



UV-Light-Induced N-Acylation of Amines with α -Diketones

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scale experiment product yield is 76%. Moreover, this system can be applied to the synthesis of several amino acid derivatives. Mechanistic studies show that benzoin is generated in situ from benzil under UV irradiation.

mides are some of the most important compounds in And organic synthesis.¹ The green and efficient synthesis of amides has gradually attracted the attention of scientists worldwide.² Amides are a ubiquitous scaffold that widely exists in drugs,³ agrochemicals,⁴ and organic functional materials.⁵ Many biologically active amides have been developed to cure diseases, such as paracetamol,⁶ safinamide,⁷ procainamide,⁸ and moclobemide⁹ (Figure 1). In addition, amides can serve as synthetic intermediates for different transformations, such as for acquiring amines and heterocycles.¹⁰



Figure 1. Representative drugs.

Traditional methods for amination mainly fall into four categories: activation of carboxylic acids and amines,¹¹ activation of carboxylic acids alone,¹² activation of amines alone,¹³ and activation of the acyl group.¹⁴ Thermal condensation of carboxylic acids with amines is displayed in route 1 (Scheme 1a), and stoichiometric or excess highly active reagents such as EDC, DCC, and HATU are added in route 2 (Scheme 1a). A series of methods for metal-catalyzed synthesis of amides have been well developed, as shown in Scheme 1b.¹⁵ In recent years, photocatalysis has emerged as a powerful tool for the construction of C-C bonds and C-Z bonds due to its cleanliness, sustainability, and simple operation.¹⁶ A few examples of N-acylation of amines with photocatalysts have been reported, as shown in step i of Scheme 1c. For example, Ke

Scheme 1. N-Acylation of Amines for the Synthesis of Amides Previous work



et al.¹⁷ reported an amination reaction of carboxylic acids and amines catalyzed by eosin Y under a white light-emitting diode (LED) lamp. Song et al.¹⁸ reported that thioacids can react with amines to prepare amides using Mes-Acr-MeBF₄ with blue light.

Although much progress has been made in this field, some limitations remain, such as heavy metal pollution, the use of excess amounts of starting materials, adding equivalents of oxidants and additives, and the requirement for external photocatalysts. Therefore, the development of environmentally friendly and efficient direct amination is still highly desirable.

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Inspired by previous works and in the course of our exploration, we found a mild protocol for direct amination of α -diketones^{19–21} and amines irradiated by UV light without the need for external additives and photocatalysts under ambient conditions (Scheme 1c, ii).

Initially, we started our investigation by using benzil (1a) and pyrrolidine (2a) to optimize the reaction conditions, and the results are depicted in Table 1. Surprisingly, the yield of 3a

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\bigcirc		+ H=N UV lar air	np .t., time	
~	1a	2a	Ť	3a
entry	1a:2a	solvent	time (h)	yield (%) ^a
1	1:1	2-MeTHF	35	43
2	1:1.5	2-MeTHF	35	69
3	1:2	2-MeTHF	35	82
4	1:3	2-MeTHF	35	81
5	1:4	2-MeTHF	35	82
6	1:2	H_2O	24	NR
7	1:2	acetone	24	ND
8	1:2	<i>n</i> -hexane	24	trace
9	1:2	toluene	24	trace
10	1:2	DMF	24	trace
11	1:2	EtOAc	24	41
12	1:2	1,4-dioxane	24	54
13	1:2	THF	24	74
14	1:2	2-MeTHF	24	71
15	1:2	CH ₃ CN	24	37
16	1:2	CH ₃ OH	24	26
17	1:2	isopropyl ether	24	58
18	1:2	THF	10	NR^{b}
19	1:2	THF	10	88 ^c
20	1:2	THF	10	94 ^d
21	1:2	THF	10	86 ^e
22	1:2	THF	8	75
23	1:2	THF	10	NR ^f
24	1:2	THF	10	ND ^g

^{*a*}Unless otherwise noted, all reactions were carried out with 1a (0.2 mmol, 42.0 mg), 2a (0.4 mmol, 28.4 mg), and a general solvent (2.0 mL) at room temperature under air conditions under one 26 W UV lamp (350–380 nm). ^{*b*}No light. ^{*c*}With two 26 W UV lamps (350–380 nm). ^{*d*}With three 26 W UV lamps (350–380 nm). ^{*e*}With N₂. ^{*f*}With a green lamp (8 W) and a white lamp (20 W). ^{*g*}With a blue lamp (12 W).

(43%) was obtained in a solvent of 2-methyltetrahydrofuran irradiated by one UV lamp for 35 h (entry 1). Next, we continued to screen the ratio of the starting materials. Two equivalents of pyrrolidine gave a $\leq 82\%$ yield, which was better than that obtained for 1.5 equiv of 2a (69%) (entries 2–5). We found that different solvents exhibited various yields (0-74%)entries 6-17). This reaction did not take place in water (entry 6). It was noted that increasing the number of lamps and the reaction time can be beneficial for this reaction (entries 19–22). Finally, the best reaction conditions were determined: 1a reacted with 2.0 equiv of 2a in THF irradiated by three UV lamps for 10 h (94%, entry 20). This reaction did not occur without light, which infers that light is indispensable for realizing the product (entry 18). The yield of 3a was 86% when the reaction was conducted under a N₂ atmosphere (entry 21), indicating that an air atmosphere is unnecessary.

With the optimized reaction conditions in hand, we first investigated the substrate scope with respect to secondary amines (Scheme 2). For cyclic secondary amines, the reaction

Scheme 2. Substrate Scope with Various Amines^a



"Reaction conditions: 1a (0.2 mmol, 42.0 mg), 2 (0.4 mmol), three 26 W UV lamps (350–380 nm), THF (2.0 mL), air, room temperature. Isolated yields.

proceeded smoothly with the desired products obtained in good yields (**3a**-**3d**, 90-94%). In particular, 2 equiv of azetidine gave **3b** in a relatively low yield under the standard condition due to the large tension of the four-membered ring. Product **3b** was obtained in a higher yield when the amount of azetidine was increased (4 equiv, 92%). For acyclic secondary amines, diethylamine and dibutylamine afforded the corresponding amides in moderate yields (**3e**, 87%, and **3f**, 70%). *N*-Methyl-1-phenylmethanamine and dibenzylamine with a certain steric hindrance still generated the target products (**3g**, 64%, and **3h**, 50%).

Next, we explored various primary amines. Isopropylamine, *tert*-butylamine, and isobutylamine were added to this reaction mixture, and they displayed almost quantitative yields (97%, 95%, and 97% for 4a-4c, respectively). Extending the carbon chain of the amine also gave an excellent yield (4e, 92%). 4-Phenylbutylamine achieved the same yield as isooctylamine (4f, 92%). Primary amines with three-membered, four-membered, or five-membered rings enabled one to obtain the target products (4g-4i, 52–90% yields). Regardless of whether the benzylamines had electron-rich groups or electron-deficient groups, good to excellent yields were obtained regardless of the

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ortho, meta, and para position groups (4j-4r, 78-97%) yields). The amine containing a ternary ring with a large tension could also form the desired product in this system (75% yield for 4s). Reactions of furfurylamine and pyridin-2-ylmethanamine with heterocycles proceeded smoothly (4t, 52%, and 4u, 70%). (Tetrahydrofuran-2-yl)methanamine and (tetrahydro-2*H*-pyran-4-yl)methanamine with heteroatoms afforded the corresponding products in moderate yields (4v, 85%, and 4w, 89%). In addition, amines containing olefin, ether, active hydroxyl, and Boc groups enabled one to smoothly obtain target products, indicating that there was good functional group compatibility in this system (4z-4ae, 62-96% yields).

In addition, several disubstituted α -diketones exhibited different activities when they reacted with pyrrolidine (Scheme 3). The results showed that electron-withdrawing -Br (5a) and

Scheme 3. Substrate Scope with α -Diketones and Amino Derivatives^{*a*}



^aReaction conditions: **1b–1e** (0.2 mmol), **2a** (2.0 equiv), three UV lamps (350–380 nm), THF (2.0 mL), air, room temperature. Isolated yields.

electron-donating -CH₃ (**5b**) in the *para* position of α -diketones led to high yields (80% and 93%, respectively). The -OCH₃ group in the *meta* position of α -diketones generated a 52% yield for amide 5c. The di-2-pyridylglyoxal-containing heteroatom (5d) afforded the product in 43% yield. Unfortunately, the N,Ndimethyl group in the *para* position of α -diketones [Se (Scheme S2) did not react in this system. Moreover, we could not find the desired product when using 1-(4-methoxyphenyl)propane-1,2-dione and 2,3-butanedione [5f and 5g, respectively (Scheme S2)]. 1,2-Di(furan-2-yl)ethane-1,2-dione [5h (Scheme S2)] was unsuccessful and found to be a mixture due to its high activity for this reaction. The wavelength of light, the activity of substrates, and the presence of α -H nitrogen atoms may affect unsuccessful reactions. In addition, aniline could not be applied to this reaction. Inspired by the N-Boc-ethylenediamine (4ae) reacting with benzil, we assumed that amino acid derivatives may also be involved in the system. As expected, reactions with L-proline tert-butyl ester (6a), methyl-1-aminocyclopropanecarboxylate (6b), tert-butyl glycinate (6c), and L-asparagine tertbutyl ester (6d) proceeded well under the reaction conditions, giving the proposed amides in moderate to good yields (59-96%). To demonstrate the practical value of this system, we carried out a scale-up reaction for benzil and pyrrolidine. Benzil could be successfully transformed in 76% yield after irradiation for 5 days (Scheme S1).

To reveal the reaction mechanism, we performed a series of control experiments. First, 2.0 equiv of butylated hydroxytoluene (BHT) or 2,2,6,6-tetramethylpiperidinooxy (TEMPO) was added to the reaction system under standard conditions, and the results showed that TEMPO can inhibit the reaction, with only a trace amount of the desired product obtained (Scheme 4a,b). The addition of BHT did not quench the reaction, which

Scheme 4. Control Experiments



may be due to 2 equiv of amines inhibiting the phenol in this system. Therefore, it is inferred that the corresponding mechanism may involve a radical path. The model reaction was carried out for 6 h, and the byproduct benzoin was detected by GC-MS (Scheme 4c). Next, we directly used benzoin (1a') as the starting material instead of 1a to react with 4-chlorobenzyl-amine under standard conditions (4I, 88% yield). At the same time, the reaction did not proceed without light (Scheme 4d). This result indicated that benzoin may be the key intermediate in this reaction. We added asymmetric diketones [1-(4-bromophenyl)-2-phenylethane-1,2-dione (1f)] to this reaction mixture and obtained two products (3a, 54%, and 5a, 36%). Moreover, benzaldehyde did not react with pyrrolidine under standard conditions (Scheme 4f).

To prove that the reaction was related to UV light, we performed light turn-on and turn-off experiments by controlling the lamps and reaction time (Figure S2). According to the graph, the yield of **3a** can increase under UV-light irradiation for 1 h with no distinct difference observed for dark irradiation for 1 h. Therefore, UV light is essential for this synthesis.

According to the previous control experiments, we propose a possible mechanism in Scheme 5. 4-Chorobenzylamine (2l) attacks diketone (1a) in the first step to form intermediate A. Next, A passes through the Norrish type II route to generate intermediate B under UV irradiation.²² However, 4b has no α -C-H on *tert*-butylamine. It is possible that hydrogen atom abstraction of THF with oxy occurs during the reaction. Then, intermediate B soon becomes an enol form compound (C) and

Scheme 5. Possible Mechanism



phenylmethanimine (**D**). Intermediate **C** can transfer to benzoin (**F**, isolated), and intermediate **D** can react with H_2O in the system to form **E** (detected by GC-MS). Then, amine will attack the carbonyl group of intermediates **F** and **B**: water will interact with hydrogen bonds via proton-coupled electron transfer (PCET) to form **H** and radical cations (**I**) under UV irradiation.²³ Next, these cations become two free radicals (**J** and **K**). The nitrogen radical (**K**) combines with the carbon radical (**J**) to afford intermediate **L**. Then, **L** removes anion **M** to form the desired amide. The quantum yield is 24.69, which may involve a radical chain reaction (for detailed data, see the Supporting Information).²⁴

In summary, we describe a mild method for the amination of α -diketones irradiated by UV light without the need for external additives and photocatalysts. This reaction showed good functional group tolerance toward various primary and secondary amides with high yields. The yield reached 97%. In addition, this protocol was applied to the synthesis of several amino acid derivatives. Mechanistic studies showed that benzoin was generated *in situ* from benzil under UV irradiation. In addition, this method provides an alternative way to synthesize amides by using a photoinduced procedure.

ASSOCIATED CONTENT

1 Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01599.

Detailed experimental procedures, characterization data, spectral data for ¹H, and ¹³C NMR data for the obtained products (PDF)

FAIR data, including the primary NMR FID files, for compounds 3a-3h, 4a-4ae, 5a-5d, and 6a-6d (ZIP)

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Notes

The authors declare no competing financial interest.

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