Synthesis of Pyrrolo[2,3-*c*] coumarin Derivatives, A Review

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Abstract: **This paper provides an extensive review of a wide range of synthesis of pyrrolo[2,3-c]coumarin derivatives documented over the past two decades. Pyrrolo[2,3-c]coumarins synthesized in the literature involve constructing the pyrrole coumarin ring through classical reaction protocols, one-pot reaction, and catalyst-free protocols starting from appropriate precursors.**

Keywords: Fisher indole reaction, amino-Claisen rearrangement, arylglyoxal monohydrate, aminocoumarin, arylglyoxal, Nef reaction.

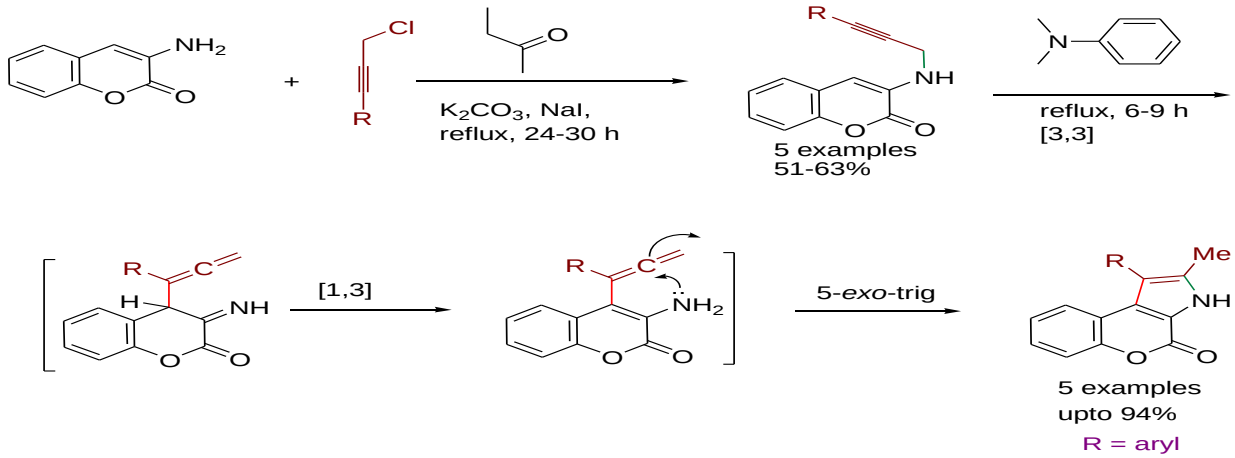
1. INTRODUCTION

Natural and synthetic coumarins and their derivatives are significant heterocycles due to their diverse biological activities. [1-9] Pyrrolo[2,3-c]c oumarin scaffolds, present in natural products have been extensively studied[10-20]. Researchers have conducted detailed syntheses of marine alkaloid lamellarin type compounds[17]. These natural products are appreciated for their structural diversity and biological activities, including multidrug-resistance reversing, anti-cancer and HIV-1 integrase inhibitory properties[21-28]. Additionally, purely synthetic pyrrolo[2,3-c]coumarins demonstrate activities such as Topoisomerase I inhibition, DYRK1A inhibition, anti-retroviral effects[29-38], and are used as neuroimaging agents. This review focuses on the synthesis of pyrrolo[2,3-c]coumarins and their derivatives from suitable precursors.

2. PREPARATION OF PYRROLO[2,3-C]COUMARIN DERIVATIVES

2.1. *Through amino-Claisen rearrangement*

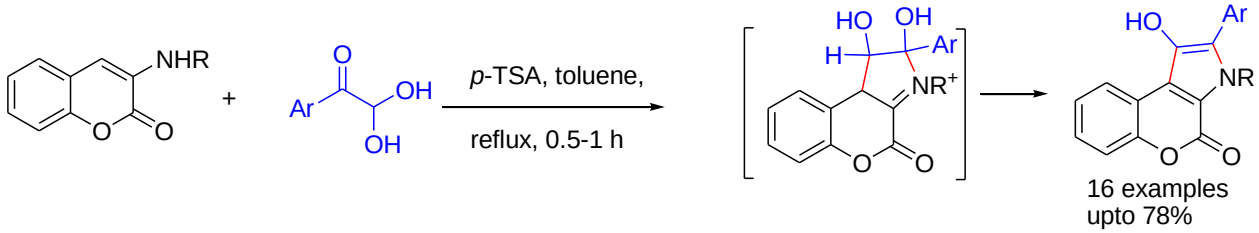
In 2008, Majumdar51[39] and colleagues developed a process to synthesize pyrrolo[2,3-c]coumarins with high regioselectivity and excellent yields using the amino-Claisen rearrangement. This transformation involved refluxing 3-N-propargylaminocoumarin in DMF, as depicted in Scheme 1. The 3-N-propargylaminocoumarins were initially prepared by reacting the 3-aminocoumarin with propargyl chloride in methyl ethyl ketone at reflux conditions with sodium iodide and potassium carbonate. The reaction proceeded via an initial [3,3]-sigmatropic rearrangement of the propargylamine moiety within the substrate, with the formation of an allenic intermediate. Subsequent 5-exo-trig cyclization of this intermediate led to the formation of the desired pyrrolo[2,3-c]coumarin products.



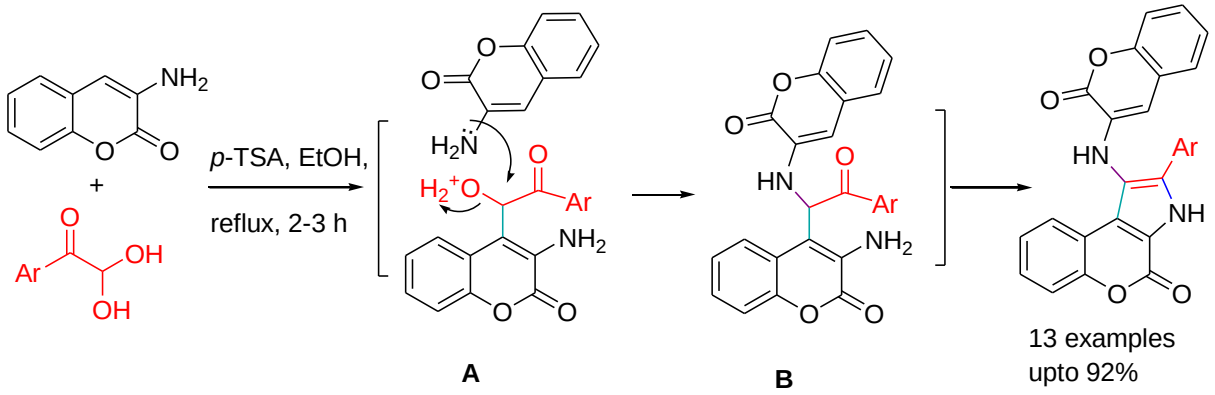
Scheme 1. Amino-Claisen rearrangement for the synthesis of pyrrolocoumarins.

2.2. *By reaction with arylglyoxal monohydrates*

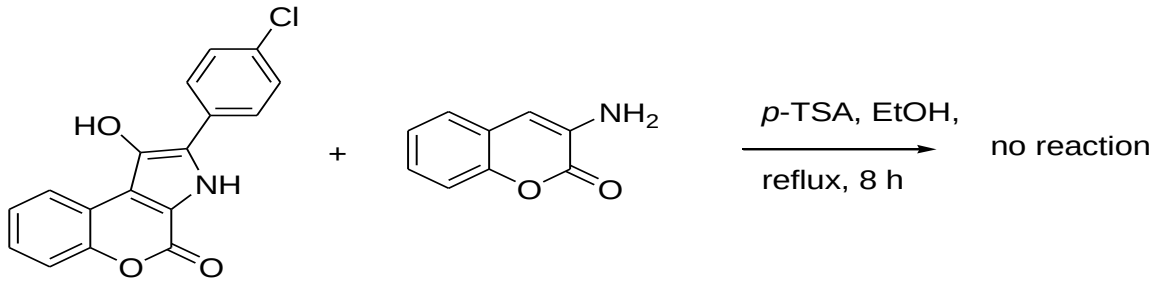
In 2017, Yang and colleagues[40] reported a method for synthesizing functionalized hydroxy pyrrolo[2,3-c]coumarins by the use of p-toluenesulfonic acid (p-TSA) in refluxing toluene through a one-pot reaction (Scheme 2). The process involved domino cyclization of 3-aminocoumarins with arylglyoxal monohydrates, yielding the desired products in moderate to good yields (54-78%). Arylglyoxal monohydrates having both electron-withdrawing and electron-donating groups were compatible with the reaction conditions. Although, arylglyoxal monohydrates substituted with ortho groups provided lower yields, likely due to steric hindrance. A notable distinction found to be seen when the reaction was conducted using ethanol as the solvent instead of toluene, under comparable reaction conditions. Here, the hydroxyl group of intermediate A underwent nucleophilic attack by the -NH2 group of another molecule of 3-aminocoumarin to form intermediate B, which subsequently cyclized with dehydration to yield the final products (Scheme 3). Interestingly, in this scenario, the second molecule of 3-aminocoumarin acted as a selective N-nucleophile rather than a C-nucleophile. However, when 3-aminocoumarin was reacted 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, no such product was observed (Scheme 4)."



Scheme 2. *p*-TSA-catalyzed one-pot synthesis of functionalized pyrrolocoumarins in toluene.

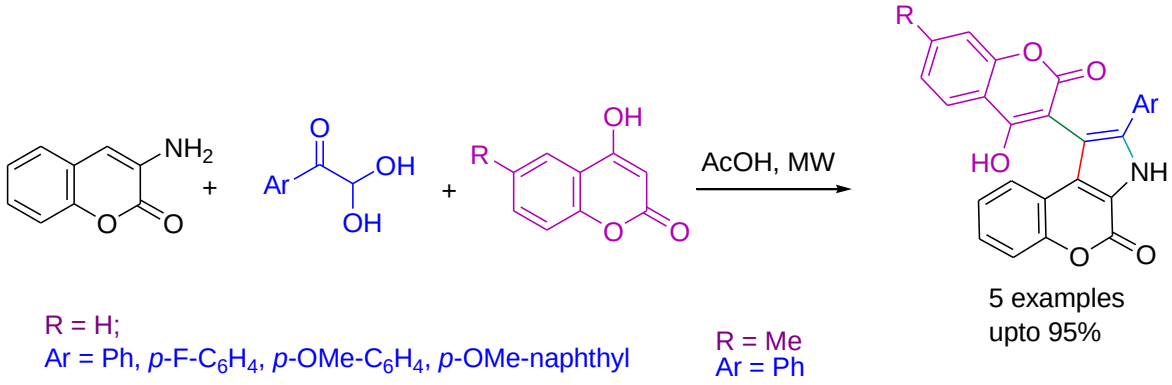


Scheme 3. *p*-TSA-catalyzed one-pot synthesis of pyrrolocoumarin derivatives in ethanol.



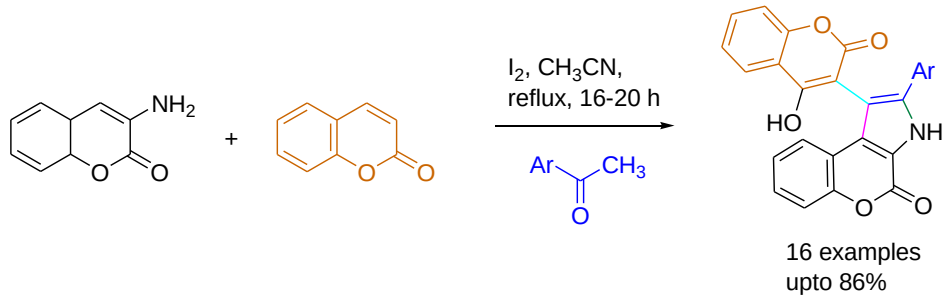
Scheme 4. Reaction of hydroxy pyrrolocoumarins and 3-aminocoumarin in presence of *p*-TSA in ethanol.

In 1978, Choudhury and colleagues[41] introduced a catalyst-free domino reaction in order to synthesize pyrrolo[2,3-c]coumarins incorporating 4-hydroxycoumarin groups in the pyrrole segment (Scheme 5). The reaction was carriedout in acetic acid medium under microwave irradiation using arylglyoxal, 4-hydroxycoumarin and 3-aminocoumarin. This three-component domino reaction included Michael addition, N-cyclization via water elimination, and subsequent hydrogen shift mechanisms.



Scheme 5. Microwave-assisted synthesis of pyrrolocoumarins in presence of acetic acid.

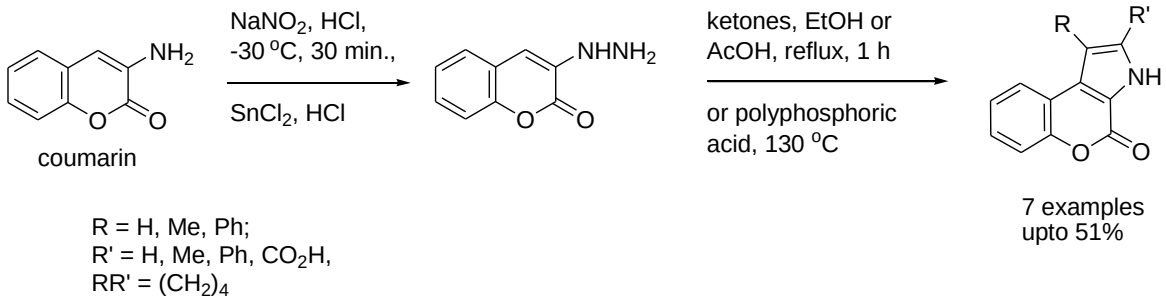
Khan and colleagues [42] described a one-pot, three-component reaction to synthesize 1-(4-hydroxycoumarinyl)-2-arylpyrrolo[2,3-c]coumarins from 3-aminocoumarins, arylglyoxals, and 4-hydroxycoumarin. This transformation took place efficiently in refluxing acetonitrile with iodine serving as a catalyst (Scheme 6). The protocol obviated the need for aqueous work-up or column chromatography, yielding the products in high yields, thereby highlighting its practical appeal.



Scheme 6. Iodine-catalyzed synthesis of functionalized pyrrolocoumarins.

2.3. *Utilizing the Fisher indole synthesis*

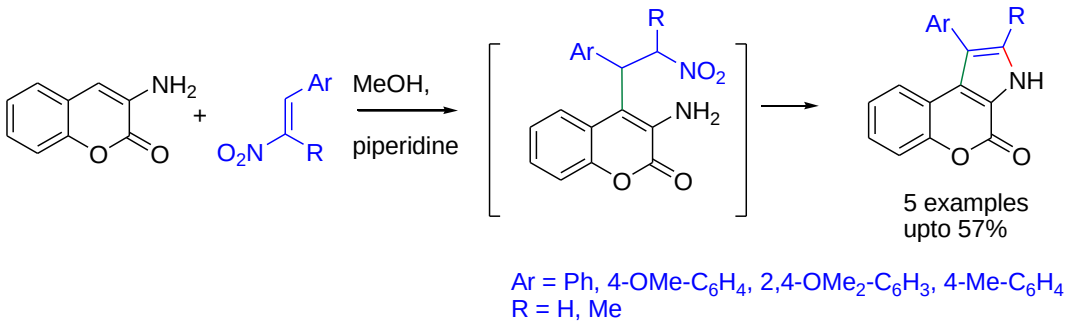
In the year 1978, Khan et al.[43] reported the Fisher indole synthesis of 3-aminocoumarin to construct pyrrolocoumarins (Scheme 7). The process involved diazotization of 3-aminocoumarin followed by reduction to yield coumarin-3-yl-hydrazine. Thereafter this intermediate underwent the Fisher indole reaction in the presence of acid, reacting directly with various carbonyl compounds to produce pyrrolo[2,3-c]coumarin derivatives, without the requirement for isolation.



Scheme 7. Synthesis of pyrrolocoumarins by Fisher indole synthesis.

2.4. *Using Nef reaction*

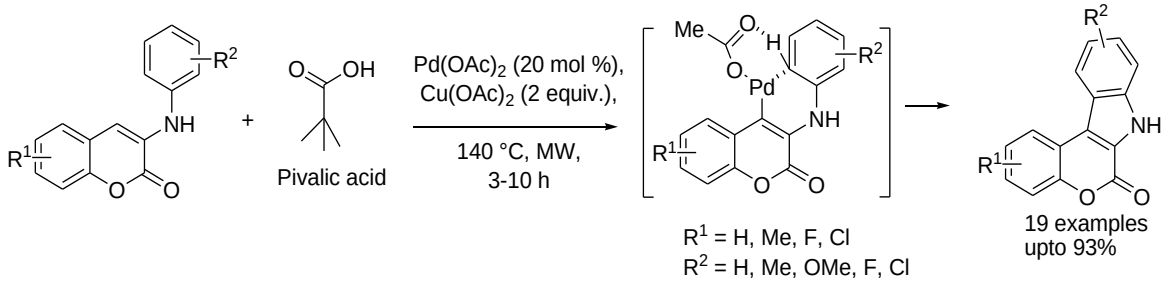
Pandya and colleagues [44] demonstrated the preparation of various 1-aryl-pyrrolo[2,3-c]coumarins using 3-aminocoumarin and different 2-aryl-1-nitroethenes in methanol and piperidine under Nef reaction conditions (Scheme 8).



Scheme 8. Synthesis of functionalized pyrrolocoumarins under Nef reaction conditions.

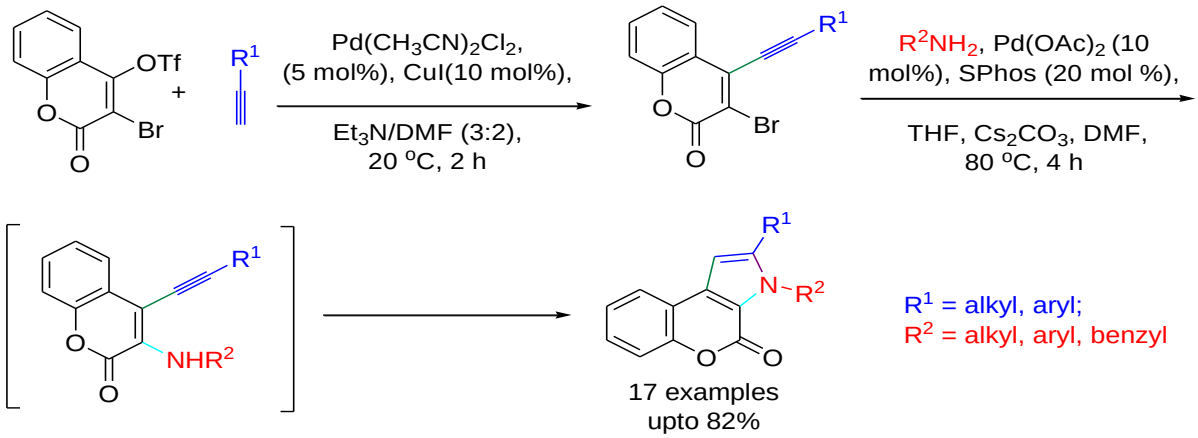
2.5. *By Palladium catalyzed reaction*

Cheng and colleagues [45] introduced a microwave-assisted palladium(II)-catalyzed, base-free cross dehydrogenative coupling (CDC) reaction for synthesizing indolo[2,3-c]coumarins. This process employed PivOH as a solvent and copper(II) acetate as an oxidant, operating at 140°C for 3-10 hours, yielding products in the range of 46-93% (Scheme 9).



Scheme 9. Microwave-assisted palladium(II)-catalyzed synthesis of indolocoumarins.

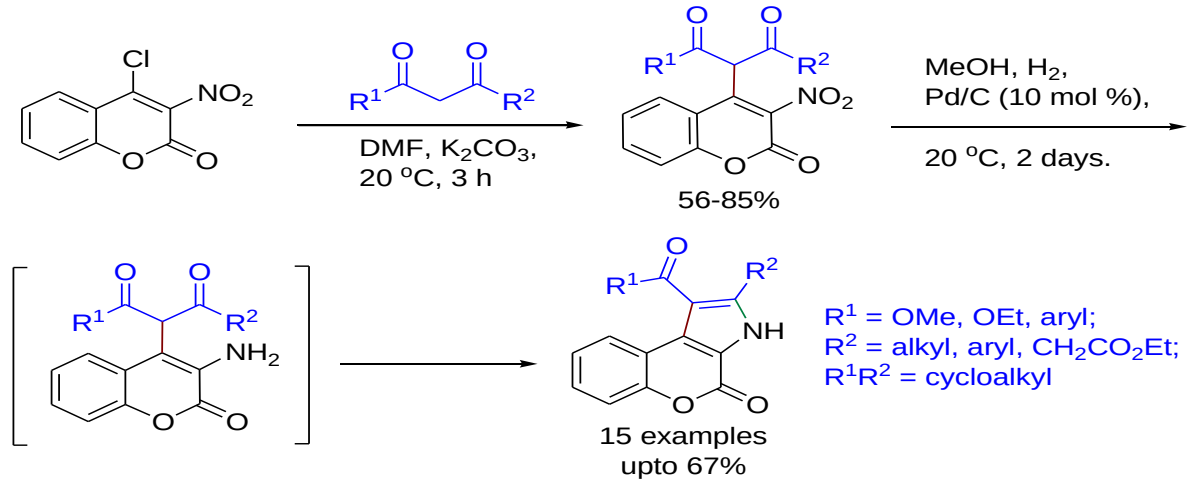
Ngo and collaborators [46] devised a practical method for synthesizing a range of pyrrolo[2,3-c]coumarins by the use of a Pd-catalyzed domino C-N coupling/hydroamination approach (Scheme 10). The pivotal step involved constructing the pyrrole ring using a 4-alkynyl-3-aminocoumarin intermediate. The palladium-catalyzedchemoselectiveSonogashira cross coupling reaction of 3-bromo-4-(trifluoromethane-sulfonyloxy)coumarin with arylalkynes in the presence of $Pd(CH_3CN)_3Cl_2$/CuI and triethylamine in DMF at room temperature afforded 4-alkynated-3-bromocoumarinsSubsequent treatment of these intermediates with alkyl/arylamines and a Pd(0) catalyst facilitated the formation of the final pyrrolocoumarins.



Scheme 10. Palladium-catalyzed multi-step synthesis of pyrrolocoumarins.

2.6. *via 3-aminocoumarin intermediates*

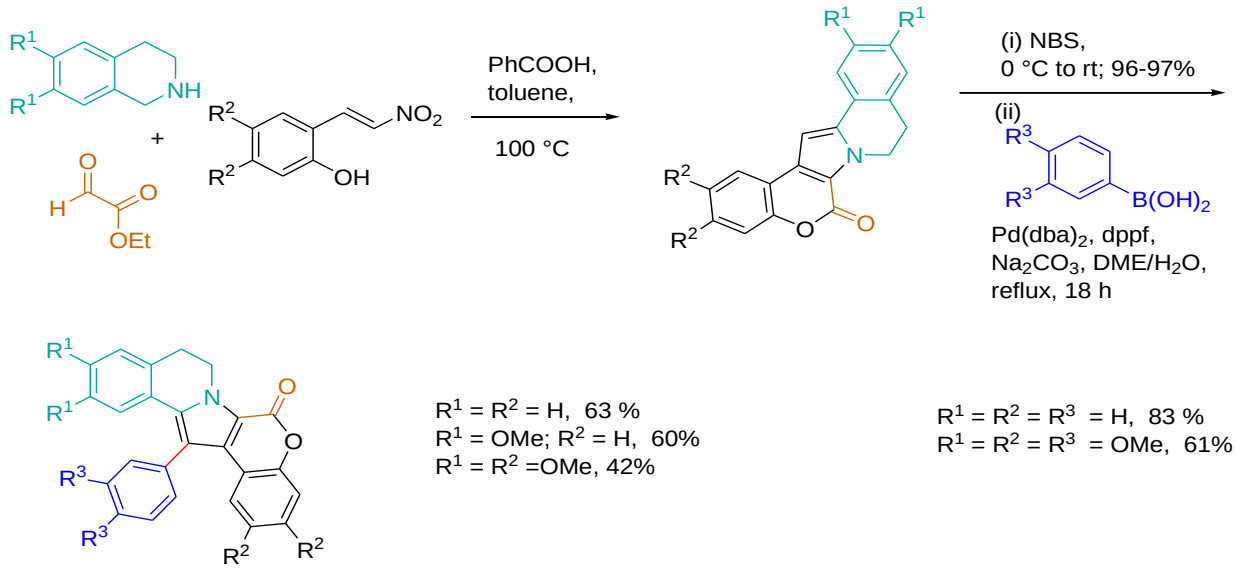
Iaroshenko and colleagues [47] synthesized 1,2-disubstituted pyrrolo[2,3-c]coumarins via base-mediated condensation and subsequent cyclization of 1,3-dicarbonyl compounds with 4-chloro-3-nitrocoumarin (Scheme 11). The reaction involved treating 4-chloro-3-nitrocoumarin with 1,3-dicarbonyl compounds in DMF solvent at 20°C in the presence of K_2CO_3, yielding the condensation products, specifically 4-substituted-3-nitrocoumarins. Subsequent hydrogenation of these condensation products with Pd/C (10 mol%) produced 4-substituted-3-aminocoumarin intermediates, which then underwent cyclization through water elimination to afford the desired pyrrolocoumarins in yields ranging from 41% to 67%.



Scheme 11. Synthesis of 1,2-disubstituted pyrrolocoumarins *via* base-mediated condensation, reduction and subsequent cyclization.

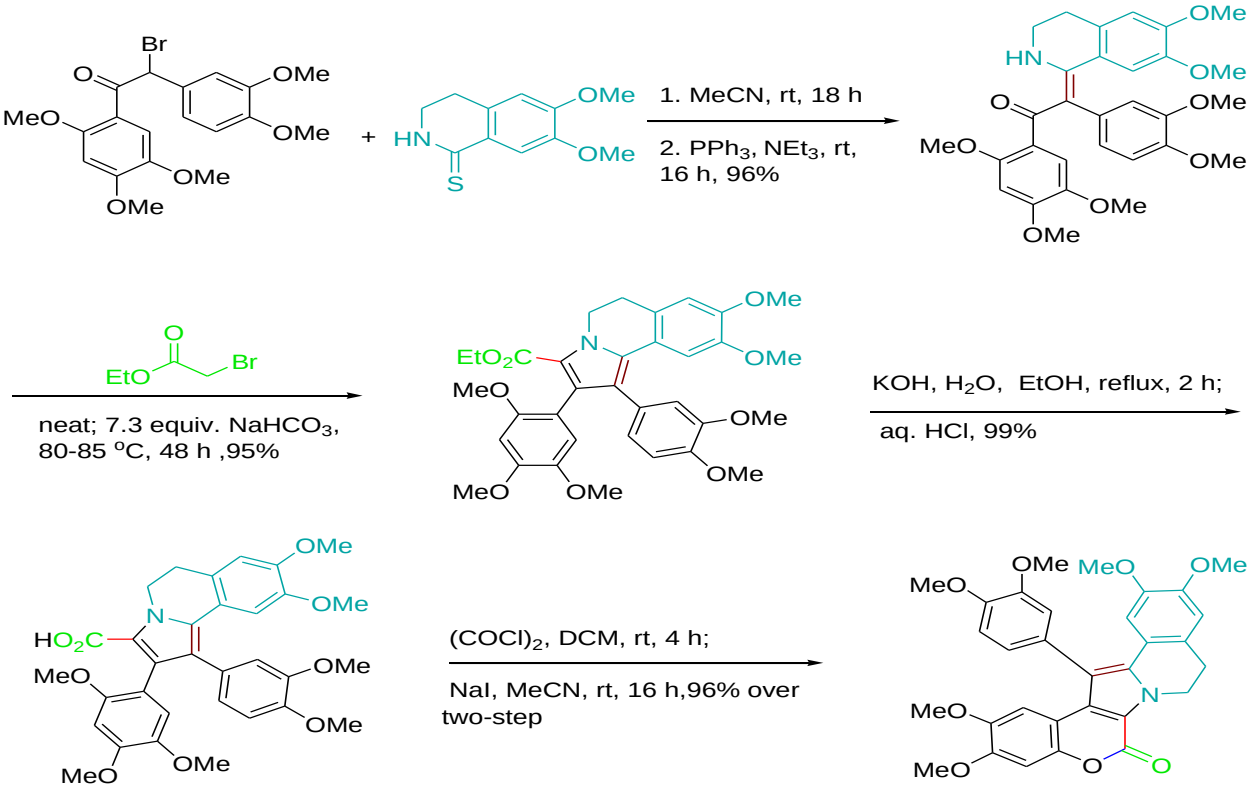
2.7. *From isoquinolines*

Wu and colleagues[48] developed an acid-mediated one-pot reaction for the efficient synthesis of the lamellarin core from (E)-(2-nitrovinyl)benzenes, ethyl glyoxalate, and tetrahydroisoquinoline (Scheme 12). The process involved a [3+2] cycloaddition of (E)-(2-nitrovinyl)benzenes with azomethine ylides, which were generated in situ from tetrahydroisoquinoline and ethyl glyoxalate. This reaction occurred in the presence of benzoic acid in toluene at 100°C, yielding pentacyclic pyrrolocoumarins. These intermediates were subsequently transformed into lamellarin structures through bromination followed by Suzuki-Miyaura cross-coupling reactions.



Scheme 12. Synthesis of lamellarin core by [3+2] cycloaddition.

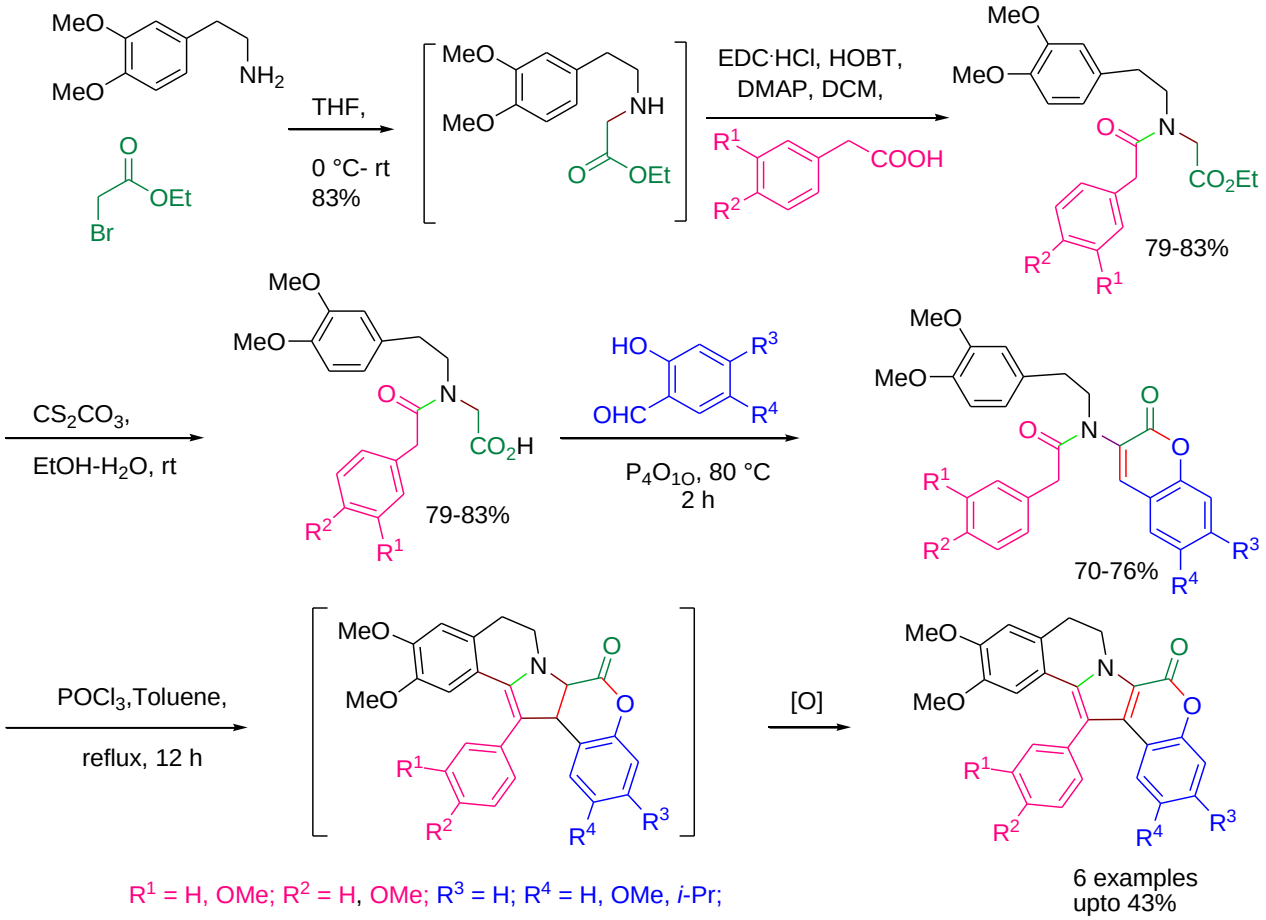
Michael and colleagues[49] established gram-scale syntheses of lamellarin derivatives from α-bromoketones and dihydroisoquinolinethione, achieving the construction of pyrrole and coumarin rings with the highest overall yields reported to date (Scheme 13). The central pyrrole core was synthesized via a [4+1] condensation involving an enaminone skeleton and ethyl bromoacetate. Subsequently, a chromenyl lactone ring was formed through a demethylative cyclization between a methoxylated aromatic system and a nearby carboxylic acid positioned on the pyrrole ring. This approach offers the advantage of avoiding additional protection and deprotection steps during the synthesis process.



Scheme 13. Gram-scale syntheses of lamellarinderivativefromdihydroisoquinolinethioneandα-bromoketones.

2.7. *From From arylethylamine*

Mandrekarand co-workers[50] devised a metal-free convergent route for synthesizing pentacyclic pyrrolo[2,3-c]coumarins, analogous to lamellarins, from 3-amidocoumarins via domino reactions. The synthesis involved Bischler-Napieralski, Michael addition, and subsequent oxidation reactions (Scheme 14). The key precursor, 3-amidocoumarins, was synthesized starting from substituted salicylaldehydes.



Scheme 14. Syntheses of lamellarinsanalogs by Bischler-Napieralski, Michael and subsequent oxidation reactions.

3. CONCLUSION

Pyrrolo[2,3-c]coumarins are valued natural products due to their extraordinary biological activities. This has spurred major interest in both natural product synthesis and the development of analogs, necessitating the advancement of effective preparative methods. In this review, we have summarized key references detailing the synthesis of pyrrolo[2,3-c]coumarins and their derivatives from appropriate precursors. These compounds are notable for their roles as both natural products and pharmacophores. We anticipate that this compilation of synthetic strategies will assist organic chemists in advancing methods for preparing these complex molecules and will encourage further exploration of their beneficial properties.

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