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REVIEW ARTICLE

A Brief Review on the Synthesis of Pyrrolo[2,3-*c*]coumarins, including Lamellarin and Ningalin Scaffolds

Prasanta Patra[a], Sibasish Manna[a], Susanta Patra[b], Khokan Samanta[c], and Debnarayan Roy[d]

[a]Department of Chemistry, Jhargram Raj College, Jhargram, India; [b]Department of Chemistry, IIT(ISM) Dhanbad, Dhanbad, India; [c]Department of Chemistry, Haldia Government College, Haldia, Purba Medinipur, India; [d]Department of Zoology, Jhargram Raj College, Jhargram, India

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CONTACT Prasanta Patra prasantaanupama1983@gmail.com

Introduction

Natural and synthetic coumarins and their derivatives are important oxygen- and nitrogen-containing heterocycles due to their numerous biological activities,[1–16] some of which have been reported in the literature as long as two centuries ago. Pyrrolo[2,3-*c*]coumarin[17–27] scaffolds are found in such natural products as the lamellarins (Types I and II), ningalin A, ningalin B and baculiferin O, as depicted in Figure 1; and as examples we may note that researchers[24,28,29] have reported in depth the total syntheses of marine alkaloid lamellarins and ningalin-type compounds. These natural products are important for their structural diversity as well as for their biological activities, including anti-cancer,[30–33] multidrug-resistance reversing,[34–35] cytotoxic, and HIV-1 integrase inhibitory[36–37] activities. In addition, purely synthetic pyrrolo[2,3-*c*]coumarins have been found to exhibit *Topoisomerase* I inhibitory, DYRK1A inhibitory, and anti-retroviral activities,[38–47] among others. In addition, these compounds are used as neuroimaging agents.[48] Here we review the recent literature on the preparation of pyrrolo[2,3-*c*]coumarins and their derivatives from suitable precursors. Although some of the methods have been discussed in related surveys,[49–50] to the best of our knowledge, this is the first review specifically covering pyrrolo[2,3-*c*]coumarins.

I. From 3-aminocoumarin by the formation of pyrrole rings

1. By Fischer indole reaction

In 1978, Khan *et al.*[51] reported the Fischer indole synthesis of 3-aminocoumarin for the construction of pyrrolocoumarins (Scheme 1). This paper was important for demonstrating the applicability of the classic Fischer methodology to pyrrolization. The diazotization of 3-aminocoumarin followed by reduction gave the coumarin-3-yl-hydrazine which, without isolation, reacted with numerous carbonyl compounds in the presence of acid *via* the Fischer indole reaction to afford pyrrolo[2,3-*c*]coumarin derivatives.

2. By amino-Claisen rearrangement

In 2008, Majumdar and colleagues[52] developed a method for the regioselective synthesis of pyrrolo[2,3-*c*]coumarins in excellent yields *via* the amino-Claisen rearrangement of

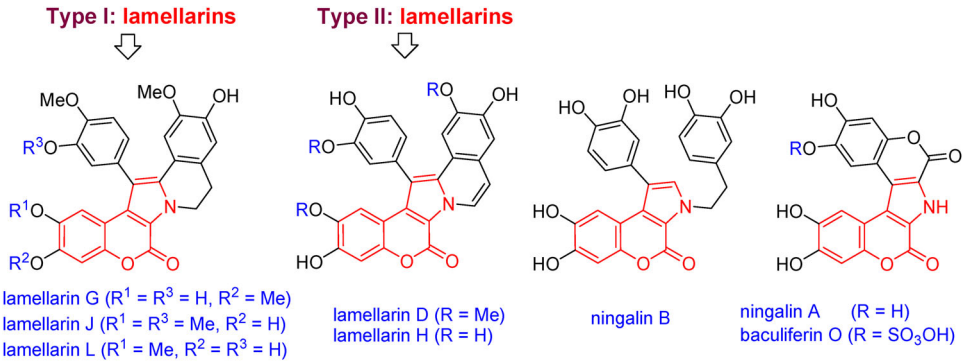
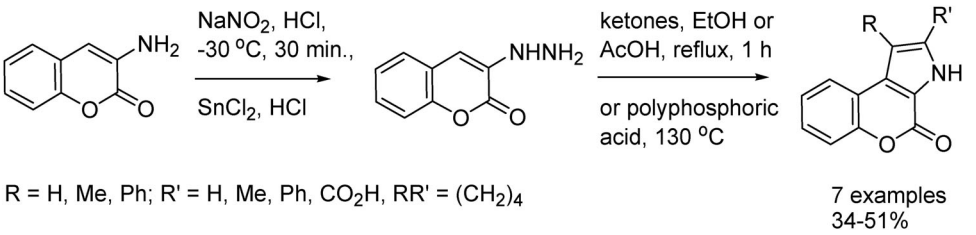
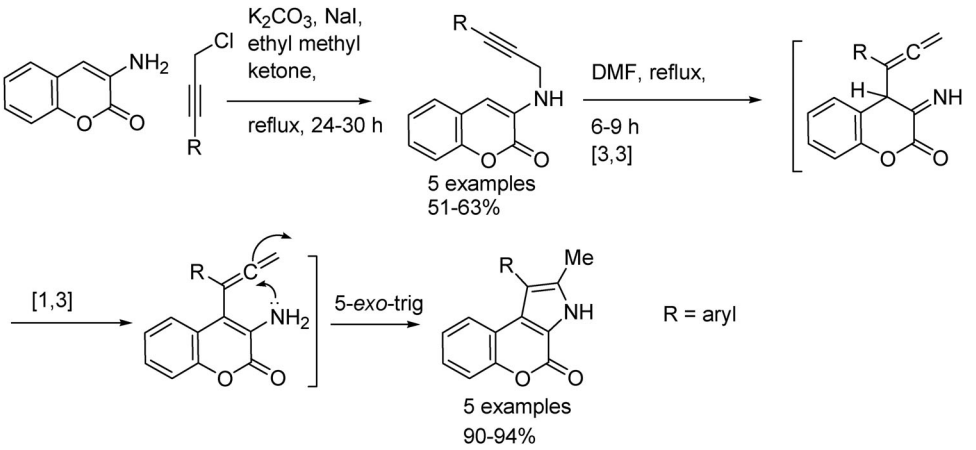


Figure 1. Examples of pyrrolo[2,3-*c*]coumarins.



Scheme 1. Synthesis of pyrrolocoumarins by Fischer indole synthesis.



Scheme 2. Amino-Claisen rearrangement for the synthesis of pyrrolocoumarins.

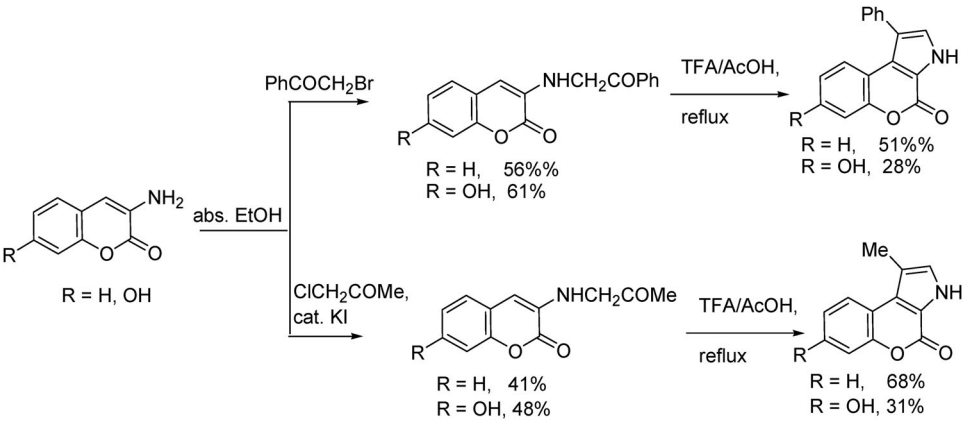
3-*N*-propargylaminocoumarin in DMF under reflux conditions (Scheme 2). The 3-*N*-propargylaminocoumarins were in turn obtained by the reaction of 3-aminocoumarin and propargyl chloride in the presence of potassium carbonate and sodium iodide in refluxing methyl ethyl ketone. The reactions went through an initial [3,3]-sigmatropic rearrangement of the propargylamine moiety of the substrate 3-*N*-propargylaminocoumarin to generate the allene intermediate, which then afforded the desired products by 5-exo-trig cyclization.

3. Reaction with α-halo ketones

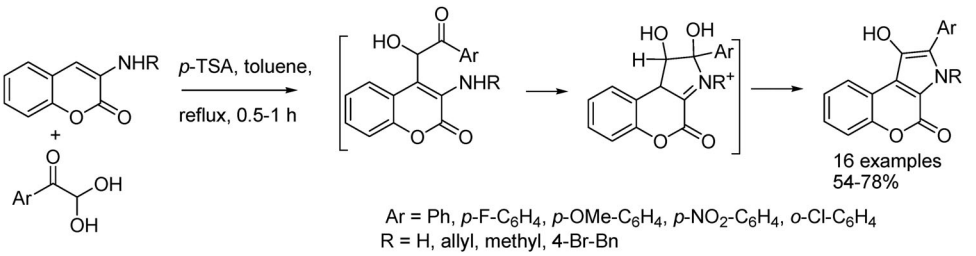
Soman and co-workers[53] synthesized 1-methyl/phenylpyrrolo[2,3-*c*]coumarins as anti-cancer agents. The reaction of 3-aminocoumarins and α-halo ketones in absolute ethanol gave the corresponding intermediates which then cyclized to the desired pyrrolocoumarins (Scheme 3).

4. Reaction with arylglyoxal monohydrates

In 2017, Yang and research partners[54] reported the synthesis of functionalized hydroxy pyrrolo[2,3-*c*]coumarins using *p*-toluenesulfonic acid (*p*-TSA) in refluxing toluene *via* a one-pot reaction (Scheme 4). Domino cyclization of 3-aminocoumarins with arylglyoxal



Scheme 3. Synthesis 1-methyl/phenylpyrrolocoumarins *via* TFA-catalyzed cyclization.

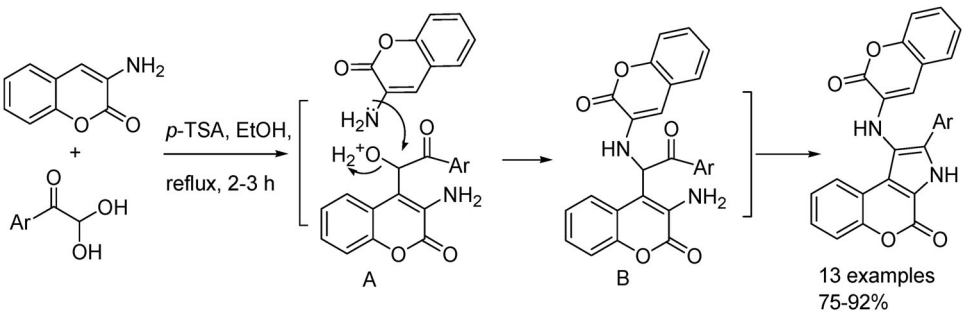


Scheme 4. *p*-TSA-catalyzed one-pot synthesis of functionalized pyrrolocoumarins in toluene.

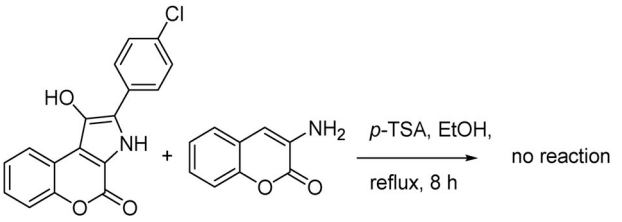
monohydrates gave the desired products in fair to good yields (54-78%). Arylglyoxal monohydrates bearing electron-withdrawing groups as well as electron-donating groups were tolerated, but arylglyoxal monohydrates having *ortho* substituents provided lower yields, presumably due to steric hindrance.

An interesting difference was noted when the reaction was carried out in the presence of ethanol as solvent, instead of toluene, under similar reaction conditions. In this case, the hydroxyl group of intermediate A underwent a nucleophilic attack by the -NH_2 group of another molecule of 3-aminocoumarin to give intermediate B which subsequently cyclized with dehydration to give the final products (Scheme 5). Here, the second molecule of 3-aminocoumarin acted as a selective *N*-nucleophile rather than a *C*-nucleophile. No such product was observed, however, when 3-aminocoumarin was treated with the appropriate hydroxypyrrolo[2,3-*c*]coumarins in ethanol at reflux in the presence of 1.0 equivalent of *p*-TSA for 8 hours (Scheme 6).

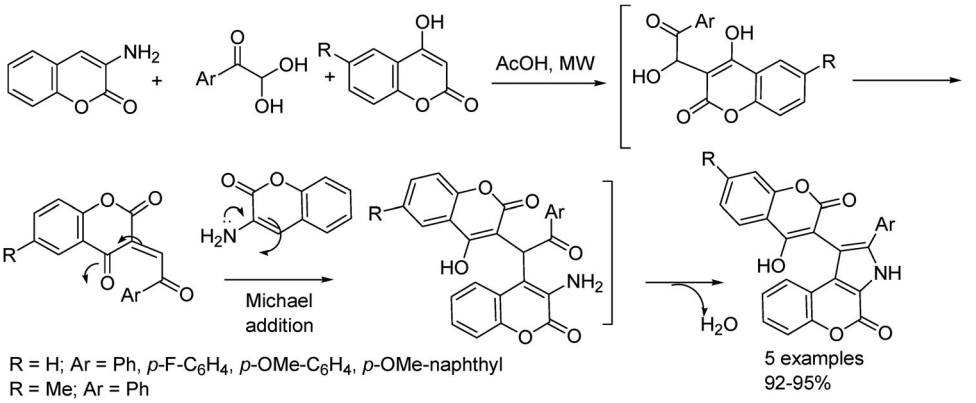
In the same year, Choudhury and research associates[55] developed a catalyst-free, domino reaction for the synthesis of pyrrolo[2,3-*c*]coumarins bearing 4-hydroxycoumarin moieties in the pyrrole part (Scheme 7). The reaction of arylglyoxal, 4-hydroxycoumarin, and 3-aminocoumarin in acetic acid under microwave gave the desired products in excellent yields. The three-component domino reactions involved Michael addition, *N*-cyclization by the elimination of water and subsequent hydrogen shift.



Scheme 5. *p*-TSA-catalyzed one-pot synthesis of pyrrolocoumarin derivatives in ethanol.



Scheme 6. Reaction of 3-aminocoumarin and hydroxy pyrrolocoumarins in presence of *p*-TSA in ethanol.

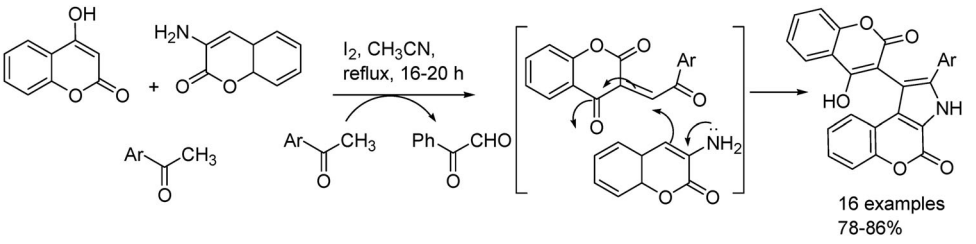


Scheme 7. Microwave-assisted synthesis of pyrrolocoumarins in the presence of acetic acid.

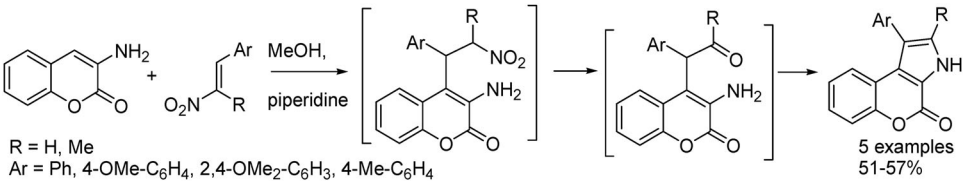
Khan and co-workers[56] reported a one-pot, three-component reaction for the synthesis of 1-(4-hydroxycoumarinyl)-2-arylpyrrolo[2,3-*c*]coumarins from 3-aminocoumarins, arylglyoxals, and 4-hydroxycoumarin in the presence of iodine as a catalyst in refluxing acetonitrile (Scheme 8). There was no need for aqueous work-up or column chromatography. Very good yields of the products help to make this an attractive protocol.

5. By Nef reaction

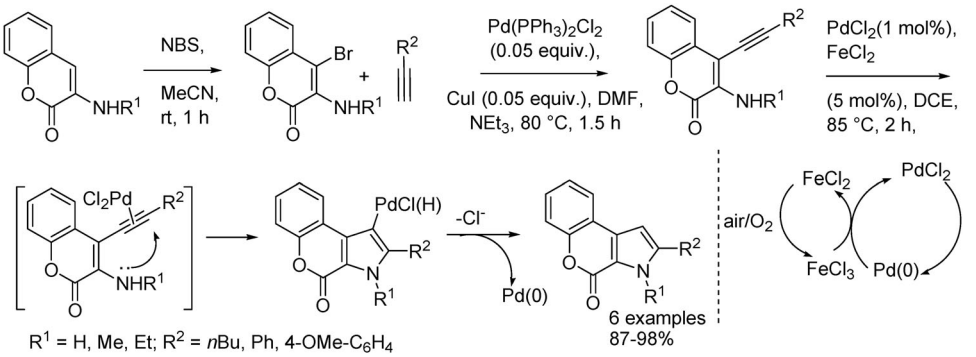
Pandya *et al.*[57] reported several 1-aryl-pyrrolo[2,3-*c*]coumarins could be prepared from 3-aminocoumarin and different 2-aryl-1-nitroethenes in MeOH and piperidine under Nef reaction conditions (Scheme 9).



Scheme 8. Iodine-catalyzed synthesis of functionalized pyrrolocoumarins.



Scheme 9. Synthesis of functionalized pyrrolocoumarins under Nef reaction conditions.

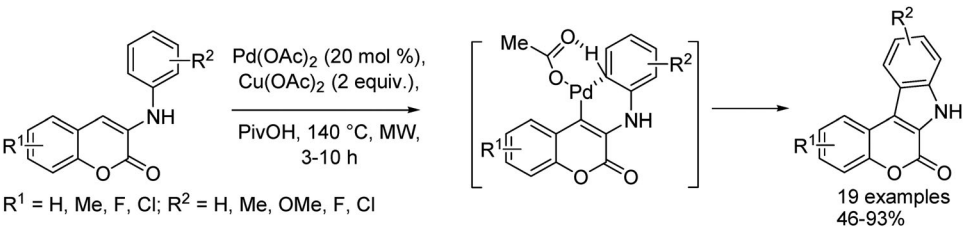


Scheme 10. Pd-Catalyzed synthesis of 2-phenylpyrrolocoumarins *via* 5-endo-dig cyclization.

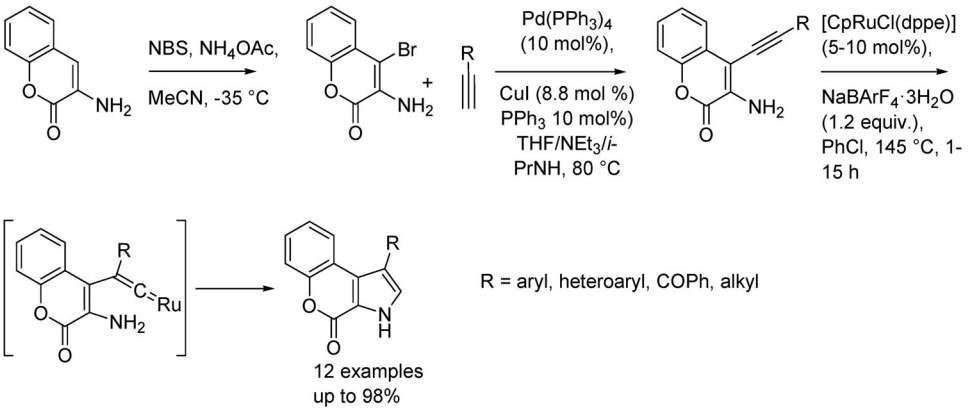
6. By Palladium catalyzed reaction

Majumdar and research partners[58] reported a highly efficient intramolecular hydroamination reaction for the synthesis of pyrrolo[2,3-*c*]coumarins from 4-alkylnyl-3-aminocoumarins in the presence of a $PdCl_2/FeCl_3$ catalytic system *via* 5-endo-dig cyclization (Scheme 10). After bromination with NBS and subsequent Sonogashira cross-coupling with phenylacetylene the corresponding 4-alkylnyl-3-aminocoumarin was achieved. The use of a less expensive catalytic system with low catalyst-loading and the high yields of the products in the cyclization are attractions of the protocol.

Oxidative intramolecular cyclization is a special type of electrophilic aromatic substitution for σ-arylpalladium(II) complexes involving direct palladation at the *ortho*-position of one arene with another arene. Chen and co-workers[59] developed the microwave-assisted palladium(II)-catalyzed and base-free cross dehydrogenative coupling (CDC) reaction for the synthesis of indolo[2,3-*c*]coumarins with copper(II)acetate as an oxidant in PivOH as a solvent at 140 °C for 3-10 hours (46-93%) (Scheme 11).



Scheme 11. Microwave-assisted palladium(II)-catalyzed synthesis of indolocoumarins.

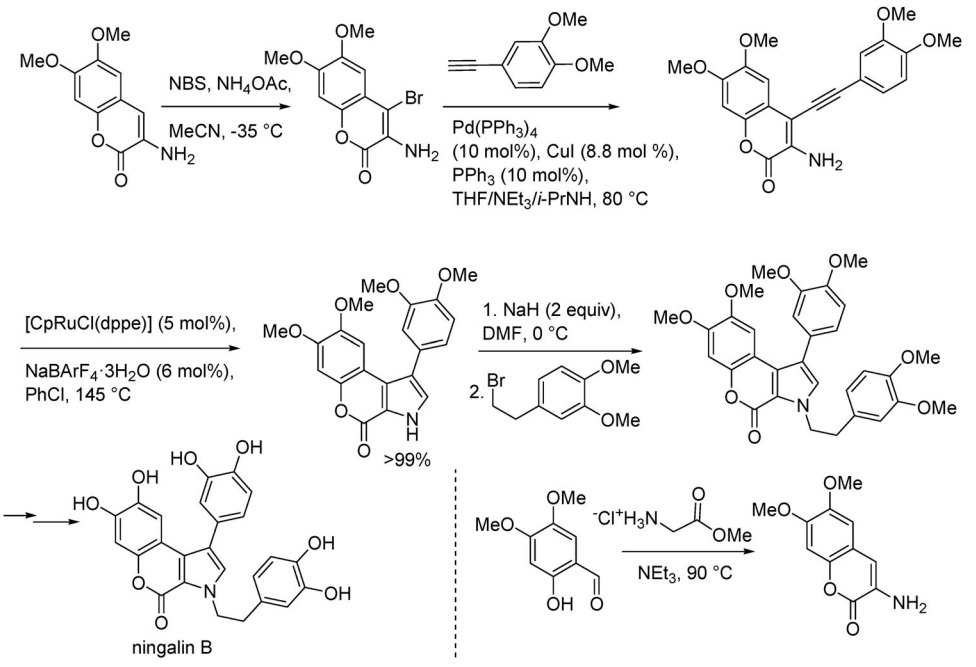


Scheme 12. Ruthenium-catalyzed cyclization for the synthesis of pyrrolocoumarins.

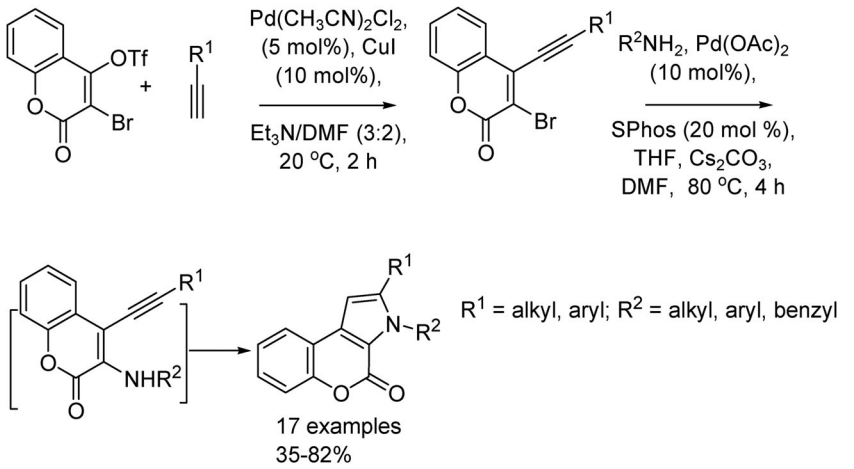
Mutoh and colleagues[60] developed ruthenium-catalyzed cycloisomerization of alkynylanilides to give 1-phenylpyrrolo[2,3-*c*]coumarins in in high yields. The reaction occcurred *via* the disubstituted vinylidene ruthenium complex that was formed by 1,2-carbon migration (Scheme 12). The authors[61] prepared diversely substituted pyrrolo[2,3-*c*]coumarins from 3-amino-4-alkynyl-coumarins in chlorobenzene at 145 °C for 1-15 hours. The amount of catalyst loading and requirement of times depend on the electronic and steric factors of the alkynyl substituent R as well as the coumarin. The key precursor 3-amino-4-alkynylcoumarins were obtained from 3-aminocoumarin by bromination with NBS and subsequent palladium(0) catalyzed Sonogashira cross-coupling with aryl acetylenes.

The authors explored the scope of this method and applied it to the total synthesis of ningalin B, key steps of which are shown in Scheme 13. When 3,4-dimethoxy salicylaldehyde was reacted with methyl aminoacetate hydrochloride in the presence of triethylamine at 90 °C, 6,7-dimethoxy-3-aminocoumarin was achieved in 43% yield. Then bromination followed by palladium(0)-catalyzed alkynylation (Sonogashira reaction) afforded the corresponding 3-amino-4-alkynyl-coumarin. Finally, the latter, on treatment with 5 mol% of the ruthenium catalyst, provided ningalin B scaffolds in 99% yield.

Ngo and research partners[62] developed a convenient approach for the synthesis of a series of pyrrolo[2,3-*c*]coumarins by Pd-catalyzed domino C-N coupling/hydroamination reactions (Scheme 14). The key step for the pyrrole ring construction of the reactions proceeded through the 4-alkynyl-3-aminocoumarin intermediate. The palladium-catalyzed chemoselective Sonogashira cross coupling reaction of 3-bromo-4-(trifluoromethane-sulfonyloxy)coumarin with arylalkynes in the presence of $Pd(CH_3CN)_3Cl_2$/CuI



Scheme 13. Ruthenium-catalyzed cyclization for the total synthesis of ningalin B.



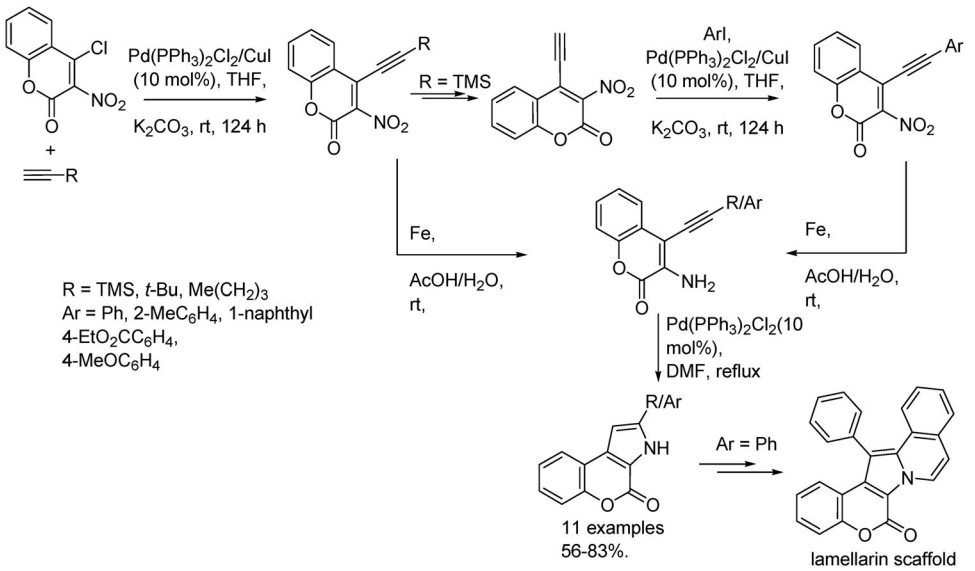
Scheme 14. Palladium-catalyzed multi-step synthesis of pyrrolocoumarins.

and triethylamine in DMF at room temperature afforded 4-alkynated-3-bromocoumarins. The latter, on treatment with alkyl/arylamines in the presence of Pd(0) catalyst, gave the final pyrrolocoumarins.

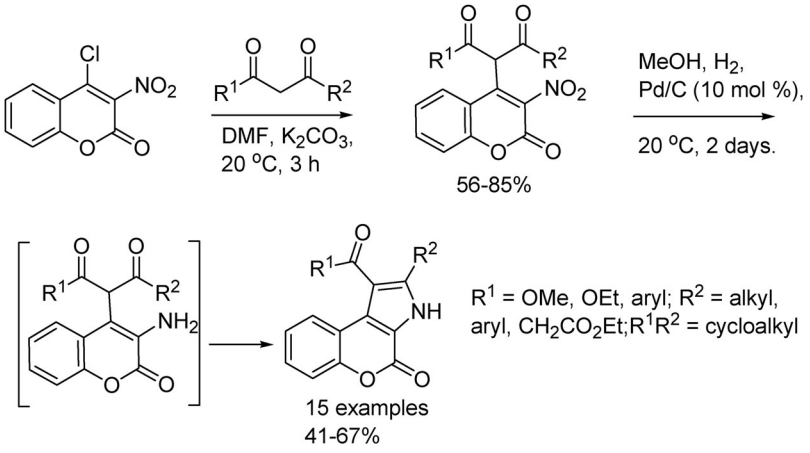
II. From 3-nitrocoumarin derivatives by the formation of pyrrole rings

1. via 3-aminocoumarin intermediates

Chen and co-workers[63] reported the multi-step synthesis of 2-substituted pyrrolo[2,3-*c*]coumarins by palladium-catalyzed C-C coupling/cyclization and reduction.



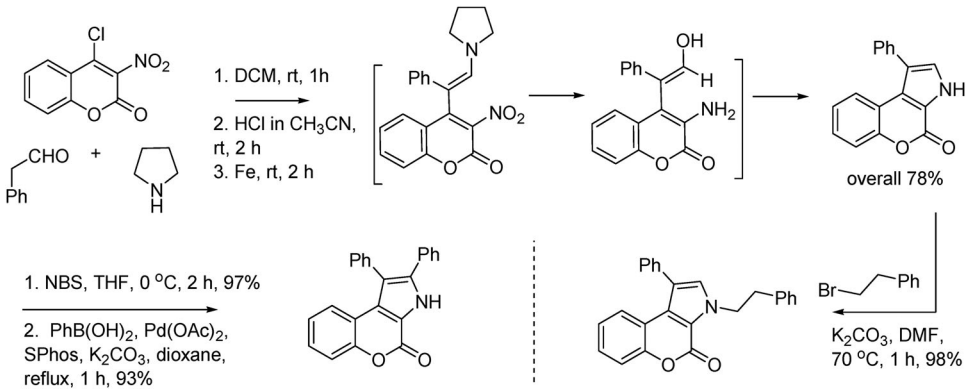
Scheme 15. Palladium-catalyzed multi-step synthesis of pyrrolocoumarins by Sonogashira coupling followed by cyclization.



Scheme 16. Synthesis of 1,2-disubstituted pyrrolocoumarins *via* base-mediated substitution, reduction and subsequent cyclization.

Cyclization of 4-alkyl/arylacetylenyl-3-aminocoumarins with $Pd(PPh_3)_2Cl_2$ in refluxing DMF gave the observed products in 56-83% yields (Scheme 15). The key 4-alkyl/arylacetylenyl-3-aminocoumarins could be prepared by reduction with iron powder from the corresponding nitro compounds. In setting the stage for the process, the reaction of 4-chloro-3-nitrocoumarins and acetylene derivatives gave the desired 4-alkyl/arylacetylenyl-3-aminocoumarins by palladium-catalyzed Sonogashira cross-coupling.

Iaroshenko *et al.*[64] synthesized 1,2-disubstituted pyrrolo[2,3-*c*]coumarins *via* base-mediated substitution and subsequent cyclization of 1,3-dicarbonyl compounds and 4-



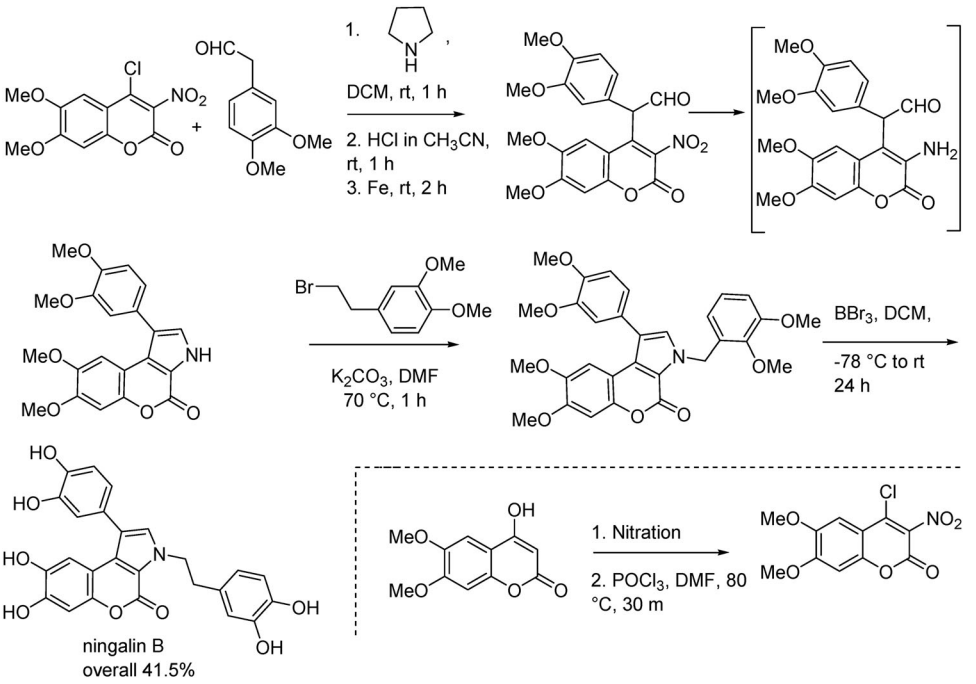
Scheme 17. Multi-component reaction for the synthesis of pyrrolocoumarin derivatives.

chloro-3-nitrocoumarin (Scheme 16). The reaction of 4-chloro-3-nitrocoumarin with 1,3-dicarbonyl compounds in the presence of K_2CO_3 in DMF solvent at 20 °C afforded the substitution products, namely 4-substituted-3-nitrocoumarins (56-85%). The hydrogenation of the condensation products in the presence of Pd/C (10 mol%) provided 4-substituted-3-aminocoumarin intermediates which then cyclized by the elimination of water to give the desired pyrrolocoumarins in 41-67% yields.

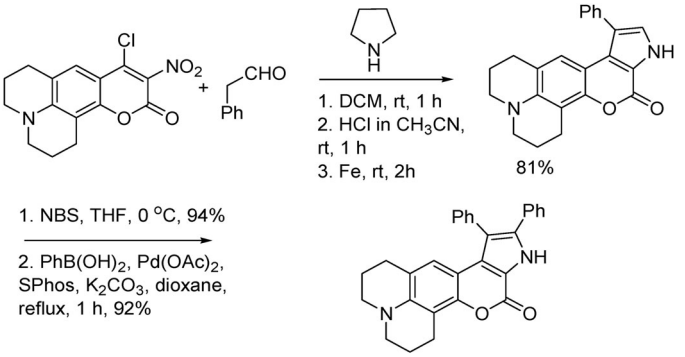
Wu and research associates[65] developed a one-pot synthesis of 1-phenylpyrrolo[2,3-*c*]coumarin, an electrochromic material, in 78% yield (Scheme 17). The reaction of 4-chloro-3-nitrocoumarin and 2-phenylacetaldehyde with pyrrolidine in methylene chloride at room temperature and then hydrolysis by HCl in acetonitrile gave the intermediate 4-substituted 3-aminocoumarin. Reduction with iron powder at room temperature and subsequent cyclization and aromatization furnished the target compound, without isolation of any intermediates. After alkylation of the 1-phenylpyrrolo[2,3-*c*]coumarin with (2-bromoethyl)benzene in base in DMF at 70 °C for one hour, the ningalin B skeleton was formed. The pyrrolocoumarin was additionally functionalized with phenylboronic acid *via* Suzuki coupling in the presence of $Pd(OAc)_2$, SPhos, and K_2CO_3 in dioxane after bromination with NBS in THF at 0 °C. This series of reactions was further extended to the total synthesis of the natural product ningalin B with an overall yield of 42% (Scheme 18) and the structurally unique pentacyclic pyrro[2,3-*c*]coumarin (Scheme 19) in 47% yield.

2. Nitro group acts as a leaving group

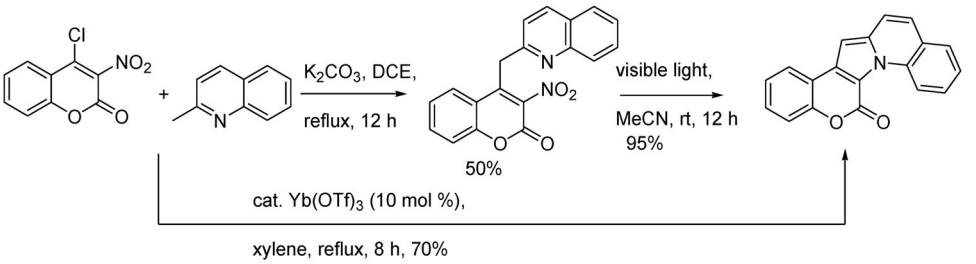
Yang and colleagues[66] reported the visible-light-mediated two-step synthesis of a novel pentacyclic fused pyrrolo[2,3-*c*]coumarin derivative (Scheme 20). In the first step 4-chloro-3-nitrocoumarin and 2-methylquinoline in 1,2-dichloroethane with base afforded 3-nitro-4-(quinolin-2-ylmethyl)coumarin in 50% yield. In the second step, the 3-nitro-4-(quinolin-2-ylmethyl)coumarin underwent intramolecular cyclization at room temperature in visible light to afford the pentacycle fused pyrrolo[2,3-*c*]coumarin in 95% yield. The synthesis of the pentacyclic product was also achieved in one step by the reaction of 4-chloro-3-nitrocoumarin and 2-methylquinoline in



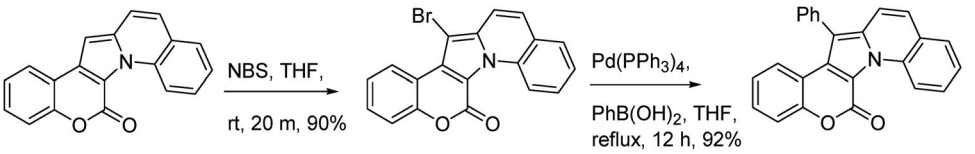
Scheme 18. Total synthesis of ningalin B from 6,7-dimethoxy 4-chloro-3-nitrocoumarin.



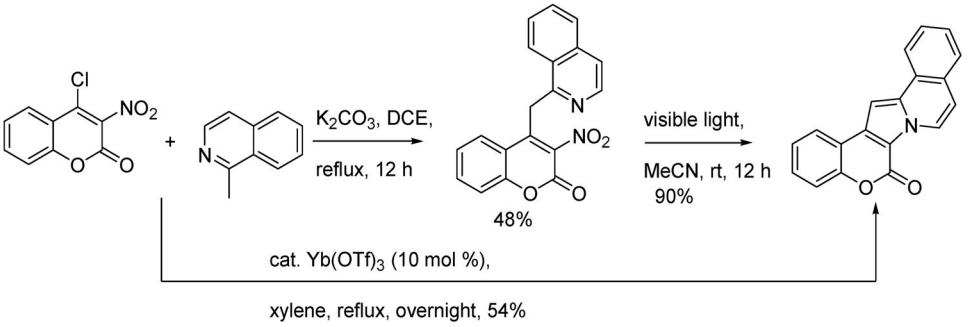
Scheme 19. Synthesis pentacyclic pyrrolocxoumarin 4-chloro-3-nitrocoumarin derivative.



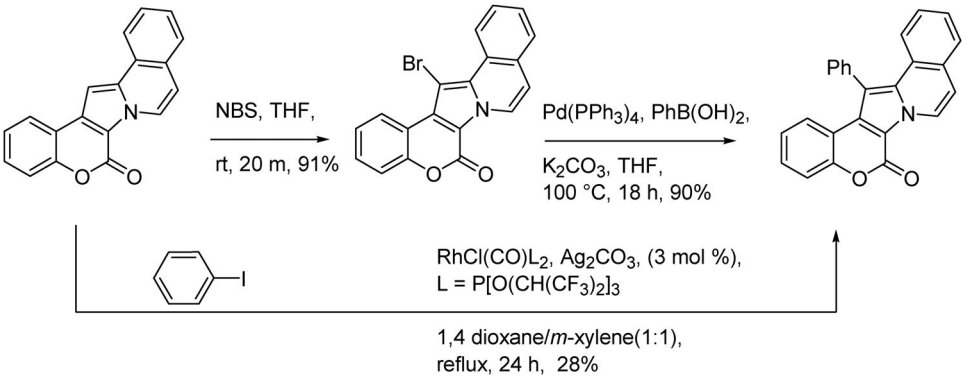
Scheme 20. Visible-light-mediated or $Yb(OTf)_3$- catalyzed synthesis of pentacyclic fused pyrrolocoumarin.



Scheme 21. Synthesis of phenyl substituted pentacyclic fused pyrrolocoumarin *via* Suzuki coupling reaction.



Scheme 22. Visible-light-mediated or $Yb(OTf)_3$-catalyzed synthesis of pentacyclic fused pyrrolocoumarin backbone of natural product lamellarin.

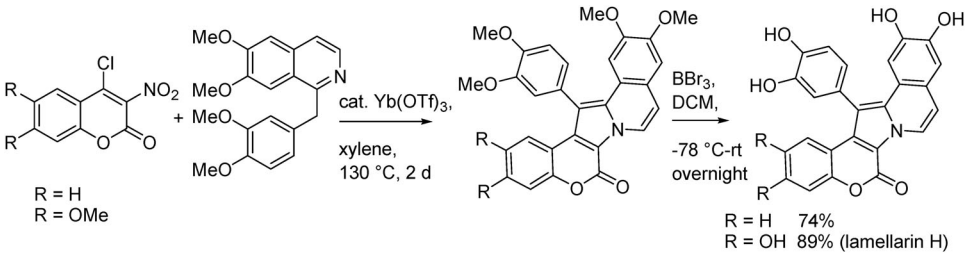


Scheme 23. Pd- or Rh-catalyzed synthesis of phenyl substituted pentacyclic fused pyrrolocoumarin.

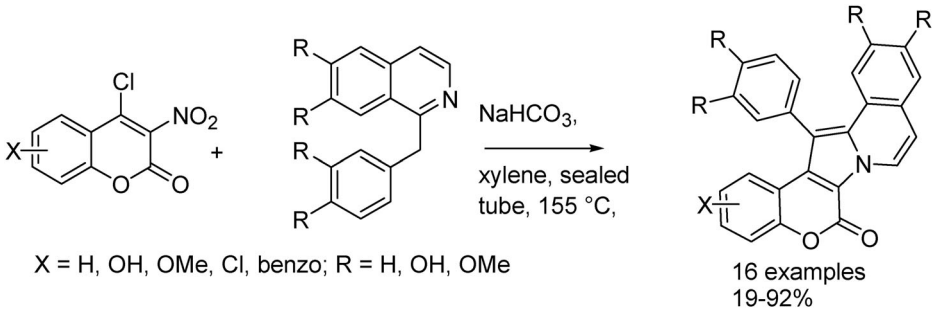
xylene at reflux in the presence of 10 mol% $Yb(OTf)_3$ catalyst, and this path gave a somewhat higher over-all yield.

Bromination of the synthesized pentacycle fused pyrrolo[2,3-*c*]coumarin with NBS in THF at room temperature and subsequent Pd(0)-catalyzed Suzuki coupling gave the phenyl substituted derivative (92%) (Scheme 21).

The authors further reported the synthesis of the pentacyclic pyrrolocoumarin backbone of lamellarin under similar reactions conditions, starting from 4-chloro-3-nitrocoumarin and 1-methylisoquinoline instead of 2-methylquinoline (Scheme 22). Phenylation could be achieved by bromination/Suzuki reaction or by direct Rh-catalyzed coupling with iodobenzene (Scheme 23).



Scheme 24. $Yb(OTf)_3$-Catalyzed synthesis of lamellarin H and its analog.



Scheme 25. Synthesis of lamellarin derivative *via* base-promoted Grob coupling.

The methodology was further exploited in the construction of other lamellarins. Coupling of 4-chloro-3-nitrocoumarin derivatives with commercially available papaverine in the presence of $Yb(OTf)_3$ in xylene furnished intermediate lamellarins which were subsequently converted to the natural product lamellarin H (R = OH).

Yang and coworkers[67] reported an efficient construction of phenyl-substituted pentacyclic pyrolo[2,3-*c*]coumarin derivatives *via* base-promoted Grob coupling of 3-nitrocoumarin and papaverine (Scheme 25).

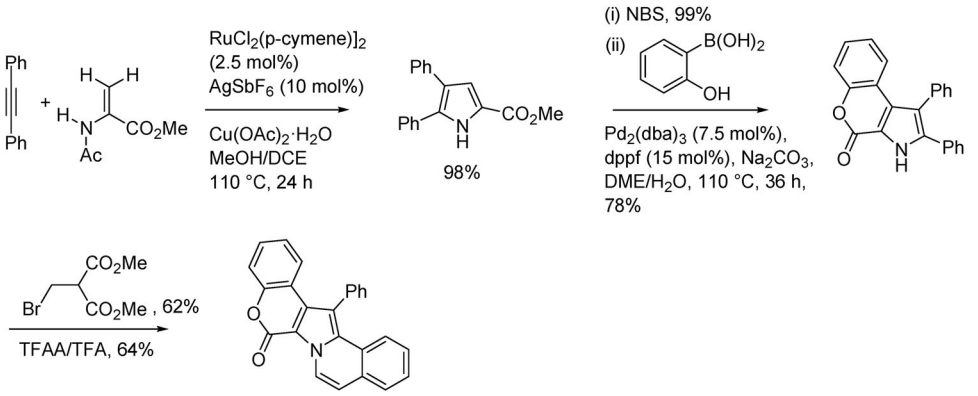
III. By the creation of both rings

1. via oxidative alkyne annulation and Suzuki coupling

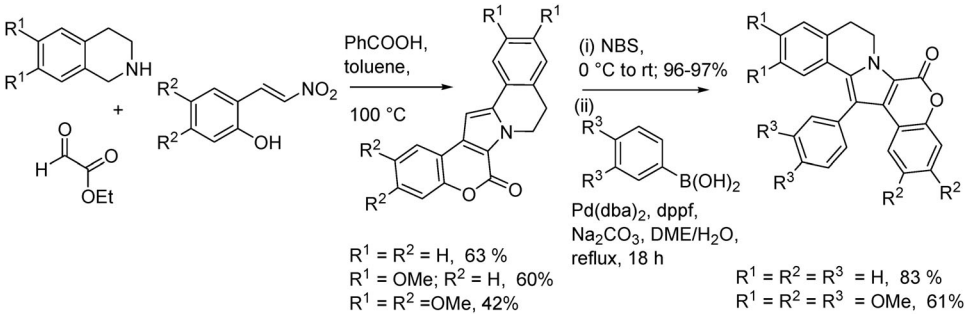
Ackermann and co-workers[68] reported formation of the lammelarin scaffold through the construction of both pyrrole and coumarin rings (Scheme 26). The pyrrole ring was synthesyzed *via* oxidative alkyne annulation using ruthenium(II)-catalyzed C–H/N–H activation. Bromination followed by palladium-catalyzed Suzuki coupling of the pyrrole furnished the corresponding diarylated pyrolo[2,3-*c*]coumarin. This could be transformed into the desired lamellarin scaffold *via* the Pomeranz-Fritsch approach.

2. From isoquinolines

Wu and research partners[69] established an acid-mediated one-pot reaction for the efficient synthesis of the lamellarin core from (*E*)-(2-nitrovinyl)benzenes, ethyl



Scheme 26. Synthesis of lammelarin scaffold by the construction of both rings.



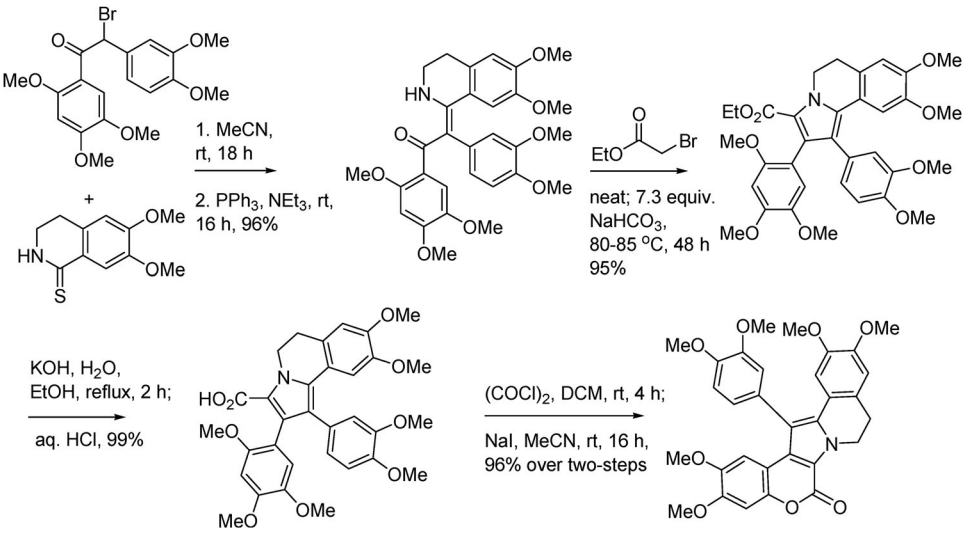
Scheme 27. Synthesis of lamellarin core by [3 + 2] cycloaddition.

glyoxalate and tetrahydroisoquinoline (Scheme 27). [3 + 2] Cycloaddition of (*E*)-(2-nitrovinyl)benzenes, and azomethine ylides generated *in situ* from ethyl glyoxalate and tetrahydroisoquinoline, afforded pentacyclic pyrrolocoumarins in the presence of benzoic acid in toluene at 100 °C. The pentacyclic pyrrolocoumarins converted to lamellarin structures after bromination and subsequent Suzuki-Miyaura cross-coupling reactions.

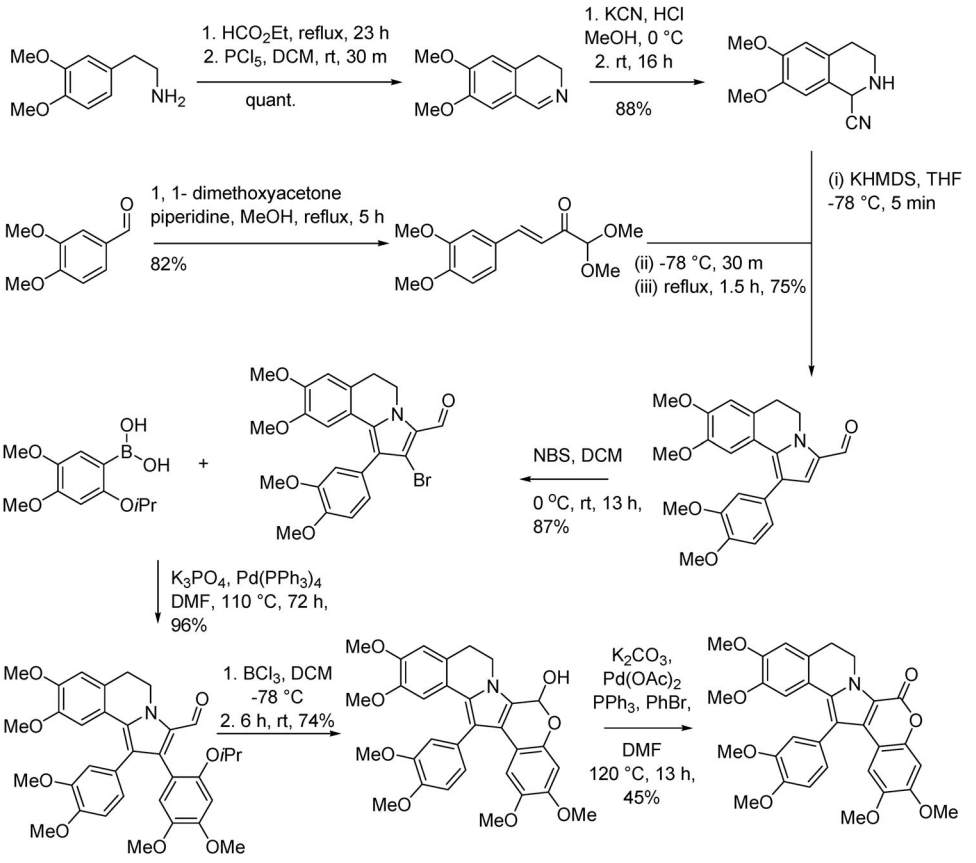
Michael and research associates[70] established gram-scale syntheses of the lamellarin derivatative from dihydroisoquinolinethione and α-bromoketones by the construction of pyrrole and coumarin rings in the highest overall yields reported to date (Scheme 28). The central pyrrole core was created in a [4 + 1] condensation between ethyl bromoacetate and an enaminone skeleton. Formation of a chromenyl lactone ring took place by a demethylative cyclization between a methoxylated aromatic system and a nearby carboxylic acid situated on the pyrrole ring. This advantage avoids the need for additional protection and deprotection steps.

3. From arylethylamine

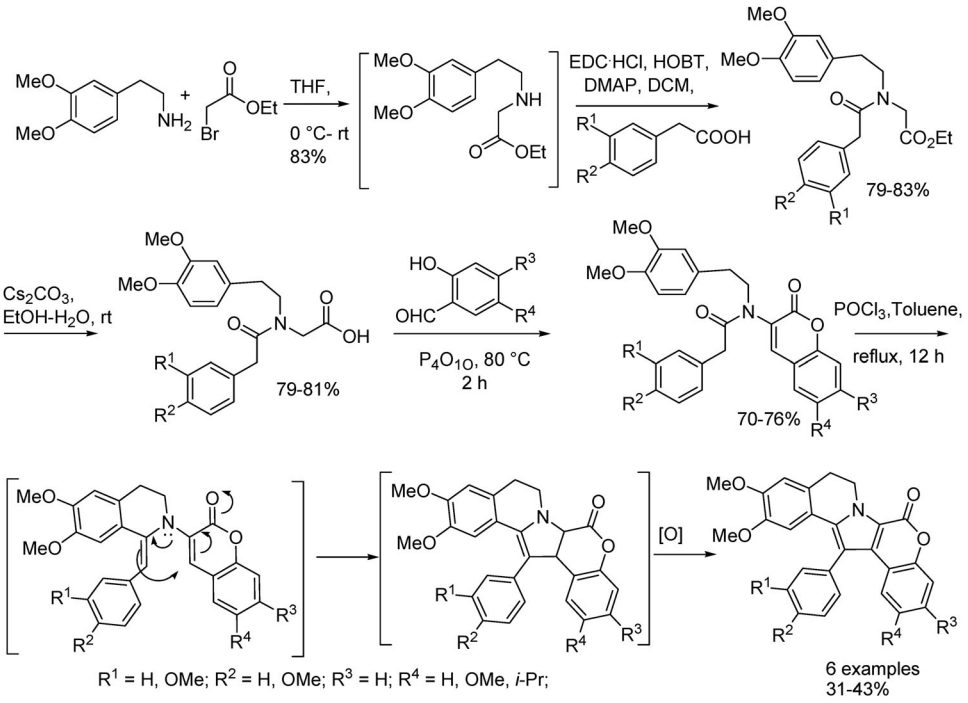
Opatz and colleagues[71] synthesized the representative lamellarin derivative (Scheme 29) based on a von Miller-Plöchl cyclocondensation of a deprotonated α-amino nitrile with



Scheme 28. Gram-scale syntheses of lamellarin derivative from dihydroisoquinolinethione and α-bromoketones.



Scheme 29. Total synthesis of lamellarin derivative by von Miller-Plöchl cyclocondensation.



Scheme 30. Syntheses of lamellarins analogs by Bischler-Napieralski, Michael and subsequent oxidation reactions.

an α,β-unsaturated ketone as the key step, then Suzuki-Miyaura cross-coupling, subsequent lactone formation and oxidation.

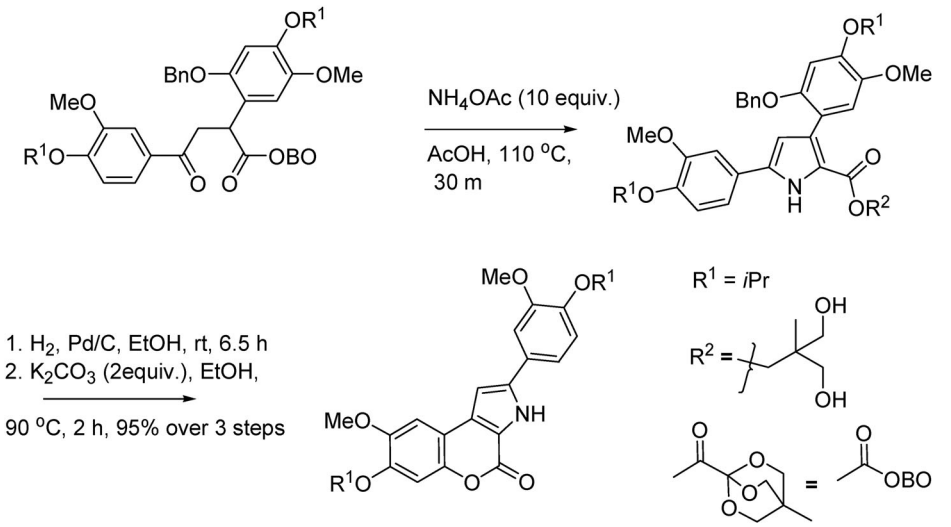
Mandrekar and co-workers[72] developed a metal-free convergent route for the synthesis of pentacyclic pyrrolo[2,3-*c*]coumarins as lamellarin analogs from 3-amidocoumarins *via* domino reactions. This entailed Bischler-Napieralski, Michael and subsequent oxidation reactions (Scheme 30). The key precursor 3-amidocoumarins could be synthesized from substituted salicylaldehydes.

4. From 1,4-dicarbonyl derivatives

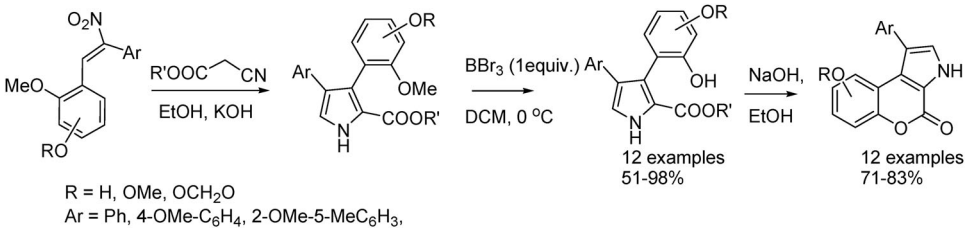
Donohoe *et al.*[73] developed an efficient high yielding method for the synthesis of pyrolo[2,3-*c*]coumarin from 1,4-dicarbonyl derivatives by the construction of pyrrole and coumarin rings *via* Paal-Knorr synthesis (Scheme 31).

5. From nitrostilbenes and ethyl isocyanoacetate

Samet and research partners[74] reported a metal-free approach for the synthesis of pyrolo[2,3-*c*]coumarins by the construction of both pyrrole and coumarin rings. In the first step, 3,4-diarylpyrrole-2-carboxylates were synthesized from nitrostilbenes with ethyl isocyanoacetate based on the Barton-Zard reaction. In the next steps, the coumarin ring was prepared by the selective O-demethylation of the *ortho*-methoxy group followed by base-induced lactonization (Scheme 32).



Scheme 31. Synthesis of pyrolocoumarin by Paal-Knorr synthesis.



Scheme 32. Metal-free synthesis of pyrolocoumarins based on Barton-Zard reaction.

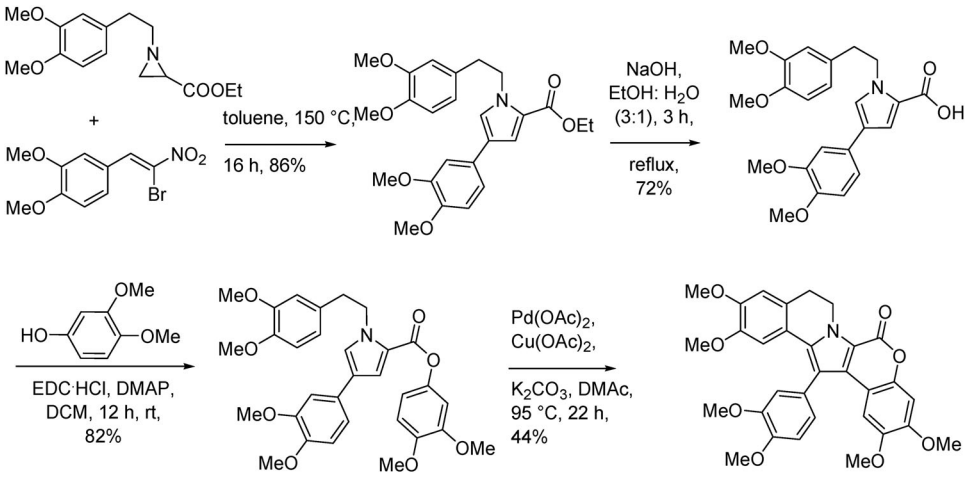
6. via a one-pot [3 + 2] cycloaddition and Pd(II)-catalyzed C-H activation

Khan *et al.*[75,76] reported the total synthesis of lamellarin derivative by the construction of pyrrole ring *via* a one-pot [3 + 2] cycloaddition as well as coumarin ring creation using Pd(II)-catalyzed C-H activation in the key steps (Scheme 33).

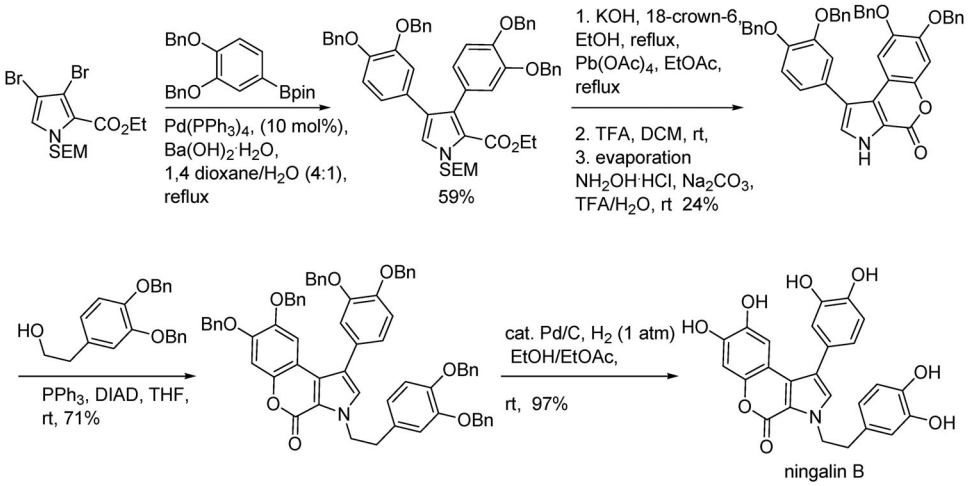
IV. By the formation of the coumarin ring

Synthesis of ningalin B starting from β,β′-dibromopyrrole

Okano and co-workers[77] established a method for the synthesis of ningalin B starting from *β,β*'-dibromopyrrole (Scheme 34). A one-pot double Suzuki-Miyaura coupling of *β,β*'-dibromopyrrole with the appropriate arylboronate ester afforded the corresponding diarylated pyrrole derivative (59%). After hydrolysis of the ester and $Pb(OAc)_4$-mediated lactone formation, removal of the trimethylsilylethoxymethyl (SEM) group was carried out to afford the pyrolo[2,3-*c*]coumarin in 24% yield over three steps from the diarylated pyrrole. Ningalin B was obtained by *N*-alkylation with phenylethyl alcohol under Mitsunobu conditions, and subsequent hydrogenolysis of the six benzyl ethers.



Scheme 33. Multi-step synthesis of lamellarins analogs using one-pot [3 + 2] cycloaddition and Pd(II)-catalyzed C-H activation in the key steps.



Scheme 34. Multi-step synthesis of ningalin B starting from β,β'-dibromopyrrole.

Conclusions

Pyrrolo[2,3-*c*]coumarins are of interest as natural products with outstanding biological activities. This has generated considerable activity in natural product synthesis and in the synthesis of analogs, making necessary the development of appropriate preparative methods. In this article, we have reviewed the significant references on the preparation of pyrrolo[2,3-*c*]coumarins and their derivatives from suitable precursors, in the main published during the period 2000 to 2020. The compounds are noteworthy for their interesting roles as natural products and as pharmacophores. We hope that this survey of the synthetic literature will assist organic chemists in further development of methods needed for the preparation of these challenging compounds and will promote more research into their useful activities.

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