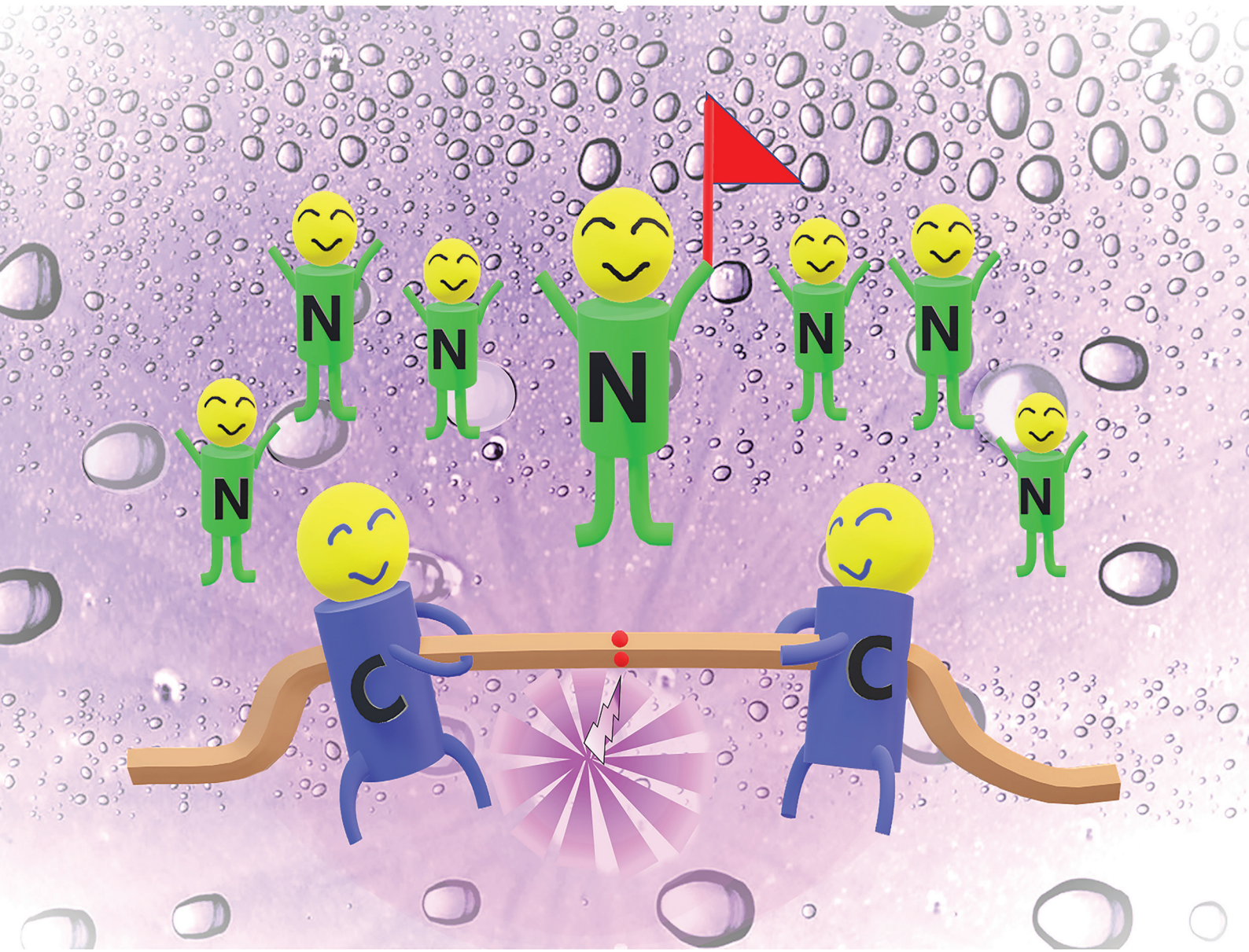
Volume 19
Number 9
7 March 2021
Pages 1869-2066

Organic & Biomolecular Chemistry

rsc.li/obc



ISSN 1477-0520

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Cite this: *Org. Biomol. Chem.*, 2021, **19**, 1970

Catalyst-free generation of acyl radicals induced by visible light in water to construct C–N bonds†

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Received 27th November 2020,
Accepted 4th January 2021

DOI: 10.1039/d0ob02364g

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We describe herein a catalyst-free and redox-neutral photochemical strategy for the direct generation of acyl radicals from α-diketones, and its selective conversion of nitrosoarenes to hydroxyamides or amides with AcOH or NaCl as an additive. The reaction was carried out under mild conditions in water with purple LEDs as the light source. A broad scope of substrates was demonstrated. Mechanistic experiments indicate that α-diketones cleave to give acyl radicals, with hydroxyamides being further reduced to amides.

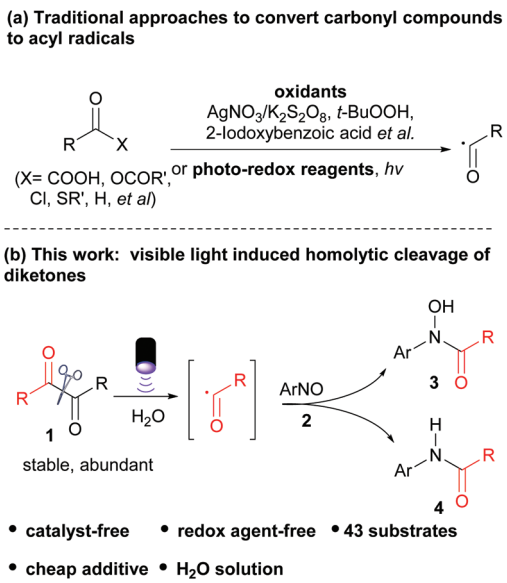
Introduction

Green chemistry is one of the most important research fields to address sustainability challenges in chemical transformations.[1] Many efforts have been made to increase resource and energy efficiency for chemical synthesis. Examples include reactions enabled by light[2] and catalyst- or metal-free reactions,[3] as well as reactions using water rather than harmful organics as a solvent.[4]

Acyl radicals are key intermediates in organic synthesis.[5] They can generally generated from α-ketoacids,[6] aldehydes,[7] acid chlorides,[8] and other acid derivatives (Scheme 1a).[9] Although these elegant strategies provide effective solutions for the direct synthesis of carbonyl compounds, most of these reactions require stoichiometric strong oxidants or photo-redox reagents. Approaches to convert readily available precursors such as diketones to acyl radicals in a mild and green manner are highly desirable, since diketones are stable, easy to handle and low cost. Although high-power Hg lamps can be used in the homolytic cleavage of α-diketones,[10] the cleavage of the C_{sp^2}–C_{sp^2} bond of α-diketones irradiated by visible light has not been reported. Also, further transformation of the resulting acyl radicals from α-diketones has rarely been explored.

Besides, amides and hydroxylamides are also important bioactive compounds in medical or agricultural studies.[11] They are frequently used as building blocks in the formation of other amine derivatives.[12] Diverse strategies have been proposed for their syntheses catalyzed by enzymes, organic catalysts, metals and others.[13] However, the direct reaction of acyl radicals with nitroso compounds is still unknown. The photo-induced catalyst-free transformation of nitroso compounds into hydroxylamides or amides has not yet been achieved. The radical chemistry of nitroso compounds remains largely unexplored.[14]

In this context, we report a general approach to convert α-diketones to acyl radicals promoted by visible light without any catalysts or redox agents under aqueous conditions (Scheme 1b).



Scheme 1 Converting carbonyl compounds to acyl radicals.

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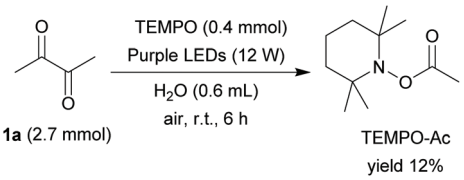
† Electronic supplementary information (ESI) available: Experimental details and spectroscopic characterization information. See DOI: 10.1039/d0ob02364g

Results and discussion

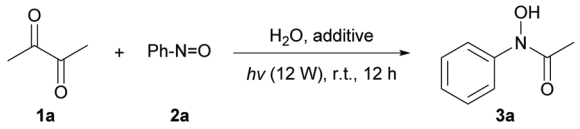
This approach proceeds *via* a homolytic cleavage mechanism (Scheme 2): biacetyl displays obvious absorption in the purple light region (λ_{max} = 417 nm, Fig. S1†) and can be activated by purple light. It cleaves to give acetyl radicals, which can be trapped by 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) to give a 12% TEMPO-Ac (Fig. S2†) or N═O group to construct C–N bonds (Scheme 1b).

This strategy was tested (Table 1) using biacetyl (**1a**) and nitrosobenzene (**2a**, 0.4 mmol) as model substrates for condition optimization with water as the solvent under purple LED irradiation (12 W) at room temperature under air atmosphere for 12 h. To our delight, the addition of acetyl radicals to the nitroso group proceeded smoothly and gave the coupling product hydroxyamide **3a** in an isolated yield of 36% (Table 1, entry 1), with by-products *N*-phenylacetamide (**4a**) and nitrobenzene (**5a**) detected by GC-MS. Compound **4a** is a reduction product from **3a**, but **5a** is a by-product from the oxidation of **2a** by O_2 in air. The acidity of the reaction system may affect this transformation. Thus, a series of additives and their amounts were examined (Table 1, entries 2–15): no product or only a trace amount of product was detected under basic conditions (Table 1, entries 2–4); with 6 equiv. of acetic acid, an 84% yield of **3a** was obtained (Table 1, entry 13). To further improve the atom efficiency of this procedure, the concentration of **1a** was further studied (Table 1, entries 16–19): **1a** can be reduced to 6.8 equiv., which gave similar yields (85%, Table 1, entry 19). An inert atmosphere was not necessary for this coupling reaction (Table 1, entries 20 and 21). Purple light gave the highest yield compared with other light (Table 1, entries 22–26).



Scheme 2 Trap of acetyl radicals by TEMPO.

Table 1 Optimization of conditions for the synthesis of **3a**[a]



Entry	Additive/equiv.	**1a**/equiv.	Yield [%]
1	—	11	36
2	K_2CO_3/1	11	N.R.
3	NaOH/1	11	N.R.
4	*N*-Methylpiperidine/1	11	Trace
5	H_2SO_4/1	11	N.R.
6	H_3PO_4/1	11	N.R.
7	Benzoic acid/1	11	15
8	**AcOH/1**	**11**	**44**
9	HCOOH/1	11	35
10	1.2 M HCl/1	11	N.R.
11[b]	AcOH/4	11	35
12[b]	AcOH/5	11	67
13[b]	**AcOH/6**	**11**	**84**
14[b]	AcOH/7	11	78
15[b]	AcOH/8	11	79
16	AcOH/6	1.1	70
17	AcOH/6	2.2	71
18	AcOH/6	4.5	78
19	**AcOH/6**	**6.8**	**85**
20[c]	AcOH/6	6.8	83
21[d]	AcOH/6	6.8	80
22[e]	AcOH/6	6.8	79
23[f]	AcOH/6	6.8	Trace
24[g]	AcOH/6	6.8	Trace
25[h]	AcOH/6	6.8	35
26[i]	AcOH/6	6.8	32

[a] Reactions were performed with **1a** and **2a** (0.4 mmol) in water (0.6 mL) at room temperature under purple LED irradiation (12 W) for 12 h unless otherwise indicated. Yields were determined after purification by column chromatography. [b] The reaction was carried out with **2a** (0.1 mmol) in water (0.15 mL). [c] The reaction was carried out under an argon atmosphere. [d] The reaction was carried out under a nitrogen atmosphere. [e] Blue LEDs were used. [f] Yellow LEDs were used. [g] Red LEDs were used. [h] Green LEDs were used. [i] UV light (254 nm) was used.

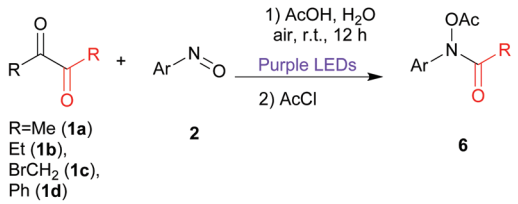
Subsequently, the optimized reaction conditions for the preparation of hydroxylamides (Table 1, entry 19) were selected for substrate study (Table 2). The reactive hydroxyl group made product **3** unstable on silica gel, which was further converted to *O*-acetyl derivative **6** in a one-pot reaction for purification purpose.

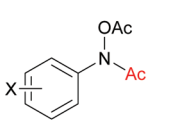
An array of functional groups including Cl (**6b**, **6g**, and **6h**), Br (**6c**, **6e**, and **6f**), 4-MeO (**6d**), 4-*tert*-butyl (**6i**), 4-acetyl (**6j**), 4-CF_3 (**6k**), methyl (**6l** and **6m**), 4-ethyl (**6n**), carboxylic ester (**6o–6q**) and phenyl (**6r** and **6s**) groups, as well as the benzothiazolyl group (**6t**), were all well tolerated and provided yields from 72% to 94% for two steps after purification (Table 2). Other α-diketones were also tested: hexane-3,4-dione (**1b**) and 1,4-dibromobutane-2,3-dione (**1c**) can be transformed into the corresponding products in moderate yields (**6u** and **6v**). Because of the resonance effect of the benzyl and carbonyl group, which makes it stable and difficult to cleave homolytically, **1d** remained unchanged after 12 h. The alkyl-substituted nitroso compounds were not stable, and thus they were not tested in this reaction.

The direct transformation of nitrosoarene (**2**) to amide (**4**) without the use of a reductant has not been reported before. Also, the synthesis of amides is fundamentally important in the pharmaceutical industry.[15] This led us to explore related chemical reactivities and mechanisms.

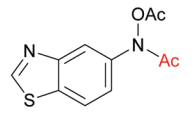
Aqueous acetone was used as the solvent for condition optimization with 0.4 mmol **2a** and 1.1 mmol **1a** as substrates (Table 3). Under the acidic conditions presented in Table 2, only a trace amount of **4a** was formed; so other additives were examined (Table 3, entries 1–5), with NaCl giving the highest yield (32%, Table 3, entry 2). Only a trace amount of **4a** was obtained with the addition of 1 equiv. of base (including *N*-methylpiperidine, DIPEA, NaOH or KOH in Table 3, entries 6–9). We were delighted to find that 76% of **4a** could be selectively formed as a major product with the use of 2 equiv. of

Table 2 Catalyst-free coupling of nitrosoarenes with α-diketones in water[a]

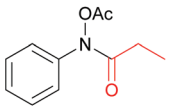




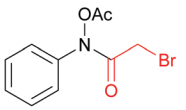
6a, X=H, 89%
6b, X=4-Cl, 85%
6c, X=3-Br, 84%
6d, X=4-OMe, 91%
6e, X=4-Br, 84%
6f, X=2-Br, 80%
6g, X=3-Cl, 84%
6h, X=2-Cl, 82%
6i, X=4-*t*-Bu, 88%
6j, X=4-Ac, 86%
6k, X=4-CF_3, 79%
6l, X=2-Me, 87%
6m, X=2,5-di-Me, 92%
6n, X=4-Et, 90%
6o, X=4-COOMe, 93%
6p, X=4-COOEt, 94%
6q, X=3-COOMe, 90%
6r, X=4-Ph, 75%
6s, X=2-Ph, 72%



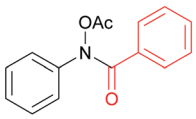
6t, 77%



6u, 44%



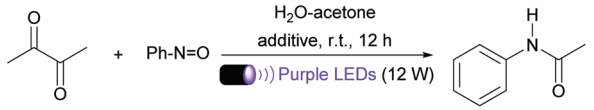
6v, 57%



6w, 0%

[a] Conditions (1): **1** (2.7 mmol, 6.8 equiv.), **2** (0.4 mmol) and AcOH (2.4 mmol) in water (0.6 mL) at room temperature under purple LED irradiation (12 W) for 12 h. Conditions (2): NEt_3 (0.1 mmol) and AcCl (0.6 mmol), 0 °C to room temperature for 1 h. Isolated yields for 2 steps.

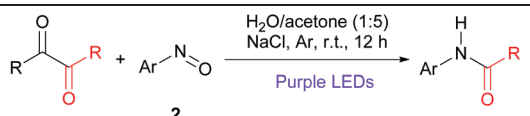
Table 3 Optimization of conditions for the synthesis of amide **4a**[a]

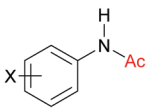


Entry	Additive/equiv.	Yield [%]
1	NH_4Cl/1	31
2	NaCl/1	32
3	$MgSO_4$/1	22
4	Na_2SO_4/1	24
5	NaBr/1	28
6	*N*-Methylpiperidine/1	Trace
7	DIPEA/1	Trace
8	NaOH/1	N.R.
9	KOH/1	N.R.
10	NaCl/2	40
11	NaCl/3	30
12	NaCl/4	31
13	NaCl/5	24
14[b]	**NaCl/2**	**76**
15[c]	NaCl/2	76
16[b]	—	21

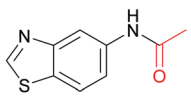
[a] Reactions were performed with **1a** (1.1 mmol, 0.1 mL) and **2a** (0.4 mmol) in water (0.6 mL) and acetone (3 mL) at room temperature in air under purple LED irradiation (12 W) for 12 h unless otherwise indicated. Yields were determined after purification by column chromatography. [b] The reaction was carried out under an argon atmosphere. [c] The reaction was carried out under a nitrogen atmosphere.

Table 4 Catalyst-free and redox-neutral conversion of nitrosoarenes to amides under aqueous conditions[a]

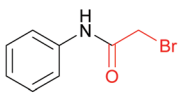




4a, X=H, 76%
4b, X=4-Cl, 68%
4c, X=3-Br, 67%
4d, X=4-OMe, 72%
4e, X=4-Br, 67%
4f, X=2-Br, 62%
4g, X=3-Cl, 65%
4h, X=2-Cl, 61%
4i, X=4-*t*-Bu, 75%
4j, X=4-Ac, 70%
4k, X=4-CF_3, 64%
4l, X=2-Me, 78%
4m, X=2,5-di-Me, 79%
4n, X=4-Et, 79%
4o, X=4-COOMe, 80%
4p, X=4-COOEt, 81%
4q, X=3-COOMe, 82%
4r, X=4-Ph, 58%
4s, X=2-Ph, 55%



4t, 73%



4u, 59%[b)]

[a] Conditions: **1a** (1.1 mmol, 2.8 equiv.), **2** (0.4 mmol) and NaCl (0.8 mmol) in water (0.6 mL) and acetone (3 mL) at room temperature under purple LED irradiation (12 W) for 12 h under argon. Isolated yields. [b] Reactions were performed with **1c** (2.2 mmol) and **2a** (0.8 mmol).

NaCl as the additive under an argon or nitrogen atmosphere (Table 3, entries 14 and 15). An inert atmosphere is needed to minimize the oxidation of **2a** to nitrobenzene (**5a**) and suppress the quenching of radical intermediates. NaCl may be involved in the electron-transfer process and is crucial for this reductive reaction, without which only 21% of **4a** was obtained (Table 3, entry 16).

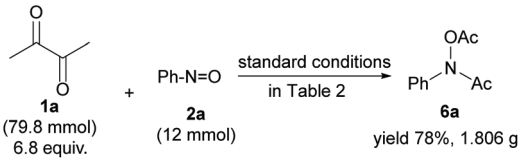
With the optimized conditions (Table 3, entry 14), the substrate scope was studied (Table 4). Besides the unsubstituted substrate (**4a**), functional groups including Cl (**4b**, **4g**, and **4h**), Br (**4c**, **4e**, and **4f**), 4-MeO (**4d**), 4-*tert*-butyl (**4i**), 4-acetyl (**4j**), 4-CF_3 (**4k**), methyl (**4l** and **4m**), 4-ethyl (**4n**), carboxylic ester (**4o–4q**), and phenyl (**4r** and **4s**) groups, as well as the benzothiazolyl group (**4t**), were all well tolerated, giving amides **4** in moderate to good yields. Likewise, the reaction of other α-diketones such as **1c** also furnished the product **4u** in a moderate yield.

Furthermore, the practicability of this transformation was demonstrated by scaling up to 12 mmol under standard con-

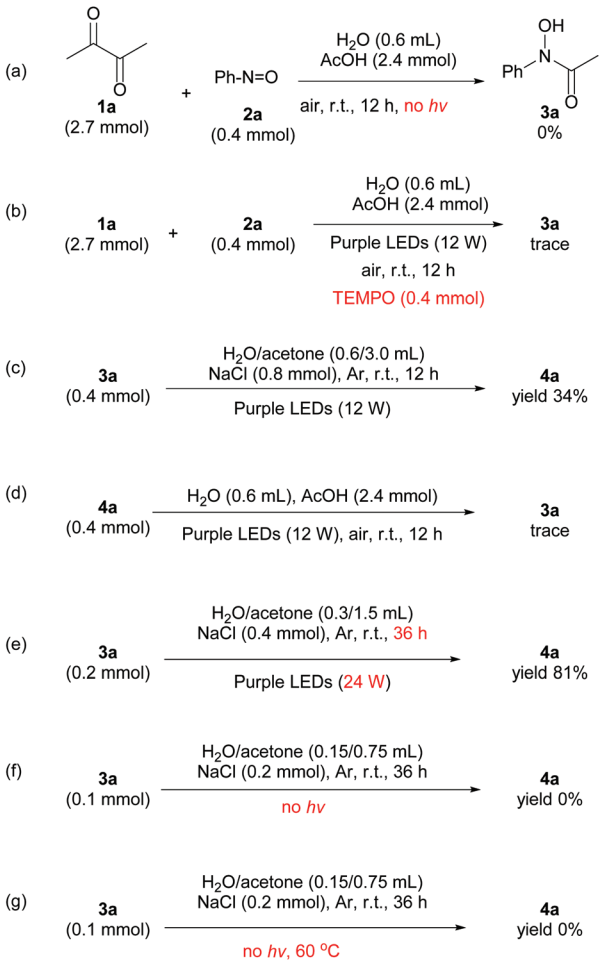
ditions to furnish 1.806 g of **6a** in 78% yield after chromatographic purification (Scheme 3).

To study the reaction mechanism, a control experiment was carried out in the dark without the irradiation of light (Scheme 4a), in which the coupling product **3a** was not detected. When TEMPO was added, only a trace amount of **3a** was detected by TLC (Scheme 4b). These results confirmed the radical nature of the reaction.

Other experiments helped to study the formation of **4a**: Compound **3a** can be partially transferred to **4a** under purple LED irradiation for 12 h (Scheme 4c), but only traces of **4a** were converted to **3a** under the corresponding optimized conditions (Scheme 4d). When the transformation of **3a** to **4a** was performed for prolonged time, 81% yield was obtained (Scheme 4e). Without the use of light (Scheme 4f) or replacing light with heat at 60 °C (Scheme 4g), no **4a** was formed. To further confirm the transformation of **3a** and **4a**, kinetic studies were performed (Fig. 1, Table 5): within 8 h, 95% nitrosobenzene (**2a**) was transferred into **3a** and **4a** (Table 5, entry 4). Yields of **3a** increased to 42% in 6 h (Table 5, entry 3), and then decreased to 17% after 12 h (Table 5, entry 5). Yields of **4a** increased over time and reached the highest after 12 h (Table 5). These results indicate that **4a** can be formed by the reduction of **3a** under irradiation of light. When **3a** was irradiated with purple LEDs in benzene in the presence of 2,6-di-*tert*-butylphenol, product **7** can be detected by GC-MS and HRMS (Scheme 5, Fig. S3 and S4†). Thus, this procedure pro-



Scheme 3 Reaction at the gram-scale.



Scheme 4 Control experiments.

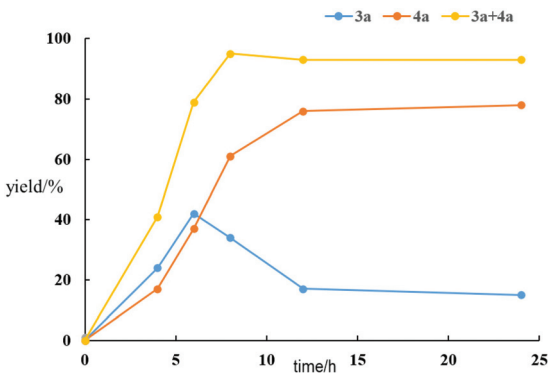
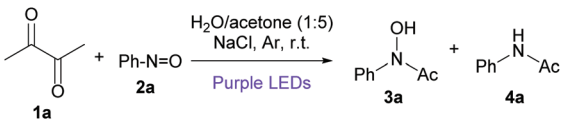


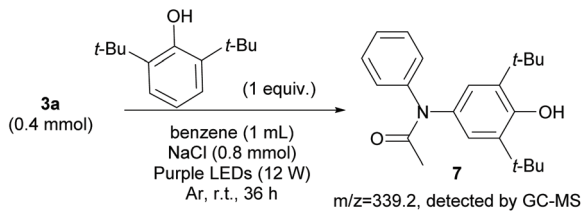
Fig. 1 Plots of product formation as a function of time.

Table 5 Study of product formation as a function of time[a]

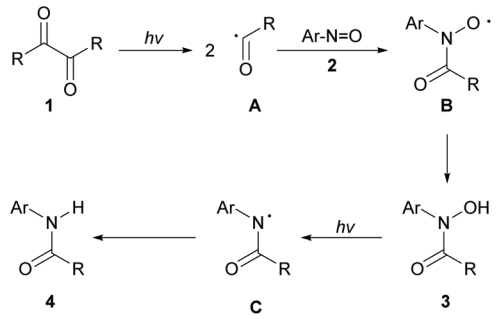


Entry	Time/h	Yield [%]		
		3a	**4a**	**3a** + **4a**
1	0	0	0	0
2	4	24	17	41
3	6	42	37	79
4	8	34	61	95
5	12	17	76	93
6	24	15	78	93

[a] Standard conditions in Table 4.



Scheme 5 Capture of radical intermediates by phenol.



Scheme 6 Proposed mechanism.

vides redox-neutral conditions for the direct reduction of hydroxylamides to amides.

A mechanism is proposed based on these observations (Scheme 6): acyl radical **A** formed *via* the homolytic cleavage of α-diketone (**1**) can add to the N═O group. This forms the radical intermediate **B** that is subsequently transformed to product **3** by hydrogen-abstraction or other pathways.[16] In the presence of NaCl, compound **3**[17] is cleaved to give the radical intermediate **C**, which finally leads to amide **4**.

Conclusions

In summary, we report the generation of acyl radicals from α-diketones *via* a redox-neutral and catalyst-free strategy under aqueous conditions induced by purple LEDs. Both hydroxylamides and amides can be selectively and directly formed from nitrosoarene compounds with acetic acid or NaCl as the only additive. Different functional groups are well tolerated and give moderate to excellent yields. Mechanistic experiments confirmed the formation of acetyl radicals after irradiation of biacetyl in water. The results demonstrate that the reduction of hydroxylamides into amides can be promoted by visible light in the presence of NaCl. While traditional approaches mostly require the use of a reductant and a transition-metal catalyst (Pd, Zn, *et al.*),[18] these redox-neutral conditions only use NaCl as the additive in water. We plan to extend this redox-neutral strategy to other systems and provide greener approaches for organic synthesis.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We thank the National Natural Science Foundation of China (no. 21801261 and 21462056), Guizhou Science and Technology Department (no. [2020]1Z003, [2014]7542, and [2014]4002), Guizhou Education Department (no. ZYDC2020123 and 20195201900) and Zunyi Medical University (no. 18zy-003) for financial support.

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