EurJOC
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A Journal of ChemPubSoc Europe

Accepted Article

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To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.201800011

Link to VoR: http://dx.doi.org/10.1002/ejoc.201800011

Supported by ACES Asian Chemical Editorial Society

WILEY-VCH

DOI: 10.1002/adsc.201((will be filled in by the editorial staff))

Synthesis of Phenanthrenes via Visible Light Photoredox Catalyzed Intramolecular Cyclization of α-Bromochalcones

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Received: ((will be filled in by the editorial staff))

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201######.((Please delete if not appropriate))

Abstract. A mild and efficient photocatalytic protocol for the synthesis of phenanthrene scaffold has been devised. The reaction involves intramolecular cyclization of α-keto radicals generated from α-bromochalcones under visible light photoredox catalyzed conditions. The high product yields, wide substrate scope and complete regioselectivity are noticeable attributes of the reaction.

Keywords: Phenanthrene; visible light; photoredox; α-keto radical; intramolecular

Introduction

The phenanthrene motif occurs widely in nature and exhibits several medicinal properties such as analgesic, antimicrobial, anticancer, antifertility, anti-inflammatory, antiallergic, antispasmolytic, antiviral etc.[1] Also, there are numerous drugs and synthetic molecules of therapeutic potential bearing phenanthrene scaffold (Figure 1).[2]

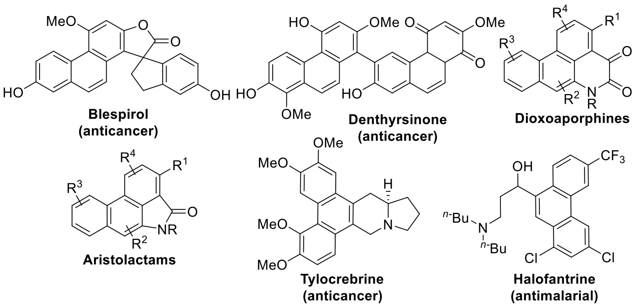


Figure 1. Phenanthrene Scaffold in natural/synthetic medicinal compounds

Further, due to their unique photophysical properties several phenanthrene based molecules and polymers found use in the material science.[3]

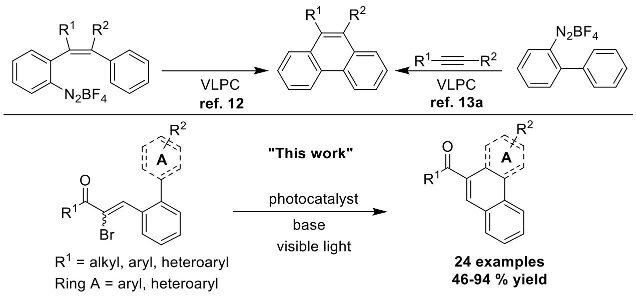
The common methods for the synthesis of phenanthrene scaffold include intramolecular[4] or intermolecular[5] cyclization of biphenyl derivatives with alkynes, intramolecular radical cyclizations of stilbene derivatives[6a] including classical Pshorr cyclization of stilbenes,[6b,c] photocyclization of stilbenes,[7] palladium-catalyzed annulation reactions of dibromoarenes[8] and transition metal catalyzed [5+5] cycloaddition between α,β-unsaturated Fisher carbene complex and o-alkynylbenzoyl system.[9]

Recently, emergence of photoredox catalysis as a greener alternative to the traditional radical reactions has led to the development of several useful protocols for C-C as well as C-heteroatom bond formation.[10] Although visible light photoredox catalyzed intramolecular radical cyclizations have been reported frequently for the synthesis of various fused polycyclic scaffolds,[11] the examples of phenanthrene synthesis under photoredox catalysis are limited.

Deronzier and co-workers first reported visible light catalyzed Pschorr reaction with $Ru(bpy)_3Cl_2$ as photocatalyst for the synthesis of phenanthrenes.[12] Zhou and co-workers reported eosin Y catalyzed [4+2] benzannulation of biaryldiazonium salts with alkynes for the synthesis of phenanthrene scaffold.[13a] Later, same strategy was practiced by Cho et al for preparing polyheteroaromatic compounds.[13b] Recently, Barriault and co-workers used gold complex for the generation of vinyl radicals via photoexcitation of $C(sp^2)$-Br bond followed by intramolecular cyclization leading to the synthesis of polycyclic molecules including phenanthrene.[14]

Recently, Reiser and co-workers reported using α-bromo chalcones as the source of α-keto radicals which were subsequently trapped by heteroarenes and alkenes yielding polycyclic molecular scaffolds under photoredox catalyzed conditions.[15a,b] Later the same group reported VLPC intramolecular cyclization of α-keto radicals into indolines,[15c] indenones and dihydroindeno[1,2-c]chromenes.[15d]

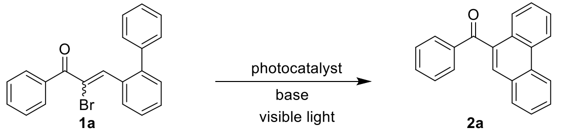
Herein we report the synthesis of phenanthren-9-yl ketones via intramolecular cylization of α-keto radicals generated from α-bromochalcones under VLPC conditions (Scheme 1).



Scheme 1. Synthesis of phenanthrene scaffold under VLPC conditions

We first investigated the proposed reaction with bromochalcone **1a** (E_{red} = -0.82 V vs. SCE; please see the supporting information) with photocatalyst [Ru(bpy)$_3$Cl$_2$] ($E_{RuIII/RuII*}$ = -0.81 V vs. SCE)[16b] and base potassium carbonate in DMF under blue light irradiation anticipating an oxidative quenching mechanism (Table 1).

Table 1. Optimization of reaction conditions.[a]



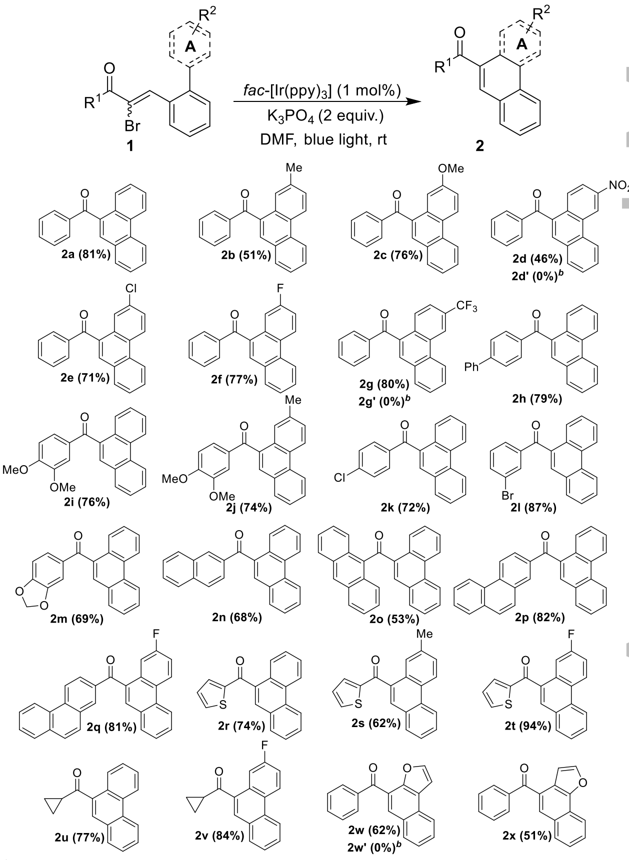
Entry	Photocatalyst (mol%), Base (equiv), Solvent	Yield (%)[b]
1	[Ru(bpy)$_3$Cl$_2$] (1), K$_2$CO$_3$ (2), DMF	21
2	[Ir{dF(CF$_3$)ppy}$_2$(dtb-bpy)]PF$_6$ (1), K$_2$CO$_3$ (2), DMF	36
3	Rose Bengal (1), K$_2$CO$_3$ (2), DMF	0
4[c]	Eosin Y (1), K$_2$CO$_3$ (2), DMF	0
5	*fac*-[Ir(ppy)$_3$] (1), K$_2$CO$_3$ (2), DMF	75
6	*fac*-[Ir(ppy)$_3$] (0.5), K$_2$CO$_3$ (2), DMF	44
7	*fac*-[Ir(ppy)$_3$] (1.5), K$_2$CO$_3$ (2), DMF	70
8	*fac*-[Ir(ppy)$_3$] (1), K$_2$CO$_3$ (2), DMSO	47
9	*fac*-[Ir(ppy)$_3$] (1), K$_2$CO$_3$ (2), MeCN	24
10	***fac*-[Ir(ppy)$_3$] (1), K$_3$PO$_4$ (2), DMF**	**86 (81)[d]**
11	*fac*-[Ir(ppy)$_3$] (1), NaHCO$_3$ (2), DMF	60
12	*fac*-[Ir(ppy)$_3$] (1), Na$_2$HPO$_4$ (2), DMF	60
13	*fac*-[Ir(ppy)$_3$] (1), K$_3$PO$_4$ (1.5), DMF	82
14	*fac*-[Ir(ppy)$_3$] (1), K$_3$PO$_4$ (2.5), DMF	87
15	**no photocatalyst**, K$_3$PO$_4$ (2), DMF	NR
16	*fac*-[Ir(ppy)$_3$] (1), K$_3$PO$_4$ (2), DMF, **no light**	NR
17	*fac*-[Ir(ppy)$_3$] (1), **no base**, DMF	52

[a] Reaction Conditions: **1a** (0.3 mmol) with specified amounts of photocatalyst and base was irradiated in solvent (2.0 mL) with a 450 nm blue LED for 3 h. [b] NMR yields. [c] Green LED. [d] Isolated yield in parentheses.

The reaction resulted into the formation of desired product **2a** in 3 hours, albeit in low yield (entry 1). Similarly, the photocatalyst [Ir{dF(CF$_3$)ppy}$_2$(dtb-bpy)]PF$_6$ (Ir^{IV}/Ir^{III*} = -0.89 V vs SCE)[16a] also afforded the desired product but only with a slight improvement in the yield (entry 2). As anticipated, no reaction was noticed when organic dye Rose Bengal (RB$^{\bullet+}$/RB* = -0.68V vs SCE) was used as photocatalyst (entry 3), however failure of Eosin Y (EY$^{\bullet+}$/EY* = -1.11V vs SCE) to provide any product was intriguing (entry 4).[17] Further, an excellent yield of product was obtained with the stronger reducing photocatalyst *fac*-[Ir(ppy)$_3$] (Ir^{IV}/Ir^{III*} = -1.73V vs SCE) which was selected for further optimization of reaction conditions (entry 5). The amount of *fac*-[Ir(ppy)$_3$] optimal for the reaction was found to be 1 mol% since a sharp decline in product yield occurred with 0.5 mol% of it (entry 6) whereas slightly lower yield i.e 70% was noted with 1.5 mol% of the photocatalyst (entry 7). The reaction when carried out in other solvents such as DMSO and MeCN proved to be much less productive in terms of yields (entries 8-9). Further, changing the base to potassium phosphate drastically improved product yield which was only moderate with other bases used i.e. NaHCO$_3$ and Na$_2$HPO$_4$ (entries 10-12). Also, optimization of the amount of base revealed that 2 equivalent of base is optimum considering the reaction yield and economy (entries 10, 13-14). The reaction failed to furnish any product in the absence of photocatalyst or visible light, substantiating the importance of both for a successful reaction (entries 15-16). However, interestingly the product could be isolated in modest yield without using base in the reaction (entry 17).

After the extensive optimization, we proceeded to examine the scope of α-bromochalcones **1** in the reaction (Table 2).

Table 2. Scope of α-bromochalcones **1**[a]



[a] Reaction Conditions: **1** (0.3 mmol), K$_3$PO$_4$ (0.6 mmol, 2.0 equiv) and *fac*-[Ir(ppy)$_3$] (0.003 mmol, 1.0 mol%) were irradiated in anhydrous DMF (2.0 mL) with a 450 nm blue LED for 3 h. [b] Please see reference **18**

The α-bromochalcones with various R^1 groups including aryl, heteroaryl as well as aliphatic moieties were utilized successfully in the reaction. Moreover, the substituents in the β-biaryl part (R^2) were varied to include the neutral, electron releasing as well as electron withdrawing groups. The reaction worked smoothly under optimized conditions to afford the products in high yields in most of the cases. The reaction provided phenanthrene-aryl ketones where the aryl part could be benzene **(2a-m)**, naphthalene **(2n)**, anthracene **(2o)** as well as phenanthrene ring **(2p-q)**. Also, the phenanthrenyl-heteroaryl ketones **(2r-t)** were isolated in excellent yields under the optimized reaction conditions. The reaction also successfully afforded the phenanthrene-alkyl ketones **(2u-v)** in high yields. Finally, changing the ring "A" from aryl to heteroaryl also worked well yielding positional isomers naphtho[2,1-b]furan-4-yl(phenyl)methanone **2w** and naphtho[1,2-b]furan-4-yl(phenyl)methanone **2x**.[18] This is specially noteworthy that our strategy provides both the positional isomers **2w** and **2x** by selecting the appropriate substrate, whereas only **2x** is accessible through the cascade cyclization of α-keto radical with furan as reported by Reiser and co-workers due to the preferential addition of the α-keto radical on the C-2 position of furan ring.[15a]

It is also important to note that in case of substrates **1d**, **1g**, and **1w**, the reaction exhibited complete regioselectivity in favour of the products **2d**, **2g** and **2w** over the other regioisomers **2d'**, **2g'** and **2w'**, respectively.[18] The structure of **2w** was confirmed by comparing with the reported structure[15a] whereas the structures of **2d** and **2g** were assigned on the basis of spectroscopic data and X-ray analysis of **2g** (Figure 2).[19]

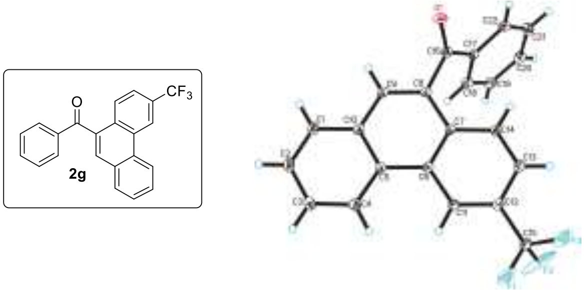
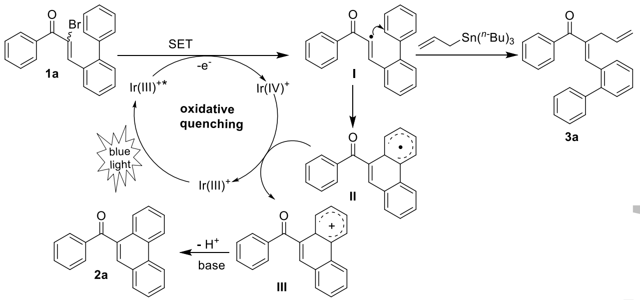


Figure 2. ORTEP diagram drawn with 10% ellipsoid probability for non-H atoms of the crystal structure of compound **2g** determined at 293 K

On the basis of our observations during photocatalyst screening and ~~from~~ literature reports the reaction possibly follows the oxidative quenching mechanism (Scheme 2). Initially, the photocatalyst [*fac*-Ir(III)(ppy)$_3$] excited by blue light in the state [*fac*-Ir(III)(ppy)$_3$*] reduces the bromochalcone **1** by single-electron transfer. The α-keto radical **I** thus generated adds on to the aryl ring intramolecularly leading to the generation of radical **II**. The generation of radical species **I** was confirmed by trapping with allyltributyltin to furnish product **3a** (please see the supporting information). The oxidation of radical intermediate **II** effected by the strong oxidant [*fac*-Ir(IV)(ppy)$_3$]$^+$ completes the catalytic cycle and produces cyclohexadienyl cation **III**. Finally, cation **III** undergoes deprotonation in the presence of base to provide the corresponding phenanthrene product **2**.



Scheme 2. Plausible mechanism

Conclusion

In conclusion, we established a simple methodology for the synthesis of phenanthrene scaffold by employing conveniently accessible starting materials. The reactions take place at room temperature in short reaction time with photocatalyst *fac*-[Ir(ppy)$_3$] under visible light photoredox catalyzed conditions. The highlights of the methodology are wide substrate scope, complete regioselectivity, and accessibility of positional isomers in case of heteroaryl substrates.

Experimental Section

General procedure for the photoredox catalyzed intramolecular cyclization

In an oven dried 5 mL snap vial equipped with a magnetic stirring bar, the α-bromochalcone **1** (0.3 mmol), K_3PO_4 (0.13 g, 0.6 mmol, 2.0 equiv) and photocatalyst *fac*-[Ir(ppy)3] (0.002 g, 0.003 mmol, 1.0 mol%) were dissolved in anhydrous DMF (2 mL). The resulting reaction mixture was degassed by three "pump-freeze-thaw" cycles via a syringe needle. The vial was irradiated using 450 nm blue LEDs with a cooling device maintaining the temperature around 25 °C. After 3 h of irradiation (TLC monitoring), the reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using hexane/ethyl acetate as eluent to afford the pure product **2.**

Acknowledgements

SBN thanks UGC, New Delhi for the Ph. D. fellowship. We thank SAIF division of CSIR-CDRI for the analytical support. We thank Dr. Tejender S. Thakur of Molecular and Structural Biology Division, CSIR-Central Drug Research Institute for supervising the X-ray Data collection and structure determination of **2g**. We are also thankful to Ms. Shachi Mishra and Dr. Atul Goel, of Medicinal and Process Chemistry Division, CSIR-Central Drug Research Institute for determining the redox potential value of **1a** by cyclic voltammetry. We gratefully acknowledge Department of Science & Technology (DST), New Delhi for the financial support (Project Ref. No.: EMR/2016/006975). CDRI Communication No: 9623

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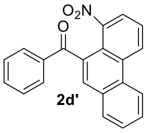
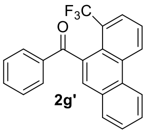
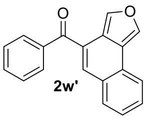
[18] Structure of **2d’**, **2g’**, **2w’**:



2d'



2g'



2w'

[19] Crystal structure of compound **2g** has been deposited at the Cambridge Crystallographic Data Center and allocated the reference no. CCDC 1578791.

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FULL PAPER

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Adv. Synth. Catal. **Year**, *Volume*, Page – Page

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