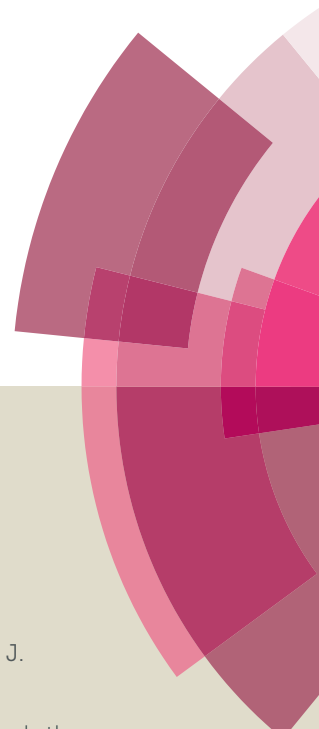
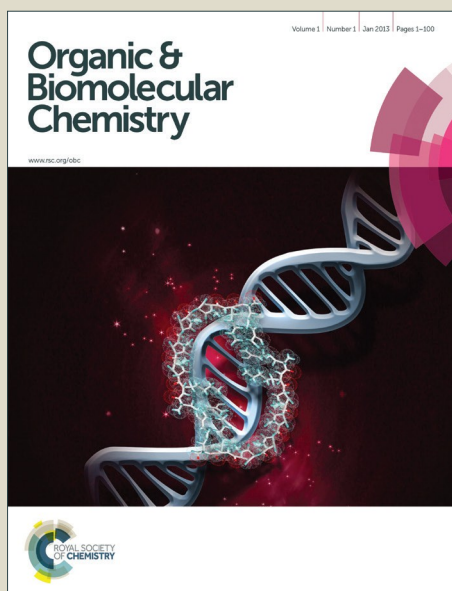


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Novel and Efficient Transformation of Enamides into α -Acyloxy Ketones *via* Acyl Intramolecular Migration Process

Xiaoqiang Zhou,^a Haojie Ma,^a Jinhui Cao,^a Xingxing Liu,^a and Guosheng Huang^{a*}Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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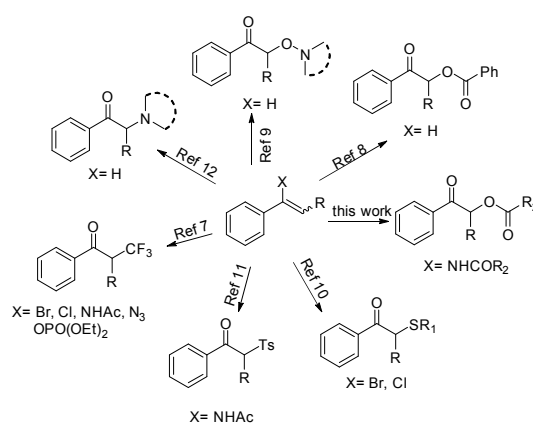
Hydrogen peroxide and anhydride mediated transformation of enamides to afford substituted α -acyloxy ketones is described. This transition-metal-free cascade reaction owned a broad substrate scope and high efficiency. The acyl intramolecular migration procedure successfully achieved this acyloxylation process under mild conditions and increased the atom efficiency.

Constructing α -acyloxy carbonyl moieties is a hot topic in organic synthesis, not only because α -acyloxy ketones motifs are common building blocks widely found in natural products and pharmaceuticals, but also because they are used as versatile synthons for further transformations.¹ Although various procedures² including hypervalent iodine mediated α -oxidation of ketones,³ ethynylcarbinols⁴ and terminal alkynes⁵ have been developed for the synthesis of α -acyloxy ketones motifs, most of them have been accomplished with harsh reaction conditions, multistep preparations and excessive hypervalent iodine reagents. Thus novel and efficient methods for the synthesis of α -acyloxy ketones motifs, by virtue of simple operation, high atom efficiency, saving energy, time and labor, remain highly desirable.

Alkene functionalization with single operation exhibits important role, because this conversion can increase molecular diversity.⁶ Recently, a series of leading works about the transformation of alkene to α -C-H functionalized ketones have been documented in C-C,⁷ C-O,^{8,9} C-S^{10,11} and C-N¹² bond formation reactions (Scheme 1). Enamides, as versatile and powerful building blocks, not only have been broadly used in constructing substantial bioactive N-heterocyclic motifs¹³ including our own contributions¹⁴, but also have been employed for building α -C-H Functionalized Ketones. In 2014, Lei's group reported a radical oxytrifluoromethylation of enamide to form α -trifluoromethylated ketone.⁷ In 2015, Du's

group also reported a facile synthetic route towards β -keto-sulfone derivatives by TBAI/TBHP mediated oxidative coupling of enamides with sulfonyl hydrazides through a radical process.¹¹ Utilizing the functional group which was wasted in these transformation^{7,11} to furnish molecular diversity is still a challenge. During our preparation of this manuscript, Park et al. reported a transformation of 1,2-azido acetate into α -amido ketones through acyl intramolecular migration procedure.¹⁵ Herein, we describe a novel and efficient procedure which employs hydrogen peroxide and anhydride for α -acyloxylation of enamides leading to α -acyloxy ketones. The intramolecular migration of the acyl group in this transformation increases the atom efficiency. We consider this synthetic technology can enrich the utilization of enamides chemistry.

Scheme 1. Synthesis of α -C-H Functionalized Ketones from Alkene derivatives



The initial reaction of **1a** was carried out in the presence of 2.0 equiv oxone as oxidant and 2.0 equiv Ac₂O which could protect enamide keeping stable as additive in water at room temperature with air bath. Interestingly, the desired α -acyloxy ketones motif **2a** was isolated in 30% yield (Table 1, entry 1). The efficiency of several oxidants was tested, and the results illustrated that oxone and H₂O₂ (30%) could promote this

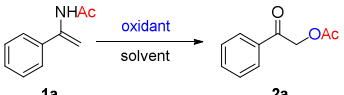
^a State Key Laboratory of Applied Organic Chemistry, Key Laboratory of Nonferrous Metal Chemistry and Resources Utilization of Gansu Province, Department of Chemistry, Lanzhou University, Lanzhou, 730000, China. E-mail: hgs@lzu.edu.cn; Fax: +86-931-8912582

Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

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conversion (Table 1, entries 2-6). With the consideration of the economic cost and environmental protection, H₂O₂ was used as an ideal oxidant to improve the efficiency. Control experiments confirmed that the reaction did not occur in the absence of Ac₂O (Table 1, entries 7 and 8). While when the substrate **1a** was added just only in the mixture of H₂O₂ (30%) and Ac₂O, the yield of **2a** was increased remarkably to 81% yield (Table 1, entry 9). Increasing the dosage of H₂O₂ (30%) and Ac₂O, **2a** was given with a higher yield (Table 1, entry 10). Furthermore, carrying out the mixture in a water bath could give the paralleled result without increasing the dosage of reagents (Table 1, entry 11). In addition, using propionic anhydride or isobutyric anhydride as additive could give the same result, which indicated that the acetyl group at acyloxylation product **2a** was derived from enamide **1a** itself (Table 1, entries 12 and 13). Moreover, when **1a** was carried out under nitrogen atmosphere, it could transform to α -acyloxy ketone **2a** smoothly, which suggested that oxygen was not the oxygen donor in this conversion (Table 1, entry 14). Also, when the substrate was extended to 10 mmol, the desired ketone can be given with a good yield (Table 1, entry 15). Finally, the optimized reaction conditions were obtained as follows: enamides was added in a mixture of 5 equiv of H₂O₂ (30%) and 5 equiv of Ac₂O and the mixture was stirred with a water bath at room temperature under air for the desired time.

Table 1. Optimization of the Reaction Conditions^a


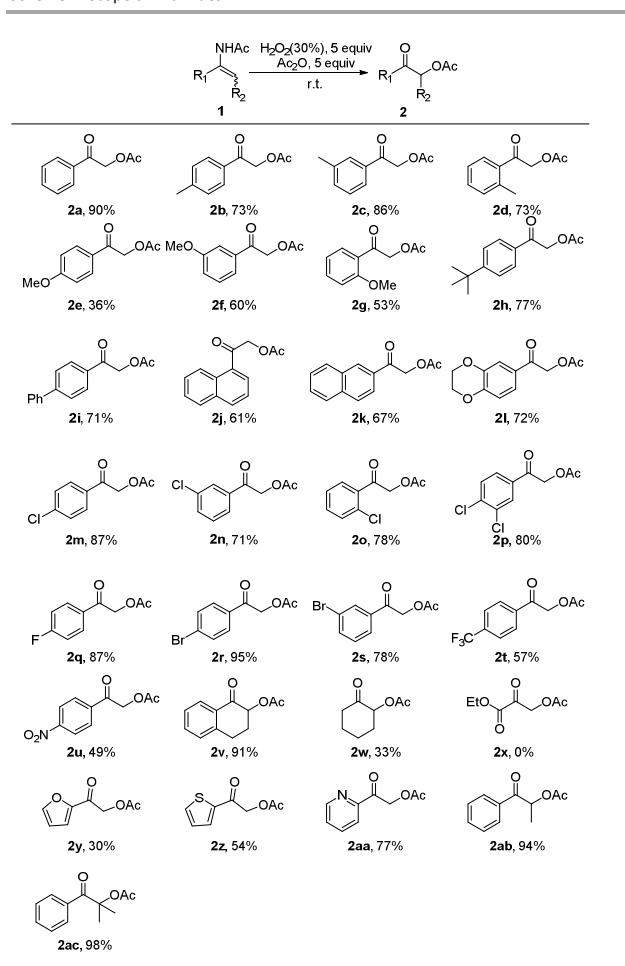
entry	oxidant	additive	solvent	time/min	yield ^b / %
1	Oxone	Ac ₂ O	H ₂ O	120	30
2	TBHP	Ac ₂ O	H ₂ O	120	0
3	DTBP	Ac ₂ O	H ₂ O	120	0
4	BPO	Ac ₂ O	H ₂ O	120	0
5	K ₂ S ₂ O ₈	Ac ₂ O	H ₂ O	120	0
6	H ₂ O ₂	Ac ₂ O	H ₂ O	120	15
7	H ₂ O ₂	HOAc	H ₂ O	120	0
8	H ₂ O ₂	-	-	120	0
9	H ₂ O ₂	Ac ₂ O	-	10	81
10 ^c	H ₂ O ₂	Ac ₂ O	-	10	89
11 ^d	H ₂ O ₂	Ac ₂ O	-	10	90
12 ^c	H ₂ O ₂	(EtCO) ₂ O	-	10	88
13 ^c	H ₂ O ₂	(<i>i</i> -PrCO) ₂ O	-	10	86
14 ^{d,e}	H ₂ O ₂	Ac ₂ O	-	10	85
15 ^{d,f}	H ₂ O ₂	Ac ₂ O	-	60	83

^a reaction conditions: **1a** (0.2 mmol), oxidant (2 equiv), additive (2 equiv) and solvent (1 mL), the mixture was stirred at room temperature under air for the desired time. The reaction was monitored by TLC. H₂O₂ (30%) aqueous solution was used. ^b isolated yield. ^c oxidant (5 equiv), additive (5 equiv). ^d The reaction was carried out with a water bath. ^e under nitrogen atmosphere. ^f **1a** (10 mmol), oxidant (2 equiv), additive (2 equiv).

With a set of optimized conditions in hand, we examined the scope of this acyloxylation process. Delightfully, this new acyloxylation reaction displayed a high degree of functional-group tolerance and proved to be a quite general procedure

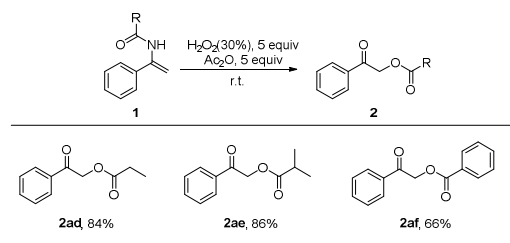
(Scheme 2). Aryl enamides with methyl, methoxyl, tertiary butyl, 1,4-dioxine, phenyl, chloro, fluoro, bromo, trifluoromethyl and nitryl on the aromatic rings all gave the corresponding α -acyloxy ketones in moderate to excellent yields. Enamides with electron-withdrawing groups such as chloro, bromo, and fluoro achieved better results than with electron-donating groups (**2b-2i**, **2m-2s**), and electron-donating group methoxyl at para-position only obtained desired **2e** in 36% yield. Also 1- or 2-naphthyl substituted enamides survived well, providing the prospective **2j** and **2k** in good yields, respectively. Also, the employment of aliphatic enamides rooted in α -tetralone and cyclohexanone can respectively transformed successfully (**2v-2w**), whereas the use of ethyl 2-acetamidoacrylate could not give the presumptive ketone (**2x**). Furthermore, the heterocyclic enamides derived from furan-2-yl, thiophen-2-yl and pyridine-2-yl ketones were tolerated in this transformation (**2y-2aa**). Additionally, α -methylated *E/Z* enamides mixture and α -dimethylated enamide performed well in this reaction respectively to obtain expectant ketones with stoichiometric yields (**2ab-2ac**).

Scheme 2. Scope of Enamides

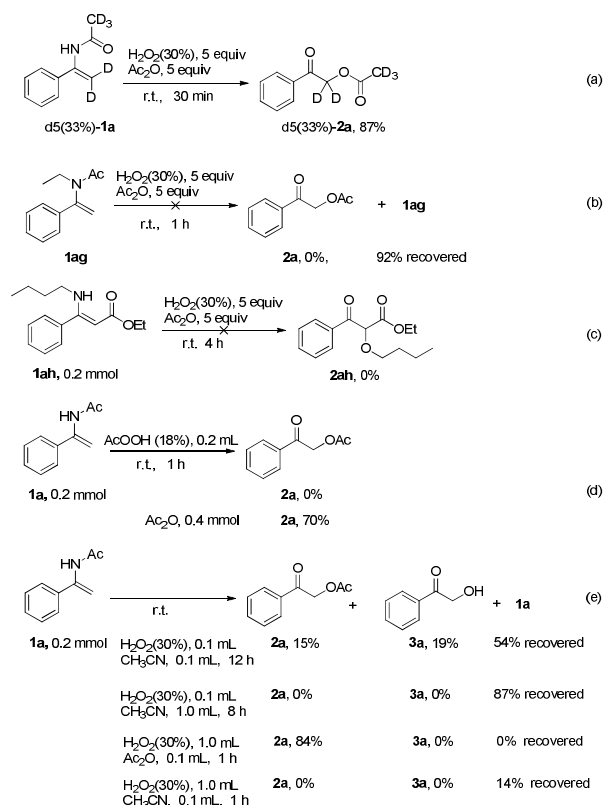


It was noteworthy that when *N*-propionyl, *N*-isobutyryl and *N*-benzoyl enamides were investigated, and acyloxylation reactions proceeded smoothly to give the corresponding α -acyloxy ketones in good to excellent yields (**2ad-2af**), which further confirmed that the acyl group at acyloxylation products were derived from enamides (Scheme 3).

Scheme 3. Scope of Enamides with Different Acyl Groups



Scheme 4. Control Experiments

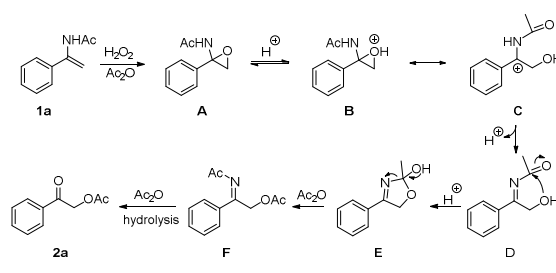


To gain mechanistic insight into this transformation, some control experiments were carried out. Some deuterium labeling experiments illustrated that there is no proton transfer process in the reaction system (Scheme 4, a). The desired **2a** was not generated when *N*-ethyl enamide **1ag** was employed under standard conditions, and 92% yield of the intact starting material **1ag** was recovered. This result showed that the reaction might undergo an N-H hydrogen atom

abstraction process (Scheme 4, b). Moreover, the employment of enamide **2ah** which changing the aryl group of enamide into alkyl substituent could not succeed this cascade transformation, this result demonstrated that acyl group is imperative for this intramolecular migration process (Scheme 4, c). Subsequently, peracetic acid solution, which can be easily prepared using hydrogen peroxide and anhydride, was evaluated in this conversion with a disappointing result. After anhydride was added to reaction mixture, this acyloxylation reaction can occur smoothly. The result proved that peracetic acid could not perform this procedure independently (Scheme 4, d). When using a bit of acetonitrile to dissolve enamide, hydrogen peroxide could produce small amount of desired **2a** and its hydrolysis product α -hydroxy-ketone **3a**. While using abundant of acetonitrile to dissolve enamide, all these reactions were inhibited, and starting material **1a** was recovered with 87% yield. Furthermore, abundant H_2O_2 and little CH_3CN or Ac_2O were employed to carry out this procedure, respectively. Only Ac_2O could promote this reaction. These procedure turned out that anhydride can promote the acyloxylation of enamide and inhibit the hydrolysis of α -acyloxy ketone, acetonitrile just acts as solvent in this reaction which can dilute the concentration of H_2O_2 and reduce the reaction rate. (Scheme 4, e).

Though the exact reaction mechanism is still not clear, a probable mechanism is proposed as shown in Scheme 5 on the basis of above results. Initially, this reaction might be initiated by the oxidation of enamide **1a** with hydrogen peroxide, providing *N*-acylaminoepoxide intermediate **A**. Subsequently, the ring opening of **A** and subsequent deprotonation procedure generated intermediate **D**. Then intermediate **F** was formed by an acyl intramolecular migration process and a followed substitution reaction of imine with Ac_2O . Finally, the hydrolysis of intermediate **F** afforded the desired ketone **2a**.

Scheme 5. Proposed Mechanism



Conclusions

In conclusion, we have demonstrated a transition-metal-free α -C-H functionalization of enamides to give α -acyloxy ketones compounds, which are used as versatile synthons for organic synthesis and pharmaceutical chemistry. Just mixing enamides to a solution of hydrogen peroxide and anhydride at room temperature can successfully realize this acyloxylation process through acyl intramolecular migration process. Simple

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operation with inexpensive reagents, high atom economy, saving energy, time and labor make this novel and efficient protocol attractive.

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