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Communcation

One-Pot Synthesis of Acyloxycarbonyl compounds from ketones using Pybox-Copper(II) catalysts

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we have described the first one-pot and efficient method for the synthesis of acyloxycarbonyl compounds from ketones compounds catalyzed by Pybox Cu(II) complex under mild conditions. A series of α-acyloxylation of ketones products were obtained in good and excellent yields.

α-acyloxylation of ketones represent an important organic synthetic intermediates in organic synthesis and versatile building blocks in natural products and pharmaceuticals.[1] Thus, many efforts have been devoted to efficient synthetic approaches to α-acyloxylation of ketones and its derivatives using different synthetic method by many research groups. A variety of protocols have been reported including transition-metal-catalyzed and organocatalysts methods. In 1998, Ohfune and coworker reported the copper-catalyzed insertion of α-diazoketones into carboxylic acids to give α-acyloxyketones.[2] In 2009, the Cadierno group described the addition of carboxylic acids to propargyl alcohols leading to α-acyloxyketones catalyzed by Ru complexes.[3] However, in contrast to transition metal catalyst, the organocatalysts have been further extensively explored for catalyzed α-acyloxylation of ketones formation including dimsyl anion[4], (hypo)iodite[5], N-heterocyclic carbene (NHC)[6], amine[7], 2-tritylpyrrolidine[8] as well as Bu_4NI[9]. Although these organocatalys-catalyzed reactions are robust to synthesize a variety of α-acyloxylation molecular architectures with a series of functional groups, transition metal catalyzed reaction of propiophenone generate α-acyloxylation products is not reported.

Herein, we reported an one-pot and efficient method for the synthesis of α-acyloxylation of carbonyl compounds in the presence of both moisture and air catalyzed by Pybox Cu(II) complex. Treatment of a variety of ketones with [(Dm-Pybox)Cu(II)Br_2] and $K_4[Fe(CN)_6]\cdot 3H_2O$ provides the α-acyloxylation of ketones products in 67-97% isolated yield. The transformation is regiospecific in the discrimination of electron-deficient intermediate in the case of nonsymmetrical substrates.

Recently, we developed an efficient method for the synthesis of α-amination of ketones and esters under aerobic oxidative conditions using [(Dm-Pybox)CuBr_2] complex as catalyst through α-bromo carbonyl intermediate.[10] In the continued effort to develop environmentally benign protocols for the synthesis of biologically and pharmacologically active compounds[11], we attempted to extend this nucleophile-catalyzed aerobic oxidation protocol to the synthesis of aromatic α-cyano ketones from ketones and potassium hexacyanoferrate as the CN^- source.[12] When propiophenone and potassium hexacyanoferrate were applied to the reaction conditions, previously, the expected 2-methyl-3-oxo-3-phenylpropanenitrile was not observed; instead, an unexpected compound was obtained as the major product.

With this rather unexpected result in hand, we started our study using the model reaction as shown in Table 1: propiophenone (0.5 mmol) and potassium hexacyanoferrate(II) (2.4 equiv.) in DMF (1 mL). However, no reaction took place after heating the mixture at 110 ºC for 9 h only with or without ligand (Table 1, entry 1 and entry 2). The α-acyloxylation product was obtained in 48% yield when using $CuBr_2$ as catalysts (Table 1, entry 3); However to our delight, 90% yields of desired product were observed using 2,6-bis[4',4'-dimethyloxazolin-2'-yl]pyridine (Dm-Pybox) as the ligand (Table 1, entry 4). Then, we chose [(Dm-Pybox)Cu(II)Br_2] complex as the catalyst to test the influence of solvents on reaction yield (Table 1, entries 5-7). To our delight, DMF is the best solvent for this transformation. However, lower yield was obtained with lower catalyst loading 5 mol% [(Dm-Pybox)Cu(II)Br_2] and required longer reaction time of 16 hours (Table 1, entry 8). The yield remains unchanged with 15 mol% of [(Dm-Pybox)Cu(II)Br_2] and reaction time shorter 6 hours (Table 1, entry 9). To ascertain that O_2 is necessary (as shown in proposed mechanism later on) for the reaction to proceed, a control reaction was carried out in presence of N_2. In absence of O_2, only 9% of desired product were obtained (Table 1, entry 10), which clearly demonstrates the role of O_2 in this reaction. Finally, the amount of $K_4[Fe(CN)_6]\cdot 3H_2O$ was also surveyed, 9% desired product was obtained in the presence of 10% CN^- source (Table 1, entry 11). It is proved that equivalent $K_4[Fe(CN)_6]\cdot 3H_2O$ was necessary

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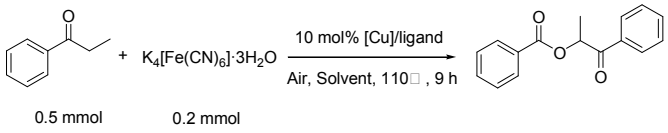
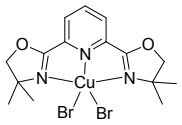
for the reaction to proceed. A control experiment with the 20% TEMPO showed no reaction (Table 1, entry 12). This result might support the formation of intermediate **E** through radical mechanism pathway in Scheme 2.

Table 1 Initial Studies toward α-acyloxylation of propiophenone



0.5 mmol 0.2 mmol



[(Dm-Pybox)Cu(□)Br2] ≡ **Cu complex**

Entry	Cu catalyst (10 mol %)	Ligand (mol%)	Solvent	Yield (%)[a,b]
1			DMF	NR
2		L	DMF	NR
3	$CuBr_2$		DMF	48
4	**Cu complex**		DMF	90
5	**Cu complex**		DMSO	11
6	**Cu complex**		NMP	NR
7	**Cu complex**		DMF	91
8	**Cu complex**		DMF	73[c]
9	**Cu complex**		DMF	92[d]
10	**Cu complex**		DMF	9[e]
11	**Cu complex**		DMF	9[f]
12	**Cu complex**		DMF	NR[g]
12	**Cu complex**		DMF	50[h]
12	**Cu complex**		DMF	33[i]

[a] Isolated yield; [b] reaction condition: 1mL DMF as solvent, under air, 110℃; [c] 5 mol% catalyst, reaction time: 16 h; [d] 15 mol% catalyst, reaction time: 6 h; [e] under N_2; [f] 0.0083 mmol $K_4[Fe(CN)_6]\cdot 3H_2O$; [g] 20mol% TEMPO was added; [h] 1.2 mmol CuCN; [i] 1.2 mmol $Zn(CN)_2$.

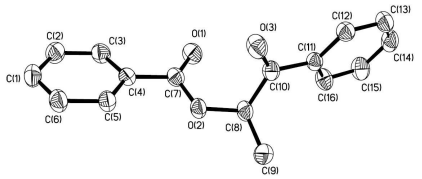
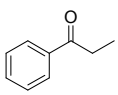
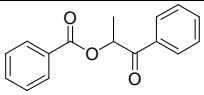
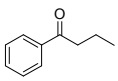
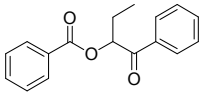
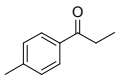
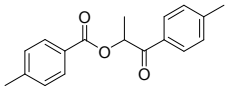
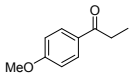
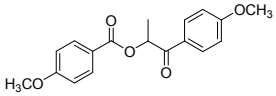
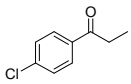
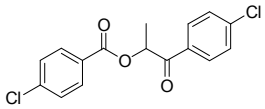
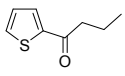
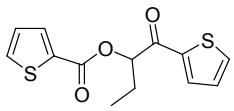
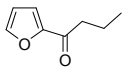
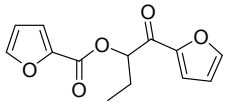


Fig. 1 Molecular structure of **1a** with thermal ellipsoids drawn at the 30% level, all hydrogen atoms are omitted for clarity.

To explore the generality and scope of the present α-oxyacylation synthetic method, several ketones compounds were examined as substrates under the optimized reaction conditions. Propiophenones derivatives, which are substituted with electron-donating or electron-withdrawing groups, gave the corresponding α-benzoyloxy ketones **1a**-**5a** in good to excellent yields. The configuration of **1a** was determined by X-ray crystallographic analysis (Fig. 1). More specifically, the efficient conversion of electron-deficient ketones was achieved at low temperature (Table 2, entry 5). Notably, 2-butyrylfuran and 2-butyrylthiophene were also tested, and these reactions proceeded smoothly to give α-heteroaryl heteroaryl ketones (**6a** and **7a**) in good and moderate yields in the presence of 15 mol% [(Dm-Pybox)Cu(II)Br_2]catalysts.

Table 2 [(Dm-Pybox)Cu(II)Br_2] catalyzed α- oxyacylation of ketones.

Entry	Substrate	Product	Time (h)	Yield (%)[a,b]
1		 **1a**	9	90
2		 **2a**	8	97
3		 **3a**	8	94
4		 **4a**	8	93
5		 **5a**	10	73[c]
6		 **6a**	15	87[d]
7		 **7a**	15	79[d]

[a] Isolated yield; [b] reaction condition: 0.5 mmol carbonyls, 0.2 mmol $K_4[Fe(CN)_6]\cdot 3H_2O$, 10 mol% [PyboxCu(Ⅱ)Br_2], 1mL DMF as solvent, under air; [c] 90℃; [d] 15 mol% [(Dm-Pybox)Cu(II)Br_2].

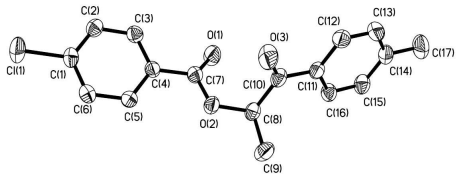


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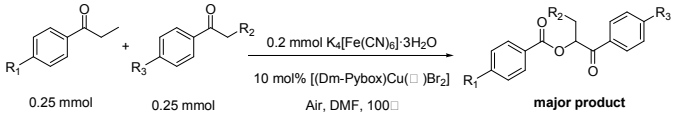
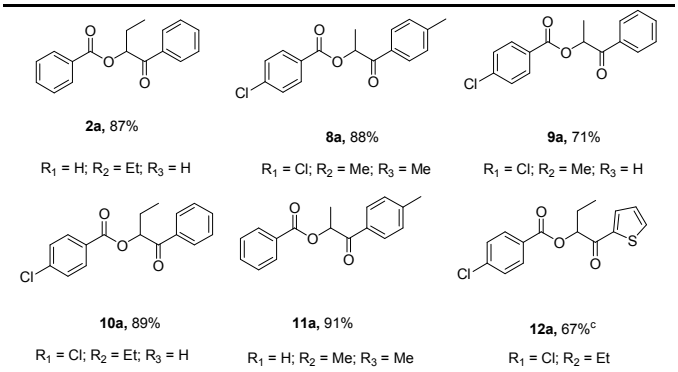
Fig. 2 Molecular structure of **8a** with thermal ellipsoids drawn at the 30% level, all hydrogen atoms are omitted for clarity.

Table 3 Studying the reaction selectivity toword α-oxyacylation of ketones[a, b].

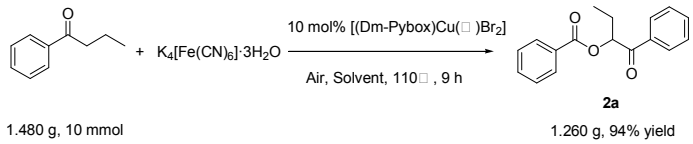




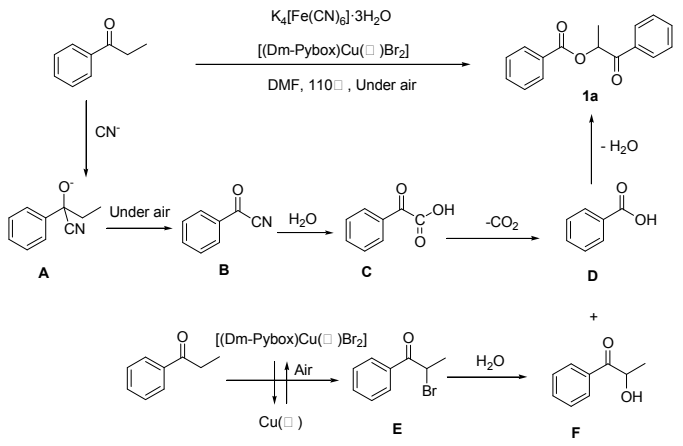
a: Isolated yield; b: reaction condition: 1 mL DMF as solvent, 0.2 mmol $K_4[Fe(CN)_6]\cdot 3H_2O$, 9 h, under air, 100℃； c: 20 h

In general, the selectivity of the reaction is determined by electronic effects, the control experiments were carried out to test the selectivity of α-oxyacylation of ketones reaction. Thus, equimolar amounts of 1-p-tolylpropan-1-one and 1-(4-chlorophenyl)propan-1-one were heated in the presence of 10 mol% [(Dm-Pybox)Cu(II)Br_2] catalysts and 2.4 equivalents of CN^- in DMF to give **8a** in 88% yield (Table 3). No other side products were observed in this transformation. The configuration of **8a** was also determined by X-ray crystallographic analysis (Fig. 2). Electron-withdrawing groups on aromatic ring substrate 1-(4-chlorophenyl)propan-1-one more favor form the intermediate, and then obtained the asymmetry α-oxyacylation product. Propiophenone and 1-phenylbutan-1-one were also transformed well under the standard conditions, desire products 1-oxo-1-phenylpropan-2-yl 4-chlorobenzoate (**9a**) and 1-oxo-1-phenylbutan-2-yl 4-chlorobenzoate (**10a**) were obtained in 71% and 89% yields, respectively (Table 3). Interestingly, the hetercycle substrate 1-(thiophen-2-yl)butan-1-one underwent this transformation to provide **12a** in aceptable yields.

To further evaluate the practical utility of the catalyst system, the model reaction was carried out on a gram scale under the optimized conditions, and the desired product was obtained in 94% yield (Scheme 1).



Scheme 1 Gram-scale synthesis of **2a**



Scheme 2 Proposed catalytic mechanism toward α-oxyacylation of ketones.

To gain further insights into the reaction mechanisms of the Cu-catalyzed cross-coupling reactions, several starting materials, such as benzoic acid or benzoyl cyanide, have been added to investigate the viability of the intermediate. The desired products were observed in both conditions indicating that the benzoic acid and benzoyl cyanide involvement of the mechanism process (see Supporting Information (SI)). Based on the documented precedents and experiment results, the reaction mechanism was proposed as shown in Scheme 2. Initially, cyanohydrin intermediate **A** formed by cyanide addition to propiophenone. Then, intermediate **A** could also undergo oxidation to yield benzoyl cyanide (**B**) under aerobic oxidation conditions, which is hydrolyzed in situ to give the benzoic acid (**C**) under wet organic solvents.[13] and then decarbonylation formation of (**D**), On the other hand, propiophenone would undergo bromination at the α-carbonyl to generate 2-bromo-1-phenylpropan-1-one (**E**) in the presence of [(Dm-Pybox)Cu(II)Br_2] catalyst.[14] Then, intermediate **E** was further hydrolyzed to afford 2-hydroxy-1-phenylpropan-1-one (**F**), which could react with intermediate **D** to afford final product. The intermediate **F** is supported by the isolation and MS spectra. And Cu(II) catalyst were regenerated in the presence of oxygen-mediated reoxidation of Cu(I).

Conclusions

In conclusion, we have described the first one-pot and green efficient method for the synthesis of α-acyloxylation of ketones compounds catalyzed by Pybox Cu(II) complex under mild conditions. A series of α-acyloxylation of ketones products were obtained in good and excellent yields. This method provides an excellent alternative to organocatalysts. And a detailed reaction mechanism is still under investigation.

Acknowledgment

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Notes and references

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† Electronic Supplementary Information (ESI) available: Additional copies of NMR spectra and CCDC 1012733 and 1012734 crystallographic information files (CIFs) for complex **1a** and **8a** are available, See DOI 10.1039/:

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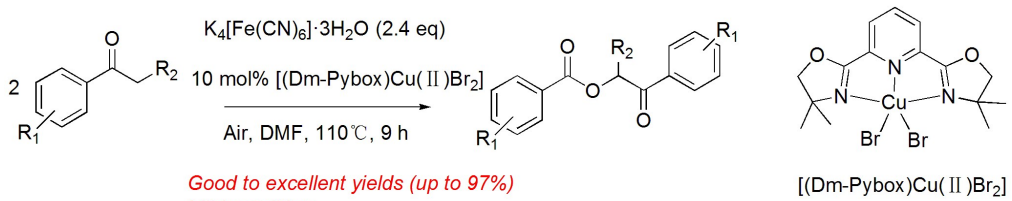
Table of Content

One-pot and efficient method for the synthesis of acyloxycarbonyl compounds from ketones compounds catalyzed by Pybox Cu(II) complex have been obtained under mild conditions.



Good to excellent yields (up to 97%)
Mild condition
Gram scale synthesis

[(Dm-Pybox)Cu(Ⅱ)Br_2]