Recent Advances on Metal-Free, Visible-Light-Induced Catalysis for Assembling Nitrogen- and Oxygen-Based Heterocyclic Scaffolds

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Abstract: Heterocycles are important class of structures, which occupy a major space in the domain of natural and bioactive compounds. For this reason, development of new synthetic strategies for their controllable synthesis became of special interests. The development of novel photoredox systems with wide-range application in organic synthesis is particularly interesting. Organic dyes have been widely applied as photoredox catalysts in organic synthesis. Their low costs compared to the typical photocatalysts based on transition metals make them an excellent alternative. This review describes proceedings since 2015 in the area of application of metal-free, visible-light-mediated catalysis for assembling various heterocyclic scaffolds containing five- and six-membered rings bearing nitrogen and oxygen heteroatoms.

Keywords: photocatalysis; photoredox; visible-light-induced catalysis; photoredox cyclization; organic dyes; heterocycles

1. Introduction

Heterocycles are a very important class of structural motifs that can be found in many pharmaceuticals and natural products [1–3]. Numerous of them contain five- or six-membered rings bearing different heteroatom, like nitrogen or oxygen. Drimetine G, for example, is composed of three heterocyclic rings and indicates anticancer and antibacterial activities; others like Captopril is an ACE inhibitor used for the treatment of hypertension (Figure 1) [4–7]. As a consequence of potent bioactivity of many heterocycles, significant efforts have been devoted toward the development of new synthetic strategies for their preparation [3].

During the last years, application and development of visible-light-mediated catalysis in organic chemistry became a topic of immense importance [8,9]. It is due to the fact that opposite to many reactions, a light source is used to generate reactive species without the need to apply stoichiometric activators [10,11]. To fulfill the needs of the solar energy usage, structurally diverse compounds based on transition metals have been developed [12]. To pursue the ideal chemical transformation, light-emitting diodes (LEDs) or compact fluorescent lamps (CFLs) are used as a light source because of their low costs, reasonable energy consumption, and general availability.

To create heterocyclic scaffolds, comprehensive photocatalytic strategies based on various metal complexes have been already disclosed [13–20]. However, their metal-free analogues play a significant role in terms of green chemistry [21] and medicine because of the high toxicity of many transition-metal complexes [22–24]. Organic dyes capable of visible-light-spectra absorption are generally less expensive and less toxic compared to the classical iridium or ruthenium catalysts. Thanks to high air stability, they are also easy to handle. For this reason, organic dyes act as an attractive alternative to transition-metal
complexes [25–27]. Figure 2 shows the examples of most commonly used metal-free catalysts in photoredox chemistry.

This article presents the coverage of the recent advances in the application of metal-free, visible-light-mediated catalysis for assembling five- and six-member heterocyclic scaffolds containing nitrogen and oxygen heteroatoms. We are mainly focusing on the new metal-free photochemical reactions discovered after the year 2015 in the synthesis of aromatic and non-aromatic heterocycles. The article is organized into three chapters, which describe synthetic strategies for the preparation of nitrogen-containing heterocycles, oxygen-containing heterocycles, and heterocycles containing more than one heteroatom.

Figure 1. Selected example of current drugs containing heterocyclic scaffold.

2. Application of Visible-Light-Mediated Catalysis in Synthesis of Heterocyclic Compounds

Many organic compounds isolated from nature contain five- or six-membered heterocyclic scaffolds. These compounds are very interesting due to their potent bioactivities and applications as therapeutic drugs. For example, many heterocyclic derivatives, like emetine, papaverine, theophylline, etc. containing heterocyclic scaffold are used as life-saving pharmaceuticals [28]. Moreover, heterocyclic systems very often act as suitable intermediates in the synthesis of more complex molecules [29]. As part of their well-defined structure, they may contain N-, O-, S-, or other heteroatoms. Among the reaction strategies that lead to heterocycles, many of them use heavy metals, or require harsh reaction conditions [30]. Therefore, development of more sustainable approaches for constructing highly functionalized heterocycles have gained a considerable interest.
Figure 2. Examples of metal-free photoredox catalysts.

2.1. N-containing Heterocycles

7 Rose Bengal
8a) R = H; 2,4,6-Triphenylpyrylium
8b) R = Me; 2,4,6-Tri(p-tolyl)pyrylium
8c) R = F; 2,4,6-Tris(4-fluorophenyl)pyrylium
8d) R = Cl; 2,4,6-Tris(4-chlorophenyl)pyrylium

9 DCA (9,10-dicyanoanthracene)

10 QuCN⁺ (3-cyano-1-methylquinolinium)
11a) R = H; Eosin Y
11b) R = Na; Eosin Y disodium salt
12 Mes-Acr-Me⁺ (10-methyl-9-mesitylacridinium)

13 Methylene Blue
14 TX (Thioxanthone)
15 1-AAQ (1-Aminoanthraquinone)

16 1-Butyl-7,8-dimethoxy-3-methylalloxazin
17 PQ (9,10-Phenanthrenequinone)

18a) R = H; Tetraiodofluorescein
18b) R = Na; Erythrosine B
19 3,7-Di(4-biphenyl)-1-naphthalene-10-phenoxazine
20 NHPI (N-hydroxypthalimide)

Figure 2. Examples of metal-free photoredox catalysts.
2.1. N-containing Heterocycles

2.1.1. Aromatic Heterocycles

Nitrogen bearing heterocycles constitute the majority in the field of heterocyclic chemistry. Various biologically active natural or synthetic products prevail the substituted indole motif. For example, some of the 2-substituted-indoles have been found as the successful leukotriene-modifier drugs in cardiovascular disease [31], others gain therapeutic interest in the treatment of cancer, HIV, heart disease, allergies, etc. [32]. To construct functionalized indoles, Kshirsagar and co-workers disclosed a photoredox-catalyzed vicinal thioamination of alkynes [33]. In this context, Eosin Y 11a catalyzed radical cascade annulation generates various 3-sulfenylindoles 22 in up to 86% yield (Scheme 1a). This metal and strong-oxidant-free synthesis is based on the proposed mechanism presented in Scheme 1b. Eosin Y 11a (EY) is first excited by the blue LED irradiation to EY*, which is then reduced to EY** by oxidizing thiophenol to the radical species 24. Re-oxidation of EY** to its ground state takes place by air oxygen producing O2•− species. Deprotonation of thiophenol cation radical 24 by the O2•− gives hydroperoxyl radical 28 and radical 25, which undergoes addition to the triple bond of 21 and produces another radical 26. Subsequent intramolecular cyclization followed by N2 release delivers intermediate radical 27. Finally, hydrogen atom transfer (HAT) from hydrogen source present in the reaction mixture gives product 22.

![Scheme 1](image-url)

Scheme 1. (a) Vicinal thioamination of alkynes, mediated by Eosin Y; (b) Proposed mechanism for vicinal thioamination of alkynes, mediated by Eosin Y.

2,3-Disubstituted indoles can also be obtained by cyclization of arylsulfonyl chlorides with ortho-azidoarylalkenes [34]. This transition-metal free process described by Gu group, emerges as an efficient protocol, exhibiting high functional-group tolerance. Various indoles 31 can be prepared in up to 84% yield (Scheme 2a). Mechanism of this annulation is shown in Scheme 2b. Excited Eosin Y 11a (EY) is responsible for reduction by SET of benzenesulfonyl chloride 30 to aryl radical 32 and EY**. Formed phenyl radical 32 undergoes addition to the triple bond of 29 forming radical intermediate 33, which subsequently undergoes intramolecular cyclization with the azide group to N-radical intermediate 34 with extrusion of nitrogen. Finally, H-atom abstraction from cyclohexadiene

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(CHD) by 34 forms desired product 31 and CHD radical 35, which closes the photoredox cycle by SET process regenerating Eosin catalyst in its ground state (Scheme 2b).

Scheme 2. (a) Visible-light-induced cyclization of arylsulfonyl chlorides; (b) Proposed mechanism.

Fluorine-containing compounds can often be found in medicinal chemistry due to improvement bioavailability, lipophilicity, or the metabolic stability compared to their non-fluorinated analogs [35]. For this reason, the synthesis of fluorinated heterocycles is particularly interesting.

The intramolecular cyclization of various 1,6-enynes 37 can be found as a general and powerful strategy in the synthesis of indole derivatives. In this context, Kumar and co-workers proposed metal and oxidant-free visible-light-induced trifluoromethylation of alkynes 37 (Scheme 3), using 9,10-phenanthrequinone catalyst 17 under compact fluorescent lamp (CFL) irradiation [36].

Scheme 3. Dehydrogenative cascade trifluoromethylation and oxidation of 1,6-enynes.
In addition, the described protocol is also effective for constructing benzofuran or thiophene frameworks. CFL irradiation of the CF₃SO₂Na derivative generates the initiating CF₃ radical, which undergoes selective addition to the double bond acceptor, while subsequent intramolecular cyclization gives final aromatic derivatives 38 in up to 75% yield.

The cascade-type reactions have been established as a general strategy for the synthesis of highly functionalized compounds [37]. In this context, Brasholz and co-workers described a visible-light-induced photocatalytic cascade reaction in the synthesis of indoloisoquinolines 40 using amino-substituted anthraquinone 15 as photocatalyst [38]. Formation of new heterocyclic ring is based on the dehydrogenation–cyclization–oxidation cascade that converts tetrahydroisoquinolines 39 into substituted tetracyclic heterocycles 40 (Scheme 4a). A plausible reaction mechanism starts on electron transfer between amine 39 and the photoinduced anthraquinone catalyst 15 (AQ⁺) with the formation of amine radical cation 41. Hydrogen atom abstraction from 41 by superoxide radical anion converts amine 41 into iminium ion 42. Subsequent deprotonation of 42 gives nitroenamine 43, which undergoes electrocyclic ring closure to ylide 44. Finally, rearomatization followed by photoinduced catalytic oxidation leads to appropriate 12-nitroindoloisoquinoline 40 in up to 69% yield (Scheme 4b).

Pyridine core is widespread in many bioactive compounds [1–3]. The versatile methodology employing visible-light-promoted [2 + 2 + 2] cyclization of alkynes with nitriles to pyridines recently has been described by Wang and Meng group [39]. Using pyrylium salt 8d as photoredox catalysts, various 2,3,6-trisubstituted pyridines 47 can be prepared under blue LED irradiation. A wide range of functional group tolerance makes various pyridines 47 accessible in up to 79% yield (Scheme 5a). In Scheme 5b, a reasonable mechanism for this transformation is suggested. Blue LED irradiation of the pyrylium salt 8d (PC) in the presence of phenyl acetylene 45 generates the radical cation 51, which reacts with the nitrile 46 and generates intermediate 48. Subsequent addition of 48 to another phenyl acetylene molecule 45 affords intermediate 49, which undergoes intramolecular cyclization to pyridine.

![Scheme 4](image-url)
radical cation 50. Finally, reduction of 50 by pyrylium anion (PC\(^-\)) via a SET process provides the product 47 and regenerated catalyst (PC) in its ground state.

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\text{Scheme 5. (a) \([2 + 2 + 2]\) Cyclization of alkynes with nitriles; (b) Proposed mechanism.}
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Recently, visible-light-photoredox catalysis has been used for the synthesis of various quinolones as well. The Zhang group developed an impressive example of N-propargyl aromatic amine application in the synthesis of 3-arylsulfonylquinolines 55 (Scheme 6a). The authors demonstrated a visible-light-induced multicomponent cascade cycloaddition of 52 with diaryliodonium salts 53 and sulfur dioxide [40]. This three-component reaction can be achieved using Eosin Y 11a catalysts under irradiation by green LEDs in the presence of DABSO (DABCO·(SO\(_2\))\(_2\)) as sulfur dioxide source. This transformation performs effectively with a wide functional group tolerance in up to 84% yield.

On the basis of a series of control experiments, the authors proposed a plausible catalytic cycle (Scheme 6b). First, irradiation of Eosin Y 11a by green LEDs generates excited Eosin Y (EY\(^*\)), which undergoes oxidative quenching with iodonium salt 53 to appropriate aryl radical 61 and EY\(^{**}\). Subsequent reaction of aryl radical 60 with DABSO generates sulfonyl radical 56, which react regioselectively with the triple bond of 52 forming alkenyl radical 57. Intramolecular cyclization of 57 produce annulated aryl radical 58. Deprotonation of 58 generates another radical 59, which is oxidized to 60 by EY\(^{**}\) thus regenerating eosin catalyst in its ground state. Alternatively, radical 59 can be oxidized by 53 leading to the dihydroquinoline derivative 60 (path II). Finally, sulfonated 1,2-dihydroquinoline 60 undergoes dehydroaromatization to the product 55.
As an efficient strategy for the construction of phenanthridine skeleton, the radical cyclization involving an iminyl radical is often invoked [41]. To develop more efficient and greener approach, Xie group reported visible-light-mediated cyclization of O-2,4-dinitrophenyl oximes 62 to phenanthridine 63 using Eosin Y 11a under CFL irradiation (Scheme 7a) [42]. The authors proposed a plausible catalytic cycle for this valuable process (Scheme 7b). Firstly, excited Eosin EY* is reduced by (i-Pr)2NEt to Eosin EY•−, which undergoes single electron transfer (SET) with 62 and generate radical anion 64.
Fragmentation of the intermediate 64 followed by intramolecular cyclization gives radical 66, which is then deprotonated by phenoxy anion 67 to radical anion 69. Formed intermediate 69 undergoes another photocatalytic cycle with the excited state of eosin by SET leading to the final product 63 in moderate to good yields (up to 80%).

In a recent investigation, Guo applied decarboxylative cyclization of N-acyloxylphthalimides 71 with vinyl azides 70 in the synthesis of various phenanthridine 72 [43]. This tandem radical addition/cyclization process affords substituted products in up to 79% yield (Scheme 8a). The authors proposed a possible mechanism for this transformation (Scheme 8b). Firstly, irradiation of Eosin Y 11a by CFL affords the excited Eosin Y catalyst (EY*). Subsequent single electron transfer with 71 generates radical anion 73, which undergoes fragmentation to CO₂, phthalimide anion 74, and radical 76. Addition of 76 to the double bond of 75 followed by extrusion of nitrogen produce iminyl radical 77, which undergoes series of transformations: intramolecular cyclization, oxidation by Eosin Y**, and deprotonation to the final product 72.
2.1.2. Non-Aromatic Heterocycles

Non-aromatic heterocycles are an integral part of heterocycles' family. Same as their aromatic analogues they are widely distributed in nature, therefore significant efforts have been devoted to their synthesis [1–3].

In a recent investigation, Leonori reported a novel visible-light-mediated generation of 5-membered cyclic imines 81 [44]. Reaction is based on the hydroimination and iminohydroxylation cyclization of olefins 80 using Eosin Y 11a as a photoredox catalyst (Scheme 9a). In this process, non-aromatic five heterocyclic ring is formed in up to 84% yield. Based on experimental findings, a plausible reaction mechanism is depicted in Scheme 9b. The suggested mechanism is based on single electron transfer from the enhanced Eosin catalyst (EY*) to the starting material 80 with production of anion radical 82. Radical 82 undergoes fragmentation to phenoxide 85 and radical intermediate 83. Next, radical 83 undergoes 5-exo-trig cyclization to the five-membered N-heterocycle radical 84. Finally, hydrogen abstraction from 84 by cyclohexadiene (CHD) leads to the desired product 81 and CHD radical 35, which closes the photoredox cycle by SET process regenerating Eosin catalyst in its ground state.
Cyclization of N-arylacrylamides 86 have been found as a useful strategy in the synthesis of indolin-2-one compounds 88. Novák and Tóth group developed cyclization of trifluoromethylated acrylamides under visible-light conditions catalyzed by Erythrosine B 18b (Scheme 10) [45]. The elaborated arylation/cyclization sequence is initiated by aryl radical generation from diazonium salt 87, which undergoes addition to the double bond of 86 followed by radical cyclization. In this process, structurally different heterocyclic units 88 can be prepared in up to 83% yield.

Scheme 9. (a) Hydroimination and iminohydroxylation cyclization of olefins; (b) Proposed mechanism.

Scheme 10. Synthesis of 3-(trifluoromethyl)indolin-2-one derivatives under photoredox conditions.
Various dihydroisoquinolinin derivatives can be obtained by using Eosin Y 11b catalyst under visible-light conditions [46]. Huang group showed that substituted 3,4-dihydroisoquinolinones 90 can be received in a very good yields by intramolecular cyclization of appropriate amides 89 (Scheme 11a). Mechanistic pathway for this transformation is presented in Scheme 11b. It starts by the formation of excited state of Eosin catalyst (EY*) and deprotonation of 89 by DBU with anion 91 formation. Single electron transfer between anion 91 and EY* leads to the radical 92. Subsequent intramolecular cyclization followed by another SET cycle recovers ground state of Eosin catalyst together with the anion 94 formation, which undergoes protonation to the final product 90.

![Scheme 11](image)

Scheme 11. (a) Synthesis of 3,4-dihydroisoquinolinones; (b) Proposed mechanism.

Throughout the past decades, stereoselective synthesis became of special interest, both by academia and industry scientists [47]. Recently, Sivaguru group [48] demonstrated that heterocycles possessing multiple stereocenters can be prepared using photochemical chemistry by intramolecular [2 + 2] photocycloaddition (Scheme 12). By incorporating axial chirality into the system, cycloaddition process can be effectively controlled leading to the appropriate stereoisomer 96 in up to 99% yield.

![Scheme 12](image)

Scheme 12. [2 + 2] Photocycloaddition of enones.
Tetrahydroquinolines (THQ) are an important class of compounds being significant synthetic target for chemists. In this context, Guan and co-workers reported synthesis of tetrahydroquinoline derivatives utilizing Rose Bengal 7 (RB) as a catalyst under irradiation by the compact fluorescent lamp (CFL) [49]. This newer approach to the previously reported by Rueping and coworkers [50] proceeds via tandem radical cyclization of N,N-dimethylanilines 97 with 2-benzylidenemalononitriles 98 to six-membered non-aromatic heterocycles 99 in up to 74% yield (Scheme 13a). The mechanism of this transformation can be rationalized on the basis of 1O2 formation by interaction of O2 with the excited-state of Rose Bengal catalyst (RB*) (Scheme 13b). Generated singlet oxygen proceeds single electron transfer with the formation of cation radical 100. Absorbing proton by dioxygen radical anion results in the formation of amine radical 101, which react with 2-benzylidenepropanedinitrile 98 and produce the alkyl radical 102. Finally, intramolecular cyclization of 102 followed by rearomatization by the second electron transfer/proton elimination step gives the final product 99.

![Scheme 13.](image-url)

Scheme 13. (a) Synthesis of tetrahydroquinoline derivatives; (b) Proposed mechanism for synthesis of tetrahydroquinoline derivatives.

Similarly, using (N,N-dimethyl)anilines 104 for the formation of α-amino radicals, Zhang [51] and Yadav [52] group revealed an efficient [4 + 2] cyclization to the THQ analogues 106. In this process, N-hydroxyphthalimide 20 was used as an organophotoredox catalyst under white LEDs irradiation (Scheme 14a). Elaborated protocol involves C(sp3)-H activation of N-methylanilines 104 for the formation of α–amino radical 108, which undergoes [4 + 2] cyclization with maleimide 105 to form...
intermediate 109. Finally, aromatization of 109 leads to the desired product 106 in up to 94% yield (Scheme 14b).

By utilizing sulfonyl radicals, many sulfonyl containing compounds can be prepared using photoredox catalysis. The use of cheap, non-irritating sodium sulfinate opens the way to the possibility to generate sulfonyl radicals by means of visible-light-induced catalysis. Zuo et al. disclosed a tandem radical addition/cyclization concept for the synthesis of isoquinolinediones [53]. A mild radical cascade reaction is based on sulfonyl radical generation from the appropriate sodium sulfinate and Eosin Y under blue LED irradiation (Scheme 15a). In this tandem approach, a broad range of substrates and functional group are tolerated leading to the desired products in up to 82% yield. The reaction starts on generation of excited state of Eosin (EY*) by blue LEDs irradiation which is reductively quenched by sulfinate to sulfinate radical and EY•− catalyst (Scheme 15b). More stable form of radical—radical undergoes subsequent addition to the double bond of 113 generating radical, which yields radical by intramolecular cyclization. Finally, the single electron and proton transfer between EY•− and 119 delivers the desired product 115. The photocatalytic cycle is completed by the reaction of Eosin hydride with proton, which leads to the release of hydrogen from the reaction mixture.
2.2. O-Containing Heterocycles

2.2.1. Aromatic Heterocycles

Similar to N-containing heterocycles, their oxygen analogues can be also found in many natural products and pharmaceuticals [54,55], attracting broad interests by scientific community. A new route toward the synthesis of a functionalized furan ring has been recently disclosed by Lei and co-workers [56]. Lei elaborated the synthesis of this useful scaffold through the visible-light-mediated oxidative [3 + 2] cycloaddition of enols and alkynes 121 (Scheme 16a). This highly selective method of constructing substituted furans is based on the usage of Methylene Blue 13 as catalyst in combination with (NH₄)₂S₂O₈ as a terminal oxidant. General mechanism for this transformation is disclosed in Scheme 16b. First, visible-light irradiation of Methylene Blue (MB) leads to the formation of its excited-state MB*. The persulfate is then reduced by MB* to form the sulfate radical anion. Subsequent hydrogen atom transfer between 120 and sulfate radical anion forms intermediate 123, which undergoes intermolecular addition to the triple bond of alkyne 121 with the formation of radical 124. Next, intramolecular radical addition to the carbonyl oxygen forms a five-membered O-heterocycle 125 radical. Finally, oxidation of 125 by MB** followed by deprotonation leads to the final product 122.
forms a five-membered O-heterocycle radical. Finally, oxidation of by MB •+ followed by deprotonation leads to the final product.

Scheme 16. (a) Visible-light-mediated oxidative [3 + 2] cycloaddition in the synthesis of furans; (b) Proposed mechanism.

2.2.2. Non-Aromatic Heterocycles

In addition to heteroaromatic compounds, their non-aromatic oxygen-containing analogues are equally important. Butyrolactones are a class of heterocycles highly prevalent in nature, indicating many interesting bioactivities [57,58]. Given their importance, many synthetic strategies for their preparations have been elaborated, including photoredox catalysis. In 2015, Nicewicz group presented a synthesis of α-benzyloamino-γ-butyrolactones 129 via polar radical crossover cycloaddition reaction [59]. The photoredox reaction is carried out using the Fukuzimi acridinium 12 photooxidant, easily accessible oxime acids 128 and alkenes 127. Using given methodology, various lactones 129 with high functional group variations are accessible in very good yields (Scheme 17a). On the basis of the author’s previous work, they proposed a plausible reaction pathway for this interesting transformation (Scheme 17b) [60]. First, a single electron oxidation of the alkene 127 by the excited state of catalyst (PC +*) affords cation radical 137. Next, the radical 137 reacts with the oxime acid 128 resulting in the formation of the radical 130. Subsequent deprotonation of compound 130, followed by intramolecular 5-exo-trig radical cyclization furnishes N-centered radical 131. Finally, hydrogen atom transfer between 131 and 133 affords final product 129 and regenerates the acridinium catalyst 12 in its ground state. Authors indicated, however, that another mechanistic pathway without the use of H-atom donor co-catalyst might be involved.
The synthesis of structurally similar butyrolactones by metal-free visible-light-mediated catalysis has been also described by Liu [61] and Shah groups [62]. Moreover, by using amide analogues of various γ-lactams or pyrrolidines can be prepared as well [63].

An impressive example of a chiral ion-pair photoredox organocatalyst [64] in enantioselective hydroethrelyfication of alkenols in stereoselective synthesis of tetrahydrofuran analogs has been recently disclosed by Luo and co-workers [65]. The described work showed that ion pair catalysts indicate improved activity compared to Fukuzimi catalysts 12 and proves that visible-light-mediated catalysis is feasible for stereoselective transformations (Scheme 18a). This reaction is based on the three stage process: single electron transfer, cyclization, and hydrogen transfer and has been described already in detail by Nicewicz group [60]. However, it has been disclosed by the authors that the origin of the higher activity observed with an ion pair catalyst is related with cyclization/H-transfer sequence. Phosphate anion in ion pair catalyst endows a longer lifetime of the chiral photocatalysts triplet state, introduces chirality, and assists in the H-shift (Scheme 18b).
Cibulka group revealed that Flavin derivatives 16 can be a successful organic catalyst, able to perform intramolecular \([2 + 2]\) cycloaddition of 148 under 400 nm violet LEDs irradiation [66–68] (Scheme 19a). 1-Butyl-7,8-dimethoxy-3-methylalloxazine 148 under irradiation undergoes intramolecular \([2 + 2]\) cycloaddition of both styrene dienes forming bicyclic unit 149 (Scheme 19b). This photo-induced cycloaddition takes place with a broad spectrum of dienes leading to the formation of desired products 149 in good to excellent yields (up to 97%).
Scheme 19. (a) Flavin-mediated visible-light [2 + 2] cycloaddition of dienes; (b) Proposed mechanism.

Ionic approach for polyene cyclization has been extensively explored, thus constituting the main synthetic strategy of polyene ring synthesis [69]. However, stereoselective radical cyclization can also have significant benefits [70]. In this context, Zhang and Luo group [71] demonstrated visible-light-induced cyclization of polyenes in the synthesis of various oxygen-containing heterocycles (Scheme 20a). The reported protocol is based on radical cascade cyclization using Eosin Y 11a as a catalyst and green LEDs. Desired products 152 are prepared in moderate to excellent yields (up to 90%) and high stereoselectivities (d.r. > 19:1). In Scheme 20b, a reasonable mechanism for this transformation is suggested. First, excited state of Eosin catalyst (EY*) is formed upon green LEDs’ irradiation. Next, intersystem crossing (ISC) forms triplet 3EY*, which allows for electron transfer from the substrate 151 to the 3EY* resulting in the formation of the radical cation 153 and EY radical anion (EY•−). The generated radical 153 undergoes intramolecular radical cascade cyclization together with the hydrogen shift to the intermediate 154. Finally, intermediate 154 is reduced to the desired product 152, whereas Eosin radical anion (EY•−) is oxidized, regenerating catalyst and completing the photocatalytic cycle.
In addition to the sulfonated quinolines (Scheme 6), its oxygen containing analogs—cumarines can be also obtained. In this context, various alkynes undergo arylsulfonylation with arylsulfinic acid and TBHP using Eosin Y \textsuperscript{11a} as a catalyst. It is noteworthy that appropriate cumarines can be obtained in good yields with a wide functional group tolerance \textsuperscript{72}.

2.3. Heterocycles Bearing More Than One Heteroatom

An efficient and straightforward strategy for building functionalized, N- or O-bearing heteroatoms is the 1,3-dipolar cycloaddition \textsuperscript{73}. Xia, Yang and collaborators \textsuperscript{74} described visible-light-mediated anti-regioselective 1,3-dipolar cycloaddition of nitrones \textsuperscript{155} with alkenes \textsuperscript{156} (Scheme 21a). The nitrones are cyclized with styrenes and aliphatic alkenes via a polar radical crossover cycloaddition reaction using triphenylpyrrylium catalyst \textsuperscript{8b} under blue light irradiation. This transformation is based on the mechanism presented in Scheme 21b. Initially, upon blue LEDs irradiation excited state of catalysts is formed (PC*), which then oxidize double bond of \textsuperscript{156} via the reductive quenching process. Electrophilic addition of intermediate \textsuperscript{158} to nitrone \textsuperscript{155}, followed by a radical cyclization leads to the intermediate \textsuperscript{159}. This intermediate act as an oxidant enabling regeneration of the catalyst by electron transfer alongside with the product formation. The authors also suggest a possible radical chain propagation between \textsuperscript{158} and alkene \textsuperscript{155}.

Woo group \textsuperscript{75} unveiled that nitrones can be also generated in situ from oxaziridines in photoredox conditions. They described synthetic method for the preparation of 4-isoxazolines \textsuperscript{162} in a visible-light photoredox-catalyzed [3 + 2] cycloaddition of oxaziridines \textsuperscript{160} with alkynes \textsuperscript{161} (Scheme 22a). Described methodology relies on the in situ generation of nitrones from oxaziridines \textsuperscript{160} by the single electron transfer process, which undergoes [3 + 2] cycloaddition with various alkynes. On the basis of a series of experiments, the following mechanism is proposed by the authors (Scheme 22b). Excited (Acr*-Mes*) catalyst formed upon blue LEDs irradiation allows for the single electron oxidation process of aziridine \textsuperscript{160} alongside with the reduced photocatalyst (Acr*-Mes) formation. The radical cation \textsuperscript{163} is then converted into the nitrone radical \textsuperscript{164} through the ring opening process. Single-electron reduction of nitrone radical \textsuperscript{164} by Acr*-Mes regenerates catalyst and forms nitrone \textsuperscript{165}. Finally, [3 + 2] cycloaddition of nitrone \textsuperscript{165} with alkyne \textsuperscript{161} provides the product \textsuperscript{162}. 

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**Scheme 20.** (a) Visible-light-mediated radical cascade cyclization of polyenes; (b) Proposed mechanism.
Scheme 21. (a) Visible-light-mediated nitrone 1,3-dipolar cycloaddition; (b) Proposed mechanism.

Scheme 22. (a) [3 + 2] Cycloaddition of oxaziridines with alkynes; (b) Proposed mechanism.
1,2,4-Oxadiazole derivatives besides exhibiting biological activities have also found application in light-emitting diodes (OLEDs) [76]. Due to the importance of this group, Cho and co-workers developed oxidative cyclization of amidoximes under visible-light conditions [77]. Described protocol involves the intramolecular oxidative cyclization of amidoximes 166 in the presence of the triphenylpyrylium 8c catalyst and molecular oxygen as the oxidant, promoted by compact fluorescent lamp (Scheme 23a). Opposite to all previous examples, in this particular transformation T(\(p\-F\))PPT act as both an electrophilic catalyst and a photocatalyst due to the fact that reaction works also in the dark, although less efficient. The authors proposed a possible mechanism for this transformation (Scheme 23b). Reaction starts by the nucleophilic addition of 166 to the triphenylpyrylium ion 168 and generates intermediate 169, which undergoes homolytic dissociation and produce two radicals: 171 and 170. Additionally, this process is accelerated by the visible-light irradiation. The catalyst 168 is then regenerated by the molecular oxygen oxidation of 170 intermediate. Beside catalyst regeneration cycle, the radical 171 undergoes an intramolecular 1,5-hydrogen atom transfer (HAT) and produces the radical 172. Subsequent oxidation of the compound 172 to the iminium ion by molecular oxygen or excited catalyst followed by intramolecular cyclization yields the final product 167.

![Scheme 23](image)

**Scheme 23.** (a) Application of amidoximes in visible-light-driven synthesis of oxadiazolines; (b) Proposed mechanism.

Many natural or synthetic compounds containing oxazoline scaffold have been found to possess some level of interesting bioactivities [78]. Moreover, these structures are important building blocks in the syntheses of many chiral ligands in stereoselective synthesis [79]. Therefore, novel methodologies for the synthesis of these structural motifs are highly desirable. In this context, Nicewicz and co-workers...
disclosed photoredox-catalyzed hydrofunctionalization of unsaturated amides and thioamides in the synthesis of 2-oxazolines and 2-thiazolines [80]. This intramolecular functionalization is based on dual catalytic system comprised from 174 and phenyl disulphide (Scheme 24a).

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\begin{align*}
\text{Scheme 24. (a) Hydrofunctionalization of unsaturated amides; (b) Proposed mechanism.}
\end{align*}
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This mild and efficient protocol leading to the products 175 in good yields (up to 82%) tolerates also many functional groups. In Scheme 24b, a reasonable mechanism for this transformation is suggested. Excitation of acridinium catalyst 12 by blue LED irradiation generates the active oxidant (PC**), which accepts an electron from substrate 174, generating cation radical intermediate 176. Subsequent cyclization and proton loss affords cyclic radical intermediate 177. Finally, hydrogen atom transfer from thiophenol 178 generates product 175 and a thyl radical 179. The thyl radical 179 is presumed to re-oxidize the acridine radical catalyst (PC*), regenerating catalyst in its ground state.

An impressive example of visible-light-mediated generation and utilization of fluorophosgene was developed by König group [81]. Presented procedure is based on the cleavage of an aryl trifluoromethoxy ether 183 and in situ conversion of formed fluorophosgene for the synthesis of carbamates, carbonates, and urea derivatives 184 (Scheme 25a). The reported protocol is based on the single-electron reduction of 4-(trifluoromethoxy)benzonitrile 183 and its fragmentation into fluorophosgene 183a, which undergoes further intramolecular cyclization with 1,2-diamines, aminoalcohols or diols 182 (Scheme 25b). In this way, carbonates, various carbamates, and urea derivatives 184 can be prepared in moderate to excellent yields.
Scheme 24 (a), Hydrofunctionalization of unsaturated amides. (b), Proposed mechanism. This mild and efficient protocol leading to the products 175 in good yields (up to 82%) tolerates also many functional groups. In Scheme 24b, a reasonable mechanism for this transformation is suggested. Excitation of acridinium catalyst 12 by blue LED irradiation generates the active oxidant (PC+*), which accepts an electron from substrate 174, generating cation radical intermediate 176. Subsequent cyclization and proton loss affords cyclic radical intermediate 177. Finally, hydrogen atom transfer from thiophenol 178 generates product 175 and a thiyl radical 179. The thiyl radical 179 is presumed to re-oxidize the acridine radical catalyst (PC •), regenerating catalyst in its ground state.

An impressive example of visible-light-mediated generation and utilization of fluorophosgene was developed by König group [81]. Presented procedure is based on the cleavage of an aryl trifluoromethoxy ether 183 and in situ conversion of formed fluorophosgene for the synthesis of carbamates, carbonates, and urea derivatives (Scheme 25a). The reported protocol is based on the single-electron reduction of 4-(trifluoromethoxy)benzonitrile 183 and its fragmentation into fluorophosgene 183a, which undergoes further intramolecular cyclization with 1,2-diamines, aminoalcohols or diols 182 (Scheme 25b). In this way, carbonates, various carbamates, and urea derivatives 184 can be prepared in moderate to excellent yields.

Scheme 25. (a) Visible-light-mediated in situ generation and conversion of fluorophosgene; (b) Proposed mechanism.

Quinazolines are another class of heterocyclic compounds extensively studied. Itoh et al. described the synthesis of quinazolines 187 under visible-light conditions by employing coupling of primary amines 185 and aldehydes 186 (Scheme 26a) [82]. A possible mechanism as proposed by the authors is disclosed in Scheme 26b. Initially, cyclization between the diamine 185 and the aldehyde 186 takes place leading to the diamine 188. In the same time, Rose Bengal 7 (RB) is excited under irradiation followed by intersystem crossing (ISC) providing 3RB*. Subsequent energy transfer from triplet RB catalyst to oxygen produces reactive singlet oxygen 1O2 responsible for the oxidation of the compound 188 into the final product 187.
photoredox conditions. In this context, a corresponding amine formed upon cyclization of diamine triggered by Eosin Y. Sun et al. described alkoxycarbonylation–addition–cyclization sequence.

More recently, Das group also demonstrated cyclization of the diamines and aldehydes into heterocycles can be prepared in up to 81% yield (Scheme 28a).

Scheme 26. (a) Synthesis of quinazolines. (b) Proposed mechanism.

The cyano moiety is widely used in organic synthesis because it undergoes many important transformations. Sun et al. described alkoxycarbonylation–addition–cyclization sequence triggered by Eosin Y 11a under white LEDs irradiation in the synthesis of polyheterocycles 194 [86].
This visible-light-induced cascade reaction is initiated by the intermolecular radical addition of alkyl carbazate 193 to a double bond of N-arylacrylamide 192 followed by cyano-mediated cyclization. Desired poly nitrogen containing heterocycles 194 can be prepared in up to 81% yield (Scheme 28a).

![Scheme 28](image)

Scheme 28. (a) Photoredox alkoxycarbonylation–addition–cyclization sequence; (b) Proposed mechanism.

The suggested mechanism is depicted in Scheme 28b. Excited state of Eosin EY* catalyst formed upon white LEDs’ irradiation undergoes single electron transfer with TBHP producing t-butoxy radical, which detach hydrogen from carbazate 193 leading to the radical intermediate 195. Sequential dehydrogenation of 195 followed by nitrogen release provides alkoxycarbonyl radical 197. At this moment, generated radical 197 reacts with double bond of the starting material 192 leading to the intermediate 198, which undergoes intramolecular cyclization with cyano group to the radical intermediate 200 (path a). Alternatively, the radical 198 can undergo intramolecular cyclization with the aromatic ring (path b) leading to the undesired product 199 in trace amount. The radical 200 undergoes another intramolecular cyclization producing conjugated radical 201, which after oxidation by the Eosin Y cation radical (EY*+) forms intermediate 202. Final product 194 is obtained by the deprotonation of intermediate 202.

In the context of synthesis of THIQ analogues, Baruah et al. elaborated cross dehydrogenative approach toward 1,3-oxazines using visible-light-induced catalysis [87]. 1-Aminoalkyl-2-naphthols
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203 easily undergoes intramolecular cyclization using Eosin Y 11a as photoredox catalyst and green light source (Scheme 29a). On the basis of a series of control experiments, the authors proposed a plausible catalytic cycle (Scheme 29b). The excited Eosin Y (EY*) accepts an electron from the starting material 203 to form a cation radical 205. Next, the generated EY•− radical anion undergoes electron transfer with molecular oxygen regenerating the ground state Eosin Y 11a and forming superoxide radical anion. Hydrogen removal from 205 and subsequent intramolecular addition of hydroxyl to the imine group provides the final product 204 in up to 86% yield.

Scheme 29. (a) Synthesis of 1,3-oxazines under photoredox conditions; (b) Proposed mechanism.

Quinazolinone structure is another important structural unit in heterocyclic chemistry [1–3]. Idrolone, Hydromox, and sildenafil citrate are the representative drugs containing quinazolinone motif. Pan and co-workers [88] demonstrated synthesis of sulfonated quinazolinones 209 in visible-light-induced oxidative/reductive cyclization of N-cyanamide alkenes 207 (Scheme 30a). Presented strategy features mild reaction conditions and broad substrate suitability. Various complex N-heterocycles 209 can be accessed in up to 98% yield. On the basis of their experimental observations and literature studies, authors proposed the mechanism depicted in Scheme 30b. Firstly, Eosin Y 11b is irradiated by green LEDs to generate the excited-state Eosin Y (EY*). Secondly, electron transfer from Eosin to tert-butyl hydroperoxide (TBHP) generates t-butyloxy radical and OH−. Subsequent hydrogen atom removal from 214 produces sulfur-centered radical 215, which undergoes addition to the double bond of 207 and produces radical intermediate 210. Intramolecular cyclization cascade delivers radical 212, which is oxidized by EY•+ to the cationic intermediate 213 through a single-electron-transfer route regenerating the same EY in its ground state. Finally, deprotonation of 213 gives the expected product 209.
In addition to the given examples, other heterocycles containing multiple heteroatoms like imidazopyridines [89] or oxadiazoles [90] can be also obtained using metal-free visible-light-mediated catalysis.

3. Conclusions

In this review, recent advances in the synthesis of nitrogen and oxygen heterocyclic compounds via a metal-free visible-light-induced catalysis have been discussed. It has been shown that various metal-free organic dyes are effective photo-redox catalysts in the synthesis of many structurally different heterocycles containing one or more heteroatoms. Both non-aromatic and aromatic heterocyclic units are readily accessible by using visible-light-mediated catalysis in a straightforward modular way. Reported works indicate that organic dyes capable of visible-light-spectra absorption act as an attractive alternative to the transition-metal complexes. The variety of the presented examples indicates the potential use of the described methodologies in organic synthesis, drug discovery, or materials science. Moreover, the use of inexpensive organic, transition metal-free catalysts makes described protocols very practical and hold promise for broader application in industry and scientific community.

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