Review

Synthetic Strategies in the Preparation of Phenanthridinones

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Abstract: Phenanthridinones are important heterocyclic frameworks present in a variety of complex natural products, pharmaceuticals and displaying wide range of pharmacological actions. Its structural importance has evoked a great deal of interest in the domains of organic synthesis and medicinal chemistry to develop new synthetic methodologies, as well as novel compounds of pharmaceutical interest. This review focuses on the synthesis of phenanthridinone scaffolds by employing aryl-aryl, N-aryl, and biaryl coupling reactions, decarboxylative amidations, and photocatalyzed reactions.

Keywords: N-methoxy benzamides; benzanilides; 2-phenyl benzamides; ketoximes and aldoximes; C–H bond activation; C–C and C–N bond activation; arynes; carbonylation; oxidation

1. Introduction

The phenanthridinone skeleton is a common structural moiety found in bioactive alkaloids from many sources, such as oxynitidine [1], crinasiadine [2], nacriclasine [3], nacripimine [4], phanglydon [5], pancratistatin [6], oxoassoainine [7], pratosine [8], anhydrolycorinone [9], and lycoricidine [10]. Owing to the many structural derivatives of phenanthridines [11], their synthesis has been known since the beginning of the 20th century [12]. There are many classical methods available, e.g., via the Schmidt reaction [13–16], the Ullmann reaction [17], and the Beckmann rearrangement reaction [18,19], dienone-phenol rearrangement [20], and intramolecular rearrangement reaction [21]. In addition, phenanthridinones can be constructed through dichromate oxidation [22], internal cyclisation of a benzene intermediate [23–25], and other conventional methods [26,27]. However, these classical reactions have their limitations due to the requirement of additional steps for the synthesis of the key starting materials, and the generally poor to moderate overall yields. Promptly, these techniques were replaced by using non-traditional methods employing environmentally friendly chemicals, microwave-assisted reactions and catalytic approaches. These more recent techniques offer numerous advantages like shorter reaction times, improved yields, acceleration of sluggish transformations, and cleaner reaction products.

Phenanthridinones are important heterocycles, as they are used as prospective agents for anticancer treatment [28–30], and for antiviral and nerve disorders [31,32]. They possess different pharmacological properties of current interest as a class of HMG-CoA reductase inhibitors [33], anti-HIV [34], anti-hepatitis C virus [35], immunomodulatory activity [36], antibacterial and antifungal activities [37], and treatment of ischemic injuries [38] and other activities [39,40]. Interestingly, they are also estrogen receptor modulators (SERMs) [41], tyrosine protein kinase inhibitors [42], and neurotrophi activity enhancers [43]. Phenanthridinones are known to be inhibitors of poly ADP-ribose polymerase (PARP) family proteins [44–51]. PJ34 [N-(6-oxo-5,6-dihydrophenanthridin-2-yl)-N,N-dimethylacetamide.HCl] is a phenanthridone drug which is a selective inhibitor of...
poly(ADP-ribose) polymerase [52–54]. PJ38 is yet another lead molecule of the phenanthridinone family, which is active as a PARP inhibitor. The synthetic bioactive analogue ARC-111 is well known for its pharmacological activities, and is reported as topoisomerase-1 targeting antitumor agent [55] (Scheme 1).

![Scheme 1. Selected examples of biologically important phenanthridinones.](image)

This review focuses on modern techniques like transition metal-catalyzed coupling reactions, transition metal free coupling reactions, aryne-mediated coupling reactions, amidation reactions through decarboxylation, photo-induced reactions, oxidation reactions, and anionic cycloisomerization reactions for phenanthridinone synthesis.

2. Simultaneous Aryl–Aryl and \( N \– Aryl \) Coupling Reactions for Phenanthridinone Synthesis

Transition metal-mediated aryl–aryl and \( N \– Aryl \) bond forming reactions are powerful synthetic tools for constructing highly complex molecules [56,57]. They have been recently employed in the key steps of the total synthesis of nitrogen containing natural products, as well as for the construction of heterocycles in medicinal chemistry in a one-pot fashion or multi step processes due to high efficiency and compatibility with numerous functional groups. One-pot C–C/C–N bond forming reactions have been used in drug discovery [58]. In this section, simultaneous aryl–aryl and \( N \– Aryl \) coupling reactions are described.

2.1. C–C and C–N Bond Formation via a One-Pot Synthesis

Simultaneous C–C and C–N bond forming reactions played pivotal roles for the synthesis of biologically relevant phenanthridinones. The most atom efficient protocols are based on one or more C–H-activation steps, avoiding excessive use of halogenated derivatives. The Snieckus group and Rault group prepared phenanthridinones by using transition metal-catalyzed C–C and C–N bond formation coupling reactions in a two-step process [59,60]. The use of \( N \– methoxybenzamides \) 2 became a fruitful direction for the
development of C–H activation methodology (Scheme 2). In 2011, Wang and colleagues demonstrated the synthesis of biologically important phenanthridinones through a one-pot formation of C–C and C–N bonds using palladium-catalyzed dual C–H activation of N-methoxybenzamides using phenyl iodide and silver oxide as oxidant [61]. Later, the following transformation was realized under the catalysis with binaphthyl stabilized palladium nanoparticles [62]. Further, non-halogenated arenes could be engaged in analogous phenanthridinone synthesis [63]. Multiple oxidative C–H bond activation and C–C/C–N bond formation steps in a one pot fashion are the benefits of this process. The utility of the methodology was disclosed through crinasiadine natural product synthesis. In continuation, N-methoxybenzamides could be annulated with aryl boronic acids [64] or aryl silanes [65] to form phenanthridinones under rhodium-catalysis. In general, the reactions start with the formation of pallada- or rhodacycles, which further react with the coupling partner.

![Scheme 2](image)

**Scheme 2.** Phenanthridinone preparation from N-methoxybenzamides.

In 2002, Caddick and his colleagues reported the synthesis of phenanthridinones using o-halobenzamides through an intramolecular Heck reaction [66]. In 2004, Ferraccioli, Catellani and colleagues reported the synthesis of phenanthridinones 6 using o-halobenzamides 4 and aryl iodides 5 as starting materials (Scheme 3) [67]. In this case, the use of norbornene was necessary to mediate the reaction and achieve a C–H activation step. Interestingly, when benzamides without halogen in the ortho position were treated with 1-bromo-2-iodobenzenes under Pd-catalysis, the synthesis of phenanthridinones was successfully achieved in the absence of norbornene [68]. An efficient intermolecular dehydrogenative annulation of aryl iodides and aryl carbamic chlorides was reported for the synthesis of phenanthridinones using Pd-norbornene-catalysis [69].

![Scheme 3](image)

**Scheme 3.** Palladium-catalysed phenanthridinones from 2-bromobenzamides and aryl iodide.

2-Bromobenzamides 7 could be subjected to Pd-catalyzed homocoupling, delivering phenanthridinone derivatives 8 [70–72] (Scheme 4). In 2016, phenanthridinone synthesis was realized starting from o-halobenzamides under phosphine-free palladium catalysis in N,N-dimethylacetamide [73]. Authors also demonstrated this methodology in a scalable process by performing gram scale reactions. Later, Hu and his colleagues attempted the synthesis of N–H-phenanthridinones by using palladium-catalyzed intramolecular C–H arylation of 2-halo-2-Boc-N-arylbenzamides [74]. A variety of benzamides bearing electron-donating and electron-withdrawing groups can be coupled and produce the corresponding phenanthridinones in moderate to good yields.
Scheme 4. Palladium-catalyzed homocoupling of 2-bromobenzamides.

A decarboxylative copper-mediated coupling of benzamides 9 with ortho-nitrobenzoic acid salts 10 was realized by Miura and co-workers (Scheme 5) [75]. The C–H-activation step was achieved with the help of a quinol-8-yl directing group. After the decarboxylative coupling, cyclization occurred through nucleophilic substitution of a nitro-group by an amide moiety. The resulting phenanthridinones 11 were isolated with moderate yields. Li et al. reported a Pd-catalyzed decarboxylative ortho-arylation of N-methoxyarylarnides using aryl acyliperoxides [76].

Scheme 5. Phenanthridinone preparation using benzamides and o-nitrobenzoic acids.

In 1994, Tour and colleague reported a phenanthridinone synthesis using 2-halobenzoate and aromatic boronic acids using palladium as the catalyst [77]. However, the products were obtained with low yields and the substrate scope was not investigated. Later, Tanimoto et al. established a convenient one-step access to biologically important phenanthridinones 14 using 2-halobenzoate 12 and 2-aminophenylboronic acid 13 in a Suzuki–Miyaura cross-coupling reaction with palladium(II) acetate and 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl (SPhos) as precatalysts (Scheme 6) [78]. Interestingly, Kuwata et al. extended this strategy to synthesize the phenanthridinone alkaloids crinasiadine and N-alkylcrinasiadines from 2-aminophenylboronic acid and 2-halobenzoate [79]. Furthermore, 2-halobenzoates were proved to be an efficient substrate for preparing biologically active phenanthridinones [80–82].

Scheme 6. Palladium-catalyzed phenanthridinones from 2-halobenzoate and 2-aminophenylboronic acid.

Recently, Ding et al. reported the synthesis of phenanthridinones 17 through Pd-catalyzed cyclization of N-aryl-2-aminopyridine 15 with 2-iodobenzoic acid 16 via C(sp²)–H
bond activation (Scheme 7) [83]. The advantage of the methodology was in low catalyst-loading, and that the reaction smoothly proceeded in water. The broad substrate scope was demonstrated with high yields comparatively with previous methods. A tentative mechanism, based on experimental results, was proposed by the authors. Primarily, the substrate 15 coordinates with Pd(OAc)$_2$ via the pyridine nitrogen atom. A six membered palladacycle dimer complex 15-A is generated through directed C–H bond activation. Further, a carboxylate-directed oxidative addition generates a Pd(IV) species 15-B. This is followed by reductive elimination, resulting in the ortho-arylated product 15-C. Subsequently, the latter undergoes intramolecular acylation to generate 17.

Scheme 7. Phenanthridinone preparation from N-aryl-2-aminopyridines and 2-iodobenzoic acids.

2.2. C–C and C–N Bond Formation via Aryne-Mediated Reactions

In 2002, Lu et al. described an aryne-mediated synthetic methodology of substituted o-halobenzamides through a palladium-catalyzed annulation for the synthesis of N-substituted phenanthridinones in good yields. The advantage of this methodology is the preparation of phenanthridinones in a single step via simultaneous C–C and C–N bond formation, under relatively mild reaction conditions, tolerating a wide variety of functional groups [84]. Later, Jeganmohan and colleagues applied this concept on methyl or methoxy benzamides 18 and reported an aryne mediated cyclization using o-(trimethylsilyl)aryl triflate 19 in the presence of Pd(OAc)$_2$, organic acid and K$_2$S$_2$O$_8$ in CH$_3$CN yielding tricyclic phenanthridinone derivatives 20 in good yields. The scope of the catalytic reaction was examined with a variety of substituted N-methoxy benzamides (Scheme 8) [85]. Initially, a five membered palladacycle 18-A forms by the coordination of N-methoxy benzamide 18 to the Pd(0) species followed by ortho-metalation. Coordinative insertion of the benzyl intermediate 19-A into intermediate 18-A forms a seven membered palladacycle 18-B. This undergoes reductive elimination, as well as C–N bond formation using RCOOH, K$_2$S$_2$O$_8$
with regeneration of the Pd catalyst (Scheme 9). Furthermore, the utility of benzyne precursors was reported using palladium, copper, and nickel catalysts [86–90].

Scheme 8. Benzyne-involved preparations of phenathridinones.

Scheme 9. Proposed mechanism for the palladium-catalyzed aryne mediate cyclization.

2.3. C–C and C–N Bond Formation via Carbonylative and Carboxylative Reactions

In 2013, Zhang [91] and Zhu [92] concurrently described a phenanthridinone synthesis through carbonylation of biphenyl-2-amines 21 employing a combination of Pd(II) and Cu(II) salts under a carbon monoxide atmosphere (Scheme 10). Zhang and co-workers succeeded in developing a catalytic system that can avoid the formation of urea as side product, using a combination of Pd(OAc)$_2$ and Cu(II) trifluoroacetate in 2,2,2-trifluoroethanol. The substrate scope of the reaction was verified using various electron rich and electron deficient biphenylamines. Electronic rich biphenylamines gave higher yields compared to electronic deficient biphenylamines [91]. In the case of Zhu’s work, 1 equiv of TFA was needed for smooth conversion [92]. Moreover, Chuang and colleagues used only a palladium catalyst for oxidative insertion of carbon monoxide on N-sulfonyl-2-aminobipharyls to furnish phenanthridinone 22 [93]. Interestingly, DMF could also be used as a one-carbon-source instead of toxic carbon monoxide [94]. Ling and colleagues reported a CoCl$_2$-catalyzed carboxylation of ortho-arylanilines in the presence of diazadicarboxylates as a carbonyl source and oxygen as oxidant [95]. 10-Hydroxy-10,9-borazarophenanthrenes could be converted into phenanthridinones, including phenaglydon, through Pd(II)-catalyzed carbonylation [96].

Scheme 10. Pd-catalyzed carbonylative synthesis of phenanthridinones.
The use of non-toxic CO$_2$ as a carbonyl source for phenanthridine formation could be advantageous. For example, o-arylanilines 21 could be transformed into phenanthridinones 22 under a CO$_2$ atmosphere using transition metal free conditions (Scheme 11) [97]. Substrates bearing an electron-donating group on the aryl moiety, demonstrated higher reactivity to furnish 22 with higher yields, while electron-withdrawing groups gave lower yields. Based on experimental results, a plausible mechanism was proposed. Initially, the o-arylaniline 21 reacted with the adduct of 1,5,7-triazabicyclo[4.4.0] dec-5-ene (TBD) and CO$_2$ to produce the carbamate 21-A with the aid of MeOTf. Release of MeOH generated isocyanate 21-B at high temperature. Subsequently, internal cyclization of intermediate 21-C resulted in the formation of 21-D, which upon hydrolysis gave phenanthridinone 22. In 2021, arylisocyanates 21-B were directly transformed into phenathridinones under the action of catalytic amounts of MeOTf in DCE. That approach was used for the synthesis of amaryllidaceae alkaloids [98].

Scheme 11. Transition metal free carboxylative cyclization of o-arylanilines.

In 2019, Gao et al. developed an amino group-assisted C–H carboxylation of 2-arylanilines with CO$_2$ through Rh(I) catalysis under redox neutral condition (Scheme 12) [99]. The reaction was carried out in the presence of a phosphine ligand and $^3$BuOK as base. The advantage of the methodology is that no external oxidant was needed. The reaction started with the oxidative addition of Rh(I), followed by a reductive elimination of HX to generate a rhodacycle, which underwent carboxylation with CO$_2$. The resulting Rh carboxylate cyclized into the target product. Only N-unsubstituted 2-phenylanilines 21 participated successfully in the reaction.
3. C–C Coupling Reactions for Phenanthridinone Synthesis

Arylation of arenes has emerged as a powerful tool for the synthesis of biaryl compounds, which led to a variety of bioactive molecules [100,101]. Biaryl coupling has shown a prominent strategy to prepare bioactive phenanthridinones. The synthesis of phenanthridinones through C–C coupling reactions is discussed in this section.

Benzanilides with halogen substituent in the ortho-position were extensively used for the preparation of phenanthridinones [102–108]. Later, a dehydrogenative approach with halogen-free compounds was developed. Dong and co-workers reported an intramolecular ortho-arylation of benzanilides 23 [109]. The reaction was performed in DCE under the action of palladium (II) acetate (10 mol%) and Na$_2$S$_2$O$_8$ as oxidant. The addition of TFA was crucial for the transformation. The methodology allowed the synthesis of N-methylcrinasiadine natural product in 30% yield. Further, Murakami's group used molecular oxygen as terminal oxidant for the palladium-catalyzed arylation of benzanilides 23 towards the synthesis of phenanthridinones 24 via oxidative C–H coupling (Scheme 13) [110]. Interestingly, non-substituted benzanilide afforded the phenanthridinone in 89% yield. Chloro- and bromo-groups remained intact, while cyano-substituents were not tolerated under the reaction conditions. Later, Du, Zhao, and co-workers developed a Cu(II)-promoted conversion of N-benzoylated enaminoines into 3-hydroxyphenanthridinones [111]. Interestingly, N-formyl-2-arylanilines could be cyclized into phenanthridinones under Cu(0)-catalysis in the presence of stoichiometric amounts of selectfluor [112].

The following mechanism was proposed by the authors (Scheme 14) [110]. The palladium (II) species coordinates to the carbonyl oxygen of the amide group of the anilide via ortho-palladation, resulting in the formation of the aryl palladium species 23-A. Uncoordination of the amide bond in intermediate 23-A was followed by the rotation of the amide bond and placing the ortho-position of the benzoyl moiety in close proximity to the palladium center, leading to the second aromatic palladation to generate intermediate 23-B. Reductive elimination gives phenanthridinone 24 and palladium (0). Palladium (II) was regenerated by the action of molecular oxygen and benzoic acid.
Benzanilides 25 could be cyclized into phenanthridinones 26 under transition metal free conditions. For instance, benzanilide 25 (X=H) underwent the desired transformation in the presence of phenyliodine (III)-bis (trifluoroacetate) (PIFA) (Scheme 15) [113]. The reaction was possible for electron-rich substrates. Bhakuni et al. developed a transition metal free aryl arene coupling of halo benzamides 25 using KO\textsubscript{t}Bu, 1,10-phenathroline as ligand and AIBN as a radical initiator [114]. In 2016, Sharma et al. developed a transition metal-free microwave-assisted methodology utilizing vasicine 27 (a natural product) as a catalyst for the synthesis of phenanthridinones. The reaction proceeded through intramolecular C–H arylation with aryl halides in the presence of KO\textsubscript{t}Bu base, under microwave irradiation in sulfolane as the solvent. Remarkably, the reaction worked smoothly with less reactive aryl chlorides and reached completion after 15 min [115]. Bromides could be analogously cyclized in the presence of 1-(2-hydroxyethyl)-piperazine (28) and DMAP in mesitylene (Scheme 15) [116].

Lautens and colleagues reported a synthesis of remarkable ortho-aminated phenanthridinones 31 to be produced by reacting wide scope of benzamides 29 with O-benzoyl-hydroxylamine 30 under palladium-norbornene catalysis. Various hydroxylamines could also be used, although less efficiently (Scheme 16) [117].
4. **N–Aryl Coupling Reactions for Phenanthridinone Synthesis**

An N–Aryl coupling reaction opened avenues for the synthesis of heterocycles, that are abundant in natural products [118]. In addition, N–arylation coupling reactions proved to be a good strategy to prepare pharmaceutically important phenanthridinone derivatives. In this section, phenanthridinone synthesis, using metal catalyzed N–arylation coupling reactions and transition metal free N–arylation coupling reactions, is discussed.

Oxidative intramolecular palladium-catalyzed C–H amination of arenes for the synthesis of phenanthridin-6-one in 63% yield was reported in 2012 [60], employing the procedure for the synthesis of quinolones (Scheme 17) [119]. The removal of the tosyl group took place at the same time. Later, Gui and colleagues developed a copper-catalyzed approach for the preparation of phenanthridin-6-ones from 2-phenylbenzamides 32 (R=H) through an intramolecular N-arylation bond-forming process under basic conditions [120]. Ortho-arylation of benzamides proceeded smoothly in the presence of CuI (10 mol%), KO\(_2\)Bu (2 equiv), and a phosphine ligand (20 mol%). Heating the reactant in o-xylene at 120 °C for 18 h was needed to produce the target molecules in 40%–92% yield. Only N-unsubstituted amides could be used. Later, hypervalent iodine-mediated processes for the cyclization of N-methoxybenzamides 32 (R-OMe) were developed. Jiang, Xue, and coworkers used catalytic amounts of iodobenzene and peroxy acids as oxidants [121,122]. The reactions were performed in 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) under an air atmosphere. These consecutive C–H functionalization reactions can be used efficiently to construct 2-substituted-phenanthridinones at room temperature with moderate to high yields. Interestingly, when the reaction was carried out in the presence of TBAB, a bromide was introduced in para-position of nitrogen [121]. In addition, it has been recently shown that N-methoxy amides could be also cyclized into phenathridinones under electrochemical conditions [123].

![Scheme 17](image)

**Scheme 17.** C–H amidations for the synthesis of phenanthridinones.
Wang et al. reported an oxidative arene C(sp²)–H amidation for the synthesis of phenanthridiones using amide 33 and NIS as iodinating reagent (Scheme 18) [124]. Primarily, N-iodosuccinimide reacts with amide 33 to form N-iodinated compound 33-A. It undergoes an N–I homolytic cleavage providing amide N-radical 33-B under thermal conditions. Subsequently, 5-exo-cyclization on to the aromatic ring of intermediate 33-B afforded intermediate 33-C, or 6-endo cyclization gave benzolactam intermediate 33-D. Benzolactams could also be obtained through a ring expansion via C–N bond migration. Further rearomatization gave product 34. When the substrate was bearing OTBS-group, the intermediate 29-C delivered spirolactam 35. Later, Verma et al. reported a cyclization of 2-phenylbenzamides for the preparation of phenanthridiones using iodine, succinimide, and di-tert-butylperoxide (DTBP) as oxidant [125]. It has been shown that 2'-iodo-[1,1'-biphenyl]-2-carboxamide could be cyclized into phenanthridine under Ni-catalysis in the presence of boronic acid [126].

Other useful substrates for the synthesis of phenanthridiones via a C–N bond forming route are 2-arylbenzonitriles 36. Fabis and co-workers reported a potassium hydroxide mediated anionic ring closure of fluorine-substituted benzonitriles 36 (X = F) [127,128]. Later, Chen et al. reported a copper-catalysis of annulation of bromide-substituted benzonitriles 36 (X = Br) (Scheme 19) [129]. Furthermore, the utility of copper catalysis was extended to the synthesis of phenanthridione containing bioactive natural products [130,131]. Benzonitriles with an alkyne moiety in ortho-position could undergo an anionic cycloaromatization when treated with sodium methylate in methanol, delivering condensed phenanthridiones [132,133].
5. Decarboxylative Reactions for Phenanthridinone Synthesis

Efficient C–C bond formation via transition-metal-catalyzed decarboxylation of aromatic carboxylic acids is a known strategy in organic synthesis [134]. This approach can afford unconventional alternatives to perform various types of C–C and C–heteroatom bond-forming reactions. In 2012, Shen and colleagues have achieved an efficient protocol for forming biaryl compounds through palladium-catalyzed intramolecular decarboxylative coupling of arene carboxylic acids with aryl bromides, yielding various cyclized heterocycles, including phenanthridinones [135]. Later, intramolecular decarboxylative amidation of unactivated arenes was achieved under transition metal free conditions (Scheme 20) [136]. Na$_2$S$_2$O$_8$-promoted decarboxylative cyclization of biaryl-2-oxamic acids 37, gave phenanthridinones 38 with high efficiency. It was observed that the wide scope of the desired products was obtained in good to excellent yields. As electron-withdrawing groups on the aromatic ring did not lower the reaction efficiency, a radical reaction pathway is followed.

Scheme 20. Transition metal free synthesis of phenanthridinones from biaryl-2-oxamic acids.

6. Photo-Mediated Reactions for Phenanthridinone Synthesis

Recently, photocatalyzed reactions proved to be a valuable method for the synthesis of heterocycles and biologically active compounds [137]. Firstly, Mondon et al. investigated the photocyclization of benzanilides to furnish unsymmetrically substituted phenanthridinones [138]. Later, Prabhakar et al. reported an improved phenanthridinone synthesis by using the photocyclization of boron complexes, followed by hydrolysis [139]. In 2017, a facile photo reductive protocol was developed to remove benzyl o-protective groups from phenanthridin-6-ol via blue light irradiation [140]. Furthermore, Moon and colleagues synthesized phenanthridinones 40 through a visible-light-promoted direct oxidative C–H amidation [141]. In this photocatalytic system, oxidative intramolecular C–H amidation of benzamide 39 was achieved through amidyl radicals. Those could be generated by homolysis of the N–H bond of simple amide precursors via single-electron transfer under blue LED irradiation. The scope of the methodology was further extended to different derivatives of benzamides. Interestingly, halides such as fluoro, chloro, bromo, and iodo substituents were tolerated under the reaction conditions (Scheme 21). Subsequently, the applicability of the method was verified with respect to substrates bearing p-methoxyphenyl (PMP) groups.
on the amide nitrogen. This worked well with the optimized system and provided the desired products easily. When meta-substituted substrates were employed, the formation of the C–N bond took place exclusively at the more sterically accessible C–H bond of the aryl ring, affording only one regioisomer.

Scheme 21. Visible light-induced synthesis of phenanthridinones through direct oxidative C–H amidation.

Recently, Itoh et al. developed a transition metal free alternative for visible light-mediated cyclization of benzamides 39 into phenathridinones 40 (Scheme 22) [142]. As a photocatalyst, 1-chloroanthraquinone 41 was employed. The reaction was performed under air atmosphere. The proposed mechanism is similar to the transformation on Scheme 21. Photoexcited catalyst oxidizes benzamide 39 to generate an amidyl radical 39-A, capable of intramolecular cyclization. The subsequent radical 39-B traps oxygen, giving peroxy radical 39-C. The latter is reduced and subsequently aromatized by elimination of hydroperoxide anion. In comparison with the Ir-catalyzed reaction, this transformation tolerates alkyl-substituted amides (R^3 = Ar, Alk).

Scheme 22. Visible light-induced synthesis of phenanthridinones in the presence of 1-chloroanthraquinone catalyst.

7. Miscellaneous Reactions

In 2017, Yaragorla and colleagues developed a Ca(II)-catalyzed one-pot reaction between oxindole 41 and styrenes, furnishing phenanthridinones 42 in moderate to good yields (Scheme 23) [143]. The reaction starts with a dehydrative cross-coupling, delivering the isolable intermediate 43. A sigmatropic rearrangement in the latter leads to the formation of allene 44, capable of intramolecular cyclization into compound 45. This spirocycle 45 could be transformed into the desired phenanthridinone 42 under oxidation-induced ring rearrangement.
Scheme 23. Ca(II)-catalyzed oxidative one-pot domino sequence towards phenathridinones.

A multicomponent approach for phenathridinone synthesis was developed by Alzaydi and co-workers [144]. The reaction between ortho-aminoacetophenone 46, ethyl cyanoacetate, sulfur and alkyne was carried out in the presence of AcOH/NH$_4$OAc under increased pressure in a Q-tube (Scheme 24).

Scheme 24. Multicomponent approach towards phenathridinones.

It was shown that unsaturated carbonyl compounds 47 could react with dimethyl glutaconate 48 to produce phenathridinones 49 in excellent yields (Scheme 25) [145]. The reaction took place in methanol at rt under the action of sodium hydroxide. The sequence started with the Michael addition of glutaconate 48 to the activated double bond of 47, giving intermediate 50. Double bond migration, followed by intramolecular cyclization gave cyclohexadiene 51, which underwent an intramolecular cyclization into a non-aromatic phenanthridinone. Spontaneous aromatization delivered the desired product 49.
8. Conclusions

Phenanthridinones have attracted the attention of organic and medicinal chemists because of the diverse pharmacological and biological properties of their alkaloids. Due to promising pharmacological profiles and unique structural features, coupled with low natural abundance, many synthetic methodologies have been developed. Here, we reviewed the synthetic strategies that can achieve phenanthridinone formation. Due to serious efforts in the development of modern synthetic methods, the construction of the phenanthridinone framework through C–C and C–N bond formation reactions via dual C–H bond activation has evolved. Still, the created approaches suffer from the need for pre functionalized substrates, limited substrate scope and scalability, leaving space for new discoveries. We believe that the most crucial developments in sustainable and efficient syntheses of phenanthridinones might evolve from the fields of photocatalyzed or electrochemical C–H functionalizations, conceivably combined with the flow chemistry.

Funding: This paper has been supported by the RUDN University Strategic Academic Leadership Program. The research was funded by RFBR and Moscow city Government according to the project № 21-33-70007.

Conflicts of Interest: The authors declare no conflict of interest.

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