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Visible-light-triggered, metal- and photocatalyst-free acylation of *N*-heterocycles

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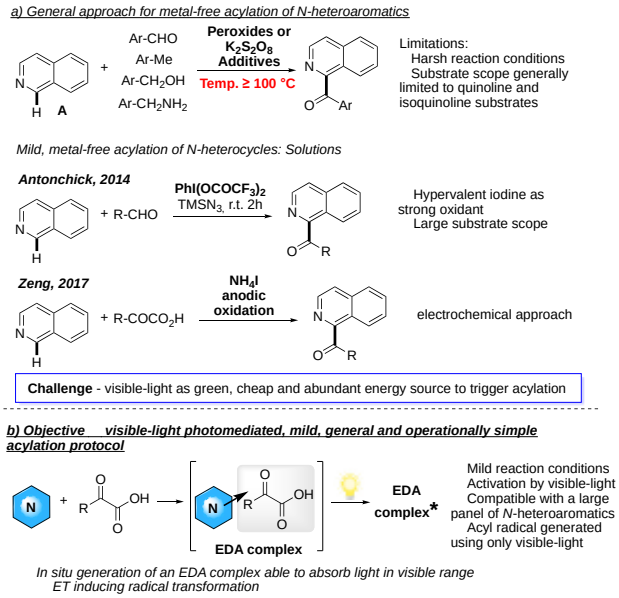
ABSTRACT: A photoinduced acylation of *N*-heterocycles is explored. This visible-light triggered reaction occurs not only under extremely mild reaction conditions, but also does not require the presence of a photosensitizer. The mechanistic studies suggest formation of EDA complexes prompt to harness the energy from visible-light. Compatibility with a large panel of α-keto acids as acyl precursors and an array of *N*-heterocycles clearly showcase the synthetic potential of this handy and green acylation protocol.

INTRODUCTION

Over the last decade visible-light induced photocatalysis has been attracting a swelling attention of the scientific community.[1] Indeed use of sunlight or simple household bulbs to promote challenging carbon-carbon and carbon-heteroatom bond formations under mild, environmentally benign and operationally simple protocols is extremely attractive. Nevertheless, since a large majority of organic molecules are not able to absorb visible-light, the photocatalytic transformations generally require the presence of a photosensitizer, such as expensive Ru- and Ir-based complexes or organic dyes. However, the strong reductive or oxidative potentials of those excited photocatalysts may induce a number of unexpected side reactions and thus limit the synthetic potential of such systems. Recently, following the pioneering discovery of Mulliken who formulated in 1952 the charge transfer theory,[2] it was demonstrated that in situ formation of an electron donor-acceptor (EDA) complex between two components of a reaction mixture[3] may allow a photosensitizer-free transformation.[4] Irradiation of colored EDA complexes with sunlight or household bulbs induces electronic transition (as frequently witnessed by a color change of the solution), into an excited electronic state, prompt to further trigger a radical process.

N-Heterocycles are key structural motifs of natural products and prevalent units in medicinal chemistry. In particular, quinolines bearing a benzoyl substituent exhibit various biological activities like antitussive, antipsychotic, antispasmodic, anxiolytic, antibacterial, antifugial and anticancer activities.[5] Over decades, different strategies have been designed to access decorated quinolines and amongst them direct functionalization via C-H modification has established itself as the most direct and step-efficient approaches.[6] In this context, the radical functionalization developed by Minisci[7] has attracted a great deal of attention although this protocol calls for a use of a silver salt catalyst. Targeting more environmentally benign protocols, several strategies for metal-free acylations have been designed. Acylated quinolines may thus be reached via radical transformations using aldehydes,[8] methyl arenes,[9] arylmethanol derivatives[10] or benzylamines[11] as coupling partners, in combination with oxidants at high reaction temperature (Scheme 1a).[12] However, due to the relatively harsh conditions, functional group tolerance of such transformations is limited and none of them allow functionalization of an array of heterocycles with both, aliphatic and aromatic acyl precursors. More recently, only two mild and metal-free alternative strategies towards acylation of *N*-heterocycles have been disclosed independently by Antonchick and Zhang. The protocol developed by Antonchick calls for the use of hypervalent iodane reagents[13] whereas Zhang's system astutely applies electrochemical approach.[14] In clear contrast, use of visible-light to mediate acylation of quinoline derivatives as well as many others families of *N*-heterocycles is elusive.[15] Such a modern strategy would certainly provide a truly sustainable and operationally simple protocol to access a variety of acylated compounds, in particular if both aromatic and aliphatic acyl moieties might be introduced.

Scheme 1. Radical acylation of *N*-heterocycles and new photo-mediated approach.



Targeting a truly mild and green synthetic approach toward benzoyl *N*-heterocycles, we surmised that if α–keto acids are used as coupling partners, photoinduced generation of an acyl radical[16] should be possible at room temperature (Scheme 1b).

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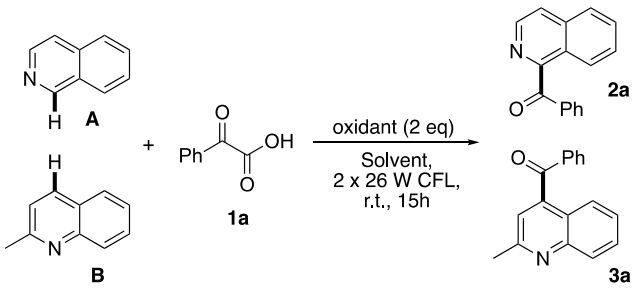
Indeed, α–oxocarboxylic acids, abundant and non-toxic precursors, are readily converted into the corresponding acyl radicals under visible-light irradiation. Furthermore, a capacity of *N*-heterocyclic compounds to play a key role in energy transfer (ET) reactions has been widely demonstrated.[17] In contrast, while α–keto acids were unknown for EDA complex formation, their conjugate □-system makes them a reasonable candidates for ET transformations.[18] Accordingly, generation of such unprecedented EDA complexes between *N*-heterocycles and α–keto acids could be an appealing solution to trigger the photosensitizer-free acylations.

Herein we report an unprecedented general strategy for the visible-light mediated acylation of heteroaromatics. The expected reactivity is achieved in the absence of any photosensitizer, rendering this mild protocol a truly handy and eco-friendly route toward functionalized *N*-heterocycles.

RESULTS AND DISCUSSIONS

To assess the feasibility of the targeted photosensitizer-free, visible light triggered transformation, coupling between **A** and phenyl glyoxylic acid **1a** was performed under household bulb irradiation and using different oxidants (Table 1; entries 1-4). Remarkably, the expected product **2a** was formed in a presence of PIDA, oxone and $K_2S_2O_8$. The optimal 69% yield was obtained using persulfate and when conducting the reaction in DCE/H_2O mixture (Table 1 entry 4). Notably, this solvent mixture turned out to be the optimal reaction medium as decreased efficiency was observed in acetone, MeCN and DMSO (Table 1, entries 5-7). Importantly, the coupling was unproductive in the dark (Table 1, entry 8). Successively, in order to rapidly evaluate versatility of this protocol, a more general character of this transformation was probed by exploring the functionalization of 2-methylquinoline **B**. Gratifyingly the desired acylation also takes place under photosensitizer-free conditions (Table 1 entry 9). Aqueous medium turned out to be particularly beneficial furnishing **3a** in 65% yield (Table 1 entry 10). Furthermore, the reaction proceeds smoothly under non-inert atmosphere and when using non-degassed solvents showcasing the robustness of this system. The photo-triggered character was again demonstrated (Table 1, entry 11). Interestingly, although a trace amount of **3a** was produced in absence of $K_2S_2O_8$ (Table 1, entry 12), this oxidant is essential to reach high conversion of the starting material and molecular oxygen is not suitable to promote this coupling (Table 1, entries 13-14).

Table 1. Optimization tolerance towards no study.

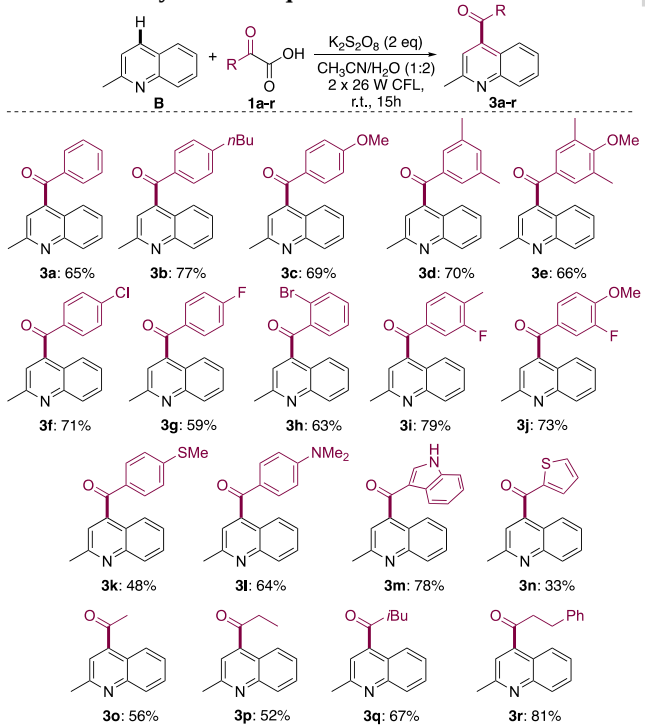


entry	substrate	Oxidant	Solvent	Yield[a]
1	A	PIDA	DCE	12
2	A	Oxone	DCE	54
3	A	$K_2S_2O_8$	DCE	54
4	A	$K_2S_2O_8$	DCE/H_2O (1:1)	69
5	A	$K_2S_2O_8$	Acetone	23
6	A	$K_2S_2O_8$	MeCN	41
7	A	$K_2S_2O_8$	H_2O	70
8[b]	A	$K_2S_2O_8$	DCE/H_2O (1:1)	nr
9	B	$K_2S_2O_8$	MeCN/H_2O (1:2)	61
10	B	$K_2S_2O_8$	H_2O	65
11[b]	B	$K_2S_2O_8$	H_2O	nr
12[c]	B	$K_2S_2O_8$	MeCN/H_2O (1:2)	17
13[d]	B	$K_2S_2O_8$	MeCN/H_2O (1:2)	12
14[e]	B	$K_2S_2O_8$	MeCN/H_2O (1:2)	14

[a] NMR yield using CH_2Br_2 as internal standard; [b] reaction conducted in dark at 40 °C; [c] no $K_2S_2O_8$ and under air atmosphere; [d] no $K_2S_2O_8$ and under O_2 atmosphere; [e] no $K_2S_2O_8$ and under argon atmosphere.

With the optimized conditions in hand, the scope of this reaction was explored with respect to α–oxocarboxylic acids (Scheme 2).[19] This new protocol turned out to be highly efficient for an array of aromatic α–oxocarboxylic acids. Electron-donating motifs such as alkyl or methoxy substituents were well tolerated when introduced at *para*- or *meta*-positions, delivering **3b-e** in 66 to 77% yield. Fluoro- and chloro-substituted **1f** and **1g** performed equally well. Remarkably, relatively sterically congested, *ortho*-Br-substituted **1h** was a highly active coupling partner (**3h** isolated in 63% yield). α–Oxocarboxylic acids bearing both, electron-donating and electron-withdrawing moieties (**1i-j**) were also potent substrates and even strongly coordinating thioether and amine groups were accepted, furnishing **3k** and **3l** in synthetically useful yields of 48 and 64%. This strategy is also an efficient handle to install an acyl group bearing heteroaromatic motifs, as exemplified by the synthesis of indole-substituted **3m** and thiophene-derived **3n**. The panel of available acylated quinolines was supplemented by effective couplings with several aliphatic α–keto acids, furnishing **3o-r** in 52-81% yield. In particular, acetylation producing **3o** is difficult under other metal-free protocols.[8-11]

Scheme 2. Acylation of quinaldine with α–keto acids.[a]



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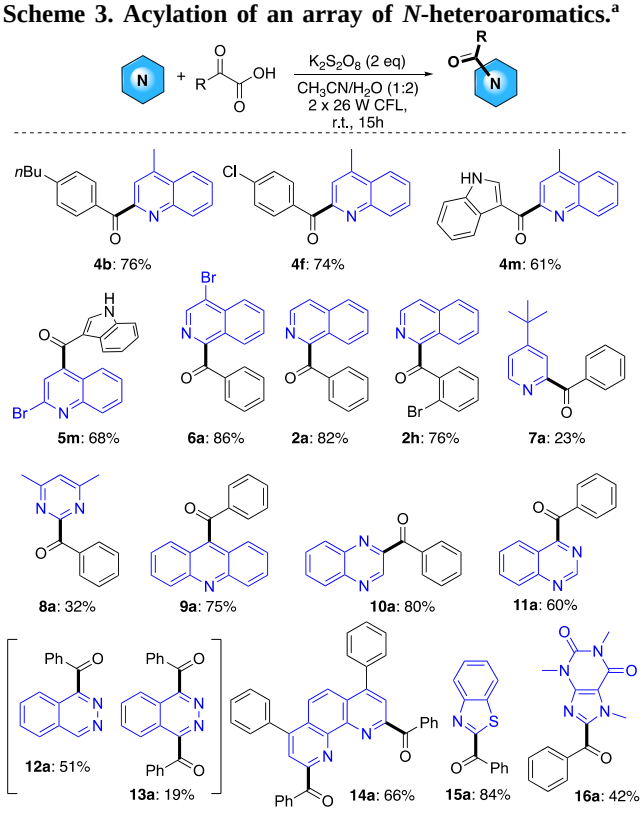
[a] Reaction conditions: **B** (0.25 mmol), $K_2S_2O_8$ (0.50 mmol), **1** (0.50 mmol), in CH_3CN/H_2O (0.5 mL / 1mL), 2 x 26 W CFL, 15h, under air atmosphere, isolated yields.

To explore the potential of this transformation further, various *N*-heterocycles were submitted to the reaction conditions (Scheme 3). 4-Me-Quinoline, lepidine, showed a comparable reactivity as its 2-substituted congener, delivering **4b**, **4f** and **4m** in respectively, 76, 74 and 61% yields. Interestingly, bromine substituent, a useful handle for further diversification, was well tolerated on both quinoline scaffolds, as **5m** and **6a** were provided in 68 and 86% yield respectively, and on the α–oxocarboxylic acids, as illustrated by isolation of isoquinoline derivative **2h** in 76% yield. In contrast, acylation of a pyridine congener was less efficient, furnishing **7a** and **8a** in rather low yields. High-yielding and regioselective transformations occured for acridine, quinoxaline and quinazoline (**9a, 10a** and **11a**). In the case of phthalazine, monofunctionalized **12a** was isolated in 51%, together with 19% of its diacylated congener **13a**. 1,10-Phenanthroline scaffold may also be diversified using this protocol, furnishing 2,9-diacylated derivative **14a**. The plethora of available functionalized heterocycles was complemented with acylated benzothiazole **15a** and caffeine **16a**.

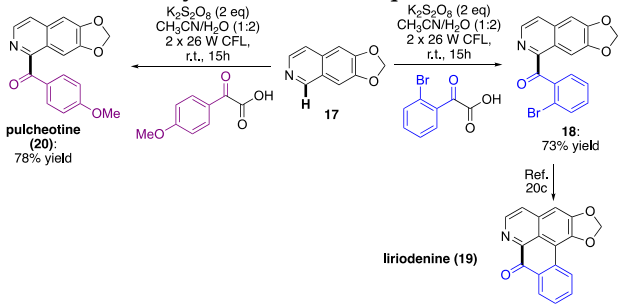
Scheme 3. Acylation of an array of *N*-heteroaromatics.[a]



[a] Reaction conditions: see scheme 2.

Regarding extremely mild, robust and simple reaction conditions, this new method seems particularly attractive for the synthesis of more complex molecular scaffolds. In particular, isoquinoline alkaloids are widely represented natural products.[20] Accordingly, we embarked on developing a new synthetic route towards a direct precursor of liriodenine **19** and pulcheotine **20** (Scheme 4). Both isoquinoline alkaloids may be obtained from a common precursor [1,3]dioxolo[4,5-g]isoquinoline **17,** build-up in 4 steps and 78% overall yield following a standard procedure (for details see Supporting Information).[20e,21] Subsequent acylation of **17** with 2-(4-methoxyphenyl)-2-oxoacetic acid **1c**, delivered the desired pulcheotine **20** in 78% yield. In addition, photo-mediated coupling of **17** with 2-(2-bromophenyl)-2-oxoacetic acid **1h** was equally productive, furnishing **18**, a direct precursor of liriodenine **19**,[20c] in 73% yield.

Scheme 4. Synthesis of isoquinoline alkaloids.



To gain a better understanding of this photo-induced process, mechanistic studies were conducted (Scheme 5). First, the radical character of this coupling was confirmed as no expected product was generated upon addition of TEMPO or 1,1-diphenylethylene (DPE), providing instead adducts **21** and **22** (Scheme 5a). The "on-off" experiment further showed the key role of the light (Scheme 5b). Subsequently, formation of the acyl radical was investigated (Scheme 5c). In the dark and in the absence of $K_2S_2O_8$, only a trace amount of **21** was formed but, as expected, the acyl radical formation was productive under light irradiation and the presence of $K_2S_2O_8$ clearly accelerates this process.

Spectroscopic studies were then undertaken to unravel how energy from visible-light is apparently harnessed during the reaction without participation of a photosensitizer (Scheme 6a). UV-Vis measurements between 300 and 400 nm revealed no absorption band for $K_2S_2O_8$ while a very weak band could be detected for the quinoline **B** (□ = 330-380 nm). Significantly stronger absorption band was detected in near UV-light (□ > 300 nm) with shoulder up to 380 nm for **1a**. This result seems coherent with the observed slow photodecarboxylation and generation of the acyl radical when reacting **1a** with TEMPO (Scheme 5c).[16g] Furthermore, as **1a** absorbs weakly within 330-380 nm range, a standard acylation reaction was performed using UV-A pen as a light source. The expected product **3a** was afforded in 66% yield indicating that UV-A light might be suitable to promote this transformation.[22] In order to study a generation of the EDA complex, spectroscopic data of mixtures between different components were also recorded. Remarkably, immediately after mixing solution of **B** with **1a**, a color change from light yellow to light orange was evidenced and the optical absorption spectra showed a bathochromic displacement and a strong absorption increase in the visible region (330-700 nm), clearly supporting EDA complex generation (**EDA-A**). Besides, a characteristic batochromic band shift and a stronger absorption were also witnessed for a solution containing the heterocycle **B** and $K_2S_2O_8$, indicating presence of a second type of EDA complex (**EDA-B**).[3h] Following the Job's plot method,[23] the stoichiometry of **EDA-A** in solution was found to be 3:1 (excess of quinaldine) and, in an identical way, a maximum absorbance of the **EDA-B** complex was observed for 3:1 mixture of quinaldine and potassium persulfate (for details see Supporting Information) (Scheme 6b). Besides, association constants of 0.91 M^{-1} and 3.57 M^{-1} for **EDA-A** and **EDA-B** complexes respectively, were determined using Benesi-Hildebrand equation[24] (for details see Supporting Information). In order to confirm that the absorption of the light by the EDA complexes in the visible region (400-700 nm) may induce the acyl radical formation, the standard reaction was performed using two band-

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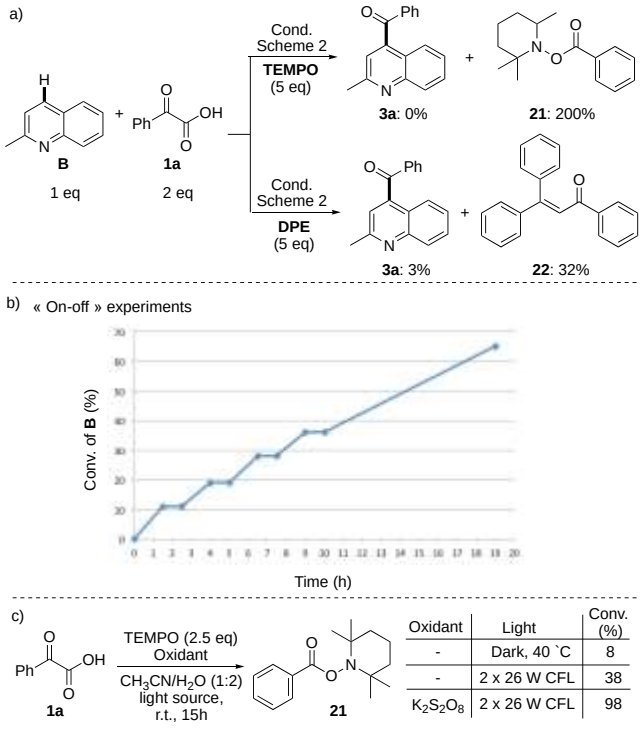
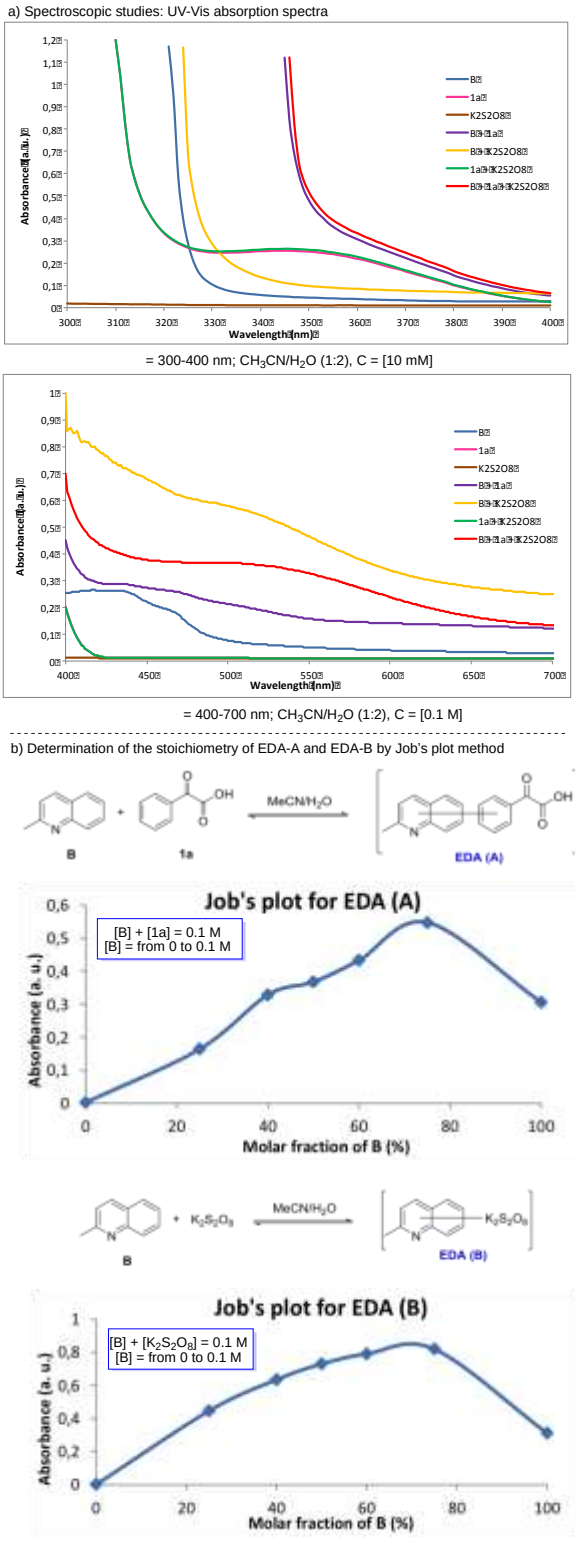
pass filters λ > 400 nm (on each CFL). In accordance with the spectroscopic data, the acylation occurred smoothly (**3a** isolated in 62% yield).

Based on these studies and literature precedents, the mechanism of the overall transformation may be proposed with the key question concerning the generation of the acyl radical (Scheme 7). Arguably, three different pathways may be envisioned: A) Direct generation of the acyl radical triggered by a low absorption of light by α–keto acid in the range of 330-380 nm (CFL light emission spectra shows weak emission around 360 nm); B) Generation of the **EDA complex A**, absorbing the visible-light and thus enhancing photodecarboxylation of **1a**; C) Generation of the **EDA complex B**, promoting homolytic cleavage of $S_2O_8^{2-}$ to produce $SO4^{\bullet-}$ triggering decarboxylation of the α–keto acid and generation of the acyl radical. Importantly, participation of persulfate might be essential in all cases, in accordance with the low efficiency of this transformation in absence of this reagent. At this stage clear differentiation between these pathways remains challenging and coexistence of several routes to access the acyl radical is plausible. In addition, spectroscopic features of various α–keto acids might further influence the feasibility of these three pathways in every individual case. Once the acyl radical is afforded, addition on the protonated heteroarene takes place and following HAT involving $SO4^{\bullet-}$, deprotonation and rearomatization deliver the expected acylated *N*-heterocycles.

Scheme 5. Mechanistic studies.



Scheme 6. Characterization of the EDA complexes.



Scheme 7. Proposed mechanism.

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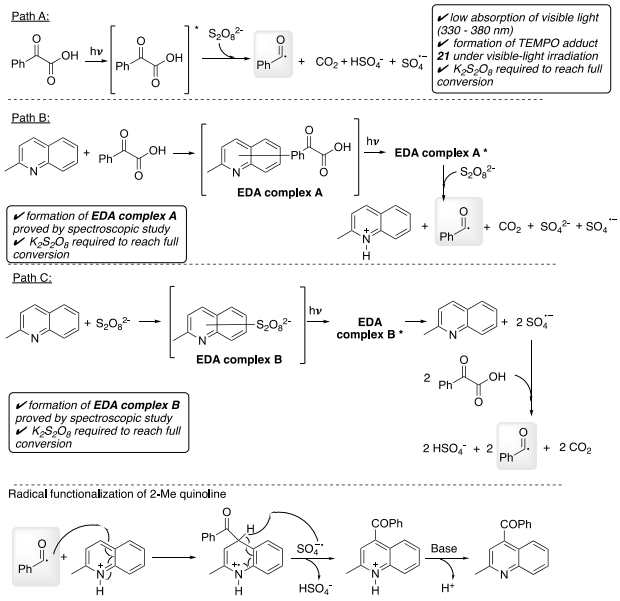

CONCLUSIONS

In conclusion, an unprecedented, mild and catalyst-free visible-light protocol for C-H acylation of *N*-heterocycles was developed. Remarkably, the energy from visible-light is harnessed in the absence of any external photosensitizer, arguably via formation of photoactive EDA complexes, thus inducing formation of the acyl radical and subsequent C-C bond formation event. The scope of this radical reaction is wide, with respect to both acyl-derivatives and *N*-heterocyles, clearly showing its appealing synthetic features. Accordingly, this strategy paves the way toward mild, operationally simple and environmentally benign synthesis of biologically relevant isoquinoline alkaloids.

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