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Carbonylation of Tertiary Carbon Radical: Synthesis of Lactams

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Herein, we disclose an interesting iron-catalyzed approach for the carbonylation of tertiary carbon radical. The tertiary carbon radical generated from a 1,5-hydrogen atom transfer can be captured by CO gas smoothly. Various six-membered lactams were constructed chemo-selectivity in high yields.

Since the first example of free radical carbonylation was discovered by Coffman and co-workers in 1951,¹ the free radical carbonylation reaction has received much attention during the past decades.² There is no doubt that the direct carbon radical carbonylative transformation is an efficient method for the synthesis of carbonyl-containing compounds. Among all the types of carbon radicals, primary and secondary carbon radicals are more frequently studied in carbonylation reactions compared with tertiary carbon radical. In general, there are two reasons might explain the challenge: 1) the tertiary carbon radical is easy to be oxidized into the corresponding olefins; 2) CO trapping is difficult due to the obvious steric hindrance and the formed tertiary acyl radical undergoes a rapid decarbonylation process (Scheme 1a). This phenomena was described by Ryu and co-workers in 1998.³ They described a δ -C-H carbonylation reaction of saturated alcohols through 1,5-hydrogen atom transfer to synthesis δ lactones. However, the carbonylation of tertiary carbon radical was failed. Except one successful case with special adamantane carbon radical.4

On the other hand, the selective activation of diverse alkane C-H bonds is general challenging. Most of the successful examples depend on the activation of symmetrical alkanes such as methane, ethane, and cyclic alkanes.^{5,6} 1,5-Hydrogen atom transfer offers an effective and applicable approach for the selective activation and functionalization at δ -C-H bond.⁷ In 1883, Hoffman reported the first example of C-H

functionalization via 1,5-HAT to the synthesis of pyrrolidine derivatives.⁸ This nitrogen radical reaction now was named as Hofmann-Löffler-Freytag (HLF) reaction. While various improvements about this reaction were explored by different groups over the last hundreds years, most of these methods provide access to construct C-halogen, and C-heteroatom bonds. For the less reported C-C bond formation, activated alkenes were normally selected to capture the new generated carbon radical.⁹ Using CO gas as radical acceptor gives another route for the synthesis of carbonyl-containing compounds has not been reported. Last but not least, important lactam compounds can be directly produced.



Scheme 1. Tertiary carbon radical carbonylation.

Based on these backgrounds and our continuing interest in carbonylation chemistry, we turn our attention on the tertiary carbon radical related carbonylative transformation. Initially, 5-methylhexan-2-one O-benzoyl oxime¹⁰ 1a was selected as the model substrate for testing this tertiary carbon radical carbonylative transformation. The reaction was performed by using 1a, copper as the catalyst in 1,4-dioxane under pressure of CO (40 bar) at 100 °C. Unfortunately, no desired carbonylation product was detected and the start material was also decomposed (Table 1, entries 1-2). With the changing of the catalyst from copper to Fe(OTf)₂, a mixture of two isomers 2a and 3a can be obtained in 45% yield (Table 1, entry 3). To our delight, the start material 1a can be transferred into the desired product in 85% yield (Table 1, entry 8) when Fe(acac)₃ was applied as the catalyst. Many other iron catalysts were also explored, but the results were inferior to Fe(acac)₃ (Table

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1, entries 4-7). Then we continued to optimize this reaction with different solvents. The yield can be further improved to 88% by using CH₃CN as the solvent (Table 1, entry 9). Other solvents, such as DCE, DMSO, DMF, THF, and toluene gave a little lower yields or no conversion (Table 1, entries 10-14). As it is difficult to purify the two isomers 2a and 3a, and part of iminyl product 2a will decompose during purification process in silica column. We try to explore other condition which can transfer 2a into 3a absolutely. After screening various organic bases, we found that adding 1.2 equivalent of pyridine into the reaction mixture produced the single product 3a at 89% yield (Table 1, entry 15, 81% isolated yield). Furthermore, the reaction efficiency dropped slightly when decreasing the loading of Fe(acac)₃ and the pressure of CO (Table 1, entries 19-20). The molecular structure of the observed products could be unambiguously determined by X-ray diffraction analysis of **3a** as shown in figure 1.¹¹ The final optimized conditions were found to be: 10 mol% Fe(acac)₃ and 1.2 equivalent of pyridine in CH₃CN under 40 bar CO at 100 °C which gave 3a in 81 % isolated yield.

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Table 1. Optimization of the reaction conditions.^a

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	BZO ^{s N}	[Catal]	HN +	$\overline{\mathbf{X}}$
	1a		2a	3a
Entry	Catalysts	Solvents	Additives	Yield ^b
1	Cu(OTf) ₂	1.4-dioxane		0%
2	CuI	1.4-dioxane		0%
3	Fe(OTf) ₂	1.4-dioxane		45%
4	Fe(OTf) ₃	1.4-dioxane		31%
5	$FeSO_4H_2O$	1.4-dioxane		60%
6	$Fe(acac)_2$	1.4-dioxane		71%
7	$Fe(Pc)_2$	1.4-dioxane		26%
8	Fe(acac) ₃	1.4-dioxane		85%
9	Fe(acac) ₃	CH ₃ CN		88%
10	Fe(acac) ₃	Toluene		0%
11	Fe(acac) ₃	DCE		65%
12	Fe(acac) ₃	DMSO		83%
13	Fe(acac) ₃	DMF		68%
14	Fe(acac) ₃	THF		60%
15	Fe(acac) ₃	CH ₃ CN	Pyridine (1.2 equiv)	89% (81%) ^c
16	Fe(acac) ₃	CH ₃ CN	Et_3N	69%
17	Fe(acac) ₃	CH ₃ CN	(1.2 equiv) DIPEA (1.2 equiv)	76%
18	Fe(acac) ₃	CH ₃ CN	TMEDA (1.2 equiv)	72%
19	Fe(acac) ₃	CH ₃ CN	Pyridine (1.2 equiv)	81% ^d
20	Fe(acac) ₃	CH ₃ CN	Pyridine (1.2 equiv)	84% ^e

^a Reaction conditions: **1a** (0.20 mmol), catalysts (10 mol%), <u>solvents</u> (3 mL), additives, CO (40 bar), 100 °C, 20 h. ^b GC yields of the hixture 2a and 3a were determined by using hexadecane as the internal standard. ^c Isolated yield is in parenthesis. ^d 20 bar CO. ^c Fe(acac)₃ (5 mol%). DCE = 1,2-dichloroethane; DMSO = dimethyl sulfoxide; DMF = *N*,*N*-dimethylmethanamide; THF = tetrahydrofuran; Et₃N = triethylamine; DIPEA = *N*,*N*-Diisopropylethylamine; TMEDA = Tetramethylethylenediamine.



Figure 1. Molecular structure of **3a** in the crystal. Displacement ellipsoids correspond to 30% probability (CCDC 1886524).

With the optimized reaction conditions in hand, we next examined the substrate scope of this reaction with a range of oxime esters. As shown in Table 2, the reaction tolerated different size of aliphatic rings on the ketone moiety. Both cyclopropane and cyclobutane substituted substrates gave the corresponding desired lactams in 70% and 68% yields respectively (**3b**, **3c**). It is interesting that cyclopentane substrate gave the tetra-substitution lactam as the major product in 54% yield, which is very hard to access by other method (**3d**). The ester functional group also worked well in the standard condition and gave the target product in 50% yield (**3e**). In addition, we changed the tert-alkyl moiety and found that the carbonylation of tertiary radical in cyclic and acyclic systems proceed smoothly to deliver the corresponding spiro-lactams and lactams in moderate yields (**3f**, **3g**, **3h**, **3i**).

Subsequently, we examined the left moiety scope with aromatic systems. In the beginning, some cyclohexanone byproducts were detected when the reactions were performed at standard conditions, which might derive from the direct addition of iminyl radical to the aromatic ring systems.¹² After changing the reaction condition into lower concentration and higher pressure of CO, the byproducts were almost inhibited.¹³ The phenyl group bearing electron-donating groups such as methyl, tert-butyl, and methoxy group at para or meta position gave the desired product in good yield (3j, 3k, 3l, 3m), especially for the methoxy group at para position producing the product in 90% yield (3n). The methoxy functional group at ortho position only gave the product in 53% yield due to part of decomposition of start material (30). The substrates with electron-withdrawing groups (bromide, fluoride) at ortho and para position only gave moderate yields compared with electron-donating groups (3p-3s). Moreover, 4-methyl-1-(naphthalen-1-yl)pentan-1-one O-benzoyl oxime and 4-methyl-1-(thiophen-3-yl)pentan-1-one O-benzoyl oxime also worked well in the standard condition and gave the corresponding product in 40% and 71% respectively (3t, 3u). Finally, we further tested this carbonylative transformation with secondary carbon radical. As we expected, 45% yield of the

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desired product can be produced from the corresponding carbon radical (3v).





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^a Reaction condition A: 1a (0.20 mmol), Fe(acac)₃ (10 mol%, 7.0 mg), pyridine (1.2 equiv., 19.3 mg), CH₃CN (3 mL), CO (40 bar), 100 °C, 20 h.^b Reaction condition **B**: 1a (0.20 mmol), Fe(acac)₃ (10 mol%, 7.0 mg), pyridine (1.2 equiv., 19.3 mg), CH₃CN (6 mL), CO (50 bar), 100 °C, 20 h.

In our control experiments, the model reaction was totally inhibited by adding 1.5 equivalents of TEMPO, and the oxidation alkene product 3a' could be detected by GC-MS (Scheme 2). Based on our results and literature,¹⁴ a potential mechanism is proposed (Scheme 3). The catalytic cycle begins with the formation of a reduced iron species $Fe^{(n)}$, which is generated from the reduction of the Fe(acac)₃ precatalyst in the presence of CO. Then, the Fe⁽ⁿ⁾ species induced a SET reduction of oxime esters to give the iminyl radical A and Fe⁽ⁿ⁺¹⁾. The iminyl radical next undergoes a 1,5-hydrogen atom transfer to produce the new tertiary carbon radical B, which will be captured by CO gas to form the intermediate C. Subsequently, the Fe⁽ⁿ⁾ is regenerated by means of single

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electron oxidation of radical **C** to acyl carbocation intermediate **D**. Finally, **D** undergoes a nucleophile ring close process to provide the six-membered product **E**, which will be transformed into the final six-membered lactams **F** through a facile base-mediated double bond isomerization.



Scheme 2. Control experiments.



Scheme 3. Proposed mechanism.

In summary, an interesting protocol for the carbonylation of tertiary carbon radical has been developed. Various oxime esters were synthesized from easily accessible ketones, which can be reduced by cheap iron catalyst to provide the corresponding iminyl radical. The unstable tertiary carbon radical was generated through a 1,5-hydrogen atom transfer. We succeed to capture this tertiary carbon radical with CO to construct different six-membered lactams in high yields and excellent chemo-selectivity, which is very difficult to access via other methods.

Conflicts of interest

There are no conflicts to declare.

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