OL | Organic Letters

Letter

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

pubs.acs.org/OrgLett

Visible-Light-Induced Radical Acylation of Imines with α-Ketoacids Enabled by Electron-Donor−Acceptor Complexes

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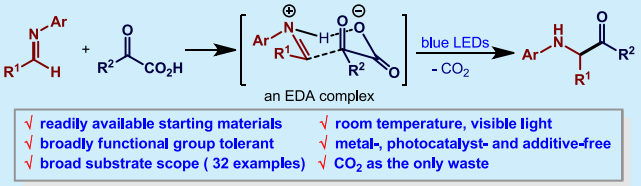
Supporting Information

ABSTRACT: A visible-light-induced radical acylation of imines with α-ketoacids has been achieved, enabled by an electron-donor−acceptor (EDA) complex. This EDA complex-mediated process eradicates the use of a photocatalyst. Visible light is used as the sole promoter for this reaction, and CO_2 is the only side product. Substrates with amide, cyanide, ester, ether, halides, and heterocycles were compatible. This radical acylation allows access structurally diverse α-amino ketones (32 examples) in up to 90% isolated yields.



Over the past decade, visible-light-driven photocatalysis has emerged as a synthetically valuable tool to induce radical reactions. This strategy takes advantage of the redox potential of the excited photocatalyst under visible-light irradiation.[1] The success of this catalytic mode has largely relied on the use of an exogenous photocatalyst, which harvests visible light energy and utilizes it for the transformation of non-visible-light-absorbing reactants into products through either an electron-transfer or energy-transfer pathway.[2] In contrast, photoabsorbing electron-donor−acceptor (EDA) complexes[3−5] generated by the molecular noncovalent interactions between electron donors and acceptors can be excited by visible light to generate radical species for the synthetically valuable transformations without an exogenous photocatalyst. These visible-light-induced and photocatalyst-free organic transformations have received increasing attention due to their mechanistically novel and economic features.[6] Despite these significant advances, more synthetic applications of EDA complexes are in need of further investigation.[7]

α-Amino ketones are an important class of biologically relevant molecules.[8] Efforts have been made by the synthetic community to develop efficient and general methods for their synthesis.[9] Several ionic methods, such as hydrogenation of α-ketoketimines,[10] cross coupling of aldehydes with imines,[11] and amination of enols,[12] have been established. Considering the importance of α-amino ketone derivatives, we envisaged that the synthesis of α-amino ketones could be achieved through radical cross couplings of α-aminoalkyl radicals[13] and acyl radicals[14] (Figure 1a). It is known that α-aminoalkyl radicals can be generated from imines through one-electron reduction under photochemical conditions.[15] α-Ketoacids[16] can be involved in EDA complexes as electron donors and, thus, serve as the precursors of acyl radicals under irradiation. Motivated by these works, as well as our continuing research interest in EDA complexes,[17] we propose that an imine and an α-ketoacid can engage in an EDA complex. Upon visible-light irradiation, this complex dissociates into an α-aminoalkyl radical and an acyl radical, respectively. Cross coupling of these two radicals gives α-amino ketone (Figure 1b). This EDA complex-mediated process eradicates the use of a photocatalyst. Visible light is used as the sole promoter and CO_2 is the only side product.

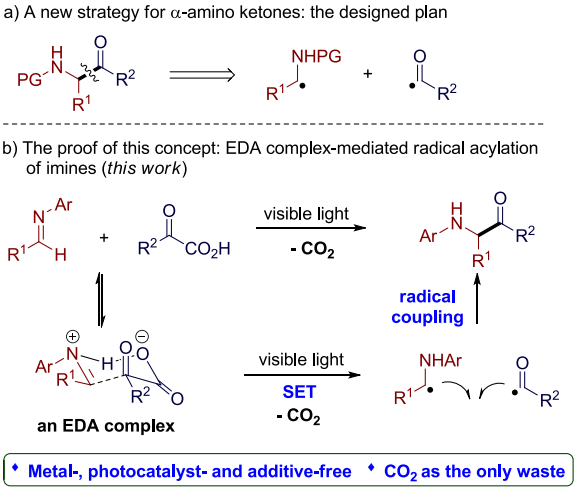


Figure 1. Synthesis of α-amino ketones by radical couplings.

This hypothesis was examined using imine **1a** and 2-oxo-2-phenylacetic acid (**2a**) as the coupling partners. After shining light on a mixture of **1a** (1 equiv) and **2a** (1 equiv) in CH_2Cl_2 with a 90 W blue LEDs for 12 h, the desired acylation product **3a** was indeed observed, but in a moderate 48% GC yield (Table 1, entry 1). Solvents were then screened to improve the yield of this reaction (entries 2−5), but no solvent was

Received: April 3, 2019

DOI: 10.1021/acs.orglett.9b01169
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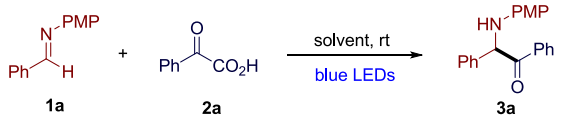
Table 1. Reaction Condition Optimization[a]



entry	solvent	1a/2a	3a[b] (%)
1	CH_2Cl_2 (1 mL)	1:1	48
2	$PhCF_3$ (1 mL)	1:1	24
3	1,4-dioxane (1 mL)	1:1	12
4	DMF (1 mL)	1:1	7
5	EtOAc (1 mL)	1:1	13
6	CH_2Cl_2 (1 mL)	1:1	23
7	CH_2Cl_2 (2 mL)	1:1	63
8	CH_2Cl_2 (2 mL)	1:1.5	80 (73[c])
9[d]	CH_2Cl_2 (2 mL)	1:1.5	NR

[a]Reaction conditions: a solution of **1a** (0.10 mmol) and **2a** in the indicated solvent was irradiated by blue LEDs for 12 h. [b]GC yields. [c]Isolated yield. [d]In dark. PMP = *p*-methoxyphenyl. NR = no reaction.

superior to CH_2Cl_2. The improvement of light transmission of the reaction mixture led to better yield (63%) when the reaction solution was diluted (entry 7). The use of 1.5 equiv of **2a** resulted in 80% GC yield (73% isolated yield, entry 8). No reaction could be observed without irradiation (entry 9).

After determining the optimized conditions, we proceeded to explore the scope and limitations of this visible-light-induced radical acylation. As shown in Figure 2, aldimines

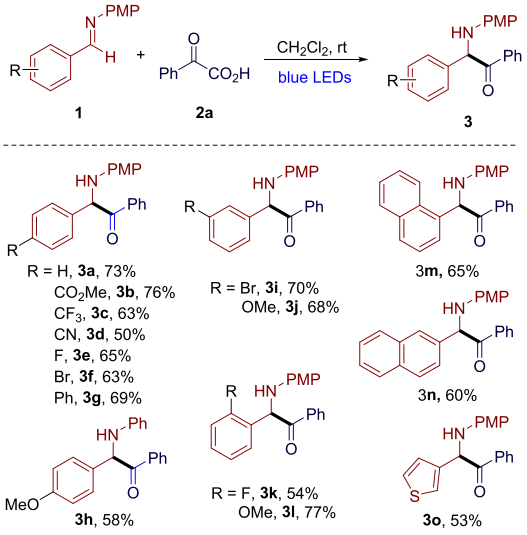


Figure 2. Scope of imines. Reaction conditions: a solution of **1** (0.10 mmol) and **2a** (0.15 mmol) in CH_2Cl_2 (2 mL) was irradiated by blue LEDs for 12 h. The yields were based on the isolated products.

derived from different functionalized benzaldehydes were acylated with α-ketoacid **2a**. In all cases, good reactivity was observed in the presence of both electron-withdrawing and electron-donating groups on the aryl ring, giving products **3a**–**o** in good yields (50–77%). Functional group tolerance was investigated. Remarkably, substrates with functional groups, such as ester (**3b**), cynide (**3d**), halogen (**3e**, **3f**, **3i**, and **3k**), aryl (**3g**), ether (**3h**, **3j**, and **3l**) and heterocyles (**3o**), could be tolerated in this reaction. Both *meta*-substituted aldimine and *ortho*-substituted aldimines could go through this transformation smoothly (**3i**–**3l**, 54–77% yields).

We next examined the scope of α-ketoacid components. As described in Figure 3, this protocol was amenable to α-

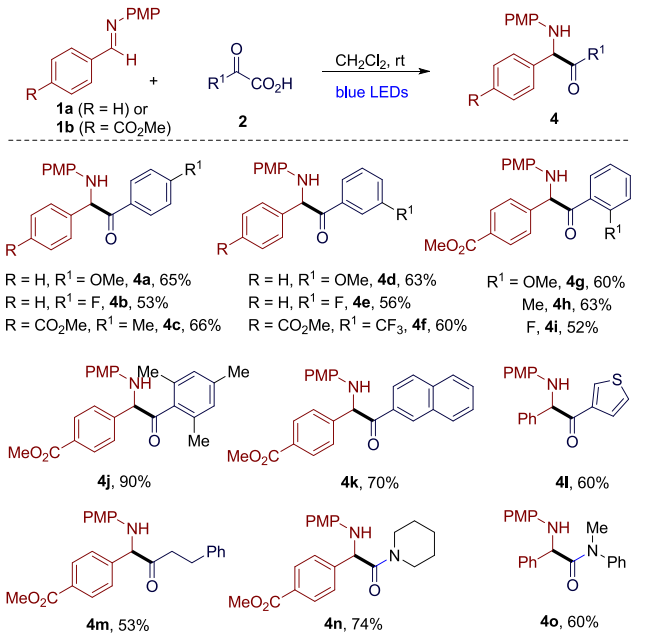


Figure 3. Scope of α-ketoacids. Reaction conditions: a solution of **1a** or **1b** (0.10 mmol) and **2** (0.15 mmol) in CH_2Cl_2 (2 mL) was irradiated by blue LEDs for 12 h. The yields were based on the isolated products.

ketoacids with different substituents of the benzene ring no matter the electronic property and position, affording the corresponding products **4a**–**4j** in 52–90% yields. It is worth noting that 2-oxo-2-mesitylacetic acid worked well to deliver the product **4j** in excellent yield (90%). 2-Naphthyl- and 3-thiophene-yl-substituted α-ketoacids were also suitable substrates (70% yield for **4k** and 60% yield for **4l**, respectively). As further detailed in Figure 3, aliphatic α-ketoacid could also serve as the efficient coupling partner to give the acylation products **4m** in 53% yield. Remarkably, this protocol was also applicable to α-ketoamides **2o** and **2p** to give 2-aminoamide derivatives **4n** (74% yield) and **4o** (60% yield).

The utility and practicality of this radical acylation reaction were elaborated by a gram-scale preparation of α-amino ketone **3b**. As shown in Figure 4a, 5 mmol of imine **1b** could be acylated with α-ketoacid **2a** under our established conditions, and a comparative isolated yield of **3b** (70%, 1.32 g) was obtained. The overall efficiency of this reaction could be

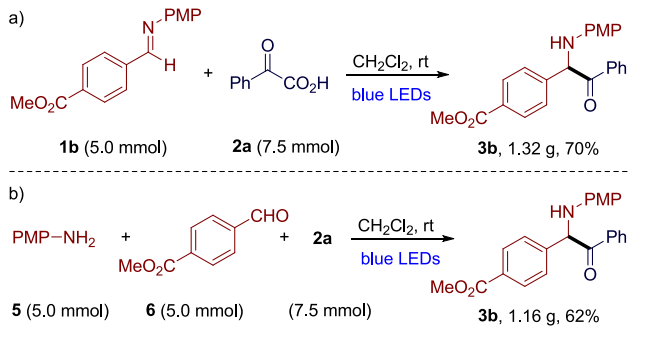


Figure 4. Gram-scale and one-pot synthesis of **3b**.

DOI: 10.1021/acs.orglett.9b01169
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further improved with the generation of the imine in situ. A three-component reaction of aromatic amine **5**, aldehyde **6** and α-ketoacid **2a** could also give the product **3b** (62%) on a gram scale (Figure 4b).

To understand this transformation, a number of control experiments and analytical surveys were performed. Termination of the desired reaction with TEMPO and observation of TEMPO-trapped product **7** by high-resolution mass spectrometry implied that this reaction involved radical pathway (Figure 5a). The radical nature of this reaction could be further

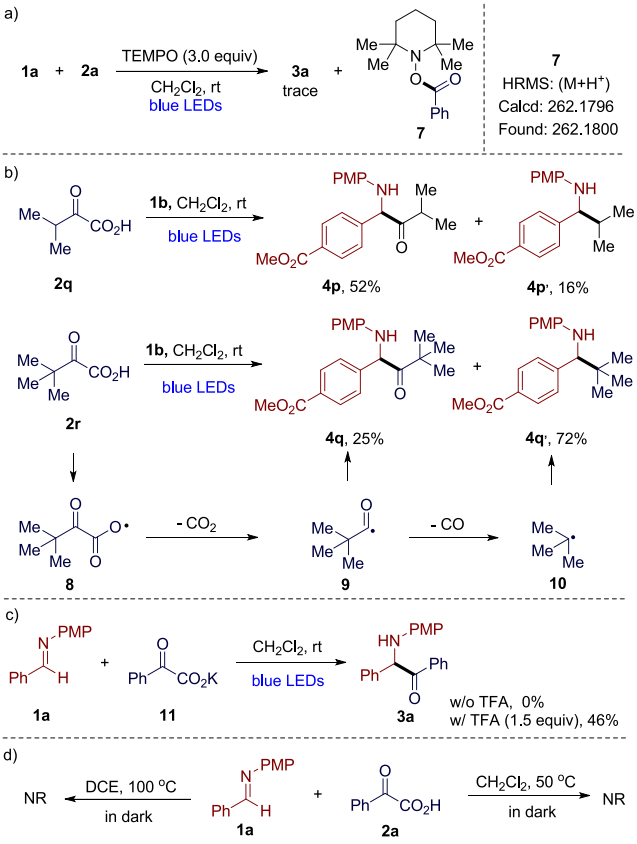

Figure 5. Control experiments.

confirmed by using α-ketoacids **2q** and **2r** as the acyl radical precursors. As described in Figure 5b, when **2q** and **2r** were employed to react with **1b**, the desired products **4p** and **4q** were generated in 52% and 25% isolated yields, respectively, together with alkylation byproducts **4p′** (16% yield) and **4q′** (72% yield). This observation could be explained by the generation of acyl radicals and the existence of a simultaneous decarboxylation process (release of CO_2) and decarbonylation process (release of CO).[14,18] When potassium 2-oxo-2-phenylacetate **11** was used instead of its acid, no reaction took place. The addition of trifluoroacetic acid (TFA) into this reaction mixture promoted the formation of the desired product (Figure 5c). This phenomenon implied that proton was crucial to this transformation. The desired reaction could not be observed in the dark, even by heating to 100 °C, which verified this reaction was a photochemical process rather than a thermodynamic one (Figure 5d).

This photochemical reaction was proposed to be enabled by an EDA complex between an imine and an α-ketoacid, which could be supported by the observation of a bathochromic shift and a charge transfer band in the UV−vis spectrum of the mixture of imine **1a** and α-ketoacid **2a** (Figure 6a). The **1a**/**2a** stoichiometric ratio in the EDA complex was determined to be 1:1 using Job's method (Figure 6b).[19]

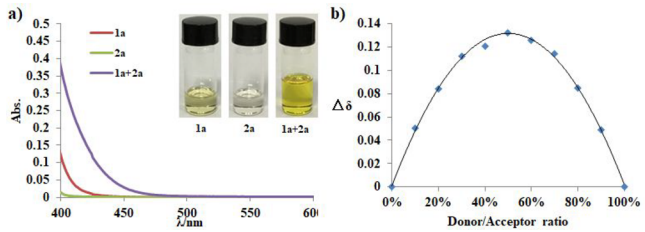

Figure 6. (a) Optical absorption spectra of the reaction components. (b) Job's plot between **1a** and **2a**.

On the basis of these experimental phenomena, a mechanism for this radical acylation reaction is posited. As shown in Figure 7, imine **1a** interacts with α-ketoacid **2a**

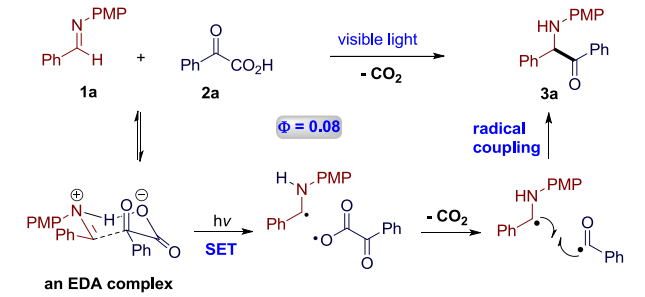

Figure 7. Proposed mechanism.

reversibly to generate an EDA complex. Upon visible-light irradiation, this complex is excited and then dissociates into a pair of radicals. After the release of CO_2 from the carboxylic radical, the resultant acyl radical couples with the α-aminoalkyl radical to give the final product **3a**. The quantum yield of this reaction was determined to be 0.08 (for details, see the SI), and this experiment strongly implies that this reaction proceeds through a cross radical coupling rather than a radical propagation.

In summary, we have established a visible-light-induced radical acylation of imines with α-ketoacids via EDA complexes. This mild decarboxylative acylation can proceed without any photocatalyst or additive. Visible light is used as the sole promoter and CO_2 is the only side product. Substrates with amide, cyanide, ester, ether, halides, and heterocycles were compatible. The radical-based methodology presented here allows to access structurally diverse α-amino ketones (32 examples) in up to 90% isolated yields.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01169.

Full experimental and characterization data for all compounds (PDF)

DOI: 10.1021/acs.orglett.9b01169
Org. Lett. XXXX, XXX, XXX−XXX

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

Financial support from National Natural Science Foundation of China (21672098 and 21732003) and the National Key Research and Development Program of China (2018YFC0310900) is acknowledged.

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