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Intramolecular Transamidation of Secondary Amides via Visible-Light-Induced Tandem Reaction

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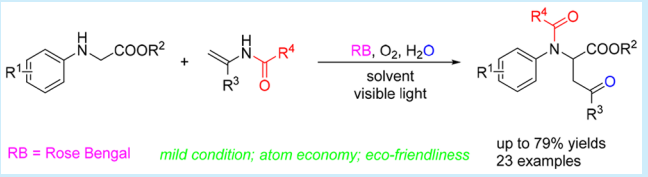
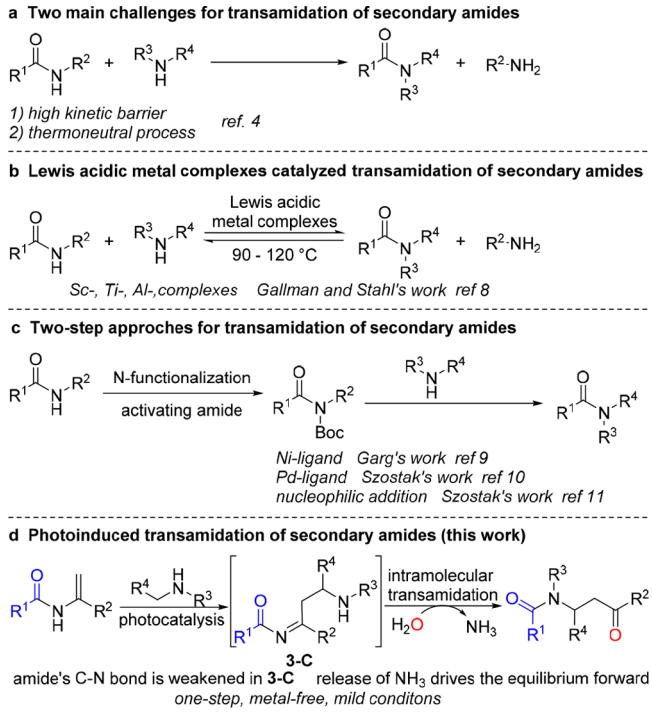
Supporting Information

ABSTRACT: Transformation of secondary amides to *N*-acylimines was used as an effective strategy to activate otherwise unreactive amide bonds. In this tandem reaction, the Rose Bengal-catalyzed photo-oxidative coupling of arylglycine esters and enamides generates *N*-acylimines, which undergo intramolecular transamidation and imine hydrolysis to afford bioactive acyl Mannich base derivatives under metal-free and mild conditions.



Amide bonds not only are the key linkages of peptides, proteins, and some synthetic polymers but are also present in a great number of modern pharmaceuticals and biologically active compounds.[1] Traditional methods for construction of amide bonds are often associated with significant drawbacks such as waste, expense, and harsh reaction conditions. Therefore, development of new approaches to amide bond formation is one of the highest priority areas in sustainable organic synthesis.[2] Transamidation can serve as an attractive strategy to prepare amides, avoiding the use of carboxylic acids which need harsh conditions or stoichiometric coupling agents.[3] However, transamidation is hindered by its kinetic and thermodynamic challenges (Scheme 1a).[4] The high kinetic barrier is due to the amide N−C(O) bond resonance stabilization, which makes the amide bond robust.[3a,5] Transamidation is a mostly thermoneutral process and tends toward an equilibrium between substrates and products.[3b,6] Primary amide transamidation is relatively common,[7] but transamidation of secondary amides that are ubiquitous in proteins and synthetic amide derivatives is still a great challenge. To the best of our knowledge, only a few secondary amide transamidations have been reported.[8−11] Catalytic direct transamidation by Lewis acidic metal complexes was developed by Gellman and Stahl, but mixed amides of reactants and products were obtained due to the equilibrium between substrates and products (Scheme 1b).[8] Very recently, an elegant two-step strategy was used for secondary amide transamidation, which involves first preparing Boc-activated secondary amide derivatives. With this strategy, Garg's group developed the Ni-catalyzed secondary amide transamidation,[9] and Szostak's group reported the Pd/NHC complexes catalyzed secondary amide transamidation.[10] The Szostak group also developed metal-free transamidation of secondary amides by nucleophilic addition (Scheme 1c).[11] Therefore, development of efficient and mild methods for transamidation of secondary amides is desirable.

Scheme 1. Two Main Challenges and Various Means of Secondary Amide Transamidation



We assumed that the ground state N−C(O) can be destabilized when secondary amides are transformed to *N*-acylimines, and transamidation equilibrium can be driven forward by hydrolysis of imines to release NH_3 just like primary

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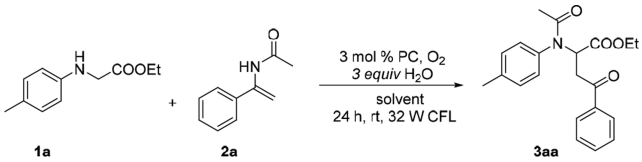
Org. Lett. XXXX, XXX, XXX−XXX

amide transamidation. Therefore, to verify our idea, we designed a tandem reaction in which the visible-light-induced aerobic oxidative coupling of arylglycine esters with enamides forms *N*-acylimines, which undergo intramolecular transamidation, producing corresponding imines; the hydrolysis of the imines gives the final product Mannich base derivatives (Scheme 1d). In the past decade, visible-light-induced photoredox catalysis has emerged as a powerful platform for design and implementation of valuable transformations through single electron transfer pathways.[12] From the viewpoint of green chemistry, organic dyes as photocatalysts are cheap and environmentally friendly.[13] Rose Bengal (RB) as a common organic dye has been widely used in photo-oxidative reactions.[14] Furthermore, Mannich base derivatives are highly important and useful compounds because aminoalkyl chain motifs exist widely in a variety of natural products, pharmaceuticals, agrochemicals, and so forth.[15] *N*-Acyl Mannich bases have specifically been found to be potential antimicrobial agents[16] and useful synthetic intermediates.[17] This reaction has three key features: (1) direct synthesis of acyl Mannich bases via the visible-light photocatalytic N−H functionalization of secondary amines; (2) one-step transamidation of secondary amides under mild conditions; (3) atom economy and using oxygen and water as clean, abundant, and sustainable chemical reagents.[18]

Our initial investigation focused on the reaction between ethyl *p*-tolylglycinate **1a** and *N*-(1-phenylvinyl)acetamide **2a** (Table 1). In the presence of 3 mol % of $Ru(bpy)_3Cl_2$, a solution of **1a** (0.4 mmol), **2a** (0.2 mmol), and water (0.6 mmol) in MeCN (1.0 mL) was irradiated with a 32 W compact fluorescent light bulb (CFL) under oxygen at ambient temperature for 24 h, and the desired product ethyl 4-oxo-4-phenyl-2-(*N*-(*p*-tolyl)-acetamido)butanoate (**3aa**) was obtained in 53% yield (Table 1, entry 1). Several other common metal and organo-photocatalysts were examined (Table 1, entries 2−6), and RB was found to be the most effective for this reaction (Table 1, entry 6). Thus, RB was chosen as the photocatalyst for the reaction. Next, other common solvents were also screened, but none achieved the yield observed with MeCN (Table 1, entries 7−11). Notably, a good yield of 79% was obtained when a MeCN/AcOH (9:1, v/v) solvent system was used (Table 1, entry 12). We speculate that acidic solvent may promote the intramolecular transamidation,[19] and acidic conditions favor hydrolysis of imines. Interestingly, no reaction was observed when AcOH alone was used as a solvent (Table 1, entry 13). As expected, no desired product was detected in the absence of water, and the reaction became messy (Table 1, entry 14). Finally, the control experiments suggested that photocatalyst, light, and oxygen were essential for this reaction to proceed (Table 1, entries 15−17).

Table 1. Selected Optimization Experiments[a]



1a **2a** **3aa**

entry	photocatalyst	solvent	yield (%)
1	$Ru(bpy)_3Cl_2$	MeCN	53
2	methylene blue	MeCN	13
3	fac-$Ir(ppy)_3$	MeCN	21
4	eosin Y	MeCN	39
5	$Ir(ppy)_2(dtbbpy)PF_6$	MeCN	48
6	RB	MeCN	65
7	RB	acetone	56
8	RB	DMSO	43
9	RB	DMF	38
10	RB	ethanol	35
11	RB	THF	26
12	RB	MeCN/AcOH 9:1	79
13	RB	AcOH	nr
14[b]	RB	9:1 MeCN/AcOH	messy
15[c]		9:1 MeCN/AcOH	trace
16[d]	RB	9:1 MeCN/AcOH	trace
17[e]	RB	9:1 MeCN/AcOH	nr

[a]Reaction conditions: **1a** (0.4 mmol), **2a** (0.2 mmol), H_2O (0.6 mmol), and photocatalyst (3 mol %) in solvent (1.0 mL) were irradiated using a 32 W CFL in O_2 at room temperature for 24 h; isolated yields are provided. [b]Standard conditions without water. [c]Standard conditions without photocatalyst. [d]Standard conditions without O_2. [e]Standard conditions without light.

With the optimized conditions in hand (Table 1, entry 12), we decided to examine the arylglycine ester scope (Scheme 2). First, different ester groups (Me, Bn) were explored, and corresponding products **3ba** and **3ca** were obtained. Second, a range of groups at the *para*-position of the benzene rings of arylglycine esters were surveyed, and both electron-withdrawing (Cl and Br) and electron-donating groups (Me and OMe) were compatible with this reaction under applied conditions, affording corresponding products **3aa** and **3da**−**3ga**. Next, mono- and di-Me substituents on *meta*-position of the benzene rings of arylglycine esters were tested, and they proved suitable for this reaction, affording the corresponding products **3ha** and **3ia**. However, no desired products were detected for the reactions with *ortho*-Me-substituted *N*-phenylglycine ester and *N*-naphthylglycine ester, probably due to the stereohindrance effect. To further investigate the generality and practicability of this photoinduced tandem reaction, an array of enamides **2** was examined (Scheme 2). Phenyl enamides with both electron-donating and electron-withdrawing groups at the *para*-position of the benzene rings worked smoothly, affording the corresponding acyl Mannich bases (**3ab**−**3ag**) in moderate to good yields. Because phenyl bromides are widely known as electrophiles in traditional cross-coupling reactions, to further capitalize these products, phenyl enamides **2** with *meta*-bromo and *ortho*-bromo at the benzene rings were examined. The *meta*-bromophenyl enamide afforded the desired product **3ah** in good yield, but the corresponding product **3an** of *ortho*-bromophenyl enamide could not be detected, potentially due to the stereohindrance effect. The *meta*- and *para*-dichlorophenyl enamides were tested, which gave the corresponding product **3ai**. Notably, xenyl and 2-naphthyl enamides were compatible with the reaction under the applied conditions (**3aj** and **3ak**). The heterocycle-based enamide also reacted smoothly with **1a**, affording product **3al**. This reaction was also applicable to *N*-propionyl enamide, and the propionyl Mannich base **3am** was obtained. In addition to aliphatic acyl enamides, both electron-donating and electron-withdrawing aromatic acyl enamides worked well in this reaction to give aromatic acyl Mannich bases **3aq** and **3ar** in good yields. In addition, note that the nonterminal olefin-derived enamides were not effective with this tandem reaction (**3ao** and **3ap**), probably because of the steric hindrance of the substituent group at nonterminal olefins. For those reactions where the desired products were not obtained, most of the starting materials (enamides **2**) were consumed; the reaction got very messy. We

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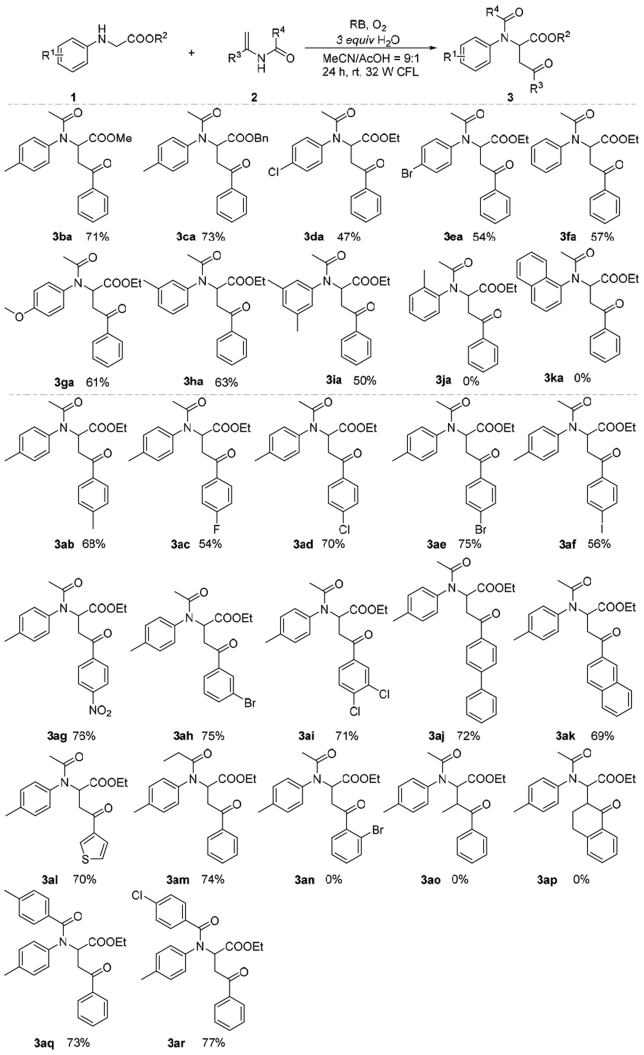
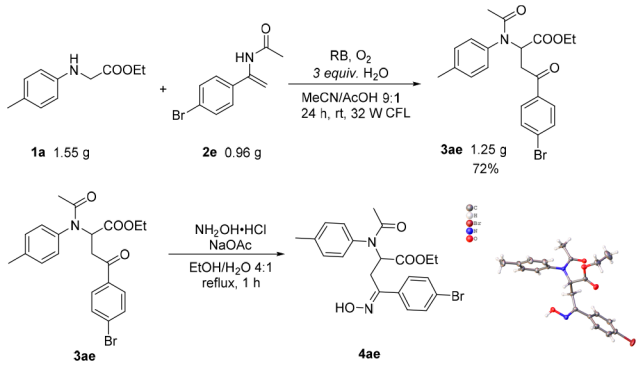
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 2. Scope of Substrates[a]

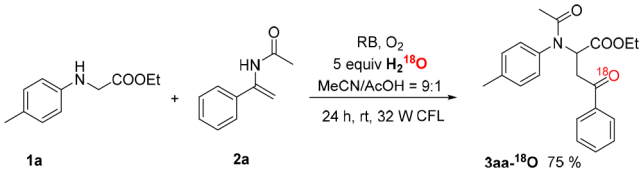


[a]Reaction conditions: **1** (0.4 mmol), **2** (0.2 mmol), H_2O (0.6 mmol), and RB (3 mol %) in MeCN/AcOH = 9:1 (1.0 mL) was irradiated using a 32 W CFL in O_2 at room temperature for 24 h; isolated yields are provided.

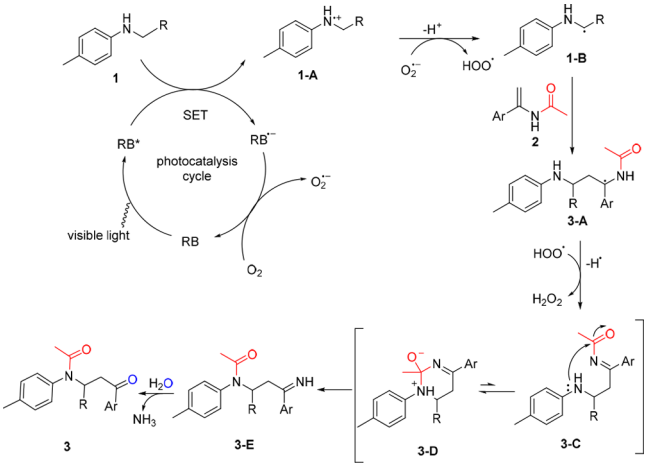
Scheme 3. Scale-up Experiment and X-ray Analysis



Scheme 4. O-Labeling Experiment



Scheme 5. Proposed Possible Mechanism



tried to isolate the produced substances but failed because the reactions were too complicated.

Next, a scale-up experiment of this visible-light induced tandem reaction was conducted. A gram-scale reaction between **1a** and **2e** was carried out under the standard conditions (Scheme 3), and product **3ae** was obtained in 72% isolated yield, which proved the efficacy of this protocol. Because all of the products are liquid, in order to undoubtedly determine the structure of the products, **3ae** was converted to its corresponding oxime **4ae** which is a solid. The crystallographic data of **4ae** is shown in Scheme 3.

To gain insight into the reaction mechanism, we performed the ^{18}O-labeling experiment (Scheme 4). When the reaction was carried out in the presence of $H_2{}^{18}O$ instead of $H_2{}^{16}O$, ^{18}O product **3aa-^{18}O** was obtained mostly (Figure S11), proving that the oxygen atom in the ketone carbonyl of products originated from H_2O.

After other control experiments were conducted (see Supporting Information), a plausible mechanism was proposed (Scheme 5). Upon visible-light irradiation, RB accepts a photon to be excited from its ground state to its excited state RB* ($E_{red}[RB^*/RB^{\bullet-}]$ = +0.99 V vs SCE in MeCN).[20] RB* is single electron reduced by arylglycine ester **1** ($(E_{ox}[\mathbf{1a}/\mathbf{1a}^{\bullet+}]$ = +0.83 V vs SCE in MeCN) (see Figure S4) to form $RB^{\bullet-}$, and **1** is converted into N-cation radical **1-A**. Then, $RB^{\bullet-}$ is single electron oxidized by oxygen, leading to the ground state RB and superoxide anion radical ($O_2{}^{\bullet-}$). Subsequently, cation radical **1-A** is deprotonated by $O_2{}^{\bullet-}$ to give arylglycine ester radical **1-B** and hydroperoxyl radical $HOO^{\bullet}$. Then enamide **2** as a radical acceptor reacts with **1-B** to form the intermediate **3-A**. Hydrogen atom transfer between **3-A** and $HOO^{\bullet}$ gives *N*-acylimine **3-C** and H_2O_2. Intramolecular transamidation of **3-C** generates the imine intermediate **3-E**. Finally, the *N*-acyl Mannich base **3** is obtained by the hydrolysis of **3-E**.

In summary, we have developed the first visible-light-mediated intramolecular transamidation of secondary amides under metal-free and mild conditions. Most crucially, we have demonstrated a new design idea for transamidation through conversion of secondary amides to *N*-acylimines, which can activate the otherwise unreactive amide bonds. In this strategy, the visible-light-induced aerobic oxidative coupling of arylglycine esters

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with enamides forms *N*-acylimines that undergo intramolecular transamidation, producing the corresponding imines. The hydrolysis of the imines gives the final product Mannich base derivatives. This work also provides a new method for the synthesis of acyl Mannich bases, which are valuable in pharmaceutical chemistry and important intermediates in organic synthesis. In the future, we will focus on developing more intermolecular transamidation of secondary amides under mild conditions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02303.

Experimental procedures, mechanism studies, characterization of new compounds, and spectral data (PDF)

Accession Codes

CCDC 1823107 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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