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Photo-redox catalyzed dehydrazinative acylation of N-heterocycles via Minisci reaction†

Saira Hafeez [ID] [a] and Aamer Saeed [ID] *[b]

Visible light-induced acylation of heteroaromatic compounds have been achieved using benzoyl hydrazides as an efficient acyl source under mild reaction conditions. The photo-redox catalyzed oxidative cleavage of hydrazides leads to in situ formation of acyl radicals, which subsequently couple with various N-heterocycles to produce acylated products. This synthetic strategy performs the classic Minisci reaction in an eco-friendly and greener way with functional group tolerance and regioselectivity. Control experiments confirm the radical pathway for this transformation.
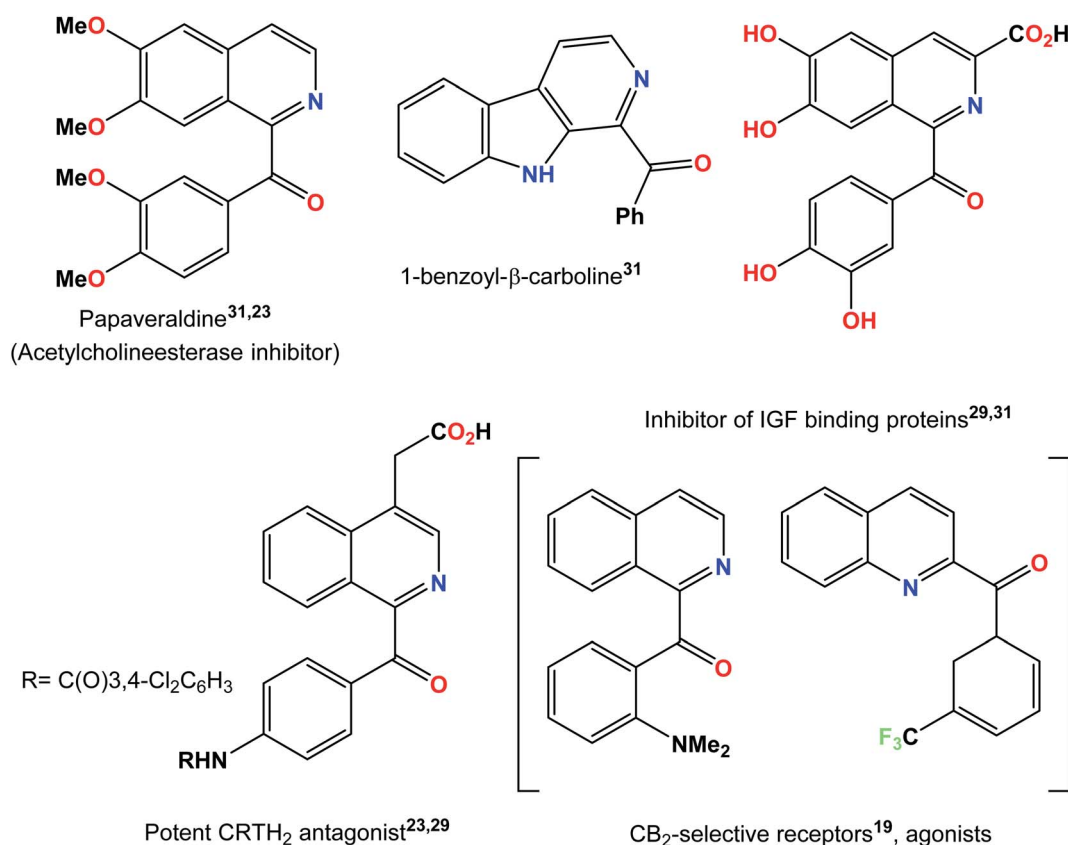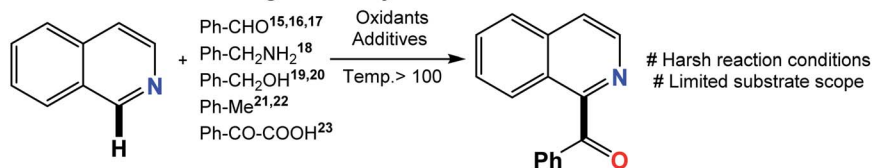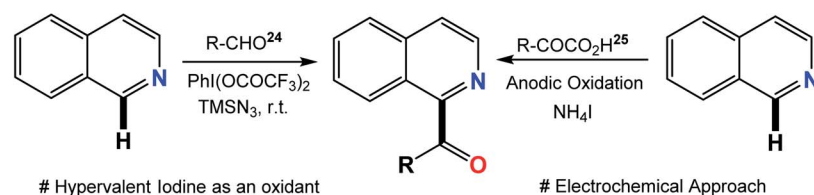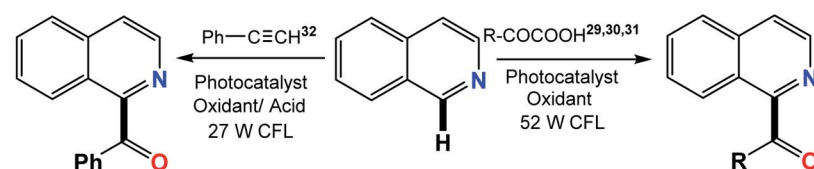
Papaveraldine[31,23]
(Acetylcholineesterase inhibitor)

1-benzoyl-β-carboline[31]

Inhibitor of IGF binding proteins[29,31]

R= C(O)3,4-Cl$_2$C$_6$H$_3$

Potent CRTH$_2$ antagonist[23,29]

CB$_2$-selective receptors[19], agonists

Fig. 1 Some acyl functionalized N-heterocycles in natural products and pharmaceutical drugs.

[a]Department of Chemistry, University of Science and Technology of China, Hefei, Anhui 230026, China

[b]Department of Chemistry, Quaid-I-Azam University, Islamabad, 45320, Pakistan. E-mail: aamersaeed@yahoo.com; asaeed@qau.edu.pk

a) General metal free strategies for acylated *N*-heteroaromatics

b) Mild, metal free acylation protocol for acylation of *N*-heteroaromatics

c) Visible light mediated approaches towards acylated *N*-heterocycles
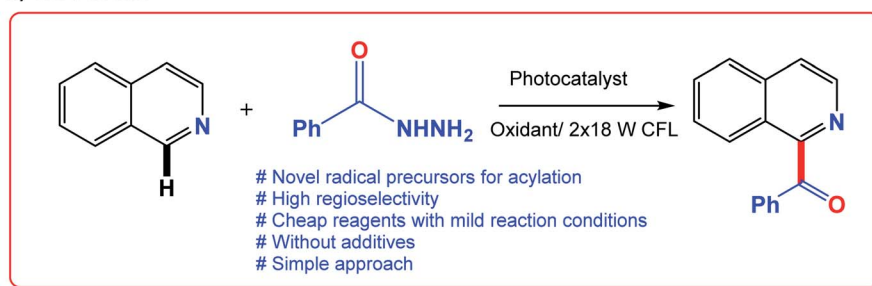

d) This Work

Novel radical precursors for acylation
High regioselectivity
Cheap reagents with mild reaction conditions
Without additives
Simple approach

Fig. 2   Previous literature reports and the current photo-mediated strategy.
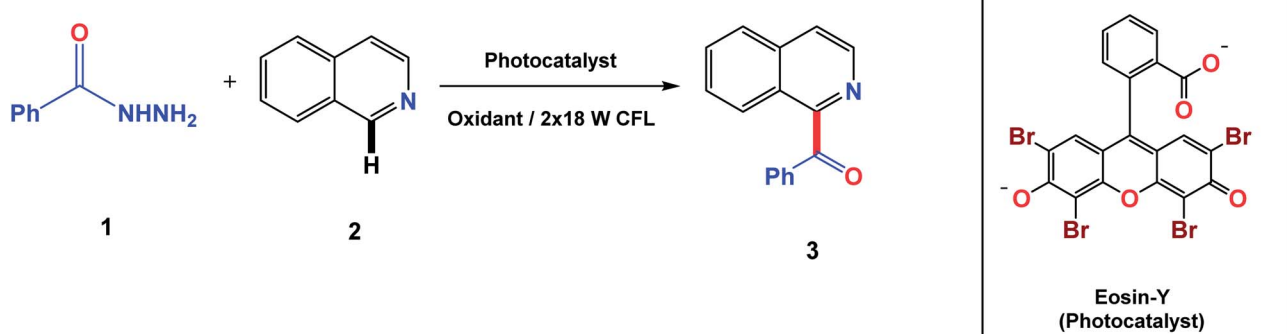
Introduction

The synthesis of natural products raises the frontiers of synthetic chemistry as it encounters the challenge to construct complex and structurally diverse molecular frameworks.[1–5] Natural products that show biological activity frequently serve as vital targets for novel drug design assemblies.[6] Efficient and powerful synthetic strategies are required to access these diverse and structurally complex assemblies, which is a multi-dimensional challenge for synthetic chemists.[7] One strategy towards the catalytic activation of organic molecules is visible light photo-redox catalysis.[8] Visible light photocatalysis has currently received growing attention from organic chemists because of its extensive applications in organic synthesis as well as its consequences for sustainable chemistry.[9]

N-heterocycles are key structural units for the synthesis of a variety of natural products with widespread application in the field of medicine. Some representative examples are shown in

Fig. 1. For example, benzoylated quinolines possess numerous biological activities like antibacterial, antifungal, and anti-cancer activities.[10–12] Different strategies have been designed, of which, Minisci radical C–H functionalization has been considered the most direct and efficient approach to access functionalized N-heterocycles.[13,14] Numerous metal-free acylation strategies have been reported *via* radical transformations including aldehydes,[15–17] benzylamines,[18] aryl methanol derivatives,[19,20] methyl arenes[21,22] and α-keto acids[23] as coupling counterparts along with oxidants at high reaction temperatures. Some milder protocols from previously reported radical precursors have also been reported by Antonchick and Zhang but with the use of hypervalent iodine as an oxidant and an electrochemical approach, respectively.[24,25] A variety of reactions resulting from visible light mediated approaches have been carried out in order to obtain more mild protocols.[26–28] In the past few years, the generation of acyl radicals for the acylation of N-heterocycles by the photo-redox strategy have been reported using α-keto acids[29–31] and terminal alkynes[32] as the acyl radical

Table 1 Optimization study of dehydrazinative acylation of isoquinoline[a]

Eosin-Y
(Photocatalyst)

Entry	Photocatalyst (mol%)	Oxidant (mmol)	Solvent (mL)	Time (h)	Yield[b] (%)
1[a]	—	$K_2S_2O_8$	DMSO/H_2O	12	11
2	Ru(bpy)$_3$Cl$_2\cdot$6H$_2$O	$K_2S_2O_8$	DMSO/H_2O	12	49
3	Eosin-Y	$K_2S_2O_8$	DMSO/H_2O	12	80
4	9-Fluorenone	$K_2S_2O_8$	DMSO/H_2O	12	62
5	Ir-PC1	$K_2S_2O_8$	DMSO/H_2O	12	56
6	Eosin-Y	TBHP	DMSO/H_2O	12	61
7	Eosin-Y	DTBP	DMSO/H_2O	12	21
8	Eosin-Y	H_2O_2	DMSO/H_2O	12	Trace
9	Eosin-Y	$Na_2S_2O_8$	DMSO/H_2O	12	62
10	Eosin-Y	$K_2S_2O_8$	DMSO/H_2O	10	64
11	Eosin-Y	$K_2S_2O_8$	DMSO/H_2O	15	76
12	Eosin-Y	$K_2S_2O_8$	DMSO	12	56
13	Eosin-Y	$K_2S_2O_8$	DCE	12	49
14	Eosin-Y	$K_2S_2O_8$	CH_3CN	12	38
15	Eosin-Y	$K_2S_2O_8$	DMF	12	25
16	Eosin-Y	$K_2S_2O_8$	CH_2Cl_2	12	23
17	Eosin-Y	$K_2S_2O_8$	MeOH	12	29
18	Eosin-Y	$K_2S_2O_8$	EtOH	12	35
19[c]	—	$K_2S_2O_8$	DMSO/H_2O	10	56

[a] Reaction conditions: **1** (0.6 mmol), **2** (0.2 mmol), oxidant (0.6 mmol), photocatalyst (5 mol%), solvent (2 mL). [b] Isolated yield. [c] Reaction at 50 °C in the absence of photocatalyst and light.

source. A visible light-induced catalytic system was also developed recently to achieve the acylation of pyridine N-oxides by the decarboxylation of α-oxocarboxylic acids using the organic dye fluorescein dimethylammonium as a new type of photocatalyst.[33] The philicity of acetonyl and benzoyl radicals has been investigated by R. H. Verschueren and co-workers recently *via* experimental as well as computational studies.[34]

In this context, the production of acyl radicals *via* the oxidative cleavage of hydrazides introduces an outstanding idea. Acyl hydrazides are a good source of acyl radicals in transition metal catalysis[35,36] but their use in the acylation of N-heterocycles *via* acyl radicals has not been reported yet. In 2017, the oxidative carbamoylation of electron deficient N-heterocycles by hydrazine carboxamide was reported by our group.[37] Therefore, in continuation of our interest with N-heterocycles, we envisioned the utility of benzoyl hydrazides as an efficient source of acyl radicals under visible light conditions using eosin-Y as a photocatalyst. Recently, eosin-Y has been reported as a direct hydrogen atom transfer photocatalyst

to generate acyl radicals from aldehydes as radical precursors.[38] The generation of acyl radicals takes place very easily by oxidative cleavage using oxidants. Traditional Minisci reactions require the use of harsh conditions such as high temperature excess amounts of radical precursors, long reaction times and poor site selectivity. The current strategy eliminates these requirements with the introduction of novel radical precursors for the acylation of heterocycles. Previously reported methods and the current photo-mediated strategy are given in Fig. 2.

Results and discussion

To initiate the study of this transformation, a model reaction between benzoyl hydrazine (**1**) and isoquinoline (**2**) was carried out under visible light from 18 W CFL bulbs in the presence of a photocatalyst and an oxidant using DMSO/H_2O (4 : 1) at room temperature. The benzoylated product was obtained with 49% yield using Ru(bpy)$_3$Cl$_2\cdot$6H$_2$O and $K_2S_2O_8$ after 12 hours (Table 1 entry 2). The influence of various photocatalysts was then
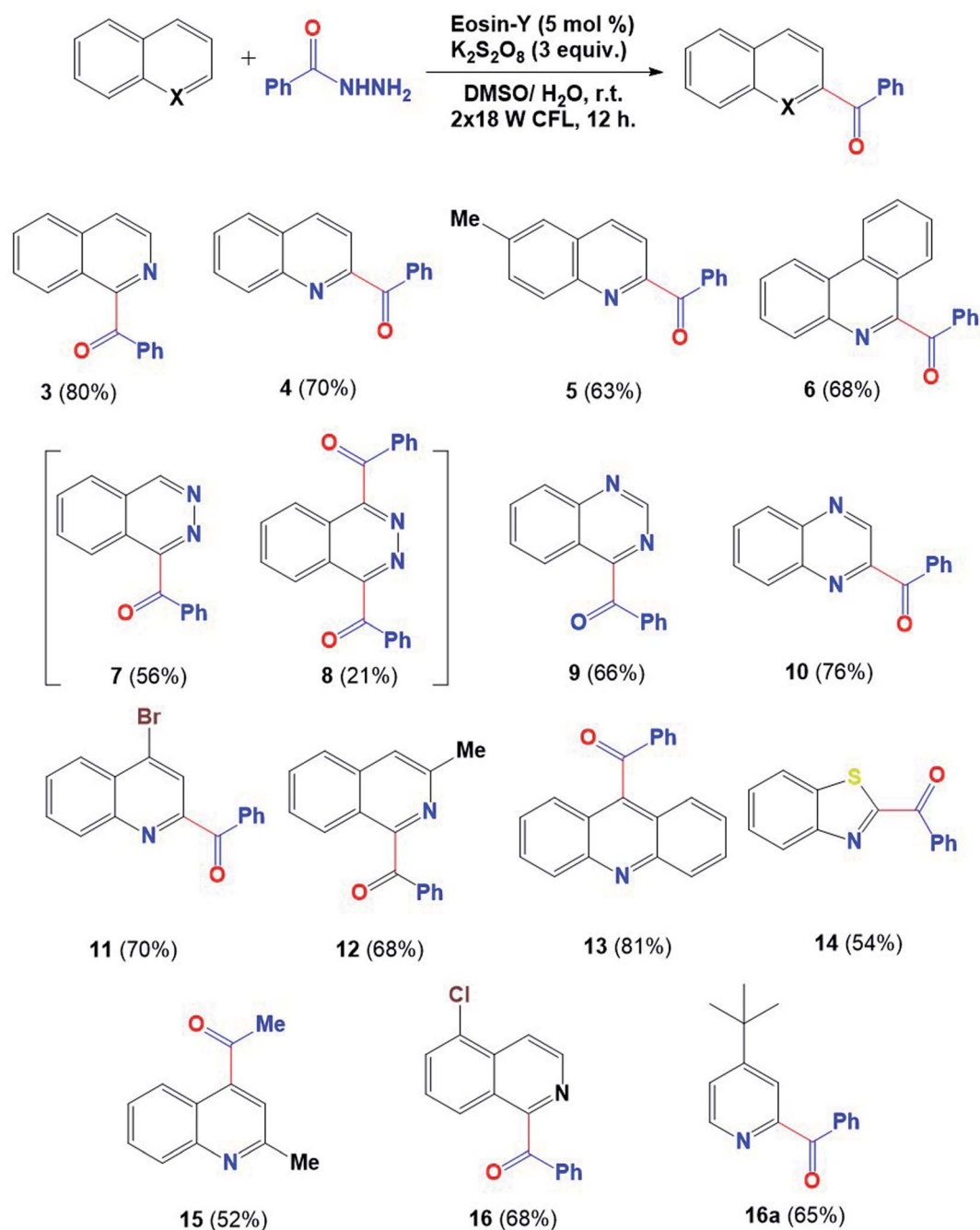
Fig. 3 Scope of heteroarenes. [a]Reaction conditions: benzoyl hydrazine (0.6 mmol), heteroarene (0.2 mmol), oxidant (0.6 mmol), solvent DMSO/H$_2$O (4 : 1) 2 mL under 36 W (2 CFL of 18 W each).
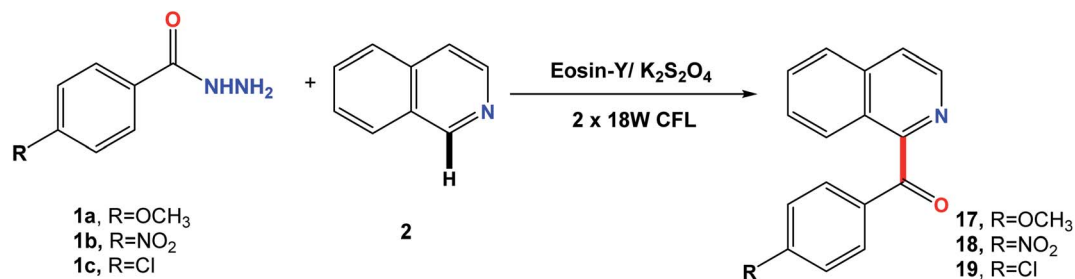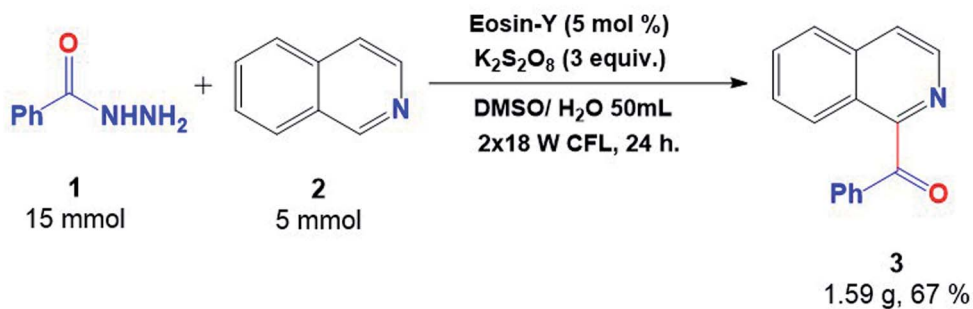

Fig. 4 Scope of acyl hydrazides.

Fig. 5 Gram-scale synthesis of **3**.

investigated which showed results with moderate to good yields (entries 3–5). The best result is obtained using eosin-Y in combination with $K_2S_2O_8$ (entry 3). Screening studies of different oxidants showed that $K_2S_2O_8$ gives the highest yield among all others tested (entries 6–9). Increase or decrease in reaction time results in low yield of the product (entries 10 and 12). The optimal solvent system (DMSO/H_2O 4 : 1) was obtained as all other solvents gave poor conversions (entries 12–18).

Having the optimized reaction conditions in hand, as indicated in Table 1 entry 3, the scope of this dehydrazinative C–H acylation was then explored with various N-heterocycles. A variety of N-heterocycles, including isoquinoline, quinoline, phenanthridine, dihydroacridine, quinoxaline and phthalazine, underwent dehydrazinative C–H acylation to produce acylated heterocycles with moderate to high yields, as shown in Fig. 3. High regioselectivity was observed in the case of quinazoline (**9**), quinoxaline (**10**) and acridine (**13**) while in the case of
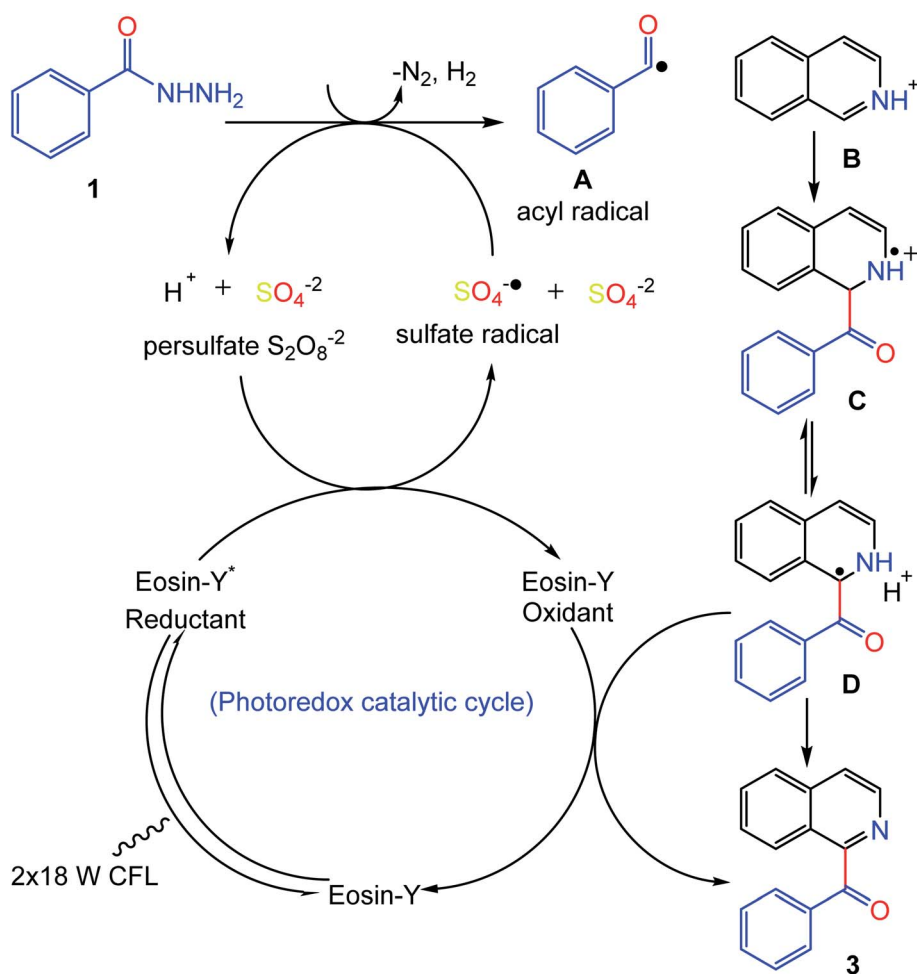

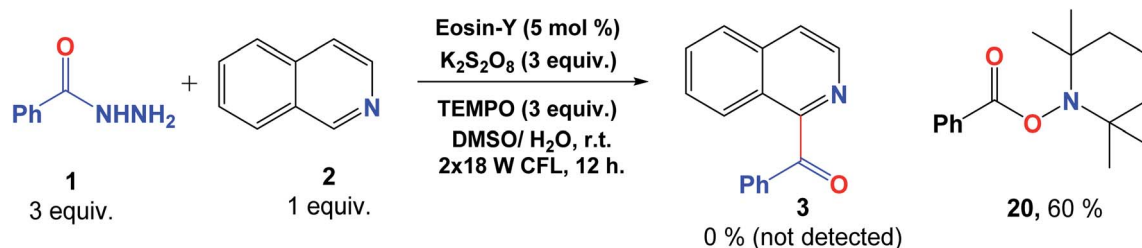**Fig. 6** Proposed reaction pathway.

Fig. 7 Control experiment confirming radical formation for this transformation.

phthalazine, a monoacylated compound (**7**) was detected with 56% yield along with a diacylated product (**8**) with 21% yield. The benzothiazole moiety may also be expanded using this protocol, furnishing its acylated product (**14**) with 54% yield. 2-Methylquinoline showed effective coupling with aliphatic hydrazide to give the acylated product (**15**) with 52% yield under optimized reaction conditions. No acylated product is formed in the case of pyridine and pyrazine under this protocol; however, *tert*-butyl pyridine furnished the acylated product with 65% yield (**16a**).

Extending the scope of the reaction with respect to the phenyl ring of **1** substituted with electron donating and withdrawing groups (**1a–1c**) showed that it worked well and could tolerate various substituents on the ring to afford **17–19**. The reaction proceeded with good selectivity and yields, using the optimized conditions mentioned above (Fig. 4).

The reaction was performed on a large scale in order to elaborate the utility and applicability of this protocol. The gram-scale reaction proceeded effectively well towards the synthesis of the acylated product (**3**) with 67% yield, clearly indicating its ability to be useful in the protocol (Fig. 5).

Based on and in comparison with previous literature reports,[22,29,30,32] a proposed reaction mechanism for this photocatalytic transformation was developed and is shown in Fig. 6. Possibly, the reaction starts with the excitation of the photocatalyst which undergoes single electron transfer (SET) in the presence of the persulfate salt, generating the sulfate radical anion $(SO_4^{-\cdot})$ and (eosin-Y oxidant). Meanwhile, benzoyl hydrazine (**1**) undergoes a removal of nitrogen and hydrogen followed by hydrogen atom transfer (HAT) with the sulfate radical anion $(SO_4^{-\cdot})$ to produce the acyl radical (**A**). Consequently, the acyl radical couples with the protonated heteroarene **B** to give the intermediates **C** and **D**. The final product **3** is produced by SET between intermediate **D** and the (eosin-Y oxidant), thus completing the photo-redox catalytic cycle by regeneration of the photocatalyst.

To confirm the proposed mechanism of this photocatalytic transformation, a reaction between benzoyl hydrazine (**1**) and isoquinoline (**2**) was conducted in the presence of the radical scavenger TEMPO. The desired acylated product **3** was not observed while the radical capture product 2,2,6,6-tetramethylpiperidino benzoate (**20**) was detected with 60% yield (Fig. 7). This observation strongly supports the proposal of the formation of radical intermediates in this reaction.

Conclusion

In conclusion, we have developed a visible light-induced acylation of N-heterocycles using benzoyl hydrazides as an efficient acyl source under mild reaction conditions. Photo-redox catalyzed oxidative cleavage of hydrazides leads to *in situ* formation of acyl radicals, which subsequently couple with various N-heterocycles to produce acylated products. This synthetic strategy performs the classic Minisci reaction in an eco-friendly and greener way with functional group tolerance and regioselectivity. Control experiments confirm the radical pathway for this transformation.

Conflicts of interest

The authors declare no conflict of interest.

Acknowledgements

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