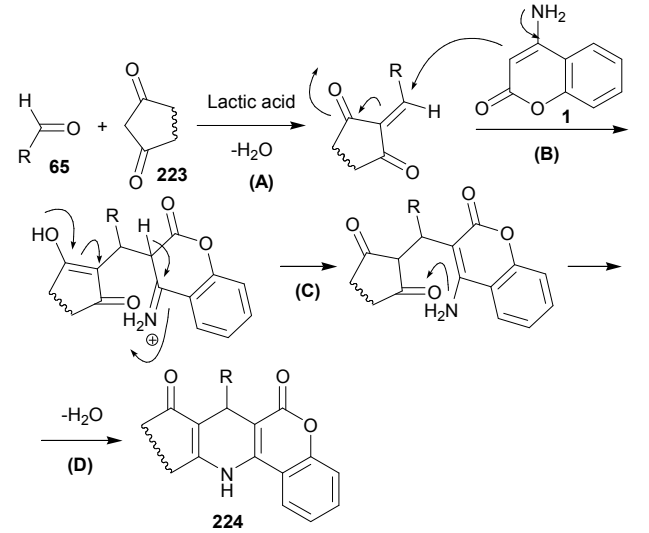
Scheme 70. Synthesis of coumarin **222**.

A multicomponent process that combines 4-aminocoumarin **1**, aromatic aldehyde **65** and indane-1,3-dione **223** in the presence of (±)-lactic acid in ethyl-*L*-lactate, leads to coumarin fused indenodihydropyridine derivatives **224** (Scheme 71),[165] which could be oxidized to the corresponding indenopyridine derivative **225** using DDQ.



Scheme 71. Synthesis of coumarin fused indenodihydropyridines **224** and its oxidized derivative **225**.

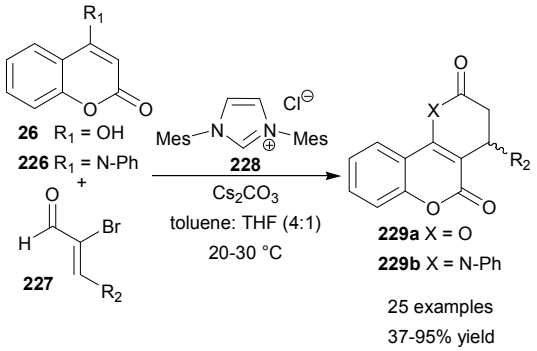
The mechanism proposed to explain this transformation involves the initial acid catalyzed Knoevenagel condensation (A), Michael addition (B), and then intra molecular cyclization (D) as presented in Scheme 72. The α-hydroxy carboxylic acid may increase the electrophilicity of both the carbonyl groups, forming H-bond, and of the Knoevenagel condensation product which in turn accelerate the Michael addition.



Scheme 72. Proposed mechanism in the synthesis of (**224**).

Umpolung of aldehydes catalyzed by *N*-heterocyclic carbine (NHC) organocatalysis constitute an unconventional protocol for the construction of carbon−carbon and carbon−heteroatom bonds.[166]

Recently, Biju and co-workers reported the lactonization and lactamization of various 2-bromoenals **227** with 4-hydroxy **26** or 4-(arylamino)coumarin **226** catalyzed by imidazolium salt **228**, proceeding via the *α,β*-unsaturated acyl azolium intermediates (Scheme 73).[167] The reaction furnished coumarin-fused dihydropyranones **229a** or dihydropyridinones **229b** respectively in moderate to good yields. When the reaction was carried out with a chiral triazolium salt, 74-86% enantiomeric excess was obtained.



Scheme 73. NHC-catalyzed annulation of heterocyclic C-H acids with 2-bromoenals.

In 2011, Yang and co-workers described the synthesis of coumarin/phenanthridine-fused heterocycles using base-mediated annulation of *N*-alkylquinolinium iodide and coumarin
as the key step (Scheme 74).[168]

The proposed mechanism for the annulation starts with a triethylamine-mediated deprotonation of the 4-methyl hydrogen on **230** to yield 1,4-dihydro-1-methyl-4-methylenequinoline **231**. The condensation of **231** and **232** affords the intermediate **233**, which then undergoes intramolecular cyclization to give the alcohol **234**. The final dehydration of **234** generates the aromatized iminium iodide **235**, which can be trapped by sodium borohydride or sodium methoxide in methanol.

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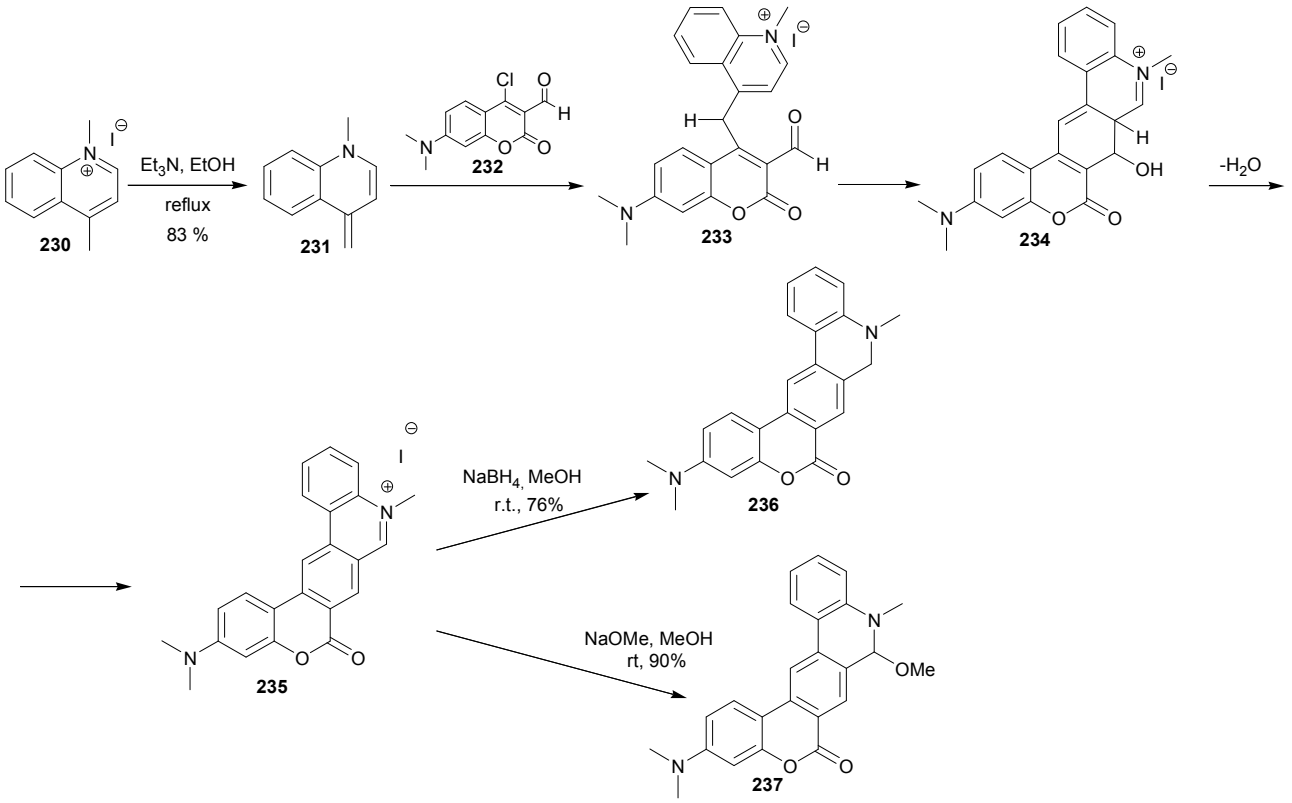
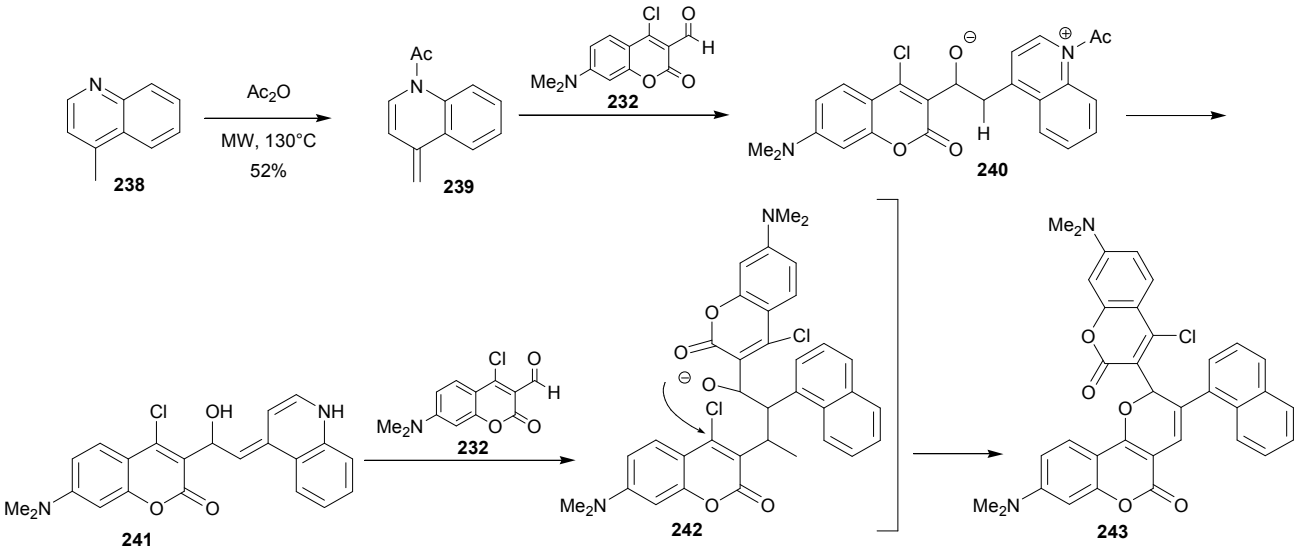


Scheme 74. Synthesis of coumarin/phenanthridine-fused heterocycles **236**-**237**.



Scheme 75. One-pot synthesis of pyranocoumarins via microwave-assisted pseudo multicomponent reactions.

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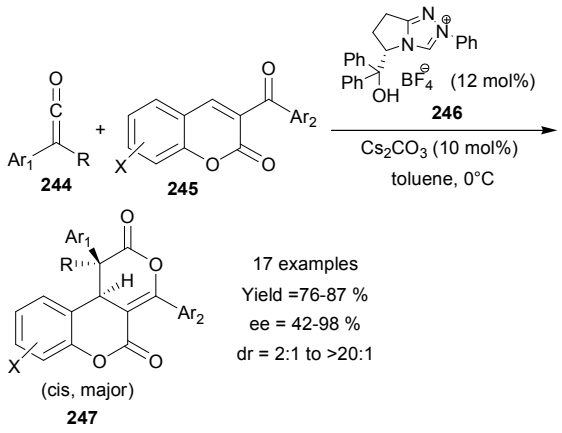
When the reaction is carried out without a base, an acetic anhydride-mediated three component condensation of carbaldehyde **232** with 4-methylquinoline **239** under microwave irradiation conditions, give quick access to the bulky substituted pyranocoumarin skeleton **243**.[169] In this case, the proposed mechanism begins with the reaction of 4-methylquinoline **238** with acetic anhydride to yield 1,4-dihydroquinoline **239**. The coupling of **239** with aldehyde **232** and subsequently loses a molecule of acetic anhydride afford alcohol **241**. The coupling of this compound, catalysed with a second molecule of **232** generates the intermediate **242**. Final cyclization of **242** followed by dehydration furnishes the final product **243** (Scheme 75).

2.5.2 Pyrans and benzopyrans

Pyrans rings constitute an important class of biologically active natural and synthetic products. In this regard, the pyran motif continues to attract the attention of synthetic chemists.[170]
NHC was demonstrated as an efficient catalyst for the formal [4+2] cycloaddition with enones to give δ-lactones with α-quaternary-β-tertiary stereocenters.[171] Thus, the reaction between disubstituted ketenes **244** and 3-aroylcoumarins **245**, afforded the corresponding dihydrocoumarin-fused dihydropyranones **247** in high yield with good to high diastereo- and enantioselectivity (Scheme 76).[172]



Scheme 76. Enantioselective synthesis of dihydrocoumarin-fused dihydropyranones **247**.

Based on the dramatic effect of the free hydroxyl group of the NHC catalyst, and the diastereo- and enantioselectivity observed, the authors proposed a transition where the enolate generated by addition of the NHC to ketene favors its Z-isomer, which minimizes the steric repulsion. The hydrogen-bonding between the hydroxy group of the NHC–ketene adduct and aroyl group of the coumarin derivative directs the facial selectivity. The endo transition state of the Diels–Alder reaction is favored and results in the cis-cycloadduct observed (Figure 3).

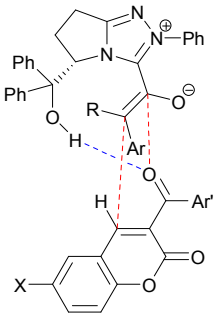
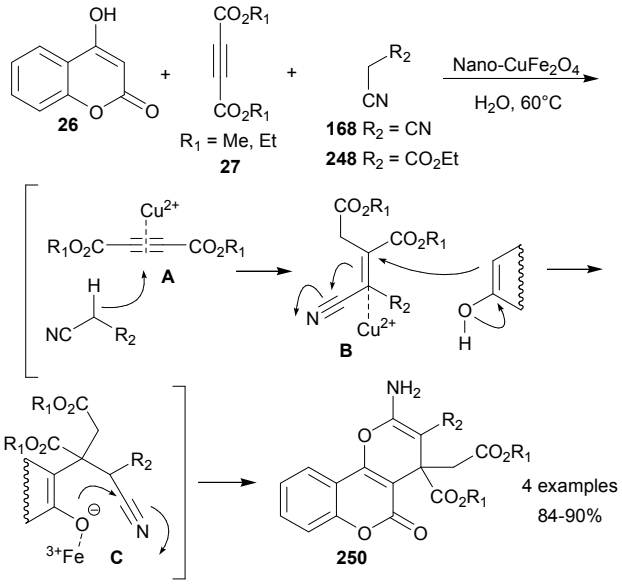


Figure 3. Proposed model for stereochemical outcome.

Considerable efforts have been devoted toward the synthesis of pyrano[3,2-*c*]coumarin derivatives **249**. Among these, a three-component reaction between 4-hydroxycoumarin **26**, nitriles **168** and **248** and aldehyde **65** has emerged as one of the most attractive process for the construction of these compounds. This transformation was carried out in the presence of a variety of catalysts and solvents (Table 1).[173-181]
A related protocol, using $CuFe_2O_4$ magnetic nanoparticles as catalyst, was developed by the Das group.[182] In this method, the benzaldehyde component **65** is changed for dialkyl acetylenedicarboxylates **27**. The mechanism suggested by the authors is summarized in Scheme 77, and involves an initial Cu^{2+} catalyzed Michael addition of dialkyl acetylenedicarboxylate **27** with alkyl nitrile derivatives to give an intermediate B, followed by a nucleophilic attack of **26** at the β-position (in regards to the nitrile group) and intramolecular electrophilic cyclization to yield **250**.



Scheme 77. Synthesis of pyrane[3,2-*c*]coumarin derivatives.

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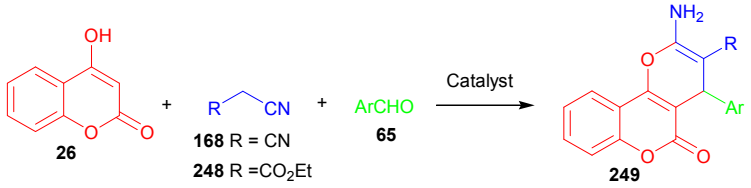
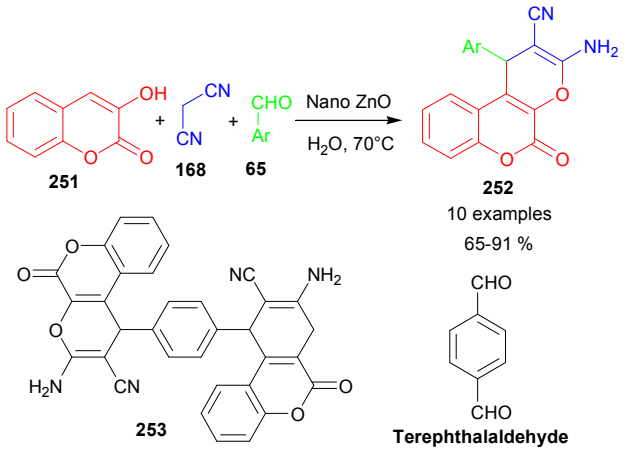
Table 1. Influence of different catalysts on the reaction of 4-hydroxycoumarin (**26**), nitriles (**168** and **245**) and benzaldehydes (**65**) to afford 3,4-dihydropyrano[*c*]chromones (**246**).



Entry	Catalyst (amount)	Solvent	T (°C)	Yield (%)	Time ([min]-h)	Ref.
1	$H_6P_2W_{18}O_{62}.18H_2O$ (1% mol)	H_2O:EtOH (1:1)	Reflux	80-90	[30]-16	156
2	TMGT[a] (10% mol)	Solvent free	100°C	64-75	[60]	157
3	MgO (3.1eq)	H_2O:EtOH (4:1)	Reflux	85-92	[30]-[37]	158
4	$(NH_4)_2HPO_4$ (10% mol)	H_2O:EtOH (1:1)	r.t.	81-95	2	159
5	TBAB[b] (10% mol)	H_2O	Reflux	84-93	[45]-[60]	160
		Solvent free	120°C	78-89	[40]	
6	DBU[c] (10% mol)	H_2O	Reflux	81-94	[5]-[20]	161
7	K_2CO_3 (10 mL saturated solution)	H_2O	110– 120 °C	87-93	[1.8]-[2.8]	162
8	Morpholine (10% mol)	H_2O	Reflux	80-90	3-4	163
9	DMAP[d] (5% mol)	EtOH	Reflux	64-98	[5]-5	164

[a] 1,1,3,3-*N*,*N*,*N'*,*N'*-Tetramethylguanidinium trifluoroacetate; [b] Tetrabutylammonium bromide; [c] 1,8-Diazabicyclo[5.4.0]undec-7-ene; [d] 4-(dimethylamino)pyridin



Scheme 78. Synthesis of dihydropyrano[2,3-*c*]chromone derivatives **252** over nano ZnO.

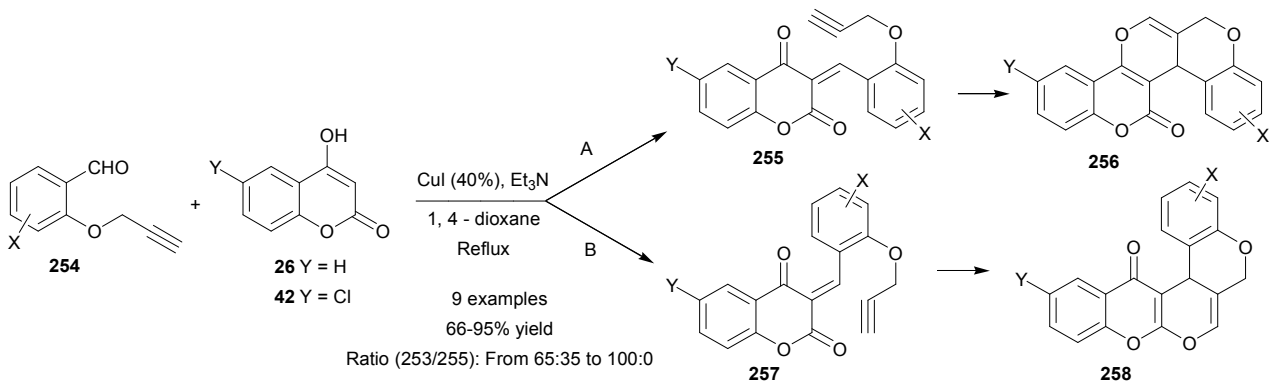
Although numerous methods exist for the synthesis of pyrano[3,2-*c*]chromene derivatives, there are few reports for the synthesis of pyrano[2,3-*c*]chromene derivatives from 3-hydroxycoumarin, which may be considered as the enol tautomer of 1,2-dicarbonyl compound hence, it is a very poor Michael donor under acidic or basic conditions.

In 2011, ZnO-catalyzed reaction of 3-hydroxycoumarin **251** in water was reported to afford dihydropyrano[2,3-*c*]chromene derivatives **252** (Scheme 78).[183] In the special case of the use of terephthalaldehyde as aromatic aldehyde, the compound obtained **253** showed self-aggregating property. It is remarkable that the formation of nanofiber from the organic molecule of low molecular weight is rather an uncommon.

In 2009, Balalaie and coworkers described a domino Knoevenagel hetero-Diels–Alder reaction of the *O*-propargylated salicylaldehydes **254** and 4-hydroxycoumarins that leads to pyrano[2,3-*c*]coumarins **256** and pyrano[2,3-*c*]chromones **258** in the presence of CuI as a Lewis (Scheme 79).[184] As a result of a competitive hetero-Diels–Alder reaction including two different heterodienes, a mixture of products was formed. It seems that two important factors control the synthesis chemoselectivity observed in this reaction: (a) more efficient HOMO–LUMO interaction for α,β-unsaturated ketone as diene and alkyne as dienophile in the intermediate **255** compared to intermediate **257**; (b) more steric hinderance in the intermediate **257** compared to **255**.

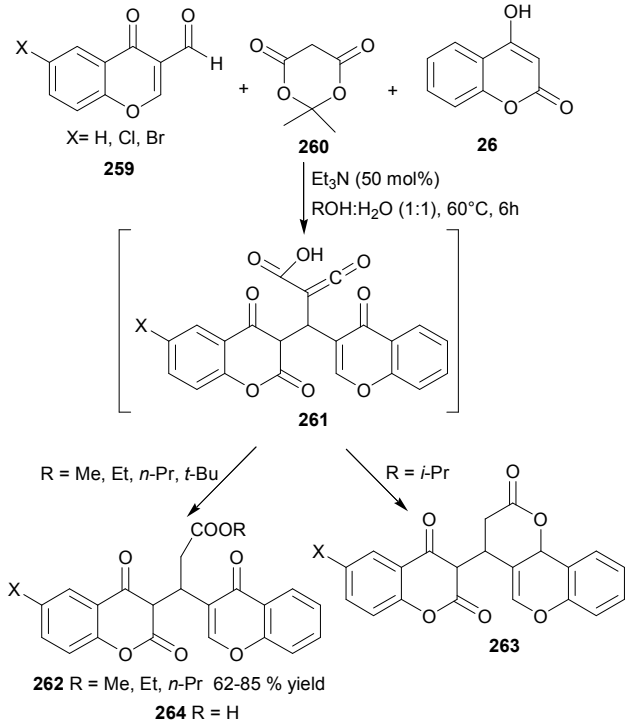
In later work, the same research group described a sequential four-component reaction of 4-hydroxyl coumarin **26**, chromone carbaldehydes **259**, Meldrum's acid **260** and primary alcohols, leading to chromone-coumarin hybrids **262** in aqueous media (Scheme 80).[185] Replacing the primary alcohol with isopropyl and *tert*-butyl alcohol, results in cyclized product chromenyl-dihydropyrano[3,2-*c*]chromene **263** or functionalized carboxylic acid **264** respectively. The proposed mechanism involves an initial Knoevenagel reaction of 3-formyl chromone **259** and Meldrum's acid **260**, followed by a Michael addition

of the deprotonated form of 4-hydroxycoumarin **26** to the alkylidene



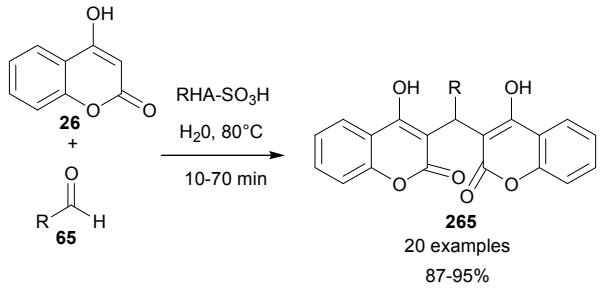
Scheme 79. CuI-catalyzed domino Knoevenagel-hetero-Diels–Alder reaction of *O*-propargylated salicylaldehydes **254** and 4-hydroxycoumarins **26** or **42**.

Meldrum's acid. After the removal of acetone, ketene **261** is formed. Nucleophilic addition of the primary alcohol to the ketene **261** after decarboxylation and tautomerization, leads the desired products **262**. Due to low nucleophilicity of isopropyl and *tert*-butyl alcohols, and low solubility of the intermediate in water, triethylamine could abstract the acidic proton of 4-hydroxycoumarin **26** and the internal nucleophilic addition to ketene after decarboxylation led to product **263**, or water could act as the nucleophile and carboxylic acid **264** was formed.



Scheme 80. Synthesis of 3-chromenyl-3-coumarinylpropanoates derivatives **262-264** through one-pot four-component reaction.

Shirini and co-workers, described the use of sulfonated rice husk ash (RHA-SO_3H) as an efficient solid acid catalyst for the condensation of 4-hydroxycoumarin **26** and aldehydes **65** in water, leading to 3,3'-(arylmethylene)-bis-(4-hydroxycoumarins) **265** (Scheme 81).[186] In this case, α,β-unsaturated aldehydes were efficiently condensed with 4-hydroxycoumarin **26** in 92 and 90% yield respectively, instead of reacting as a Michael acceptor to form the corresponding furan ring. In previous work, Das and co-workers used a similar catalyst (PEG–SO_3H) to prepare coumarin fused pyrrole system.[28]



Scheme 81. Synthesis of 3,3'-(arylmethylene)-bis-(4-hydroxycoumarin) derivatives **265** in the presence of RHA-SO_3H.

In the past decades, the chemistry of Huisgen's 1,4-dipoles has attracted much attention from organic chemists, especially in the area of heterocyclic synthesis.[187,188]

An recent example involved the use of a isoquinoline **266** and methyl or ethyl acetylenedicarboxylates in such a reaction for the preparation of compound **267a-b** (Scheme 82). However, treatment of di-*tert*-butyl acetylenedicarboxylate (**27**, R = *t*-Bu) with isoquinoline **266** afforded di-*tert*-butyl 2-(4-hydroxy-2-oxo-2*H*-chromen-3-yl)fumarate **268** in a 95% yield.[189]

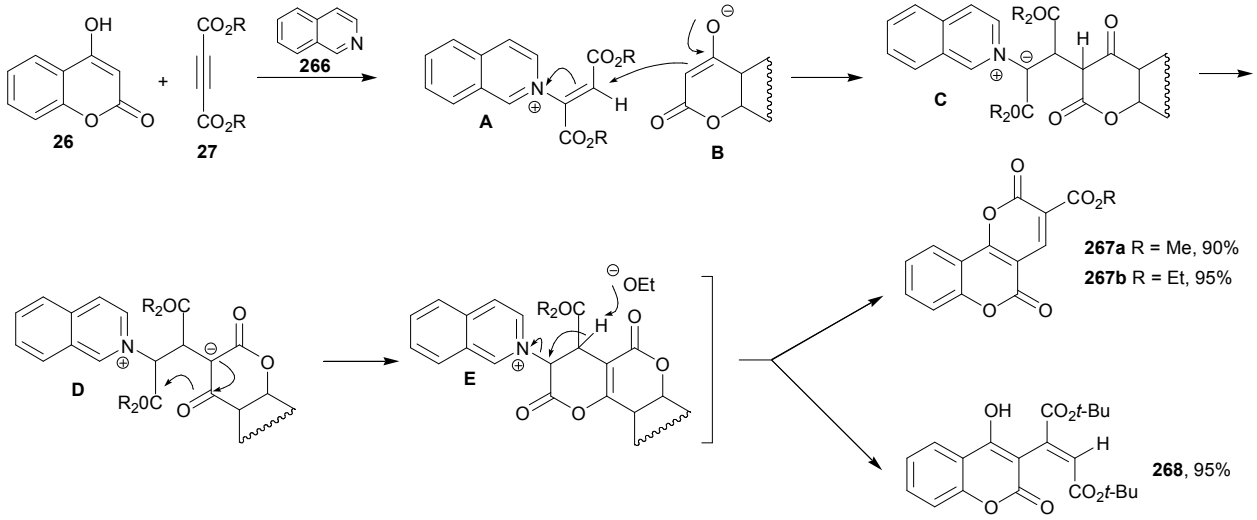
In this case, the reaction proceeded according to a mechanism where Michael addition of anion (B) to protonated zwitterion (A), followed by an intramolecular 1,3-proton transfer yielded Zwitterion intermediate (D),[190] which underwent lactonization to produce cation (E) and ethoxide anion. Finally, ethoxide anion absorbed a proton from the cation (E) and promoted the elimination of isoquinoline **266** to furnish the product **267**.

In the search for milder and more versatile reaction conditions as well as new patterns of reactivity, the use of free radicals has gained importance in synthetic organic chemistry.[191] In particular, xanthate-based radical addition processes developed by Zard and co-workers are powerful tools for constructing C–C bonds under metal-free conditions.[192] In a recent communication Miranda, Marrero and co-workers described the

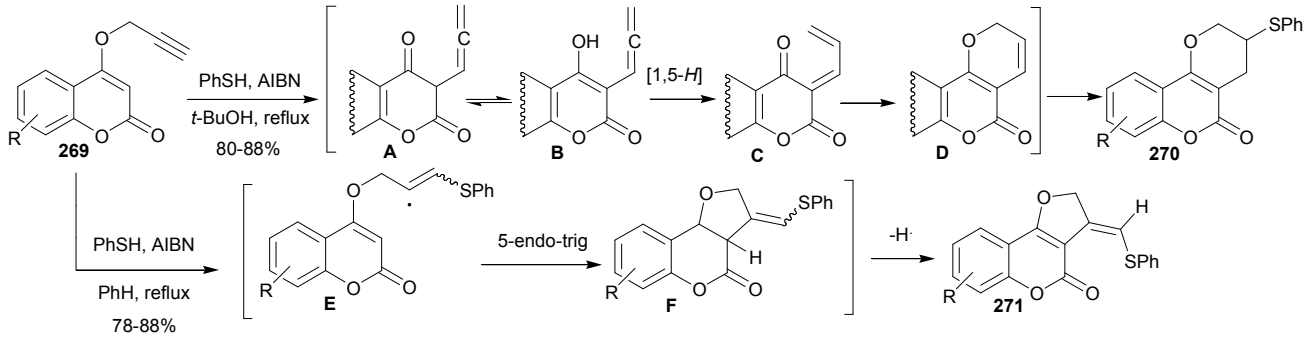
direct alkylation of flavones at the C-3 position in moderate yields using a xanthate-based oxidative radical addition procedure.[193] This methodology is a suitable synthetic tool for the direct substitution of the vinylic and unactivated C–H bond of the C ring of the flavone by an alkyl functionality under neutral conditions.

Majumdar and co-workers described a regioselective synthesis of dihydropyranocoumarins **270** and dihydrofurocoumarins **271** via a thiol mediated radical reaction (Scheme 83).[194] When dry *t*-butanol was used as solvent, 3,4-dihydropyrano[3,2-*c*]coumarin derivatives **270** were obtained whereas, when the experiments were carried out in dry benzene, furo[3,2-*c*]coumarin **271** was obtained. To explain the difference between both experiments, the authors proposed that in polar *t*-butanol, the Claisen rearrangement of ethers **269** occurs at a faster rate than the addition of thiophenol to the terminal alkyne affording the 2*H*-pyranobenzopyran ring system (D) to which the addition of a thiyl radical occurs in the presence of AIBN, to afford **270**.

Since the discovery of the direct olefination of arenes by Fujiwara *et al*.,[195] outstanding progress has been made toward improving the efficiency of oxidative C–H alkenylation of heterocycles as promising alternatives to the conventional approach.[196] In this context, some recent examples concern the C–H functionalization at the C3 position of chromones and coumarins have been reorted by the Hong group.[197, 59] With these elements, Hong and co-workers carried out a practical approach for effecting tandem C–H alkenylation/C–O cyclization via the C–H functionalization of coumarin derivatives **57** to provide convenient access to coumarin-annelated benzopyrans **272** (Scheme 84).[198]



Scheme 82. Isoquinoline-Catalyzed reaction between 4-hydroxycoumarin **26** and dialkyl acetylene dicarboxylates **27**.



Scheme 83. Thiophenol-catalyzed Claisen rearrangement and radical cyclization. Formation of furo- and pyrano-coumarin derivatives.

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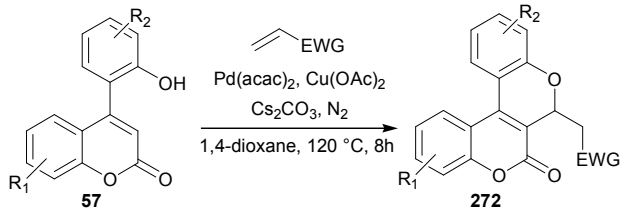
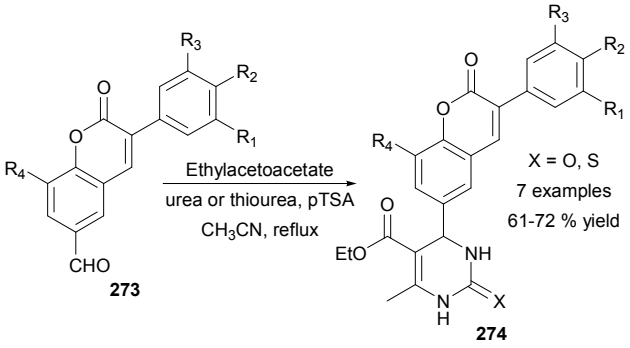


Scheme 84. The C–H alkenylation/C–O cyclization of coumarins.

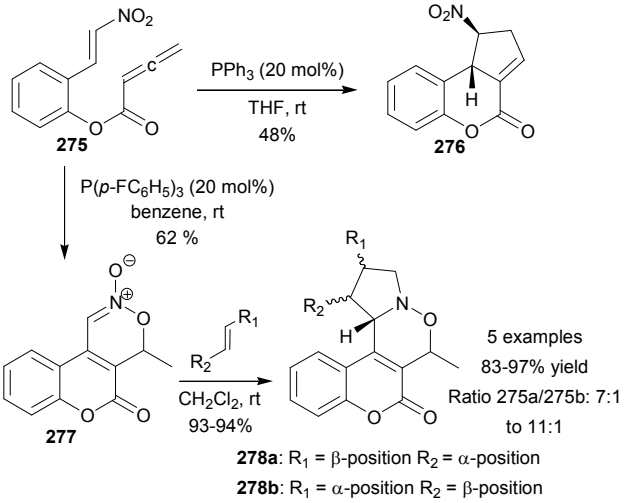
2.6 Other cycles

The concept of molecular hybridization is a useful tool in the design of new drug.[199] In 2013, Sashidhara, Bathula and coworkers reported the synthesis of a coumarin-monastrol hybrid (**271**), as potential antibreast tumor-specific agent.[200] The target compounds were synthesized as racemic mixture via the Biginelli reaction involving 3-aryl coumarin aldehydes **273** in moderate to good yields (Scheme 85). In addition, some groups have isolated enantiomerically pure monastrol. Moreover, the first successful synthesis of *R*-monastrol with 99% ee via an asymmetric Biginelli reaction was recently developed by Zhu and co-workers, applying a chiral ytterbium catalyst.[201]



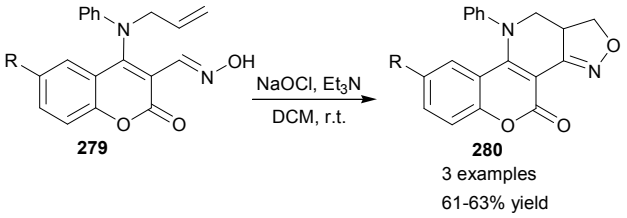
Scheme 85. Synthesis of coumarine-monastrol hybrids **274**.

In 2007, Kwon and co-workers described the conversion of 2-styrenyl allenoates **275** into cyclopentene-fused dihydrocoumarins **276** through phosphine-catalyzed regio- and diastereoselective [3+2] cycloadditions. Changing the solvent from THF to benzene promotes the conversion of the allenoate **275** into a tricyclic nitronate **277**, which was subjected to efficient face-, regio-, and exo-selective 1,3-dipolar cycloadditions with both electron-rich and electron-poor alkenes to provide tetracyclic coumarin derivatives **278** in excellent yields (Scheme 86).[202]



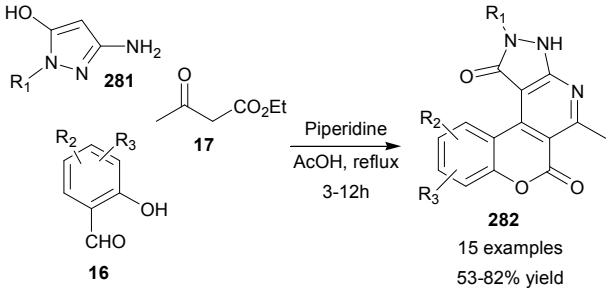
Scheme 86. 1,3-Dipolar cycloadditions of nitronate **277**.

A related more recent example of such reactivity was reported by Bhuyan and coworkers allowing a general access to dihydroisoxazolo[3',4':4,5]pyrido[2,3-*c*]coumarin **280** via an intramolecular 1,3-dipolar cycloaddition involving nitrile oxides as 1,3-dipoles (Scheme 87).[203]



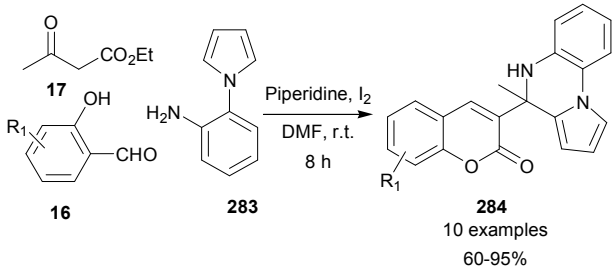
Scheme 87. Intramolecular 1,3-dipolar cycloaddition reactions of oxime (**279**).

An efficient three-component synthesis of 2,3-dihydrochromeno [4,3-*d*]pyrazolo[3,4-*b*]pyridine-1,6-diones **282** from 3-aminopyrazol-5-ones (**281**), salicylic aldehydes **16** and acetylacetic ester **17** involving an *in situ* formation of 3-acetylcoumarins and subsequent condensation with aminopyrazolones **281** has been described by Frolova and co-workers (Scheme 88).[204]



Scheme 88. MCR synthesis of 2,3-dihydrochromeno[4,3-*d*]pyrazolo[3,4-*b*]pyridin-1,6-diones **282**.

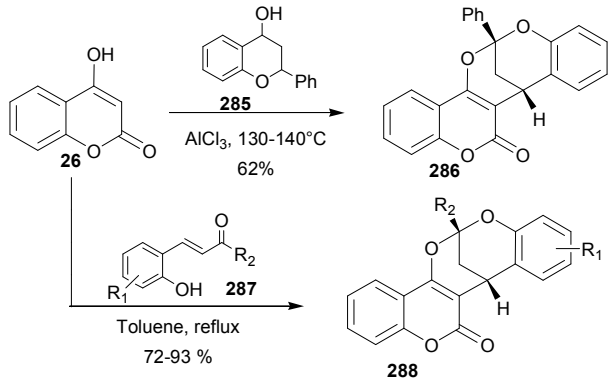
A similar strategy was developed for the synthesis of 3-(4-alkyl-4,5-dihydropyrrolo [1,2-*a*] quinoxalin-4-yl)-2*H*-chromen-2-one derivatives **281**, using piperidine-iodine as a dual system catalyst (Scheme 89).[205] In the mechanism proposed, molecular iodine plays an important role for both the formation of imine and cyclization steps.



Scheme 89. Synthesis of coumarin bearing pyrrolo[1,2-*a*]quinoxaline moiety **284**.

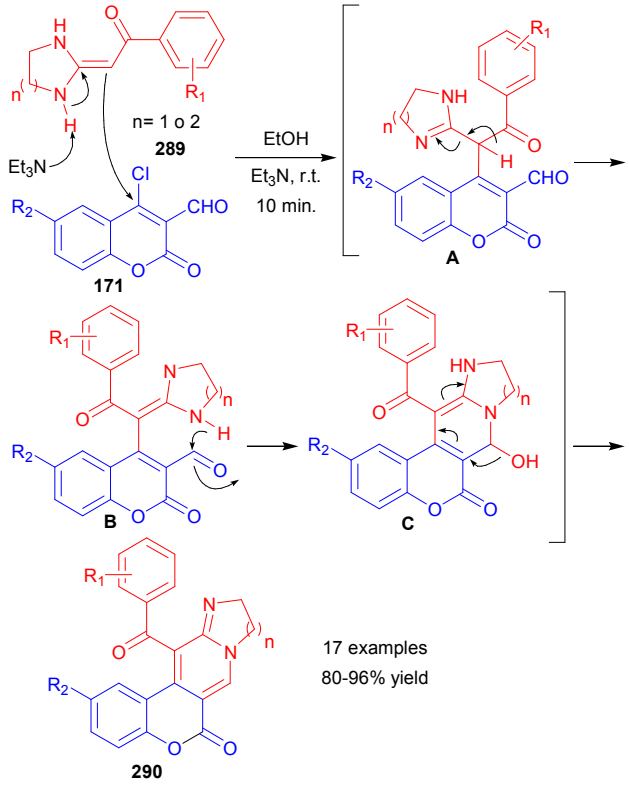
The 2,8-dioxabicyclo[3.3.1]nonane derivatives is a methylene-bridged bicyclic framework found in medicinal plant sources.[206]

These kinds of molecules could be achieved through the reactions of 2-phenylchroman-4-ol **285** with 4-hydroxycoumarin (**26**) in the presence of aluminum chloride (Scheme 90).[207] When the 2-phenylchroman-4-ol **285** partner is replaced by a cinnamaldehyde derivatives **287**, the modified evolves through a Michael addition/bicyclization sequence leading to coumarin-fused 2,8-dioxabicyclo[3.3.1]nonanes **285** (Scheme 90).[208]



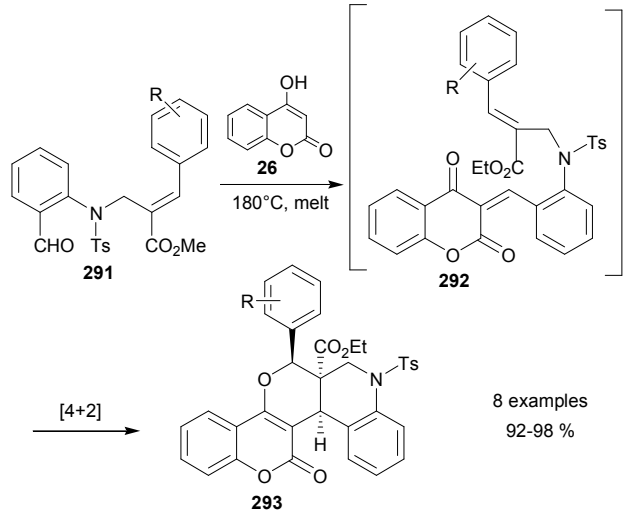
Scheme 90. Synthesis of coumarin-fused 2,8-dioxabicyclo[3.3.1]nonanes.

A one-pot protocol provided an efficient entry into 9,10-dihydro-6*H*-chromeno[4,3-*d*]imidazo[1,2-*a*]pyridin-6-one derivatives **290** (Scheme 91).[209] The authors proposed the Et_3N-catalyzed mechanism shown in Scheme 91. Reaction of heterocyclic ketene aminals (HKAs) **289** with 4-chloro-3-formylcoumarin **171**,[210] and internal elimination of HCl afford (A). The imine–enamine tautomerization of intermediate (A), subsequently intramolecular attack of the NH group at the aldehyde and elimination of H_2O give the product **290**.



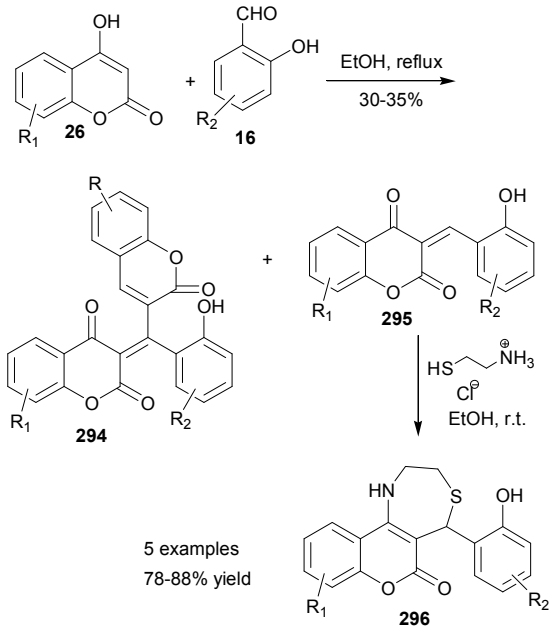
Scheme 91. Regioselective synthesis of 9,10-dihydro-6*H*chromeno[4,3-*d*]imidazo-[1,2-*a*]pyridin-6-one derivatives **290**.

Recently, Bakthadoss and coworkers developed a protocol for the efficient synthesis of structurally diverse tetra- and pentacyclic quinolinopyran tethered coumarin architectures **293** via a domino Knoevenagel intramolecular hetero-Diels–Alder strategy under solvent-free conditions.[211] Thus, a mixture Baylis–Hillman derivatives **291** and 4-hydroxycoumarin **26** was melted at 180 °C for 1 h to yield pure products in high yields and cis geometry, without a catalyst as well as solvent (Scheme 92).



Scheme 92. Synthesis of pentacyclic quinolinopyrancoumarin **290** possessing an ester functionality at an angular position.

In 2011, Shafiee and coworkers described a two step methodology for the synthesis of coumarin-fused 1,4-thiazepine (Scheme 93).[212] Thus, 4-hydroxycoumarin derivatives **26** were converted to the corresponding benzylidene derivatives **294-295**. Reaction of 2-aminoethanethiol hydrochloride with benzylidene derivatives **295** gave the corresponding fused heterocycle **296**. The low yields of the benzylidene derivatives could be due to the formation of the bis-coumarins **294**.



Scheme 93. Synthesis of coumarin-fused 1,4-thiazepines **296**.

3 Summary of biological activity

Many synthetic coumarin heterocyclic derivatives exhibit useful and diverse biological activities including kinase inhibitors, antitumor and anti-HIV therapy, antibacterials, anti-inflammatory agents, anti-coagulants, inhibitors of human carbonic anhydrase, antipsychotic or acetylcholinesterase inhibitory activity. In addition, coumarins are known to be lipid lowering agents with moderate triglyceride lowering activity. Furthermore, hydroxycoumarins are powerful chainbreaking antioxidants and can prevent free radical injury by scavenging reactive oxygen species. Their capacity of inhibition of aromatase could be useful in preventing the emergence of menopause related diseases, such as osteoporosis, increased risk for cardiovascular events /heart disease and cognitive deficiencies.

In order to provide a clear overview of biological activities of the discussed coumarins derivatives, a table detailing this topic have been added as ESI.

4 Concluding remarks

This review summarizes recent examples of coumarin heterocyclic derivatives systems construction. As is clear from this review, interest in the synthesis of coumarins fused or linked with different heterocycle derivatives has been gaining importance over the last decades, reflecting the importance of such compounds in both medical and chemical research.

In the present review, emphasis is placed on a search of innovative coumarin synthesis techniques and diverse array of biological activities of coumarins.

It is believed that the information compiled in this mini-review article will not only update scientists with recent findings of synthesis and biological activities of coumarin derivatives but also encourage them to use this promising moiety for further backbone derivatization and screening as several novel compounds with biological and chemical properties are possible.

Future goals for this field of research include the discovery, synthesis and development of compounds which display increased potency, as well as fueling structure–activity relationship studies aimed at understanding the modes of action of the most biologically active members of these classes of products.

Notes and references

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† Footnotes should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

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