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PII: S0040-4039(14)01751-1
DOI: http://dx.doi.org/10.1016/j.tetlet.2014.10.068
Reference: TETL 45297

To appear in: *Tetrahedron Letters*

Received Date: 12 July 2014
Revised Date: 2 October 2014
Accepted Date: 10 October 2014

Please cite this article as: Cheng, P., Qing, Z., Liu, S., Liu, W., Xie, H., Zeng, J., Regiospecific Minisci acylation of phenanthridine via thermolysis or photolysis, *Tetrahedron Letters* (2014), doi: http://dx.doi.org/10.1016/j.tetlet.2014.10.068

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Pi Cheng [a, b], Zhixing Qing [c], Sheng Liu [b], Wei Liu [a], Hongqi Xie [a, *] and Jianguo Zeng [a, b, c *]

[a] *Pre-State Key Laboratory for Germplasm Innovation and Utilization of Crop, Hunan Agricultural University, Changsha, Hunan 410128, China*

[b] *National Research Center of Engineering Technology For Utilization of Functional Ingredients From Botanicals, Hunan Agricultural University, Changsha, Hunan 410128, China*

[c] *School of Pharmaceutical, Hunan University of Chinese Medicine, Changsha, Hunan 410208, China*

*Corresponding authors:

Hongqi Xie: Tel: +86 731 84686560; E-mail address: xiehongqi2006@126.com;

Jianguo Zeng: Tel: +86 731 84673824; E-mail address: ginkgo@world-way.net

Graphic Abstract

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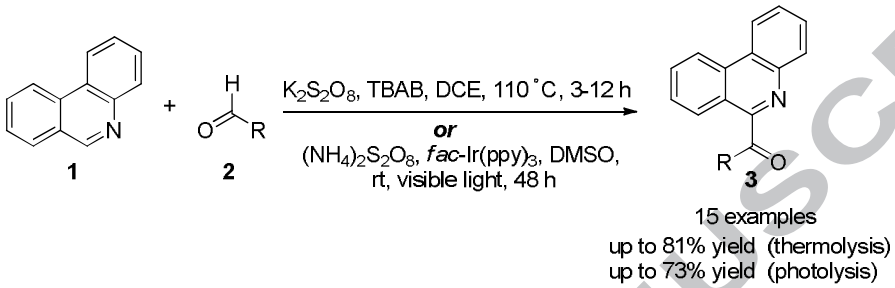
Using $K_2S_2O_8$ as oxidant and TBAB as initiator, acyl radicals generate from aldehydes substrates and couple with phenanthridine under thermal conditions at 110 °C. When $K_2S_2O_8$/TBAB is displaced by $(NH_4)_2S_2O_8$ and another 5 mol % *fac*-Ir(ppy)$_3$ catalyst is added to the reaction system, this type of coupling reaction proceeds slowly under visible light at room temperature.



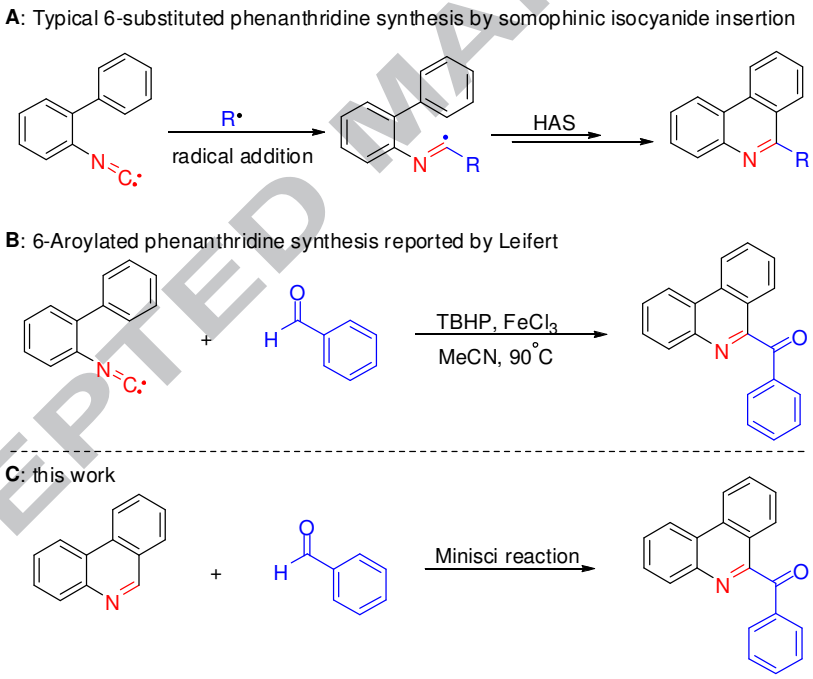
Abstract: In this study, a new type of Minisci reaction for regiospecific acylation of phenanthridine has been developed based on cross dehydrogenative coupling (CDC) strategy. Using substoichiometric amount of TBAB (tetrabutylammonium bromide, 30 mol %) and $K_2S_2O_8$ as an oxidant, acyl radicals generate from aldehydes substrates under thermal conditions followed by a regiospecific intermolecular acylation with phenanthridine. Furthermore, a preliminary research has indicated that the acylation reaction can be carried out at room temperature when $K_2S_2O_8$/TBAB is displaced by $(NH_4)_2S_2O_8$ and another 5 mol % of *fac*-Ir(ppy)$_3$ is used as photocatalyst under irradiation of visible light. This intermolecular acylation reaction provides an easy access to 6-acylated phenanthridine derivatives.

Key words: acylation, phenanthridine, Minisci reaction, photochemistry, *fac*-Ir(ppy)$_3$

The phenanthridine is a common pharmacophore existed in a wide variety of naturally occurring benzophenanthridine and phenanthridine alkaloids.[1–4] Among them benzo[*c*]phenanthridine alkaloid analogues such as NK109 exhibit potentanti-tumor activity by the inhibition of DNA topoisomerase I,[5–6] and are considered as potential anti-tumor drugs. Phenanthridines also possess a wide variety of interesting biological activities and potential pharmaceutical applications such as antibacterial,[7–8] DNA intercalator[9–10] and enzyme inhibition.[11–12] Substituted phenanthridines are also used in material science due to their significant optoelectronic properties.[13]

Because of the above reasons, diverse methods have been developed for phenanthridine synthesis in the last decades.[14–22] Along with the traditional methods,[23] phenanthridines have recently been successfully prepared by radical chemistry using cascades radical addition to 2-isocyanobiphenyls with subsequent homolytic aromatic substitution (HAS). Based on this strategy, various radical species such as sp^3 or sp^2 *C*-radicals,[24–27] *P*-radicals [28] and *Si*-radicals [29] reacted with 2-isocyanobiphenyls to give the corresponding 6-substituted phenanthridines (**A**, Scheme 1). Recently, Leifert[30] reported a new method to synthesize 6-aroylated phenanthiridne using aromatic aldehydes as *C*-radical precursor to react with 2-isocyanobiphenyls by HAS

strategy (**B**, Scheme 1). In this report, *t*-BuOOH (TBHP) was used as the oxidant and $FeCl_3$ as initiator. According to previous literature, the cross dehydrogenative coupling (CDC) provided another facile route to generate acyl radical with aldehydes as precursor for acylation of arenes.[31–33] Based on CDC strategy, electron-deficient heteroarenes[34] such as pyridine, quinolone, isoquinoline and quinoxaline could be acylated via intermolecular Minisci reaction with aldehydes.[35–36] However, this method has never been applied to synthesize 6-aroylated phenanthridine and generally needs high reaction temperature. Guided by Leifert's research, we thought that the intermolecular cross dehydrogenative coupling of aromatic aldehydes with phenanthridine could also provide corresponding 6-aroylated phenanthridines via Minisci reaction to avoid using water sensitive and toxic 2-isocyanobiphenyls (**C**, Scheme 1).

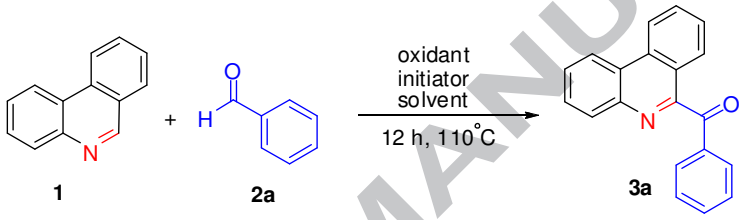


Scheme 1. Synthesis of 6-aroylated phenanthridines via radical addition to 2-isocyanobiphenyls and Minisci reaction

According to previous literatures, diverse oxidants such as $(NH_4)_2S_2O_8$[31], TBHP,[32–34] $PhI(OCOCF_3)_2$[35] and $K_2S_2O_8$[36] can be used for the CDC coupling reaction of aldehyde with various arenes, thus our reaction condition optimization began with oxidant screening. The reaction was optimized using 1.0 equiv of phenanthridine (**1**)

and 2.0 equiv of benzaldehyde (**2a**) as model substrates. In the most of times, CDC reaction was carried out in the presence of TBHP. However, experimental results in this study indicated that the intermolecular coupling of **1** and **2a** only furnished target compound **3a** in poor isolated yield when 2.0 equiv of TBHP (6M solution in decane) was used as oxidant (entry 1, Table 1). Small amount of $FeCl_3$(1 mol %) added to the reaction system could slightly improve the yield of **3a** after 9 h reaction time (entry 2, table 1). Increasing TBHP to 4.0 equiv promoted the reaction and gave **3a** in moderate yield under similar condition (entry 3–4, table 1). Although the reaction proceeded in the presence of TBHP, high yield of **3a** was not achieved.

Table 1. Optimization studies for coupling conditions [a]



entry	oxidant (equiv.)	catalyst (mol%)	solvent	Yield(%)[b]
1	6M TBHP in decane(2.0)	none	DCE	15
2[c]	6M TBHP in decane(2.0)	$FeCl_3$ (1)	DCE	18
3	6M TBHP in decane(2.0)	$FeCl_3$ (1)	DCE	23
4	6M TBHP in decane(4.0)	$FeCl_3$ (1)	DCE	37
5	$K_2S_2O_8$ (1.0)	none	DCE	10
6	$K_2S_2O_8$(2.0)	none	DCE	17
7	$K_2S_2O_8$ (2.0)	none	MeCN	NR
8	$K_2S_2O_8$ (2.0)	none	DMSO	NR
9	$K_2S_2O_8$ (2.0)	none	toluene	NR
10	$K_2S_2O_8$ (2.0)	none	DMF	NR
11	$K_2S_2O_8$ (2.0)	TBAB (10)	DCE	41
12	$K_2S_2O_8$ (2.0)	TBAB (30)	DCE	54
13[c]	**$K_2S_2O_8$ (2.0)**	**TBAB (30)**	**DCE**	**69**
14	$K_2S_2O_8$ (2.0)	KBr (30)	DCE	16
15	$(NH_4)_2S_2O_8$ (2.0)	none	DCE	51
16	$(NH_4)_2S_2O_8$ (2.0)	TBAB (30)	DCE	55

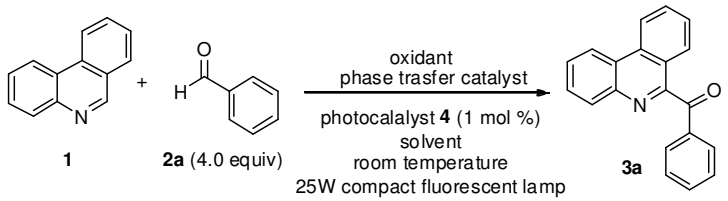
[a] **1a** (0.5mmol) and **2a** (1.0mmol) as model substrates in solvents (4 mL).
[b] isolated yield.
[c] **1a** (0.5 mmol) and **2a** (2.0 mmol) as model substrates in solvents (4 mL), 110 C for 9 h.
NR = not reaction.
DCE = dichloroethane.
TBAB = *tetra-n*-butylammonium bromide.

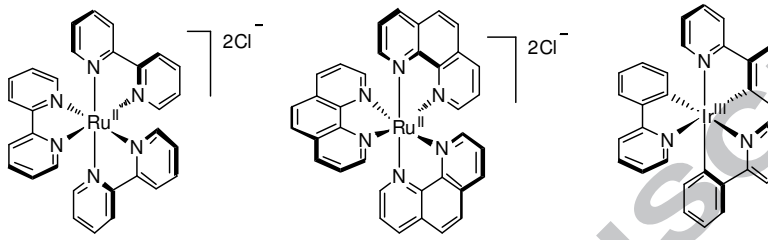
To continue oxidants screening, $K_2S_2O_8$ was used as an alternative of TBHP in this study. In the presence of 1.0 equiv of $K_2S_2O_8$, **3a** was obtained in 10% yield (entry 5, Table 1). Increasing $K_2S_2O_8$ to 2.0 equiv led to slightly promoted yield (entry 6, Table 1). After a screening of solvent, the experimental results suggested that MeCN, DMSO, toluene were not suitable for the reaction (entries 7–10, Table 1), whereas DCE was still the best suitable solvent for the reaction. When 10 mol% of TBAB was used as catalyst, the reaction furnished **3a** in 41% yield (entry 11, Table 1). Increasing the amount of TBAB to 30 mol% led to slightly enhanced yield of **3a** (entry 12, Table 1). To promote the reaction, when 4.0 equiv of benzaldehyde **2a** was used as C-radical precursor in the reaction, target compound **3a** was obtained in 69% yield (entry 13, Table 1). A further investigation of the role of TBAB in this type of Minisci reaction showed that when the same amount of KBr was used to displace TBAB, only 16% isolated yield of **3a** was achieved (entry 14, Table 1). According to previous literatures,[31, 36] TBAB possibly not only acted as a phase transfer catalyst in the reaction to dissolve persulfate anion but also a special initiator to facilitate the decomposition of $K_2S_2O_8$ to generate sulfate radical anion. Bromide ion (Br^-) of TBAB or KBr couldn't act as reductant to reduce persulfate to corresponding sulfate radical anion to promote the reaction efficiency. As a contrast, when 2.0 equiv. of $(NH_4)_2S_2O_8$ was used as oxidant, target compound **3a** was obtained in 55% and 51% yields with or without catalyst TBAB respectively (entry 15–16, Table 1). The experimental results indicated that $(NH_4)_2S_2O_8$ could decompose easily[37] or possibly possessed better solubility in DCE than $K_2S_2O_8$.

Although the optimized Minisci reaction in Table 1 could furnish **3a** in good yield, this type of acylation must be performed at high temperature using low boiling point organic solvent such as DCE. According to previous literatures, the ability of complex tris(2,2´-bipyridine) ruthenium(II) ($Ru(bpy)_3Cl_2$ **4a**, Table 2) and related transition metal complexes such as $Ru(phen)_3Cl_2$ and *fac*-$Ir(ppy)_3$ (**4b**–**4c**, Table 2) to function as visible light phtotocatalysts has been extensively investigated for room temperature organic synthesis in recent years.[38] Extensive studies demonstrated that photocatalyst can initiate single electron transfer (SET) processes and promote both reductive and

oxidative reaction under visible light irradiation. In present study, various photocatalysts were added to the reaction system as an effort to reduce the reaction temperature under irritation of 25W compact fluorescent lamp (CFL) (Table 2). After a preliminary solvents screening, we found that TBHP (6M in decane) was not suitable for the coupling reaction with **4a** ($Ru(bpy)_3Cl_2.6H_2O$) as photocatalyst in DCE and MeCN (entry 1–2, Table 2). With $K_2S_2O_8$ as oxidant and TBAB as phase transfer catalyst, no target compound was generated under irradiation of visible light in MeCN, DCE and DMSO respectively (entry 3–5, Table 2) and only trace of **3a** could be detected when the reaction was carried out in acetone after 48 h of reaction time (entry 6, Table 2). To continue the oxidants screening, $K_2S_2O_8$ was displaced by $(NH_4)_2S_2O_8$. However, desire compound was not obtained when the reaction was carried out in acetone and MeCN (entry 7–8, Table 2) in the presence of **4a** under irradiation of visible light. However, we were pleased to find that desire compound could be obtained in 38% isolated yield when DMSO was used as solvent (entry 9, Table 2). Thus, further photocatalysts screening was conducted which showed that *fac*-$Ir(ppy)_3$ (**4c**) possessed better catalytic ability than **4a** and **4b** (entry 10, Table 2) and 44% isolated yield of desire compound was achieved under the irradiation of visible light (entry 11, Table 2). To understand the role of visible light in the coupling reaction, control experiment was conducted as showed in Table 2. Only trace of desire compound could be detected when the reaction was carried out in darkness (entry 12, Table) in the presence of **4c**. It should be noted that $(NH_4)_2S_2O_8$ could decompose slowly in DMSO under visible light without any photocatalyst to give target compounds **3a** in 18% isolated yield (entry 13, Table 2). Uploading photocacalyst **4c** to 5 mol % slightly improved yield of **3a** from 44% to 52% (entry 14, Table 2). Increasing the oxidant $(NH_4)_2S_2O_8$ from 2.0 equiv to 4.0 equiv led to 58% isolated yield of **3a** when **4c** was used as photocatalyst under visible light at room temperature (entry 15, Table 2).

Table 2. Photocatalytic Minisci synthesis of **3a** [a]





entry	oxidant (2.0 equiv.)	photocatalyst (1 mol %)	phase transfer catalyst (0.3 equiv.)	solvent	time	yield (%)[b]
1	TBHP	**4a**	none	DCE	48 h	NR
2	TBHP	**4a**	none	MeCN	48 h	NR
3	$K_2S_2O_8$	**4a**	TBAB	MeCN	48 h	NR
4	$K_2S_2O_8$	**4a**	TBAB	DCE	48 h	NR
5	$K_2S_2O_8$	**4a**	TBAB	DMSO	48 h	NR
6	$K_2S_2O_8$	**4a**	TBAB	acetone	48 h	trace
7	$(NH_4)_2S_2O_8$	**4a**	none	acetone	48 h	NR
8	$(NH_4)_2S_2O_8$	**4a**	none	MeCN	48 h	NR
9	$(NH_4)_2S_2O_8$	**4a**	none	DMSO	48 h	38
10	$(NH_4)_2S_2O_8$	**4b**	none	DMSO	48 h	31
11	$(NH_4)_2S_2O_8$	**4c**	none	DMSO	48 h	44
12[c]	$(NH_4)_2S_2O_8$	**4c**	none	DMSO	48 h	trace
13	$(NH_4)_2S_2O_8$	none	none	DMSO	48 h	18
14[d]	$(NH_4)_2S_2O_8$	**4c**	none	DMSO	48 h	52
15[e]	**$(NH_4)_2S_2O_8$**	**4c**	**none**	**DMSO**	**48 h**	**58**

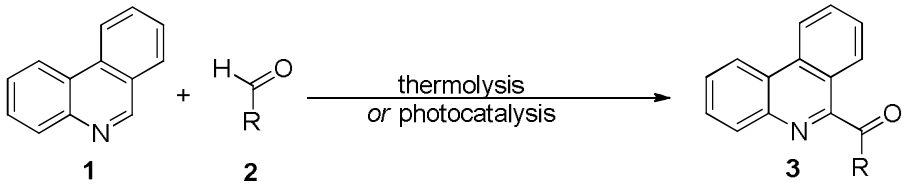
[a] **1a** (0.5mmol) and **2a** (1.0mmol) as model substrates in solvents (4 mL).
[b] isolated yield.
[c] reaction was carried out in darkness.
[d] 5 mol % of catalyst **4c** was used.
[e] 5 mol % of catalyst **4c** and 4.0 equiv. of oxidant were used.

With these optimized conditions in hand, we firstly surveyed the substrate scope of aromatic aldehyde under thermal conditions. Initially, a variety of halogen benzaldehydes were investigated by reaction with phenanthridine under standard

conditions. Phenanthridine underwent a smooth coupling reaction with chloro and bromo substituted benzaldehydes. The halogen atoms on phenyl ring didn't interfere with the coupling reaction which gave corresponding 6-aroylated phenanthridines in moderate yields (entry 2–5, Table 3). Interestingly, coupling reaction of 4-fluoro benzaldehyde with phenanthridine afforded the target compound in 80% isolated yield (entry 6, Table 3). Similarly, coupling reaction of 2-methyl and 4-methyl benzaldehydes with phenanthridine furnished corresponding aroylated phenanthridines in 58 and 64% yields respectively (entries 7–8, Table 3). It was also found that the reaction of *ortho*-substituted benzaldehydes with phenanthridine resulted in lower yields compared with *para*-substituted benzaldehydes. Similar yields of target compounds **3i** (57% yield) and **3j** (66% yield) were obtained when1-naphthaldehyde and 2-naphthaldehyde were used in the coupling reaction. Thus, it was suggested that the coupling reaction proceeded well with sterically less hindered aldehydes. To further investigate tolerance to functional group on phenyl ring of substrate under the optimized reaction conditions, 2-acetoxyl benzaldehyde was applied in the coupling reaction and gave target compound **3k** in 38%yield (entry 11, Table 3) with recovered substrates of pheanthridine and excess aldehyde detected by TLC experiment. On the other hand, the number of methoxyl group on phenyl ring didn't generate significant effects on the yields of target compounds (entries 12–15, Table 3). Generally, the electro-donating methoxyl group could facilitate the coupling reaction and give target compounds in better yields. However, it was quite interesting that reaction of 4-*N*,*N*-dimethylamino benzaldehyde with phenanthridine couldn't furnish target compound **3p** (entry 16, Table 3). The lack of reactivity of 4-*N*,*N*-dimethylamino benzaldehyde could be due to the preferential oxidation of tertiary amine in the substrate, which generated *N*-based radical or aryl radical which competes with the desired aldehyde oxidation. It should be noted that the reaction couldn't proceed with electro-deficient 4-nitrobenzaldehyde as substrates (entry 17, Table 3). Under optimized photocatalytic conditions as showed in Table 2, various aromatic aldehydes could react with phenanthridine. However, target compounds were generally obtained in lower isolated yields compared with thermolysis

conditions.

Table 3. Minisci reaction of phenanthridine with aromatic aldehydes

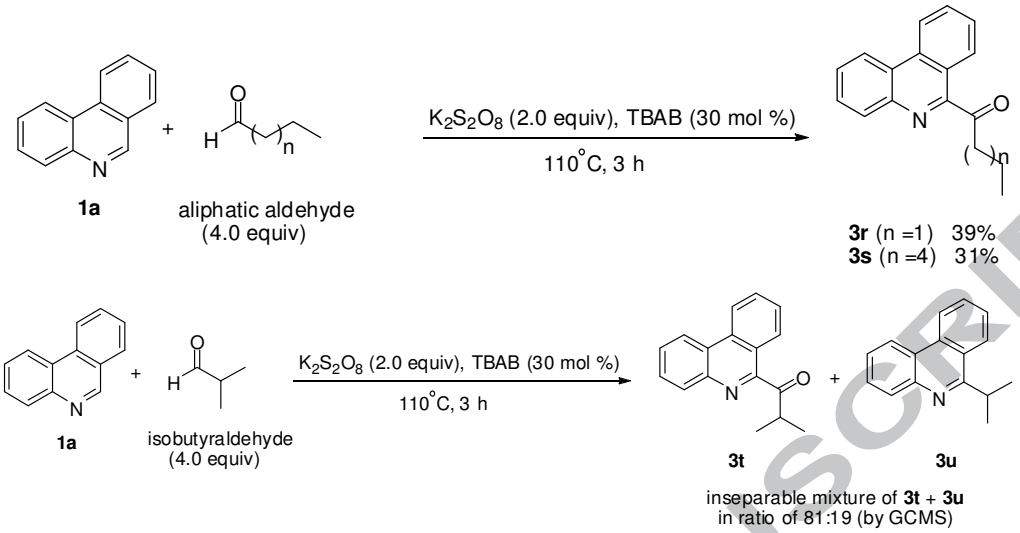


1 **2** **3**

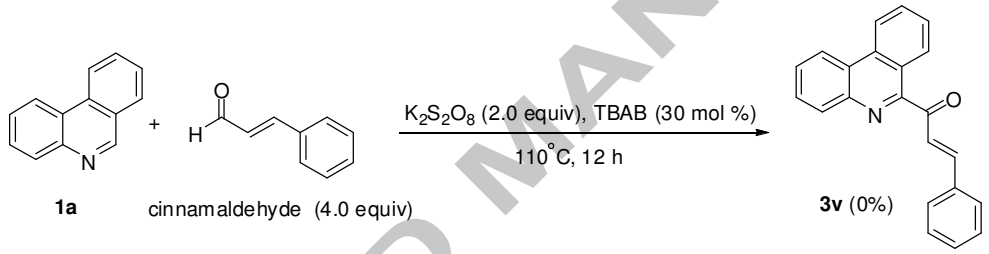
entry	Aldehyde **2**	Products **3**	Yield (%) thermolysis	Yield (%) photocatalysis
1	R = phenyl	**3a**	69	58
2	R = 2-Cl-phenyl	**3b**	54	40
3	R = 4-Cl-phenyl	**3c**	64	44
4	R^2 = 2-Br-phenyl	**3d**	50	35
5	R = 4-Br-phenyl	**3e**	65	60
6	R = 4-F-phenyl	**3f**	80	59
7	R = 2-Me-phenyl	**3g**	58	37
8	R = 4-Me-phenyl	**3h**	64	49
9	R = 1-napthyl	**3i**	57	45
10	R = 2-napthyl	**3j**	66	51
11	R =2-acetoxylphenyl	**3k**	38	27
12	R = 2-methxoylphenyl	**3l**	53	47
13	R = 4-methoxylphenyl	**3m**	70	68
14	R = 3,4-dimethoxylphenyl	**3n**	81	73
15	R = 3,4,5-trimethoxylphenyl	**3o**	77	63
16	R= 4-*N,N*-dimethylaminophenyl	**3p**	0	0
17	R^2 = 4-NO_2-phenyl	**3q**	0	0

To further expand the scope of this coupling reaction, we also investigated whether aliphatic aldehydeand α,β-unsaturated cinnamaldehyde work as substrate. When *n*-enanthic aldehydeand *n*-butanal were applied in the thermal coupling experiments, the reaction finished in 3 h under thermal conditions. Phenanthridine derivatives **3r** and **3s** were obtained in 39% and 31% isolated yields respectively (Scheme 2). However, the reaction of isopropanal with **1a** furnished the mixture of acylated (**3t**) and alkylated (**3u**) phenanthridine compounds as an inseparable mixture in a ratio of 81:19 (Scheme 2). The above experiments suggested that the stability of acyl radical and alkyl radical is crucial in the formation of products.[36] Under the optimized conditions, reaction of cinnamaldehyde with phenanthridine couldn't furnish target

compound **3v** with unreacted substrates detected (Scheme 3).

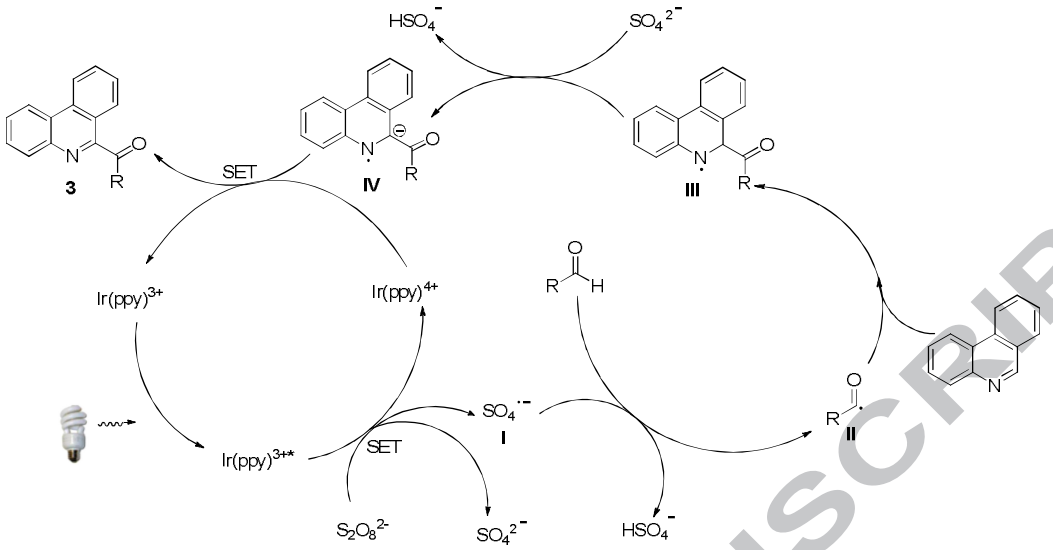


Scheme 2. Coupling reaction with aliphatic aldehydes



Scheme 3. Coupling reaction with cinnamaldehyde

On the basis of the literature precedence[31–36] and our experimental results, a possible photocatalytic mechanism was proposed in Scheme 4. Under photocatalytic conditions as listed in Scheme 4, we believe that persulfate anion can be reduced by visible light excited $Ir(ppy)_3^{3+}$* to give sulfate and sulfate radical anion **I** [37–38] together with $Ir(ppy)_3^{4+}$. The aldehyde can then undergo H-atom abstraction by radical **I** to give acyl radical **II**. Successively addition of acyl radical **II** to phenanthridine affords the corresponding amidyl radical **III**. Because of the neighboring carbonyl group, the α-proton in amidyl radical **III** is extremely acidic and can be deprotonated by the sulfate anion and then generates radical anion (**IV**). Through a single electron transfer (SET), a reductive quencher of $Ir(ppy)_3^{4+}$ by radical anion (**IV**) generates $Ir(ppy)_3^{3+}$ to sustain the photocatalytic chain along with the formation of target compound **3**. Under thermal conditions, the reaction mechanism in present study was similar to that as described in previous references. [31, 36]



Scheme 4. Proposed photocatalytic mechanism

In summary, we have developed an efficient method for the synthesis of 6-acylated phenanthridine derivatives through direct coupling of phenanthridine with various aromatic aldehydes. In the presence of $K_2S_2O_8$/TBAB, the CDC coupling of aldehydes with phenanthridine underwent smoothly in DCE under thermal conditions. When $K_2S_2O_8$/TBAB were displaced by $(NH_4)_2S_2O_8$ and another 5 mol % $Ir(ppy)_3$ catalyst was added to the reaction system, this type of coupling reaction proceeded slowly under visible light at room temperature. Persulfate was found to be an inexpensive and efficient reagent for this transformation. This Minisci reaction of acylation of electro-deficient phenanthridine was highly regioselective and provided a useful method for synthesis of functionalized phenanthridine derivatives with potential pharmacological activities.

Acknowledgement

This research was financially supported by Natural Science Foundation of China (No. 31402109), Natural Science Foundation of Hunan Province (No. 13JJ5044), Research Fund for the Doctoral Program of Higher Education, Ministry of Education of China (No. 20124320120006) and the Important Science & Technology Specific Projects of Hunan province (No. 2012FJ1004).

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Graphic Abstract

Regiospecific Minisci acylation of phenanthridine via thermolysis or photolysis

Pi Cheng [a, b], Zhixing Qing [c], Sheng Liu [b], Wei Liu [a], Hongqi Xie [a, *], Jianguo Zeng [a, b, c, *]

Using $K_2S_2O_8$ as oxidant and TBAB as initiator, acyl radicals generate from aldehydes substrates and couple with phenanthridine under thermal conditions at 110 °C. When $K_2S_2O_8$/TBAB is displaced by $(NH_4)_2S_2O_8$ and another 5 mol % *fac*-Ir(ppy)$_3$ catalyst is added to the reaction system, this type of coupling reaction proceeds slowly under visible light at room temperature.