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Communication

H₂O₂-mediated oxidative formation of amides from aromatic amines and 1,3-diketones as acylation agents via C–C bond cleavage at room temperature in water under metal-free conditions

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1,3-Diketones, as novel acylation agents, reacted with aromatic amines promoted by the commercial available H_2O_2 (30% aq.) as sole oxidant at room temperature under metal-¹⁰ free conditions in water, leading to a novel and rapid amide bond formation strategy. The reported method is highyielding, simple and mild, and it is the first example of 1,3diketones as acylation agents via C–C bond cleavage.

Selective C–C bond cleavage (activation) by transition metals, ¹⁵ similar to the recent emergence of C–H bond activation, has also attracted great attention in organic and organometallic chemistry.¹ As a unique synthetic strategy, it allows chemists to approach the desired molecules by reorganizing the existing molecular skeletons, instead of traditional retrosynthetic disconnections.

²⁰ However, the cleavage of C(sp3)–C(sp3) bond has emerged as a tremendous challenge owing to its relatively high bond strength.² To facilitate C–C bond cleavage, various processes involving the following modes have been developed, such as the relief of ring strain,³ chelation assistance,⁴ and employing functional fragment

- ²⁵ as the leaving groups, including carboxylic acids,⁵ nitriles,⁶ carbonyls,⁷ and so on.⁸ Obviously, main stream development is still restricted to the transition-metal-assisted approach to activate the inert C–C bond. Consideration from the environmental and economic point of view, the development of metal-free organic
- ³⁰ reactions has been paid much attention in modern organic synthesis, especially in the pharmaceutical industry due to the avoidance of metal contamination.⁹ However, there have been a few examples for the cleavage of the C–C single bond in the absence of transition metals.¹⁰
- 1,3-Diketones, which are inexpensive and available starting materials, have been used as the important substrates in organic

synthesis.¹¹ It should be noted that the first example of CuI-⁵⁰ catalyzed arylation/C–C bond activation of 1,3-diketones with aryl halides to α-arylketones was reported by Lei in 2010.^{7b} Later on, CuI-catalyzed tandem cyclization leading to isocoumarins from *o*-halobenzoic acids and esters or 2-halo-*N*-phenyl benzamides with 1,3-diketones was developed by Xi,^{12a} Yao,^{12b} ⁵⁵ and Fan.^{12c} On the other hand, Kuninobu and Takai developed In(OTf)₃-catalyzed synthesis of esters and amides by reactions of alcohols and aliphatic amines with 1,3-diketones via C–C bond cleavage in a retro-aldol-type reaction, regarded as an acylation reaction of alcohols or amines from another viewpoint.^{12d} Most ⁶⁰ recently, a TBHP/I₂-promoted reaction of aliphatic secondary amines with 1,3-diketones for the synthesis of α-ketoamides was also reported.^{12e}

The importance and value of amide motifs can be shown from their wide occurrence in natural products, pharmaceuticals, 65 polymers, and biological systems, and broad applications as versatile building blocks in organic synthesis.¹³ As a result, the synthesis of amides is a greatly valuable project and a variety of methods are available for their preparation, such as the acylation of amines using carboxylic acids or their derivatives;¹⁴ transition-70 metal-catalyzed amidation of aryl halides or nitriles with nitrogen-containing reagents,15 as well as the oxidative coupling of alcohols¹⁶ or aldehydes¹⁷ with amines; the direct carbonylation of alkenes or alkynes;18 and Mn- or Fe-catalyzed C-C bond cleavage with a nitrogen source.¹⁹ Nevertheless, most of the 75 reported approaches have the drawbacks, such as the use of transition metals, unstable starting materials, expensive reagents, toxic solvents and/or harsh oxidants, and drastic reaction conditions. Therefore, the more simple and green method for the synthesis of amides would be highly desirable. Hydrogen 80 peroxide (H₂O₂) is a mild and comparatively inexpensive oxidant and widely used in laboratory and industry with regard to the formation of water as the sole by-product. In a continuation to our interest in the synthesis of nitrogen-containing compounds,²⁰ herein, we firstly illustrated a novel and rapid amide bond 85 formation strategy from aromatic amines and 1,3-diketones via C-C bond cleavage promoted by H_2O_2 (30% aq.) as the sole oxidant at room temperature under metal-free conditions in water. The reported method is high-yielding, simple and mild, and it is the first example of 1,3-diketones as acylation agents (Scheme 1).

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Scheme 1 H₂O₂-mediated reaction of 1,3-diketones with amines

At the outset of this study, the optimization of reaction 5 conditions was focused on oxidant and solvent using a model reaction of pentane-2,4-dione (1a) with aniline (2a), and the results were summarized in Table 1. Gratifyingly, when the model reaction was performed in the presence of a commercial avalible H2O2 (30% aq.) without additional 10 solvent at room temperature, N-acylation of 2a underwent very smoothly and the product N-phenylacetamide (3a) was obtained in 88% yield (Table 1, entry 1). This reaction also proceeded well using cumene hydroperoxide as an oxidant and afforded 80% yield of 3a (Table 1, entry 2), whereas tert-15 butyl hydroperoxide (TBHP) and PhI(OAc)₂ exhibited relatively lower efficiency (Table 1, entries 3 and 4). However, other oxidants, such as 2,3-dichloro-5,6dicyanobenzoquinone (DDQ), 1,4-benzoquinone (BQ), di*tert*-butyl peroxide (DTBP), $(NH_4)_2S_2O_8$, and $K_2S_2O_8$ were 20 inactive and no desired product was isolated (Table 1, entries 5-9). Subsequently, the effect of solvent on the model reaction was investigated and a significant solvent effect was observed (Table S1, Supporting Information). When the model reaction was performed in toluene, only 41% yield of 25 3a was obtained. Other organic solvents, such as DMF, DMSO, DME, CH₃CN, dioxane, and THF shut down the reaction completely. With respect to the oxidant loading, 3.0 equiv. of H₂O₂ was found to be optimal. When less than 2.5 equiv. of H₂O₂ was used, the reaction was not completed 30 (Table S1). However, no significant improvement was observed with more than 3.0 equiv. of H₂O₂. It was found that the concentration of H_2O_2 (aq.) affects the reaction greatly (Table S1). H_2O_2 ($\geq 25\%$ aq.) exhibited the high efficiency to the reaction, and lower yield of 3a was obtained when less $_{35}$ than 25% of H₂O₂ (aq.) was used. The optimized reaction conditions were 30% aqueous H₂O₂ (3.0 equiv.) at room temperature for 8 h.

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Table 1 Optimization of the oxidant for the model reaction ^{<i>a</i>}	
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		oxidant neat, r. t. ►	N
of	1a 2a		3a
Entry	Oxidant	Solvent	Yield $(\%)^b$
1	H_2O_2	Neat	88
2	Cumene hydroperoxide	Neat	80
3	TBHP	Neat	52
4	PhI(OAc) ₂	Neat	15
5	DDQ	Neat	NR
6	BQ	Neat	NR
7	DTBP	Neat	NR
8	$(NH_4)_2S_2O_8$	Neat	NR
9	$K_2S_2O_8$	Neat	NR
^a Departie	n conditiona: 1a (0.50 mm	a) \mathbf{j}_{a} (0.60 mm	al) avidant (1.5

^a Reaction conditions: **1a** (0.50 mmol), **2a** (0.60 mmol), oxidant (1.5 mmol), at room temperature for 8 h. ^b Isolated yield.

With the optimized reaction conditions in our hand, a wide range of anilines (2) with pentane-2,4-dione (1a) were investigated to illustrate the efficiency and scope of this novel strategy for the synthesis of aromatic amides (Scheme 2). Anilines bearing electron-rich substituents (Me, Et, i-Pr, OMe, 45 OEt) on their para-, and meta-positions underwent the acylation transformation smoothly to give the desired anilides in good to excellent yields (82-96%, Scheme 2, 3b-f, 3h, and 3i). On the other hand, anilines with halogen groups, such as F, Cl, Br, and I on their para-, and meta-positions also gave the desired products 50 in 86–94% yields (3n-s). Disubstituted anilines, such as 2,3dimethylaniline, 2,4-dimethylaniline, 2,5-dimethylaniline, and 3.4-dimethylaniline also underwent the amidation reactions with 1a and afforded the corresponding products (3j-m) in 69-83% yields with observed steric effect. It should be noted that anilines 55 with electron-withdrawing groups, such as CH₃CO, CN, and NO₂ on their para-positions gave the desired products in moderate vields at a higher reaction temperature (70 °C) (3u-w). In addition, 2-naphthaleneamine also reacted with 1a to generate the corresponding product (3x) in 81% yield. To our great delight,

60 Scheme 2 H_2O_2 -mediated oxidative formation of amides from aromatic amines and pentane-2,4-dione $(1a)^a$





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when 4-aminophenol, 4-amino-3-fluorophenol, and 2aminophenol (**2y-aa**), which are oxidized readily in the presence of oxygen and moisture, reacted smoothly with **1a** to s give the *N*-acylated products (**3y-aa**) in 70–97% yields in the

presence of H₂O₂ (30% aq.) under air. It is obvious that *ortho*position effect was observed in the reactions of 2-substituted anilines (**2g**, **2k-m**, **2t** and **2aa**) with **1a**. It is important to note that when the reaction scale was increased up to 10 ¹⁰ mmol, 91% isolated yield of **3p** was isolated from the reaction of **1a** with 4-bromoaniline (**2p**). However, the reactions of **1a** with aliphatic primary and secondary amines (such as *n*decylamine and di-*n*-buthylamine), and aromatic secondary amine (*N*,*N*-dimethylaniline) could not afford the desired *N*-¹⁵ acylation products under the optimized reaction conditions.

 Table 2 Reactions of various 1,3-diketones with anilines^a

R ¹	$\frac{1}{2} + R^3 + R^3$	² H ₂ O ₂ (30 r. t.	$\overset{\text{(aq.)}}{\underset{R^2}{\overset{(aq.)}{\underset{R^2}{\underset{R^2}{\overset{(aq.)}{\underset{R^2}}{\underset{R^2}{\underset{R^2}{\underset{R^2}{\underset{R^2}{\underset{R^2}{\underset{R^2}{\underset{R^2}{\underset{R^2}{\underset{R^2}}{\underset{R^2}{\underset{R^2}{\underset{R^2}{\underset{R^2}{\underset{R^2}{\underset{R^2}{\underset{R^2}{\underset{R^2}{\underset{R^2}}{\underset{R^2}{\underset{R^2}{\underset{R^2}{\underset{R^2}{\underset{R^2}{\underset{R^2}{\underset{R^2}{\underset{R^2}{\underset{R^2}}{\underset{R^2}{\underset{R^2}{\underset{R^2}{\underset{R^2}{\underset{R^2}{R^2}{\underset{R^2}}{\underset{R^2}{\atopR^2}{\underset{R^2}{\underset{R^2}{\atopR^2}{\underset{R^2}$]R ³ 3)R ³		
Entry	1,3-Diketone	Amine $(R^3 =)$	Product	y ield		
1	0 0 1b	4-Me		90		
2	0 0 1b	4-MeO		92		
3	0 0 1b	4-EtO	Eto 3ad	85		
4	0 0 1c	4-Br	Br 3s	67		
5	0 0 1 1d	4-Br	Br 3ae	trace		
6		4-Br	Br Saf	trace		
7	1f	4-Br	Br 3s	89		
8	F F F	4-Br	Br 3s	65		
9	0 0 1h	4-Br	Br 3s	74 20		
10		4-Br	Br 3ag	86		
11	0 0 Ph Ph 1j	4-Me	Me Sah	0 42 ^c		
12		4-Me	Me Sb	84		
Reaction conditions: 1 (0.50 mmol), 2 (0.60 mmol), H ₂ O ₂ (30% ag.						

Leading conditions. I (0.50 minor), 2 (0.60 minor), H_2O_2 (30% aq., 1.5 mmol), at room temperature for 8 h. ^b Isolated yield. ^c 70 °C.

The H₂O₂-promoted amidation of anilines with various 1,3diketones as different acylation agents via C-C activation was also investigated (Table 2). When heptane-3,5-dione (1b) was 20 served as acylating agent like propionyl chloride reacting with 4methyaniline, 4-methoxyaniline, and 4-ethoxyaniline, the oxidative formation of amides through C-C activation of 1b with amines proceeded well to generate the corresponding amides (**3ab-ad**) in 85–92% yields (Table 2, entries 1–3). Intriguingly, 25 when 3-methylpentane-2,4-dione (1c), instead of pentane-2,4dione (1a) reacted with 4-bromoaniline, 67% yield of 3s was obtained (Table 2, entry 4). However, when 2,6-dimethylheptane-3,5-dione (1d) and 2,2,6,6-tetramethylheptane-3,5-dione (1e) was used to react with 4-bromoaniline, only a trace amount of desired 30 amides were observed owing to their steric hindrance (Table 2, entries 5 and 6). It should be noted that when asymmetric β diketones 1f and 1g were engaged in the reactions and the reactions exhibited excellent selectivity, providing product 3s in 89, and 65% yields (Table 2, entries 7 and 8).²¹ However, when 35 1i was tested under the optimized conditions, regioisomers 3s and 3ag were generated in 74, and 20% yields (Table 2, entry 9). The regioisomers may originate from the steric hindrance of the carbonyl of B-diketones. Similarly, only amide 3ag was isolated in 86% yield when asymmetric B-diketone 1i was employed in 40 the reaction (Table 2, entry 10). Aromatic β -diketone, 1,3diphenylpropane-1,3-dione (1j) was conducted in the reaction at 70 °C, leading to N-(p-tolyl)benzamide (3ah) in 42% yield (Table 2, entry 11), and 1-phenylbutane-1,3-dione (1k) was employed, the unique product N-(p-tolyl)acetamide 3b was obtained in 84% 45 yield (Table 2, entry 12). These results indicated that the activity of aromatic β -diketones is lower than that of aliphatic ones in the reaction.

To investigate the reaction mechanism, the control experiments were performed and the results were presented in 50 Scheme 3. The condensation of 1-phenylbutane-1,3-dione (1k) with aniline (2a) generated the corresponding product 4k in 90% yield at room temperature for 6 h (Scheme 3, eq. 1). When the prepared 4k was performed in H₂O₂ (30% aq., 3.0 eq.), Nphenylacetamide (3a) was generated in 94% yield, along with 55 benzoic acid in 90% isolated yield (Scheme 3, eq. 2). Meanwhile, when prepared 4a from the reaction of pentane-2,4-dione (1a) and aniline (2a) was carried out in H₂O₂ (30% aq., 3.0 eq.), 3a was isolated in 99% yield (Scheme 3, eq. 3). What's more, when a radical scavenger, 2,2,6,6-tetramethylpiperidyl-1-oxyl (TEMPO) 60 was added up to equivalent of oxidant, the reaction was completely shut down, suggesting that this reaction may involve a radical process. Though the exact mechanism is still not clear at present, a possible reaction mechanism was shown in Scheme 4. Initially, an intermediate 4k was formed via the condensation of 65 aniline (2a) with 1-phenylbutane-1,3-dione (1k). The obtained 4k then reacted with hydroperoxyl radical, which was generated in situ by the reaction of hydrogen peroxide, providing an intermediate I, followed by its reaction with hydroxyl radical, leading to II. In the following procedure, an intramolecular C-C 70 bond cleavage of II underwent to afford III and IV, which generated 3a via tautomerism. Finally, formic acid and benzoic acid were formed through the α -carbon cleavage of III by H₂O₂. Moreover, the silver mirror was detected after the reaction mixed

with Tollens' reagent. To further confirm the proposed mechanism, the Bayer-Villiger-type oxidation of 1-phenylbutane-1,3-dione (1k) and followed by the amide-ester exchange should be excluded. The results indicated that no corresponding ester 5 was formed when the Bayer-Villiger-type oxidation of 1phenylbutane-1,3-dione (1k) with 30% aqueous H_2O_2 (3.0 equiv.) at room temperature for 8 h (Scheme 3, eq. 4).



$$\frac{0}{2} \frac{0}{1 \text{ k}} \frac{1}{1 \text{ k}} \frac{1}{1$$

Scheme 3 The control experiments



Scheme 4 The possible reaction mechanism

In summary, we have developed a novel and rapid amide bond 15 formation strategy from aromatic primary amines and 1,3diketones promoted by the commercial available H_2O_2 (30% ag.) as sole oxidant at room temperature under metal-free conditions in water.²² The reported method is high-yielding, simple and mild, and it is the first example of 1,3-diketones as acylation agents via 20 C-C bond cleavage. The detailed mechanistic study and further

investigation on metal-free reactions are currently underway.

Experimental Section

All the direct oxidative coupling reactions of acetophenones with and amines were carried out under an air atmosphere. ¹H and ¹³C

25 NMR spectra were measured on a Bruker Avance 400 MHz NMR spectrometer with CDCl₃ as solvent and recorded in ppm relative to internal tetramethylsilane standard. General chemicals were purchased from commercial suppliers and used without further

purification.

30 General procedure for H₂O₂-mediated oxidative formation of amides from aromatic amines and 1,3-diketones

A 10 mL of reaction tube was charged with aniline (0.50 mmol), 1,3-diketone (0.60 mmol) and H₂O₂ (30%, aq., 1.5 mmol). After the reaction was carried out at room temperature (about 25 °C)

35 for 8 h, it was extracted twice with EtOAc. The organic layers were combined, dried over Na₂SO₄, and concentrated to yield the crude product, which was further purified by flash chromatography on silica gel to give the pure product.

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 - 22 The reaction solution was analysis by ICP-MS, and the results indicated that the general metals, such as Cu, Pd, Ni, Co, Fe, Ru, and Rh were not detected.

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Graphical Abstract

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H₂O₂-mediated oxidative formation of amides from aromatic amines and 1,3-diketones as acylation agents via C–C bond cleavage at room temperature in water under metal-free conditions

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Metal-free H₂O₂-mediated formation of amides from anilines and 1,3-diketones via C–C bond cleavage at room ¹⁰ temperature in water was developed.



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