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MINI REVIEW ON PYRIDO[2,3-*c*]COUMARINS BACKBONE OF SANTIAGONAMINE ANTIBIOTICS

Prasanta Patra[a]* and Susanta Patra[b]

[a]Department of Chemistry, Jhargram Raj College, Jhargram 721507, India
prasantaanupama1983@gmail.com
[b]Department of Chemistry, IIT(ISM) Dhanbad, Dhanbad 826004 India
patrasusanta546@gmail.com

Abstract - Santiagonamine is a natural coumarin fused pyridine, specifically pyrido[2,3-*c*]coumarin derivative having wound-healing activities and is extracted from stems and branches of the South American shrub *Berberis darwinii* Hook. It was isolated by Shamma *et al*. in 1984. Both coumarin and pyridine represent an important class of a multi tasking and multi functional scaffolds in organic synthesis. So, the syntheses of coumarin fused pyridine derivatives have an immense impact in the field of organic and pharmaceutical chemistry due to various biological activities displayed by such classes of compounds as well as for their natural occurrences. The main purpose of this review is to focus on different synthetic methodologies for the synthesis of specifically pyrido[2,3-*c*]coumarins as it is the backbone of santiagonamine antibiotics. Several methods for the synthesis of pyrido[2,3-*c*]coumarins have been described in the literature, most of which use 3-aminocoumarin as the starting material.

CONTENTS

INTRODUCTION

Coumarins, as the building block implanted in many natural products and synthesized biologically active molecules, have attracted extensive attention. These types of compounds and their derivatives are important for their rewarding biological properties,[1-7] especially for their anti-HIV,[8] and anti-biotic activities.[9] Coumarin (2*H*-chromen-2-one according to the most recent version of the IUPAC nomenclature) was first isolated from tonka beans and the flowers of melilot or sweet clover in 1820, independently by Vogel[10] and Guibourt.[11] After that, it was first chemically synthesized in 1868 by Perkin.[12] Umbelliferone[13] (sunscreen agent), warfarin[14] (anti-coagulant agent) and dicoumarol[15] (anti-coagulant agent) are significant coumarin derivatives for their widespread natural occurrences and noteworthy biological activities. Pyridine and coumarin both are very important chemical compounds for their versatile biological properties. Naturally occurring coumarin fused with pyridine (Figure 1) like schumanniophytin,[16] polyneomarline C[17] (used in Chinese herbal medicine for the treatment of malaria, hepatitis, pneumonia, syphilis, and so on), and goniothaline[18] possessing anti-malarial activity against a chloroquine-sensitive *Plasmodium falciparum* line (3D7) are also important pyridocoumarin derivatives. Santiagonamine (Figure 1) is another natural pyridocoumarin specifically pyrido[2,3-*c*]coumarin derivative having wound-healing properties.[19] Shamma *et al*.[20] isolated and determined the structure of santiagonamine in 1984. It was extracted from stems and branches of the South American shrub *Berberis darwinii* Hook. A large number of synthetic pyridocoumarins[21-34] are known to exhibit diverse biological facets, including anti-bacterial, anti-microbial, anti-malarial, antipsychotic (dopamine D4 receptor antagonists) anti-fungal, anti-cancer,[35-43] and anti-Huntington's[44] and anti-ecto-5′-nucleotidase (e5′NT) enzymatic[45] activity. In addition, these compounds act as bronchodilator agents,[46] and are used as excellent fluorescence probes.[47-52] But, great attention has been paid to pyrido[2,3-*c*]coumarin as it is the backbone of the natural product santiagonamine. In this review, we have described various synthetic approaches for the synthesis of pyrido[2,3-*c*]coumarin derivatives from suitable precursors, though most of the syntheses have been achieved from 3-aminocoumarins. To the best of our knowledge, this is the first review specifically covering pyrido[2,3-*c*]coumarins.

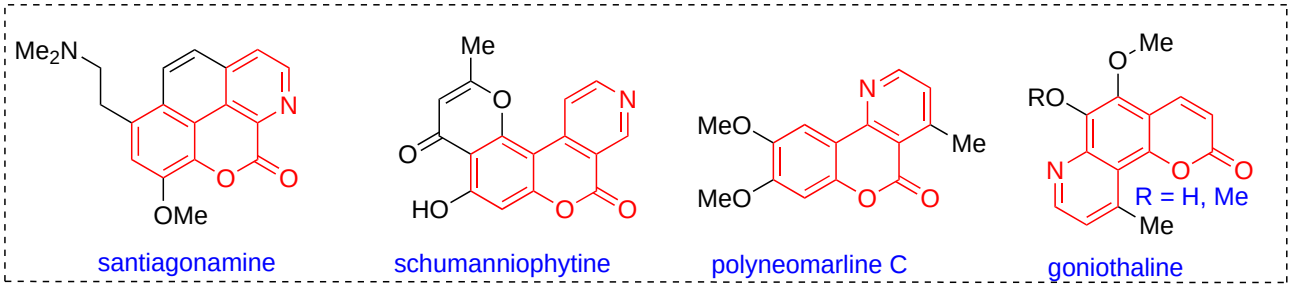


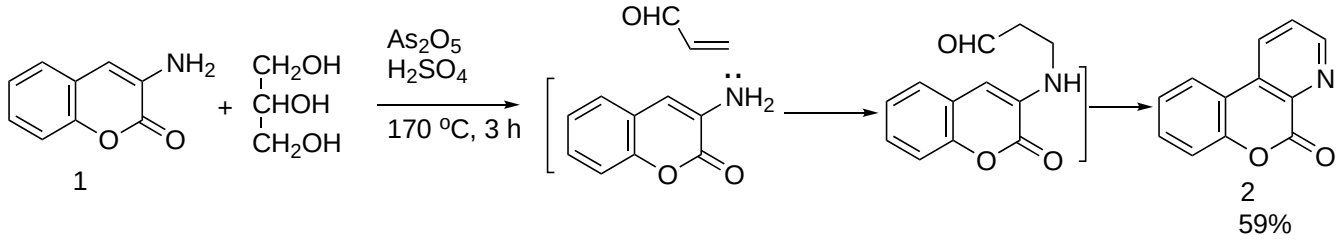
Figure 1. Pyrido/quinolinocoumarin derivatives as natural products

2. SYNTHESIS

2-1. Synthesis of Pyrido[2,3-*c*]coumarin from 3-Aminocoumarin

2-1-1. By Skraup Synthesis

Skraup synthesis is a well-known organic reaction for the synthesis of quinoline derivatives. Using this reaction protocol Khan *et al.*[53] synthesized pyrido[2,3-*c*]coumarin (**2**) by the condensation followed by thermal cyclizations of 3-aminocoumarin with glycerol in presence of arsenic pentoxide and H_2SO_4 at 170 ^oC (Scheme 1).



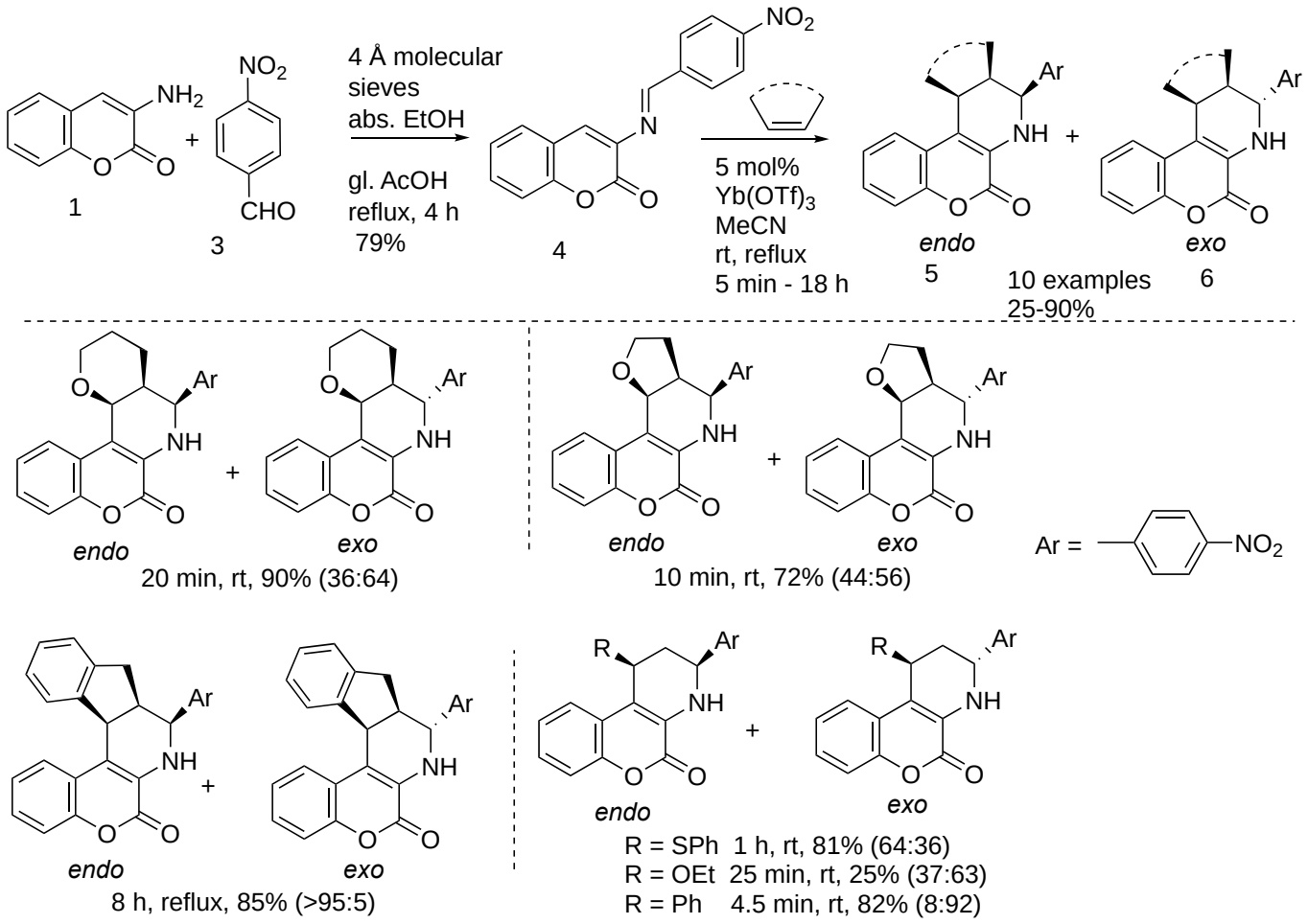
Scheme 1. Application of Skraup synthesis for the construction of pyrido[2,3-*c*]coumarin

2-1-2. By Intermolecular Povarov Reaction

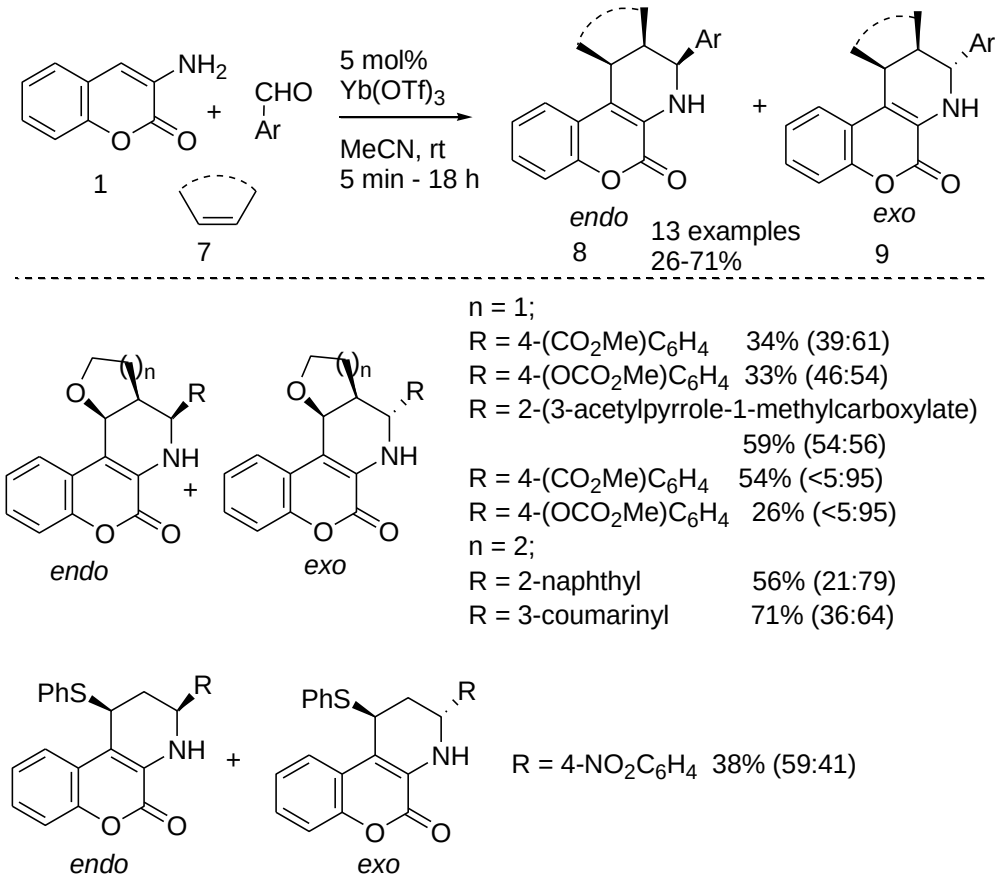
Povarov reaction (aza-Diels-Alder reaction with reverse electron-demand)[54-56] is a recognizable organic reaction involving formal [4+2] cycloaddition of aldimines derived from anilines and aromatic aldehydes with electron-rich alkenes. These types of reactions are initiated by either protic, Lewis acidic or transition metal catalysis to give 1,2,3,4-tetrahydroquinoline or other polycyclic pyridine derivatives. From time to time, the use of different types of catalysts either acids or metal catalysts with their advantages and disadvantages in the Povarov reaction is employed for the construction of fused tetrahydropyridine rings. Among them, researchers will choose the most appropriate greener and eco-

friendly methods for the synthesis of coumarin fused pyridine/quinoline derivatives that increase the interest of the research on pyrido[3,2-*c*]coumarins and their derivatives for further modifications.

In 2008, Kudaleand co-workers[57] reported the synthesis of tetrahydropyridocoumarin derivatives (**5** & **6**) *via* Povarov reaction using $Yb(OTf)_3$ as a catalyst. Intermolecular formal [4+2] cycloaddition between the azadiene (**4**) [obtained from the condensation of 3-aminocoumarin and 4-nitrobenzaldehyde] with electron-rich alkenes provided the corresponding tetrahydrocoumarin fused pyridine derivatives in moderate to excellent yield (Scheme 2). The ratio of the two diastereomers (*endo* and *exo*), requirement of the time of the reaction, and yield of the products depend on the nature of the dienophiles. Higher electron-rich alkenes provided better yield within a shorter reaction time. After that, the above reactions were carried out in one-pot conditions in presence of $Yb(OTf)_3$ as a catalyst in refluxing acetonitrile solvent and afforded the desired products (**8** & **9**) in 26-71% yield (Scheme 3).

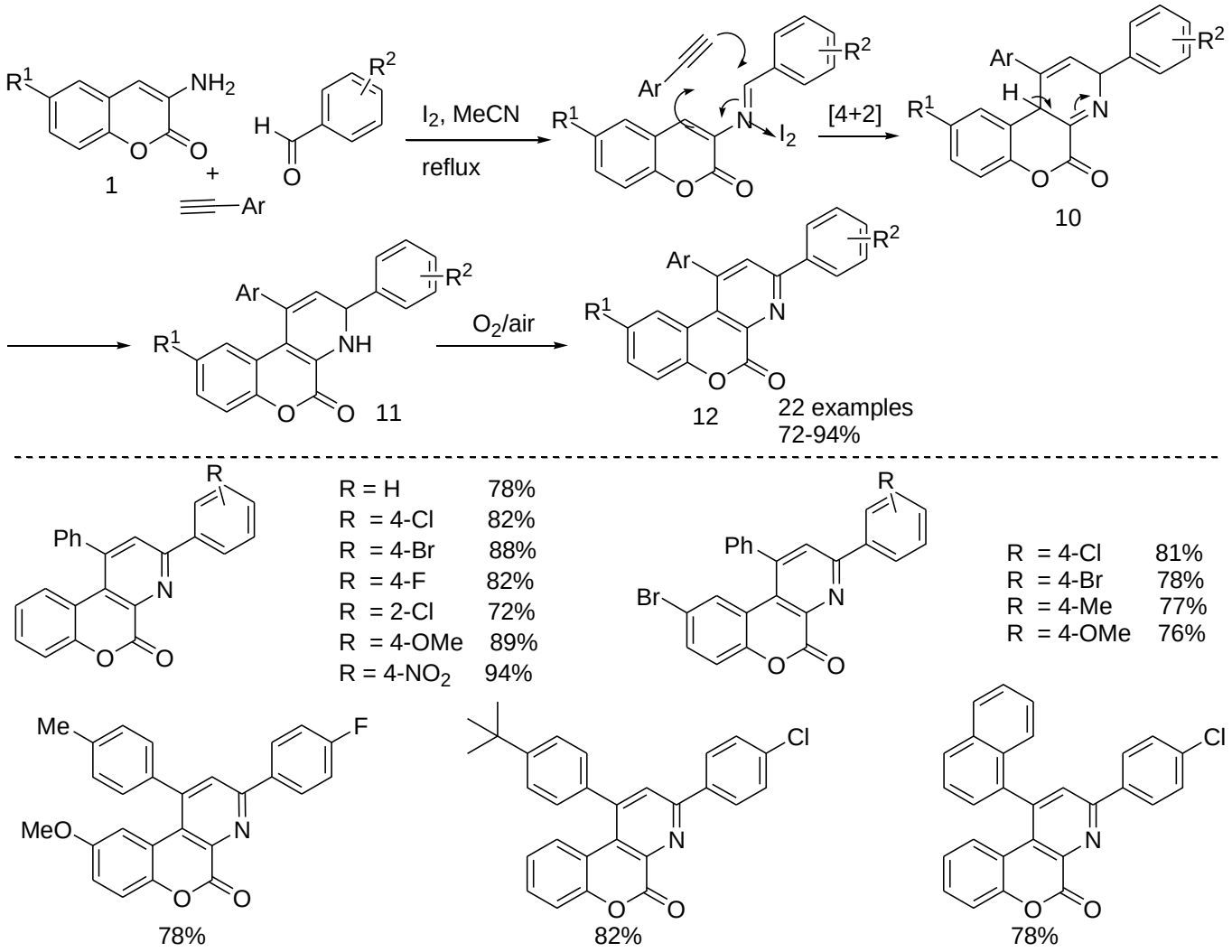


Scheme 2. Two-step synthesis of tetrahydropyridocoumarin derivatives using $Yb(OTf)_3$ as a catalyst



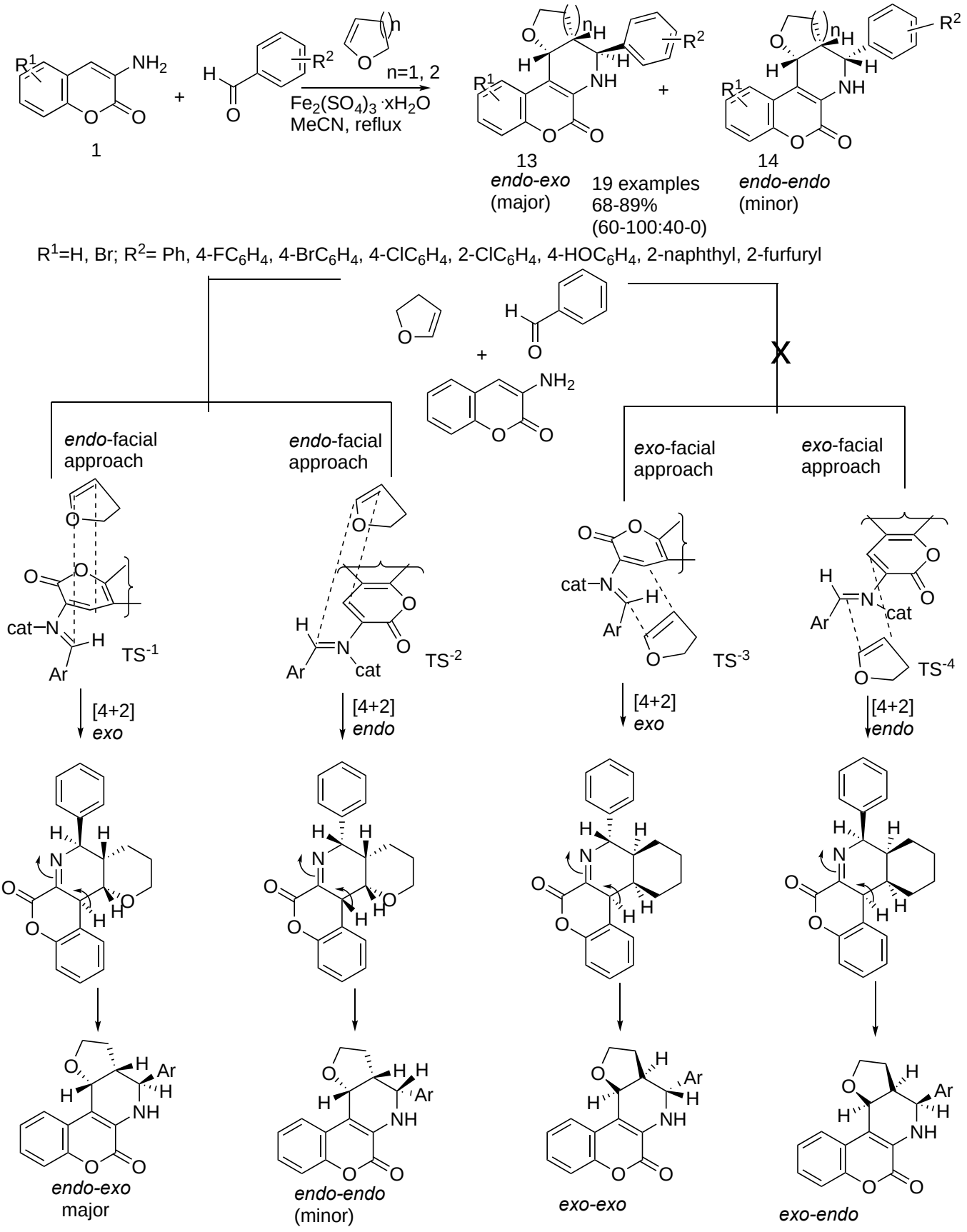
Scheme 3. One-pot synthesis of tetrahydropyridocoumarin derivatives *via* Povarov reaction using $Yb(OTf)_3$ as a catalyst

Shortly after, Khan and his group[58] reported the synthesis of pyrido[2,3-*c*]coumarin derivatives (**12**) in good to excellent yields without aqueous workup and chromatographic separation by using environmentally benign catalyst molecular I_2 *via* simple one-pot three-component condensation (Povarov reactions) reaction from a different substituent 3-aminocoumarins, aromatic aldehydes and phenylacetylenes (Scheme 4).



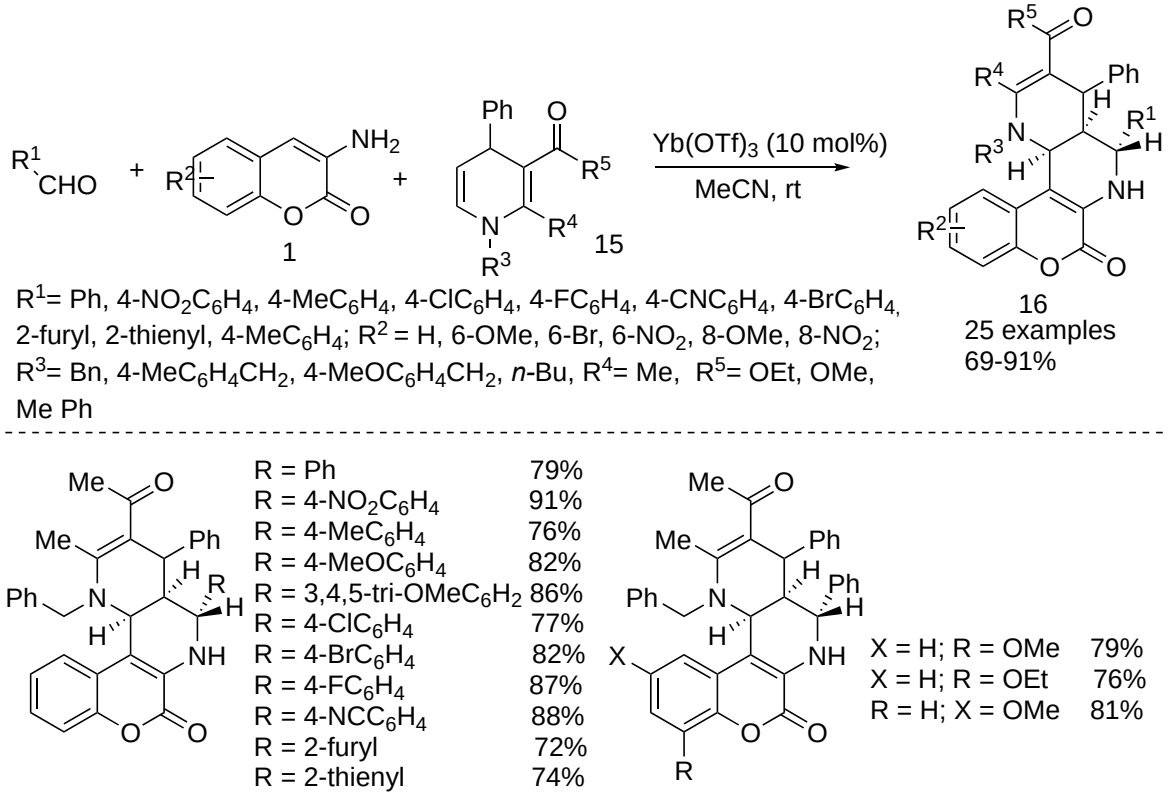
Scheme 4. Molecular I_2 promoted a one-pot three-component reaction for the synthesis of substituted pyrido[2,3-*c*]coumarins

Khan *et al.*[59] also reported the synthesis of tetrahydropyrido[2,3-*c*]coumarin derivatives (**13** & **14**) by Povarov reactions using 3-aminocoumarins, different aromatic aldehydes, and cyclic ethers in presence of hydrated ferric sulfate (Scheme 5). They also established that hydrated ferric sulfate was found to be an efficient catalyst than $Yb(OTf)_3$ for the synthesis of these compounds. The exclusive formation of *endo-exo* adducts was achieved from the *endo*-face of the dienophiles over *endo-endo* adducts.



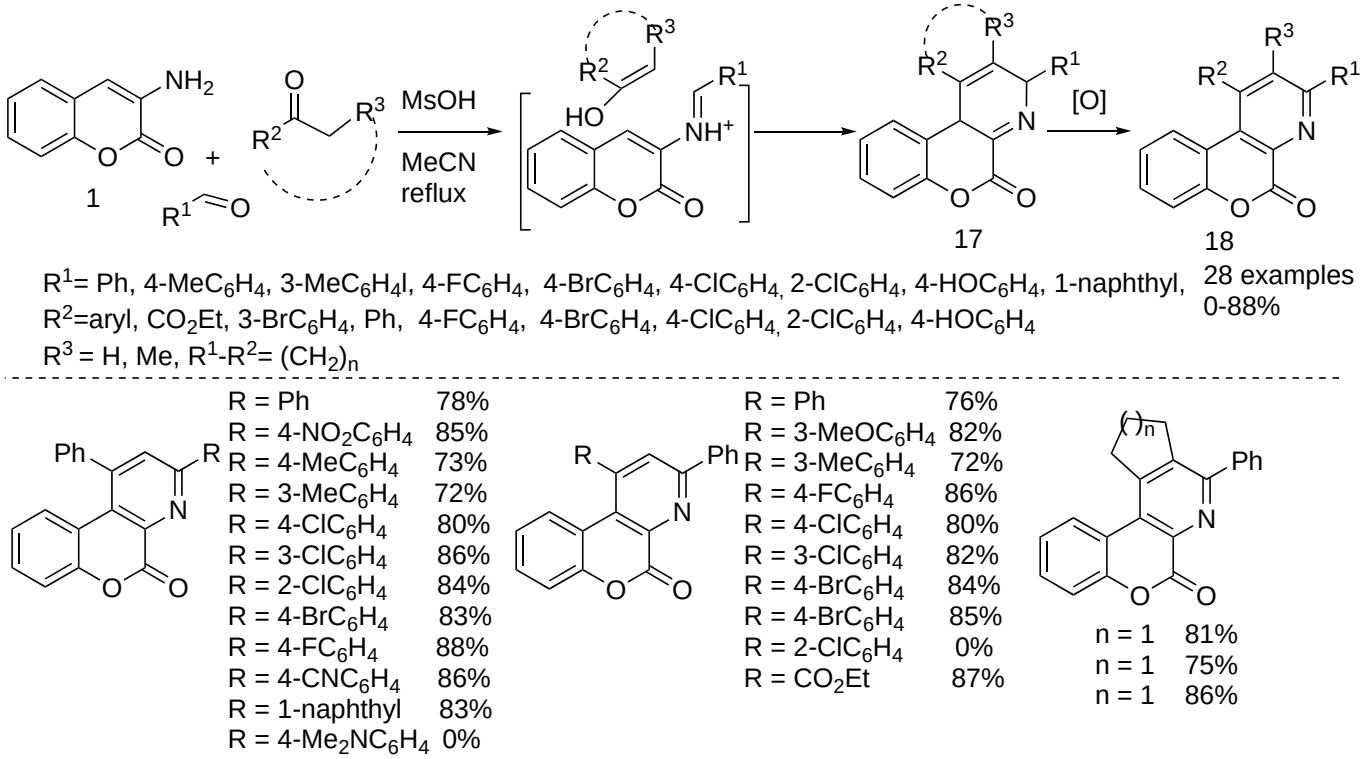
Scheme 5. Hydrated ferric sulfate promoted one-pot three-component synthesis of tetrahydropyrido[2,3-*c*]coumarins (*endo*-*exo*)

Khan *et al.*[60] developed a mild approach for the synthesis of a wide variety of substituted *exo*-tetrahydropyrido[2,3-*c*]coumarin derivatives (**16**) in 69-91% yield without any aqueous workup procedure or chromatographic separation *via* one-pot Povarov reaction (Scheme 6). The reaction of 3-aminocoumarins, diversely substituted aromatic/heteroaromatic aldehyde and nitrogen-containing electron-rich cyclic dienophiles (**15**) in the presence of 10 mol% of ytterbium(III) triflate in acetonitrile at room temperature provided the desired products (**16**).



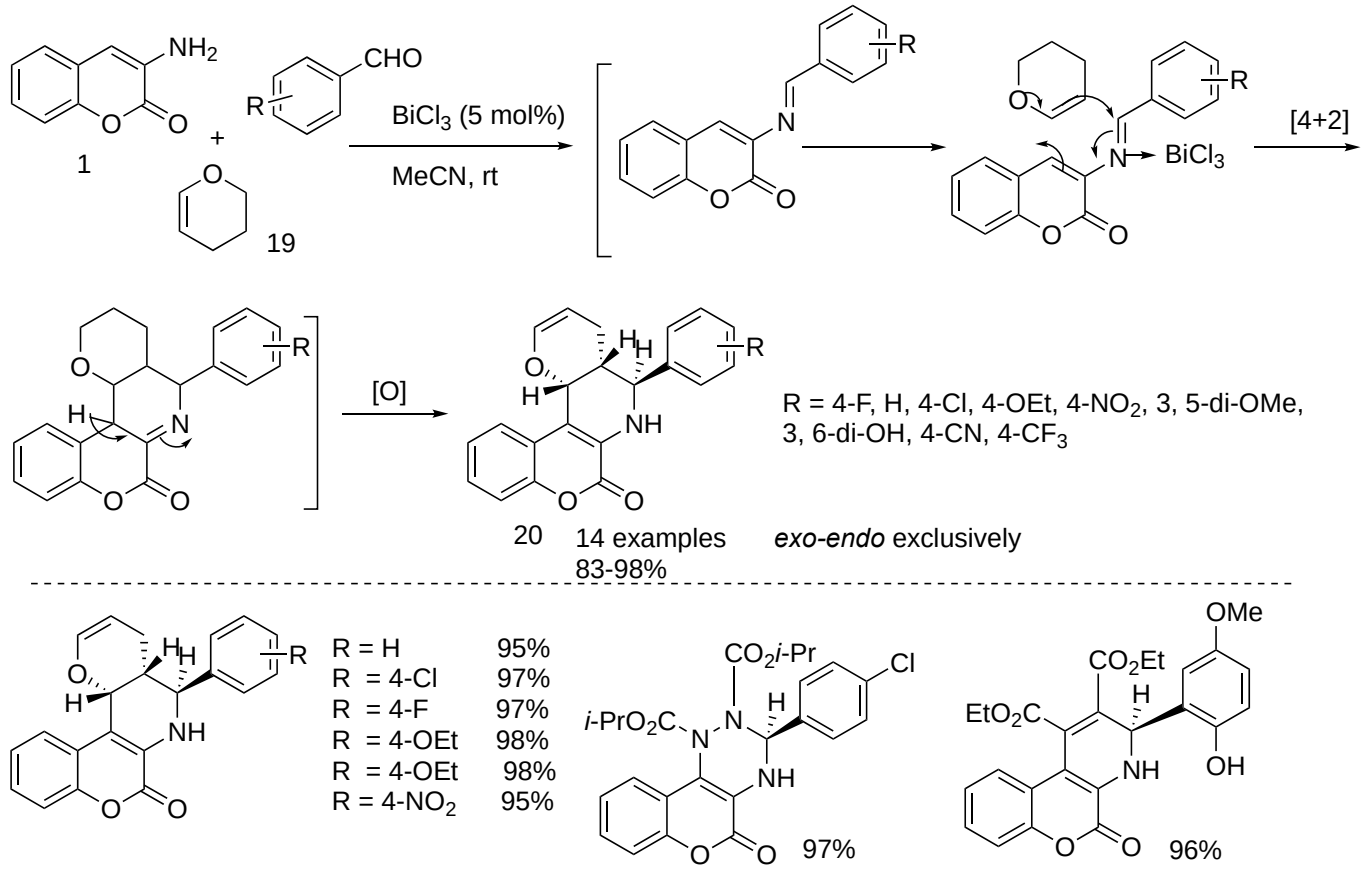
Scheme 6. $Yb(OTf)_3$ promoted one-pot three-component synthesis of *exo*-tetrahydropyrido[2,3-*c*]coumarins

Chen and co-workers[61] synthesized functionalized pyrido[2,3-*c*]coumarin derivatives (**18**) from ketones, aromatic aldehydes, and 3-aminocoumarin by an asynchronous [4+2] cycloaddition (inverse-electron-demand Diels-Alder reaction) using methanesulfonic acid in 0-88% yield (Scheme 7). According to Chen, Lewis acid $Yb(OTf)_3$ did not promote the reaction. Chen advocates that protonic acid is more efficient for the transformation of the reaction. Chen reported that among F_3CSO_3H, AcOH, F_3CCO_2H, $KHSO_4$, [DMDBSI] [$2HSO_4$], and MsOH, the use of MsOH is more efficient for this reaction. This method has many advantages like high reactivity, mild reaction conditions, simple starting materials, and the absence of a co-oxidant.



Scheme 7. Methanesulfonic acid promoted one-pot synthesis of tetracyclic pyrido[2,3-*c*]coumarins

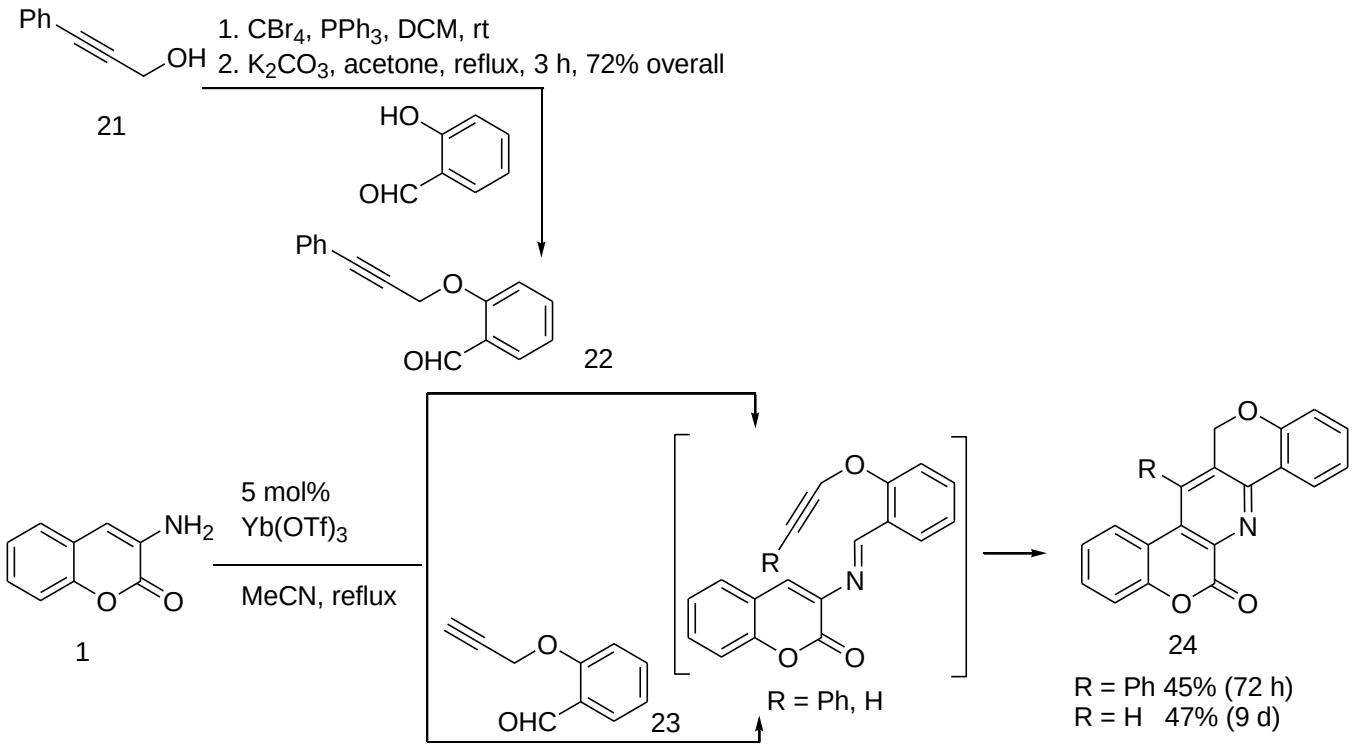
In another approach, Gurumurthy *et al.*[62] reported one-pot, three-component synthesis for the production of diastereoselective tetrahydro- and dihydropyrido[2,3-*c*]coumarin derivatives (**20**) by intermolecular Povarov reaction using $BiCl_3$ as a catalyst (Scheme 8). The reaction of aromatic aldehydes, 3-aminocoumarin, and oxygen-containing cyclic dienophiles (**19**) in the presence of 5 mol% $BiCl_3$ in acetonitrile solvent at room temperature yielded the desired cyclic pyridocoumarins in 83-98% yield.



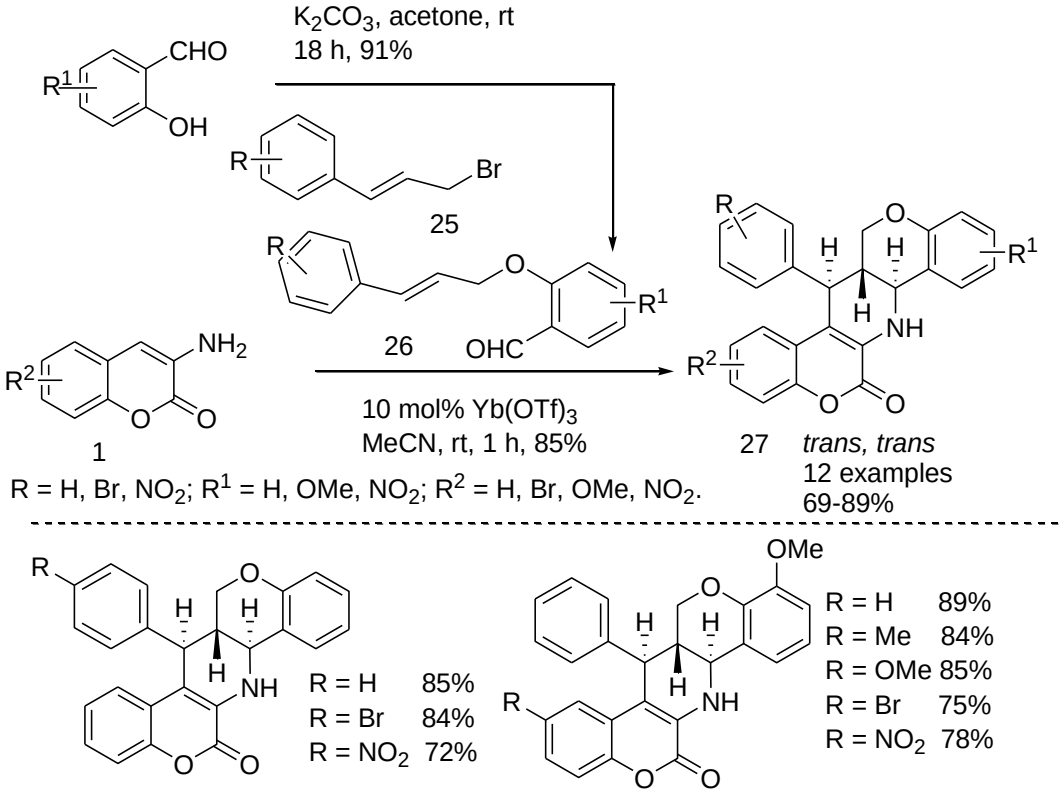
Scheme 8. $BiCl_3$ promoted one-pot synthesis of diastereoselective tetrahydro- and dihydropyrido[2,3-*c*]coumarins

2-1-3. By Intramolecular Povarov Reaction

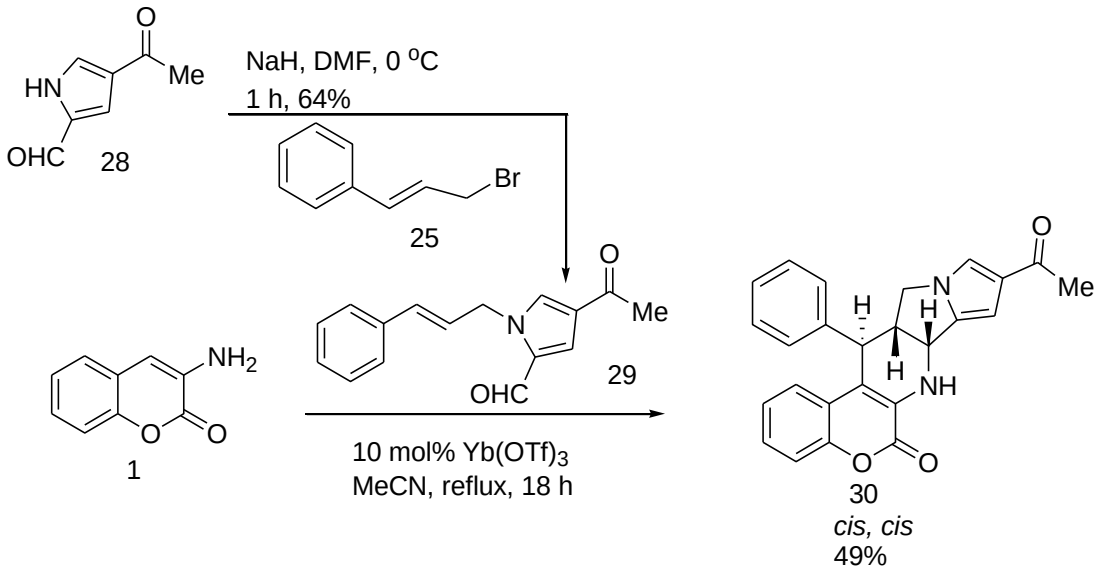
In 2011, Kudaleand co-workers[63] synthesized a series of pentacyclic coumarin fused pyridine (or tetrahydropyrirdine) derivatives (**24**, **27** & **30**) using intramolecular Povarov reactions by varying benzaldehydes bearing a pendant dienophile under similar reaction conditions (Scheme 9, Scheme 10, & Scheme 11). So, the intramolecular Povarov reactions were found to proceed under mild reaction conditions and with high *endo*/*exo* selectivity of the products. For [6,6] fused ring system, the Povarov adducts are formed with the *trans*, *trans* relative stereochemistry whereas *cis*, *trans* relative stereochemistry is observed for [6,5] fused ring systems. With respect to the mechanism, the *trans*, *trans* relative stereochemistry (*endo/exo* selectivity) of the products of [6,6] fused ring system is consistent with concerted or stepwise ring closure reaction of inverse electron-demand Diels-Alder (IEDDA) reaction where the reaction goes through the intermediacy of a secondary benzylic carbocation. The stereochemical outcome of [6,5] fused ring system is consistent either with a concerted IEDDA step, in which the *endo/exo* selectivity is opposite to that of the [6,6] fused ring system, or a stepwise ring closure leading to the most stable product.



Scheme 9. One-pot synthesis of pentacyclic pyrido[2,3-*c*]coumarins *via* intramolecular Povarov reaction using$Yb(OTf)_3$ as a catalyst

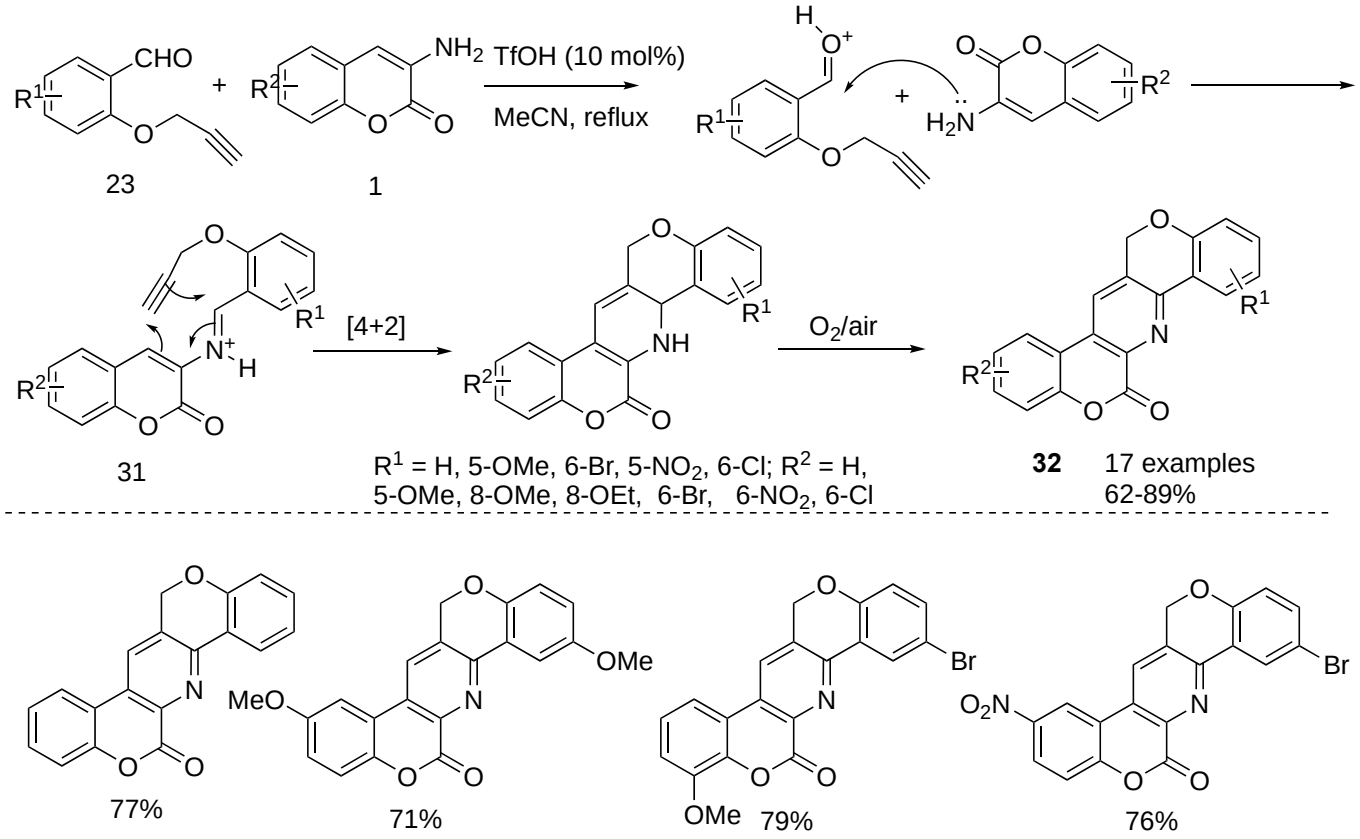


Scheme 10. $Yb(OTf)_3$ promoted one-pot synthesis of substituted pentacyclic tetrahydropyrido[2,3-*c*]coumarins (*cis*, *trans*)



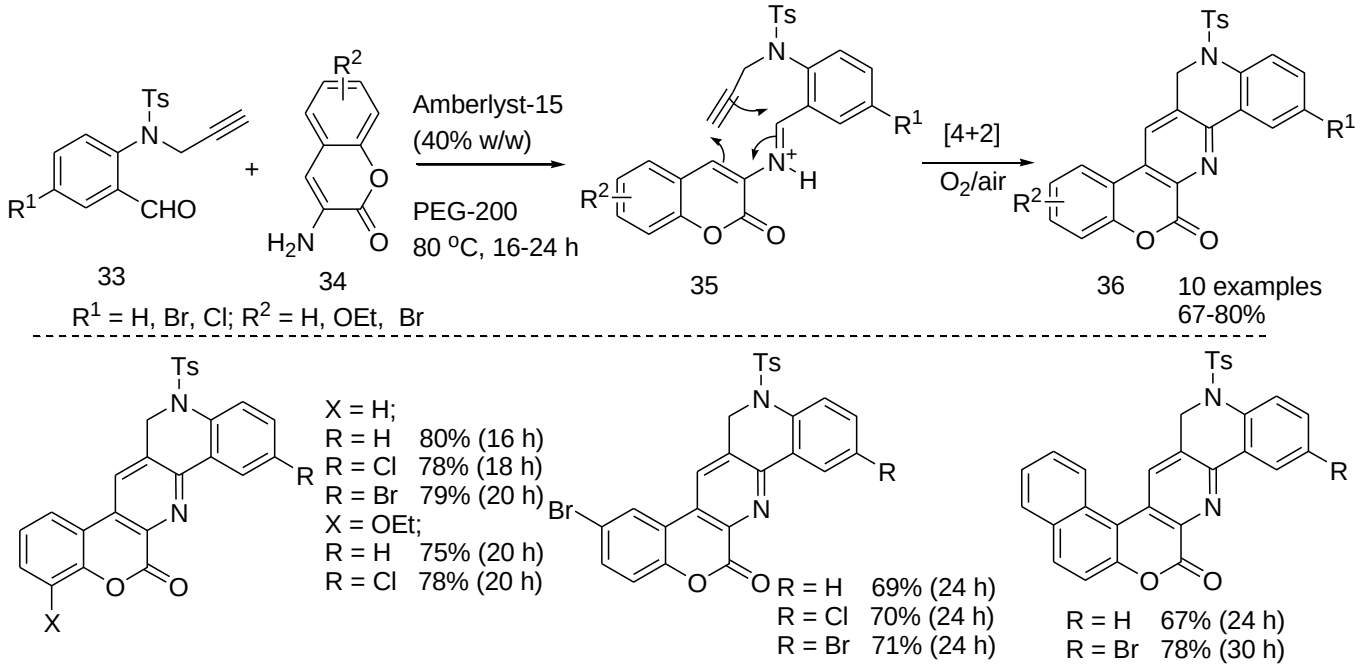
Scheme 11. $Yb(OTf)_3$ promoted one-pot synthesis of substituted pentacyclic tetrahydropyrido[2,3-*c*]coumarins (*trans*, *trans*)

Khan and co-workers[64] also reported intramolecular Povarov reaction using trifluoromethanesulfonic acid as a catalyst for the synthesis of fused pyrido[2,3-*c*]coumarins (**32**) in 62-89% yield (Scheme 12). Reaction of 3-aminocoumarins and 2-(propargyloxy)benzaldehydes (**23**) in the presence of 10 mol% of triflic acid in refluxing acetonitrile gave desired pyrido[2,3-*c*]coumarin derivatives (**32**) without any aqueous workup and chromatographic separation in a short reaction time.



Scheme 12. Trifluoromethanesulfonic acid promoted one-pot synthesis of pyrido[2,3-*c*]coumarins

Recently, Sridharan *et al.*[65] developed an efficient green protocol for the synthesis of pyridocoumarin (**36**) in 67-80% yield *via* an intramolecular [4+2] hetero Diels-Alder reaction as the key step (Scheme 13) from 2-(*N*-propargylamino)arylaldehyde (**35**) and 3-aminocoumarin derivatives. In order to obtain the best reaction conditions, authors focused on the synthesis of pyridocoumarin as a model reaction from 3-aminocoumarin (Table 1) using different catalysts, solvents and times. It was found that the reaction of 2-(*N*-propargylamino)arylaldehyde and 3-aminocoumarin in the presence of Amberlyst-15 catalyst (heterogeneous catalyst) in PEG-200 provided the desired products in 80% yield within 16 hours and it was the best reaction conditions. Synthesis of a fused pentacyclic ring in a single operation from readily available starting materials, a commercially available, transition metal-free, and recyclable catalyst, and the use of a green solvent, are the main attraction of this protocol. Though, similar compounds were reported by Sridharan and colleagues[66] in 2016, synthesized by the use of 10 mol% CuCl in refluxing toluene starting from same compounds. They reported only two examples in 74-79% yield (R^2 = H; R^1 = H 74%, Br 79%). The aforesaid method uses transiton metal catalyst, hazardous solvent toluene and coupled with the fact there is a narrow substrate scope, this method becomes less important. However, the recent Amberlyst-15 catalyzed intramolecular [4+2] hetero Diels-Alder reaction is more adequate in these regards.



Scheme 13. Amberlyst-15 catalyst in PEG-200 promoted a one-pot green approach for the synthesis of pentacyclic pyrido[2,3-*c*]coumarins

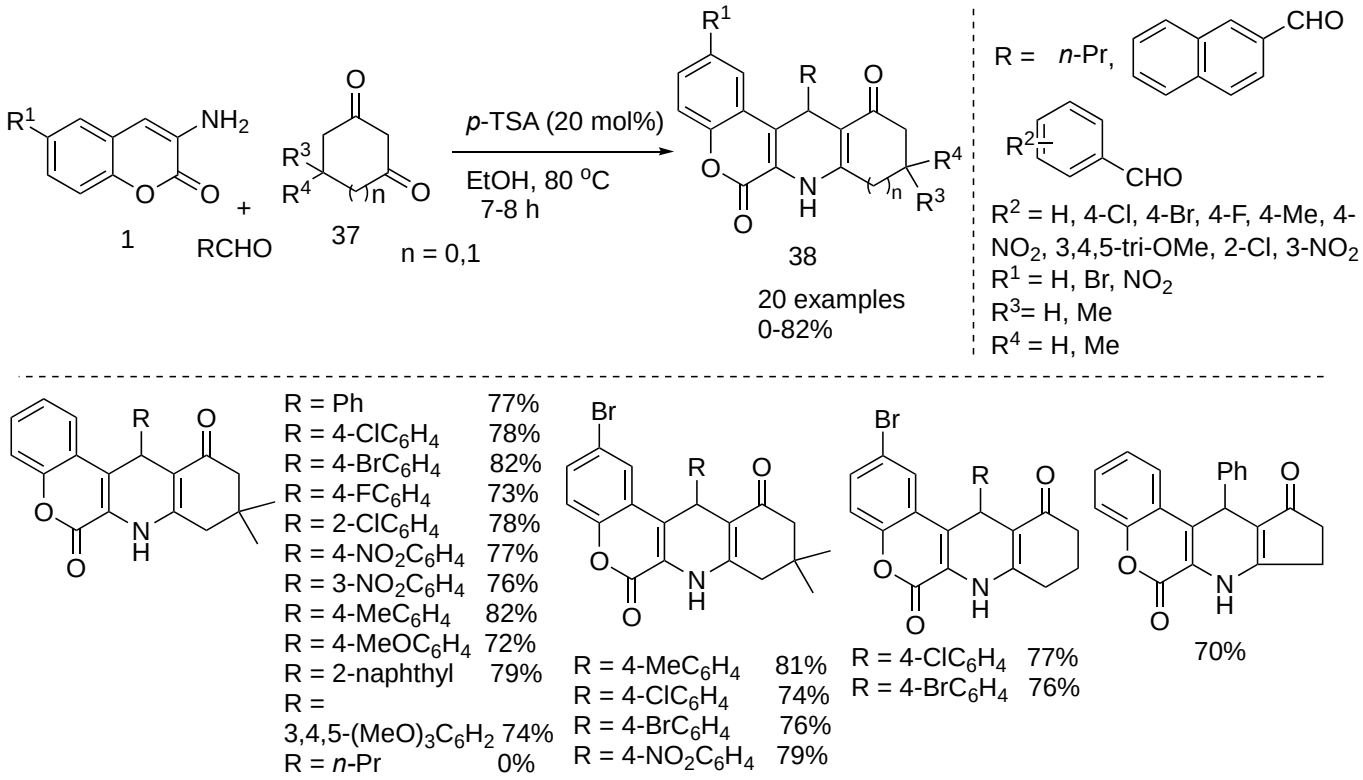
Table 1. Optimization of reaction conditions (reaction between 2-(*N*-propargylamino)arylaldehyde and 3-aminocoumarin)

Entry	Catalyst	Catalyst load (wt%)	Solvent	Time (h)	Yield %
1	Amberlyst-15	40	PEG-200	16	80
2	Amberlyst-15	20	PEG-200	36	68
3	Amberlyst-15	40	glycerol	24	43
4	Amberlyst-15	40	water	16	54
5	Montmorillonite K-10	DCM	PEG-200	24	66
6	Montmorillonite K-10	DCM	PEG-200	24	66

2-1-4. *Via* One-Pot Multi-Component Synthesis

Khan *et al.*[67] reported one-pot, three-component synthesis of pyridocoumarin derivatives (**38**) in 72-82% yield from aromatic aldehydes, 3-aminocoumarins (Scheme 14), and cyclic 1,3-diketones (**37**) in the presence of the catalytic amount of *p*-toluenesulfonic (*p*-TSA) acid in ethanol under reflux conditions without aqueous workup and column-chromatographic separation. Three new bonds and one stereocenter

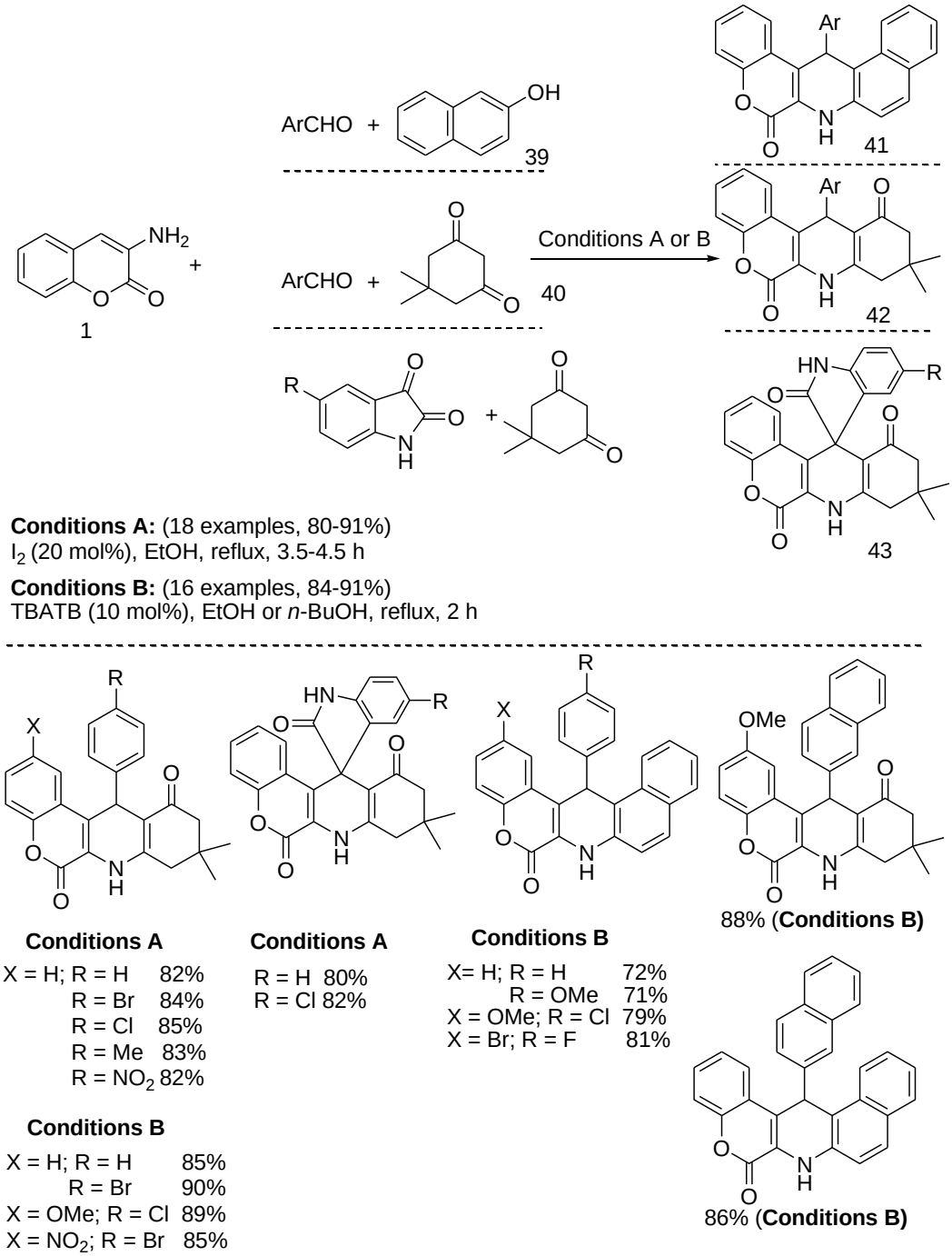
were constructed in this process in a single operation. This general method has many advantages such as the use of a wide variety of aromatic aldehydes, cyclic 1,3-diketones, different substituted 3-aminocoumarins, shorter reaction times, easy availability of the catalyst, and short reaction time.



Scheme 14. *p*-Toluenesulfonic (*p*-TSA) acid promoted one-pot synthesis of tetracyclic dihydropyrido[2,3-*c*]coumarins

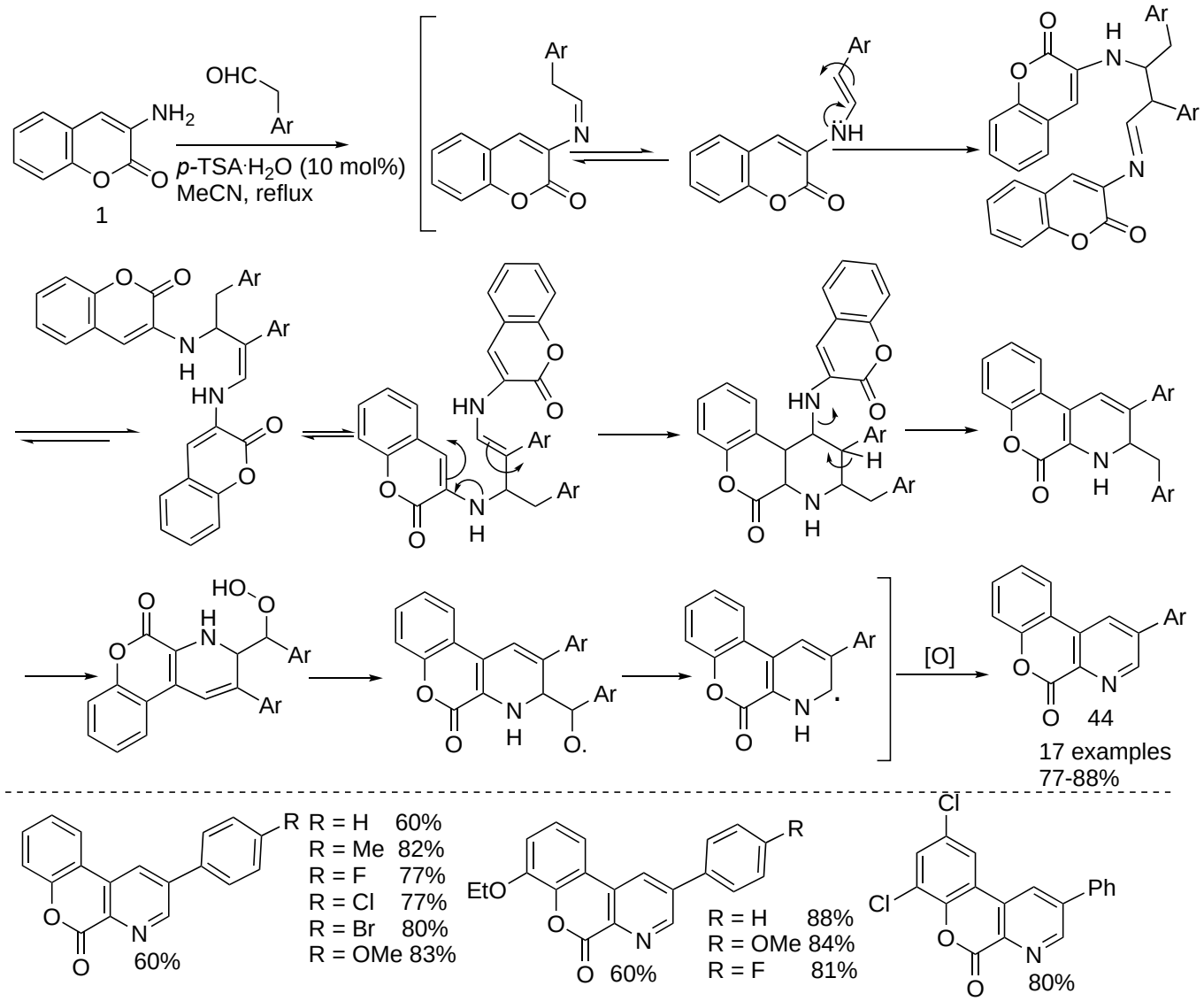
Hussain *et al.*[68] developed a simple, one-pot, and green synthetic method for the synthesis of highly substituted coumarin fused dihydropyridines derivatives (**41**) and their spiro derivatives (**43**) (Scheme 15). In the presence of molecular iodine as a catalyst in refluxing ethanol, 3-aminocoumarins reacted cyclic 1,3-diketones (**40**) and aromatic aldehydes or isatins and afforded the corresponding pyridocoumarin derivatives in 80-91% yield without any tedious chromatographic separation. Good to excellent yields, shorter reaction time, use of an inexpensive and environmentally benign catalyst are the attraction of this protocol. Synthesized compounds bearing electron-withdrawing groups such as -Cl, -Br, -F, -NO_2, and -OMe of the aromatic aldehydes provided better yields in a shorter reaction time. However, the aldehydes with electron-donating groups such as -Me and -Et also afforded good yields when the reaction was carried out in a longer time. Khan *et al.*[69] also reported simple, one-pot, and green synthetic methods for the synthesis of highly substituted coumarin fused dihydropyridines derivatives (**41**) (Scheme 15). The three-component reaction of substituted aromatic aldehydes, 3-aminocoumarins, and 2-naphthol (**39**) in *n*-

butanol using 10 mol% of *N*-tetrabutylammonium tribromide (TBATB) as a catalyst under reflux conditions afforded the desired dihydropyridocoumarins in 71-86% yield. The protocol of the reaction underwent consecutive Knoevenagel, Michael reaction followed by concomitant cyclization. The same reactions were carried out in presence of cyclic 1,3-diketones instead of 2-naphthol under similar reaction conditions gave the corresponding desired products (**42**) in relatively higher yield (Scheme 15).



Scheme 15. Molecular I_2/*N*-tetrabutylammonium tribromide (TBATB) promoted one-pot synthesis of tetracyclic dihydropyrido[2,3-*c*]coumarin

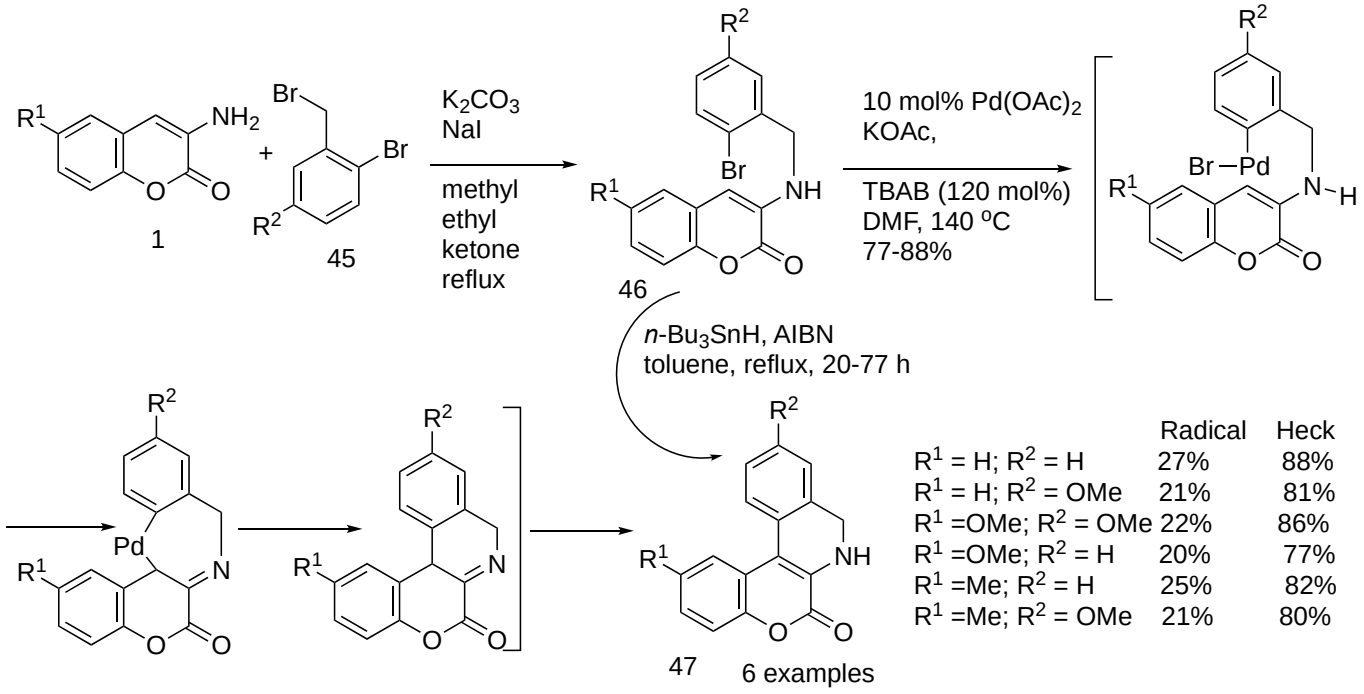
Khan and co-worker[70] synthesized 3-aryl-pyridocoumarins (**44**) in 77-88% yield *via* one-pot reaction conditions (Scheme 16). The reaction of 3-aminocoumarin and different substituted arylacetaldehyde in presence of *p*-toluenesulfonic acid monohydrate as a catalyst in acetonitrile solvent under refluxing conditions afforded the desired 3-aryl-pyridocoumarins. The plausible mechanism for the reactions involved the formation of an imine between arylacetaldehyde and 3-aminocoumarin, enamine with another imine of the same combination, then tautomerization and subsequent electrocyclic ring closure and the elimination of one molecule of 3-aminocoumarin and arylaldehyde afforded the target compounds.



Scheme 16. *p*-Toluenesulfonic acid monohydrate catalyzed synthesis of pyrido[2,3-*c*]coumarins

2-1-5. By Transition Metal-Catalyzed Synthesis

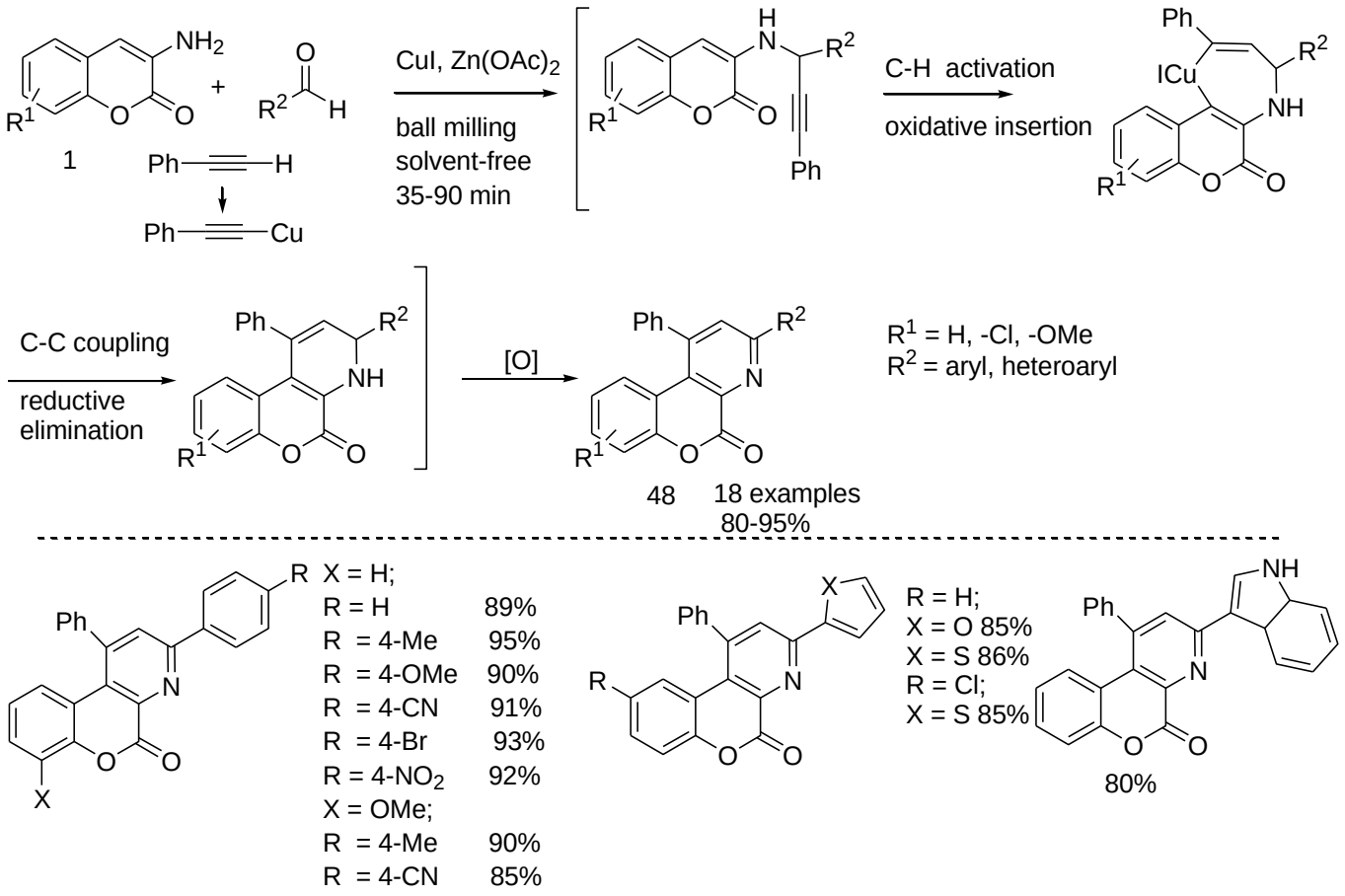
Majumdar *et al*.[71] developed two different approaches for the synthesis of dihydropyrido[2,3-*c*]coumarin derivatives (**47**) starting from 3-aminocoumarin and different substituted 2-bromobenzyl bromide (**45**) (Scheme 17). The required precursors (**46**) were synthesized in moderate to good yields by the reaction of 3-aminocoumarins and different substituted 2-bromobenzyl bromide in anhydrous methyl ethyl ketone in the presence of anhydrous potassium carbonate and a small amount of sodium iodide under reflux conditions. The synthesized precursors were cyclized by either intramolecular radical cyclization in the presence of *n*-Bu_3SnH, AIBN in refluxing toluene, or Heck coupling reaction in the presence of a catalytic amount of $Pd(OAc)_2$ in combination with TBAB, KOAc in DMF under an N_2 atmosphere at 100 ^oC. From the standpoint of the yield of the products, it was shown that palladium-catalyzed intramolecular Heck coupling reaction was found to be an excellent and straightforward approach compared to intramolecular radical cyclization.



Scheme 17. Palladium-catalyzed and radical cyclization of 2-bromobenzylic derivative of 3-aminocoumarins

Kausar and Das[72] developed a combo-catalytic, rapid, solvent-free, ball milling method for the synthesis of pyridocoumarins (**48**) in good to excellent yield from 3-aminocoumarin, aldehyde (both aryl and heteroaryl), and phenylacetylene in presence of CuI, and $Zn(OAc)_2$-catalyst (Scheme 18). The protocol of

the reactions underwent oxidative insertion by C-H activation, reductive elimination through C-C coupling, and subsequent oxidation.

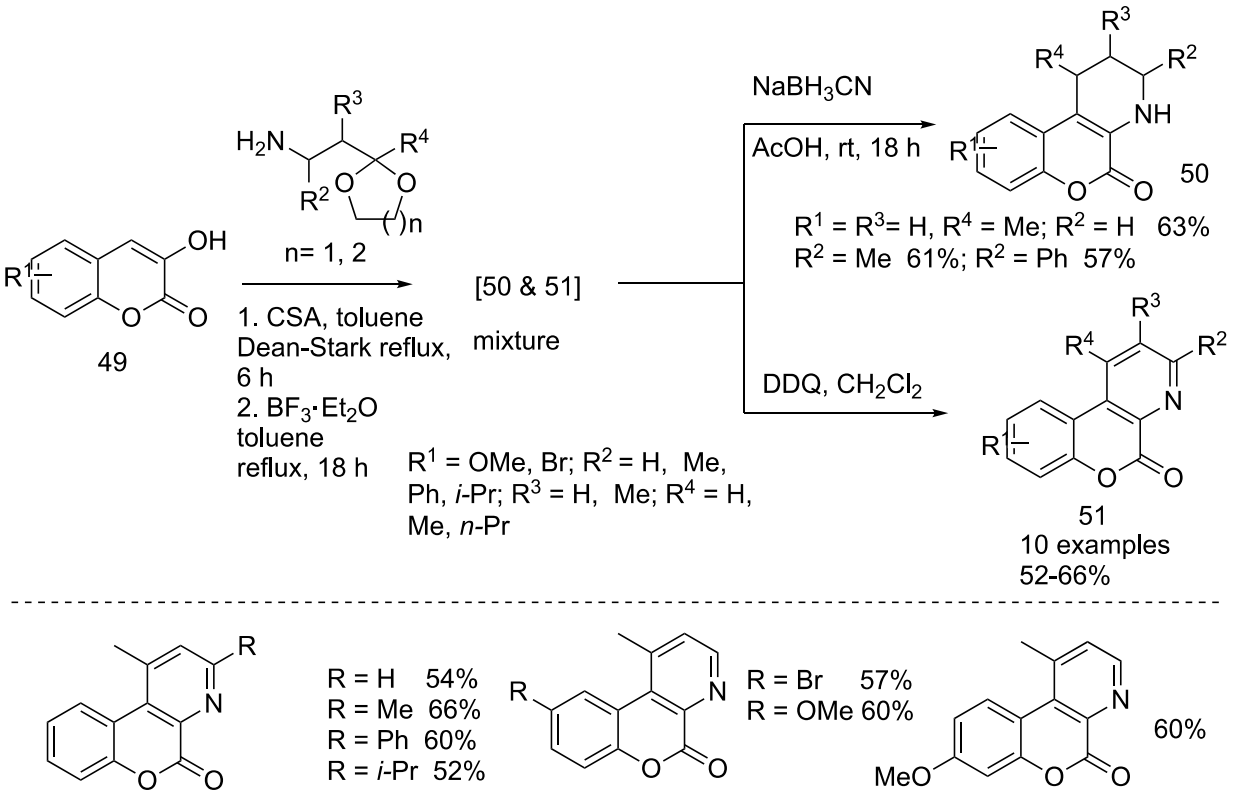


Scheme 18. Copper and zinc combo-catalytic, solvent-free, ball milling method for the synthesis of pyrido[2,3-*c*]coumarin derivatives

2-2 Synthesis of Pyrido[2,3-*c*]coumarin from 3-Hydroxycoumarin

Pave *et al.*[73] developed a method for the synthesis of substituted pyrido[2,3-*c*]coumarin (**51**) and its tetrahydro derivatives (**50**) from 3-hydroxycoumarin (**49**) *via* 3-aminocoumarin intermediate (Scheme 19). The reaction of 3-hydroxycoumarins (**49**) with protected β-aminoketones in the presence of a catalytic amount of camphorsulfonic acid (CSA) in refluxing toluene provided 3-aminocoumarin derivatives which then cyclized to pyrido[2,3-*c*]coumarins and its tetrahydro derivatives in the presence of boron trifluoride diethyl etherate complex in refluxing toluene. The mixture was converted into the corresponding pyridocoumarin derivatives in presence of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in dichloromethane without purification of any intermediates. The overall yield of the products was

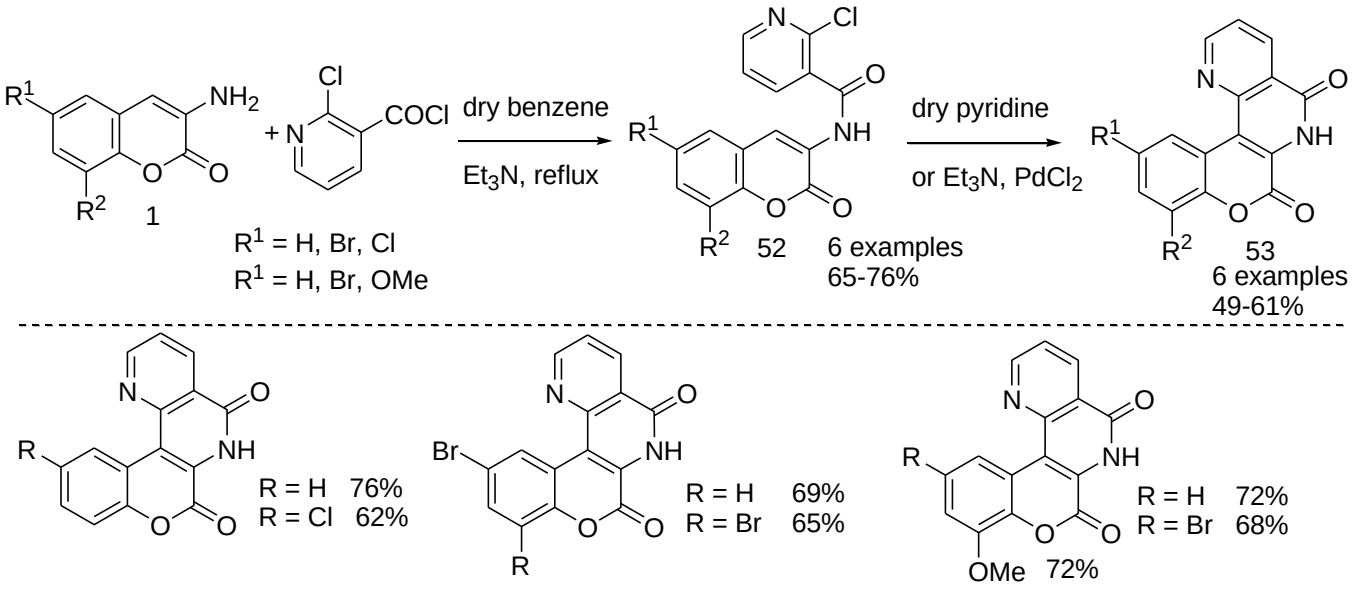
moderate to good (52-66%). On the other hand, tetrahydropyrido[2,3-*c*]coumarin derivatives were obtained in overall 57-63% yield using the same approach by using sodium cyanoborohydride in acidic conditions instead of DDQ in dichloromethane in the last step of the reactions.



Scheme 19. Camphorsulfonic acid (CSA) promoted synthesis of pyrido[2,3-*c*]coumarins and their tetrahydro derivatives

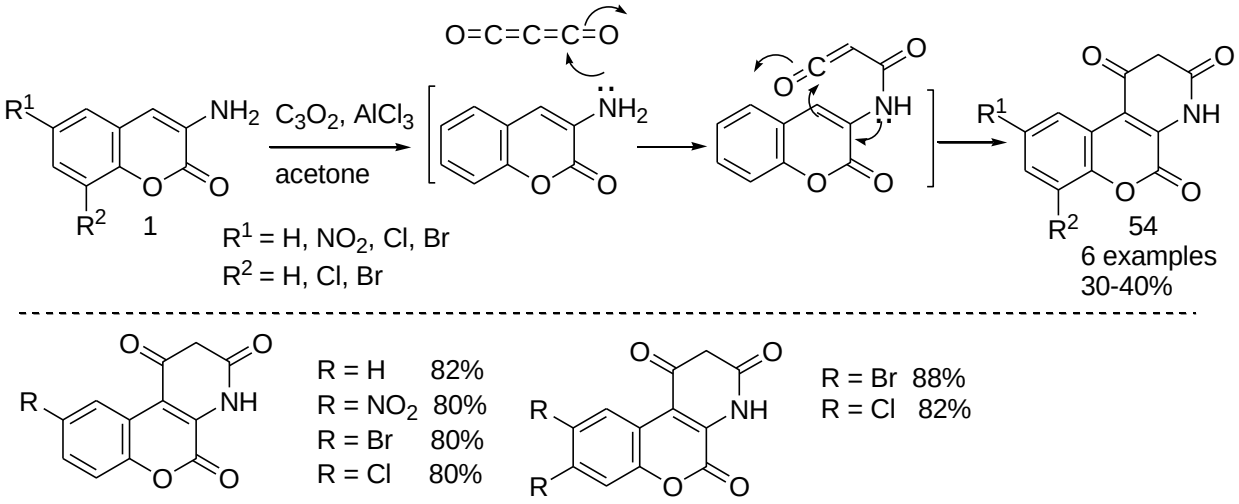
2-3. Synthesis of Pyrido[2,3-*c*]coumarinone

Prasad and co-worker[74] reported a two-step synthesis of coumarin-fused tetracyclic pyridinone derivatives (**53**). In presence of triethylamine in dry benzene solvent under reflux conditions, 3-aminocoumarin and 2-chloronicotinoyl chloride resulted in the formation of the 3-(2′-nicotinamidocoumarin derivatives (**52**) in 65-76% yield by the elimination of HCl molecule. The second step was carried out under reflux conditions in either pyridine or Et_3N in the presence of $PdCl_2$ and afforded the desired tetracyclic compounds in 49-61% yield by cyclodehydrochlorination reaction (Scheme 20).



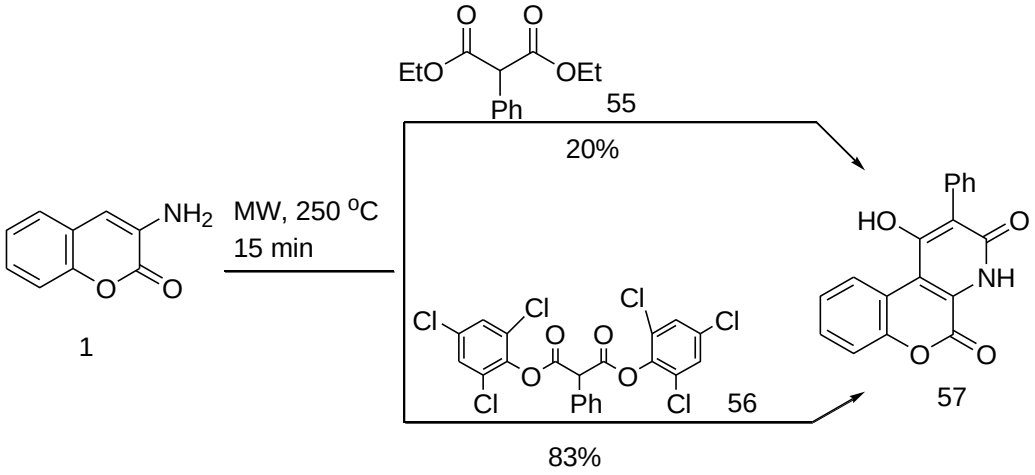
Scheme 20. Two-step synthesis of coumarin fused tetracyclic pyridinone derivatives

Bonsignore and co-worker[75] developed a method to prepare coumarin fused pyridine-dione derivatives (**54**) in 30-40% yield. Treatment of 3-aminocoumarin with carbon suboxide in the presence of a Lewis acid in acetone provided the desired compounds (Scheme 21).



Scheme 21. Synthesis of coumarin fused tetracyclic pyridine-dione derivatives from 3-aminocoumarin with carbon suboxide

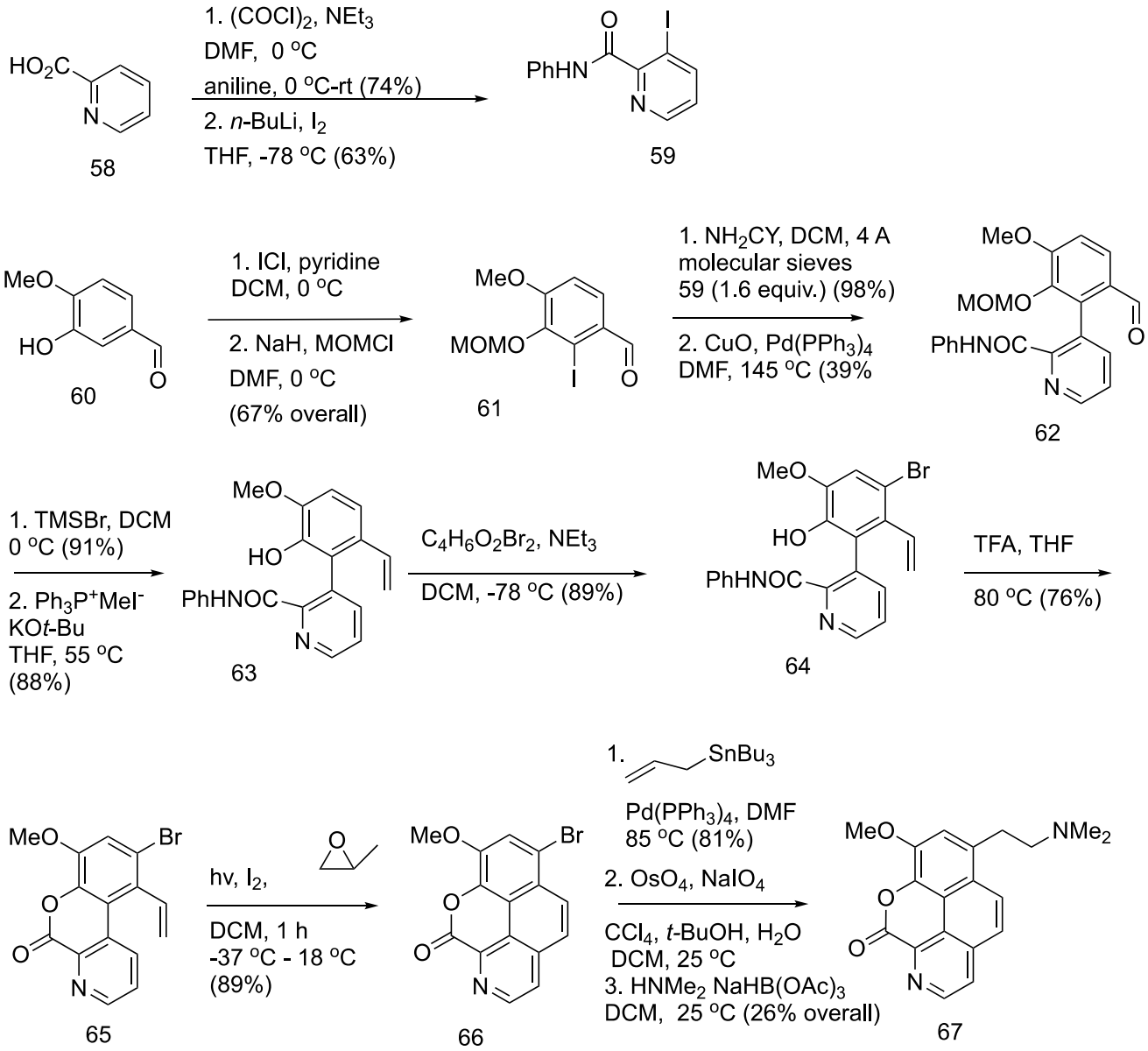
Rivkin and co-workers[76] reported the solvent-free microwave-assisted synthesis of coumarin fused pyridinone (**57**) in 20% yield from 3-aminocoumarin and diethyl malonate derivative (**55**) at 250 °C (Scheme 22). The authors used activated di-(2,4,6-trichlorophenyl)-2-phenylmalonate (**56**) instead of diethyl malonate derivative under similar reaction conditions to improve the yield of the product.



Scheme 22. Solvent-free microwave-assisted synthesis of coumarin-fused pyridinone from 3-aminocoumarin

2-4. Total Synthesis of Santiagonamine Natural Product

In 2007, Markey[77] reported the total synthesis of santiagonamine (**67**) starting from commercially available isovanillin and picolinic acid in 12 steps with overall 2.6% yield (Scheme 23). Palladium-catalyzed Ullmann cross-coupling reaction of iodinated imine of isovanillin and iodinated secondary amide of picolinic acid (**59**) provided hindered biaryl moiety (**62**). After Wittig reaction with methylenetriphenylphosphorane and subsequent bromination to achieve biaryl bromostyrene derivative (**64**), which then cyclized with trifluoroacetic acid in THF providing styrene derivative of tricyclic pyrido[2,3-*c*]coumarin (**65**). This pyrido[2,3-*c*]coumarin (**65**) underwent smooth and rapid photocyclization to yield tetracyclic bromopyrido[2,3-*c*]coumarin (**66**). Finally, installation of the side-chain of bromopyrido[2,3-*c*]coumarin to provide the target natural product santiagonamine (**67**) was achieved by sequential C-C coupling *via* Stille coupling with allyltributyltin, oxidative cleavage of alkenes into aldehyde by the action of osmium tetroxide and sodium periodate and followed by reductive amination with dimethylamine and sodium triacetoxyborohydride.



Scheme 23. Synthesis of santiagonamine natural product from commercially available isovanillin and picolinic acid in 12 steps

3. Biological Activity

Khan *et al.*[59] carried out docking studies of tetrahydropyrido[2,3-*c*]coumarin derivatives as an efficient inhibitor against human dopamine D3 receptor as possible antipsychotic drugs. The compounds having *endo-endo* stereochemistry showed better-predicted inhibition efficiency as compared to the compounds of *endo-exo* stereochemistry (Figure 2). However, compound (*endo-exo*) having R = 4-OMe demonstrated comparable effectiveness to a compound having *endo-endo* stereochemistry.

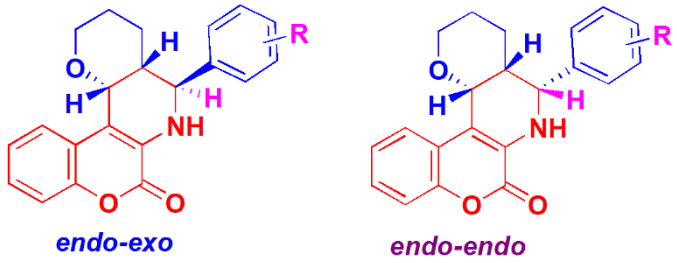
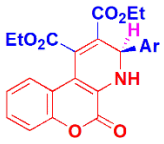
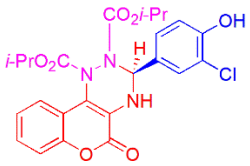
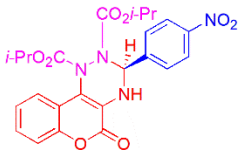


Figure 2. Tetrahydropyrido[2,3-*c*]coumarin derivatives as possible antipsychotic drugs

Gurumurthy *et al.*[62] evaluated the antioxidant activity of diastereoselective dihydropyrido[2,3-*c*]coumarin derivatives. Among the all compounds, diethyl acetylenedicarboxylate and diisopropyl azodicarboxylate derivatives with chloro functionality in the aryl part exhibited good free radical scavenging activity (FRSA) as compared to all the other derivatives at all the tested concentrations. However, the FRSA values (μg/mL) showed that the above-mentioned activity of these compounds exhibited lower than that of the reference compounds, BHT and α-tocopherol. The results in this regard are shown in Table 2.

Table 2. Inhibition compared to control (Paclitaxel)

Compounds	Concentration (mM)		
	0.5	1	2
Ar = 2,4-di-HOC_6H_3	2.43±0.01	3.88±0.01	7.42±0.01
Ar = 2-OH-4-$MeOC_6H_3$	9.58±0.01	20.05±0.01	32.12±0.01
Ar = 3-Cl-4-HOC_6H_3	4.84±0.01	5.79±0.01	10.98±0.01
	10.85±0.01	21.01±0.01	31.11±0.01
	3.27±0.01	7.06±0.01	14.59±0.01
BHT	39.78±0.01	68.52±0.01	78.54±0.01
α-tocopherol	47.72±0.01	81.68±0.01	86.42±0.01

4. CONCLUSIONS

This review has been an attempt to elaborately explain the different synthetic methods for the synthesis of pyrido[2,3-*c*]coumarin derivatives. As the structure of natural product santiagonamine is complex tetracyclic, so in the future, depending upon the significant contribution of the existing library of related reports, our review article will be a helpful steping stone for synthetic organic chemists for further development of more complex pyrido[2,3-*c*]coumarin compounds to achieve tetracyclic santiagonamine core with the help of the most appropriate greener and eco-friendly methods. In addition, this review will also help medicinal and pharmaceutical chemists to evaluate biological and fluorescence studies of reported pyrido[2,3-*c*]coumarins types compounds. From the literature, it is clear that dihydro or tetrahydro derivatives of the title compounds are found to be more biologically active than their corresponding unsaturated analogs. So, researchers may need to emphasize the structure modification by the introduction of proper functional groups like -OH, -NH_2, -CO_2H, -F etc. to improve the water solubility and also to highlight *in vivo* rather than *in vitro* experiments. However, we believe that the modifications based on the structure of pyrido[2,3-*c*]coumarin and its analogs can solve these problems in the near future.

CONFLICTS OF INTEREST

The author declares no conflict of interest.

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Dr. Prasanta Patra was born in a remote village of Paschim Medinipur, West Bengal, India. He did his M.Sc. (2006) from Vidyasagar University, Paschim Medinipur and Ph.D. (2012) in Organic Chemistry under the supervision of Prof. Gandhi Kumar Kar at Presidency University (formerly Presidency College under Kolkata University), Kolkata, India. He is an Assistant Professor of Department of Chemistry, West Bengal Education Service, since 2009. He is currently working as an Assistant Professor of Chemistry at Department of Chemistry, Jhargram Raj College. His research interest is on improvement of methodologies of heterocycles mainly γ-lactams and coumarin fused heterocyclic compounds and their biological importance.

Susanta Patra was born in 1998 in Paschim Medinipur, West Bengal, India. He did his B.Sc. (2018) from Ramakrishna Mission Vivekananda Centenary College affiliated to West Bengal State University, West Bengal, India and M.Sc. (2020) from Indian Institute of Engineering Science and Technology, Shibpur, Howrah-711103; West Bengal; India. Now he is a research scholar of the Department of Chemistry, IIT(ISM) Dhanbad, Dhanbad-826004, India. He is engaged in the synthesis of biologically active organic compounds by metal- and organo-catalysis.