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Iron-catalyzed hydroxylation of β-ketoesters with hydrogen peroxide as oxidant

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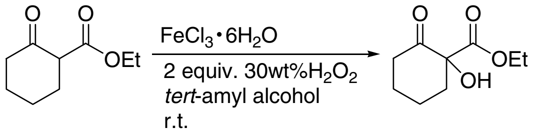
ABSTRACT

The hydroxylation of β-ketoesters was studied using simple iron catalysts and 30 wt % hydrogen peroxide as the terminal oxidant. The highest activity and yield were achieved in the presence of iron(III) chloride. Cyclic β-ketoesters could be smoothly hydroxylated in 75–90% yield. For linear β-ketoester and β-ketoamide, the chloro-substituted products were obtained.

α-Hydroxy β-ketoester is an important scaffold found in a lot of bioactive molecules.[1] The hydroxylation of 1,3-dicarbonyl compounds is a straight forward important technique in organic synthesis to access these compounds. A variety of reagents including hydrogen peroxide, *m*-CPBA, molecular oxygen, and (camphorylsulfonyl)-oxaziridines were applied in the selective oxidation of β-keto-carbonyl compounds.[1d,2] Recently, it was reported that $CoCl_2$, $CeCl_3$, and $Mn(OAc)_2$ could be effective catalyst for this transformation using molecular oxygen as oxidant.[3] Noteworthy, the asymmetric hydroxylation of β-ketoesters was also successfully demonstrated using a titanium-TADOL based catalyst and up to 94% ee was achieved.[4] Hydrogen peroxide is known to be an environmentally benign oxidant with the ease of laboratory handling. The development of general, simple and efficient catalyst system using H_2O_2 is still a challenging goal for the hydroxylation of β-keto-carbonyl compounds.

Great progress has been advanced in iron catalysis in the last decade. Various reactions such as olefin hydroxylation,[5] sulfide oxidation,[6] cross-coupling reactions,[7] heterolytic RO–OH bond cleavage,[8] hydroamination,[9] allylic alkylation or amination,[10] and alcohol oxidation[11] were investigated. Based on our recent experience in iron-catalyzed selective oxidation of olefin to epoxide and alcohol to aldehyde,[12] here we report our new findings about iron-catalyzed selective hydroxylation of β-ketoesters to the corresponding α-hydroxy-β-ketoesters. The selective hydroxylation of 2-ethoxycarbonyl-1-oxo-cyclohexane (**1**) was used as the model reaction (Scheme 1).



Scheme 1. Selective hydroxylation of 2-ethoxycarbonyl-1-oxo-cyclohexane.

Initial screening of the reaction conditions, that is, different iron salts, organic solvents, and the amount of catalyst loading revealed that 1 mol % of iron(III) chloride hexahydrate, 2 equiv of hydrogen

Table 1
Catalyst screening using **1** as model substrate[a]

Entry	Iron salts	Con.[b] (%)	Yield[c] (%)	Sel.[d] (%)
1	$FeCl_3$	79	79	99
2	$FeCl_3{\cdot}6H_2O$	82	82	99
3	$FeCl_2$	80	80	99
4	$FeBr_3$	13	13	99
5	$Fe(OAc)_2$	7	7	99
6	$Fe(NO_3)_3{\cdot}9H_2O$	7	7	99
7	$Fe_2(SO_4)_3{\cdot}5H_2O$	13	13	99
8	$FePO_4{\cdot}4H_2O$	14	14	99

[a] 1 mmol (170 mg) **1**, 1 mol % iron salt, 2 equiv (0.20 mL) 30 wt % H_2O_2, and 25 mL *tert*-amyl alcohol were added into a 50 mL reaction tube, respectively. After being shaken, the reaction vessel was allowed to react at rt for 1 h without stirring. 1 mmol (170 mg) dodecane was added as an internal standard for quantitative analysis.[14]
[b] Conversion of **1**.
[c] Calibrated GC yield.
[d] Chemoselectivity toward the desired product with respect to consumed starting material.

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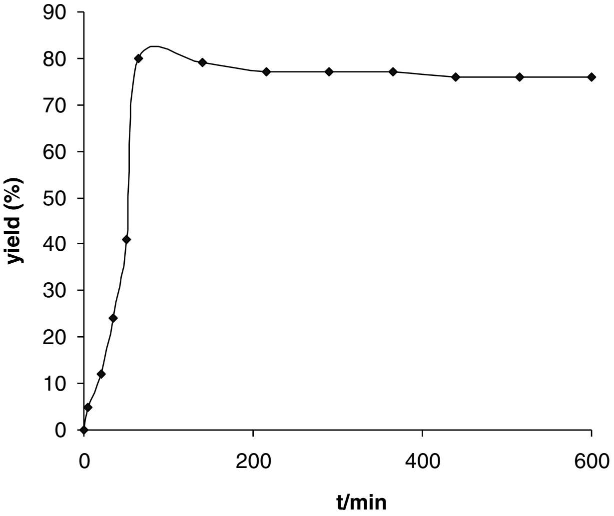
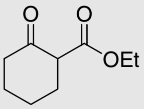
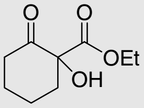
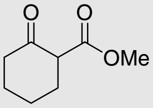
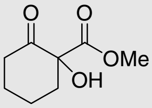
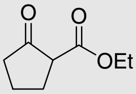
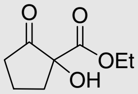
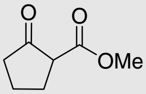
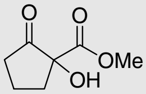
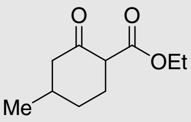
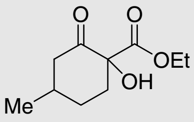
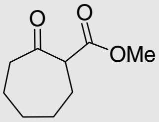
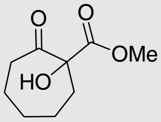


Figure 1. Yield of **1b** against time.

peroxide, and 25 mL of *tert*-amyl alcohol were suitable for the hydroxylation of **1a**;[13] 86% conversion with 70% yield could be obtained with magnetic stirring in 1 h. The usage of other solvents, such as THF, dioxane, ethanol, acetonitrile, and *N*-methyl-2-pyrrolidinone, caused lower selectivity. However, the yield of the reaction varied significantly in some cases. With careful investigation of the possible factors, it was surprisingly found that the selectivity of the reaction significantly increased from 81% to >99% with similar conversion without stirring. The addition of more iron chloride or hydrogen peroxide and with longer reaction time gave no improvement of the reaction but instead more byproducts. The results under the reaction conditions without stirring are highly reproducible, but the effect of stirring in this reaction is still not clear at this moment. Hence, all the following reactions were carried out without any stirring except specifically mentioned.

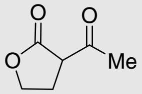
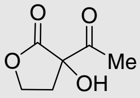
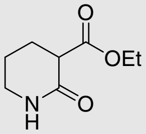
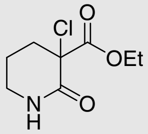
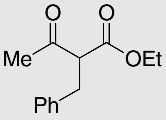
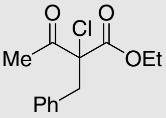
The catalytic activity of different iron salts was investigated in the presence of 1 mol % catalyst and 2 equiv, 30 wt % hydrogen peroxide (Table 1). The counter anions of iron salts highly affect the catalytic activity (Table 1, entries 1–8). The corresponding hydroxylation product was obtained in high yield when using iron chlorides as the catalysts, no matter anhydrous or hydrated, Fe(II)

Table 2
Selective oxidation of diketone compounds catalyzed by iron(III) chloride[a]

Entry	Substrate	Product	*t* (h)	Conv.[b] (%)	Yield[c] (%)	Sel.[d] (%)
1	 **1a**	 **1b**	1	82	82	99
2	 **2a**	 **2b**	0.75	75	75	99
3	 **3a**	 **3b**	8	98	90	92
4	 **4a**	 **4b**	6	98	84	86
5	 **5a**	 **5b**	0.75	89	85[e]	96
6[f]	 **6a**	 **6b**	24	90	81	90

(*continued on next page*)

Table 2 (*continued*)

Entry	Substrate	Product	*t* (h)	Conv.[b] (%)	Yield[c] (%)	Sel.[d] (%)
7[g]	 **7a**	 **7b**	0.2	91	80	88
8[h]	 **8a**	 **8c**	4	57	38	67
9[i]	 **9a**	 **9c**	15	82	60	73

[a] The same reaction conditions as given in Table 1.

[b] Conversion of starting material.

[c] Calibrated GC yield.

[d] Chemoselectivity toward the desired product with respect to consumed starting material.

[e] A mixture of diastereomers in ~1:1 (GC–MS) was obtained.

[f] The substrates and 2 equiv 30 wt % H_2O_2 were dissolved in 5 mL *tert*-amyl alcohol, and 10 mol % $FeCl_3·6H_2O$ (27 mg/20 mL *tert*-amyl alcohol) was added in 24 h.

[g] 10 mol % $FeCl_3·6H_2O$.

[h] 1 mol % $FeCl_3·6H_2O$, 2 equiv 30 wt % H_2O_2, and 15 mL *tert*-amyl alcohol were added initially. 19 mol % $FeCl_3·6H_2O$ (51 mg/10 mL *tert*-amyl alcohol) and 6 equiv 30 wt % H_2O_2 were added in 4 h.

[i] 35 mol % $FeCl_3·6H_2O$/20 mL *tert*-amyl alcohol and 6 equiv H_2O_2 were added in 15 h.

or Fe(III) (Table 1, entries 1–3). This small difference in all iron chloride catalysts indicates the reaction may be catalyzed by similar intermediates as oxidation of iron(II) chloride to iron(III) chloride by hydrogen peroxide readily takes place. Noteworthy, this reaction is also easy to be scaled up in laboratory scale. ~80% yield and ~99% selectivity maintained when 13 mmol (2.21 g) **1a** was employed.[15]

An interesting phenomenon was also observed during the reaction when using iron(III) chloride as catalyst. At the early stage of reaction, the color of the reaction mixture was yellow due to the color of $FeCl_3·6H_2O$. It turned brown immediately after the addition of β-ketoester. This color stays during the reaction even after H_2O_2 has been added. When the conversion was above 80%, the reaction mixture changed back to yellow in color. This color change was not observed in the reactions with low conversion. Hence, the formation of a new iron complex from iron chloride and β-ketoester is suspected. This phenomenon provides an opportunity to develop high throughput screening methods with direct visual aids.

Close monitoring of the reaction showed that the reaction finished fast and smoothly in 1 h (Fig. 1). Although our reaction conditions constitute typical Fenton reagent recipe,[16] the product is stable in our reaction system after its formation within 10 h.

The selective oxidation of other β-ketocarbonyl compounds was further studied (Table 2). In most of the cases, the reaction can be finished overnight. However, shorter reaction time is also feasible. The time necessary to achieve high conversion is substrate dependent, as also demonstrated in other reports.[3a,4] While **1a** and **2a**, gave higher than 75% conversion in less than 1 h, more than 6 h should be used in order to get high conversion and yield using **3a** and **4a** as starting materials (Table 2, entries 1–4). The reactivity of the preformed intermediate from iron chloride and β-ketoesters (**1a** or **2a**) governs the productivity. More iron chloride (10 mol %) and longer reaction time (24 h) can be used to produce **6b** from unreactive **6a** in good yield (81%) (Table 2, entry 6). With higher catalyst loading (10 mol %), **7a** can be hydroxylated in 80% yield with 91% conversion (Table 2, entry 7).

It is interesting to note that chlorination occurred when the catalyst loading increased. In the presence of 5 mol % iron chloride, the conversion of **8a** was ~20% with ~50% selectivity to the α-hydroxylated **8b**. When the amount of iron chloride increased to 20 mol %, the conversion could reach to 57%. However, the major product under such conditions was α-chloro-β-ketoester **8c** in 38% yield (Table 2, entry 8). For the non-cyclic β-ketoester **9a**, α-chloro-β-ketoester **9c** was the main product even with only 10 mol % of $FeCl_3·6H_2O$. Up to 60% of **9c** could be obtained when 35 mol % of catalyst was used (Table 2, entry 9). Therefore, this system has potential to develop a new oxidative chlorination protocol for the synthesis of α-chloro-β-ketocarbonyl compounds.

In summary, a simple and highly effective iron catalyst system was developed for the α-oxidation of β-ketoesters. 75–90% yield of the hydroxylation products could be obtained using cyclic β-ketoesters as starting material.

Acknowledgments

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Supplementary data

The detailed characterization results for all the products are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.07.157.

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13. The effect of N-ligands, such as pyrrolidine and imidazoles, in Refs. 12a and 12b was also tested. No better activity and yield were obtained in comparison with the merely iron chloride addition system.
14. *Typical procedure for the hydroxylation of* **1**: 1 mmol (170 mg) of **1**, 1 mol % (2.7 mg) of iron(III) chloride hexahydrate, 2 equiv of (0.2 mL) 30 wt % H_2O_2 and 25 mL *tert*-amyl alcohol were added into a 50 mL reaction tube, respectively. After being sealed and shaken, the reaction was allowed to react at rt for 1 h without stirring. After the reaction, 1 mmol (170 mg) of dedecane was added as an internal standard for quantitative analysis. Then the solvent was removed under reduced pressure and the residue was purified by column chromatography to afford the desired product. Compound **1b**: $R_f = 0.19$ (hexane/ethyl acetate = 90:10); colorless liquid; ^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 1.11–1.27 (t, J = 7.2 Hz, 3H), 1.48–1.84 (m, 4H), 1.87–2.06 (m, 1H), 2.38–2.66 (m, 3H), 4.06–4.19 (q, J = 7.2 Hz, 2H), 4.19–4.28 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 14.3, 22.2, 27.3, 38.0, 39.2, 62.3, 80.9, 170.4, 207.7; MS (EI): *m/z* (rel. int.) 186 (31), 168 (20), 142 (62), 140 (32), 130 (19), 114 (29), 113 (72), 112 (44), 111 (123), 101 (35), 95 (15), 86 (15), 85 (95), 84 (35), 83 (20), 73 (17), 68 (57), 67 (96), 57 (30), 56 (35), 55 (100), 45 (13), 43 (38), 42 (34), 41 (45), 39 (21), 29 (54), 27 (30); HRMS calcd for $C_9H_{14}O_4$ *m/z* 186.0887, found *m/z* 186.0890.
15. *Scaling up testing for the hydroxylation of* **1a**: 13 mmol (2.21 g) of **1a**, 1 mol % (35.1 mg) of iron(III) chloride hexahydrate, 2 equiv (2.6 mL) of 30 wt % H_2O_2 and 325 mL *tert*-amyl alcohol were added into a 500 mL round-bottomed bottle. After being sealed and shaken, the reaction was allowed to react at rt for 2 h without stirring. After the reaction, 13 mmol (2.2 g) of dodecane was added as an internal standard for quantitative analysis. The reactions were repeated two times. ~80% conversion, ~99% selectivity and ~80% yield were obtained. *Caution!* Although we have never faced any problem during our experiments, it needs to be mentioned that large scale usage of hydrogen peroxide may cause explosion.

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