

Iron-Catalyzed One-Pot Oxidative Esterification of Aldehydes

Xiao-Feng Wu^[a] and Christophe Darcel^{*[a]}**Keywords:** Iron / Esterification / Aldehydes / Homogeneous catalysis / Oxidation

A highly efficient, mild, and simple protocol for $\text{Fe}(\text{ClO}_4)_3 \cdot x\text{H}_2\text{O}$ -catalyzed oxidative esterification of aldehydes was developed. Several aromatic and aliphatic aldehydes reacted with simple primary and secondary alcohols, used as the solvent, smoothly in the presence of an iron salt catalyst

(10 mol-%) and hydroperoxide (4 equiv.) as an oxidant to generate the corresponding esters in good to excellent yields.

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Introduction

The development of synthetic strategies towards esters has attracted the interest of chemists for more than 100 years due to the significance and omnipresence of these compounds. The most common strategy for the preparation of carboxylic acid ester derivatives under mild conditions usually involves the stoichiometric activation of the parent acid as an acyl halide, anhydride, or activated ester (in situ or otherwise) amenable to subsequent nucleophilic substitution.^[1] An interesting and potentially valuable alternative transformation in which there has been a recent resurgence in interest is the oxidative esterification of aldehydes under mild conditions.^[2] These one-pot conventional methods reported require the use of stoichiometric heavy-metal oxidants such as KMnO_4 ,^[3] CrO_3 ,^[4] hydrogen peroxide,^[5] ozone,^[6a] oxone,^[6b] *N*-iodosuccinimide,^[7] or expensive transition-metal catalysts such as vanadium,^[8a] rhenium,^[8b] silver,^[9] palladium,^[10] ruthenium,^[11] rhodium,^[12] copper,^[13] titanium,^[14] iridium,^[15] and so on. From a viewpoint of green chemistry, this transition-metal-catalyzed oxidative esterification is expected to be a versatile procedure directly giving esters from aldehydes and alcohols. In the environmental context of today, one of the challenging issues for chemists is to develop cost-effective, green, mild, and efficient catalytic routes that minimize hazardous waste. In contrast, many catalysts are derived from heavy or rare metals and their toxicity and prohibitive prices can constitute severe drawbacks for large-scale applications. In contrast, iron is one of the most abundant metals on the earth, and one of the most inexpensive and environmentally

friendly ones. Despite the fact that the coordination chemistry of iron was widely developed in the past decades, it is really surprising that until lately, iron was underrepresented in the field of homogeneous catalysis relative to the other transition metals. However, the last few years have seen a rise in the use of iron as a catalyst, and very efficient processes that are now able to compete with other metal-catalyzed ones have emerged in the carbon–carbon bond-formation, hydrosilylation, oxidation, and even hydrogenation areas.^[16]

We disclose herein an oxidative esterification of a variety of aldehydes with simple alcohols as solvents in the presence of a catalytic amount of $\text{Fe}(\text{ClO}_4)_3 \cdot x\text{H}_2\text{O}$ in combination with H_2O_2 as oxidant at room temperature in air.

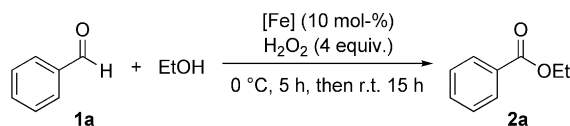
Results and Discussion

In the initial attempts to improve this iron-catalyzed oxidative esterification of aldehydes, benzaldehyde (**1a**) was chosen as a test substrate to optimize the reaction conditions (Scheme 1). An ethanol solution of **1a** was allowed to react with H_2O_2 (4 equiv.) at room temperature in the presence of a catalytic amount of iron salt (10 mol-%). It may be pointed out that the hydroperoxide water solution must be added slowly at 0 °C over 4 h to avoid the formation of the corresponding benzoic acid. After stirring for a period of one additional hour at 0 °C, and 15 h at room temperature, the reaction afforded the ester product. We then carried out extensive investigations to define the best reaction conditions, and Table 1 lists representative data obtained for the oxidative esterification with various commercially available iron(II) and iron(III) salts.

First of all, iron salts such as $\text{Fe}(\text{OAc})_2$, $\text{Fe}(\text{acac})_2$, or $\text{Fe}(\text{acac})_3$ were not able to promote any oxidative esterification reaction under our standard conditions (Table 1, Entries 1–3). By employing commercially available, classical anhydrous or hydrated FeCl_2 and FeCl_3 precursors as a catalyst, only moderate isolated yields were obtained (20–45%)

[a] UMR 6226 CNRS-Université de Rennes 1 “Sciences Chimiques de Rennes”, Equipe “Catalyse et Organométalliques”, Campus de Beaulieu, Bat 10C, Avenue du Général Leclerc, 35042 Rennes Cedex, France
Fax: +33-2-23236939
E-mail: christophe.darcel@univ-rennes1.fr

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Scheme 1. Oxidative esterification of benzaldehyde.

Table 1. Iron salt screening for the oxidative esterification of benzaldehyde.^[a]

Entry	[Fe]	Yield [%] ^[b]
1	Fe(OAc) ₂	<2 ^[c]
2	Fe(Acac) ₂	<2 ^[c]
3	Fe(Acac) ₃	<2 ^[c]
4	FeSO ₄ ·7H ₂ O	10
5	FeBr ₂	26
6	FeCl ₂	20
7	FeCl ₂ ·4H ₂ O	25
8	FeCl ₃	33
9	FeCl ₃ ·6H ₂ O	45
10	Fe(ClO ₄) ₃ ·xH ₂ O	70

[a] Reaction conditions: benzaldehyde (106 mg, 1 mmol), [Fe] (10 mol-%), EtOH (3 mL), H₂O₂ (33% in water, 4 mmol, 0.43 mL), 0 °C, 5 h then room temp. 15 h. [b] Isolated yield. [c] GC yield.

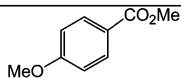
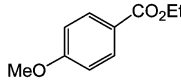
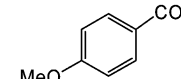
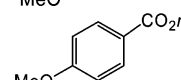
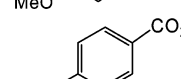
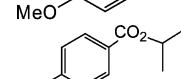
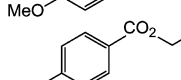
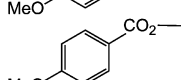
(Table 1, Entries 6–9). Interestingly, the use of Fe(ClO₄)₃·xH₂O is crucial for the success of this reaction and ethyl benzoate was obtained with a promising yield of 70% (Table 1, Entry 10).

A control experiment performed in the absence of iron salt confirmed the crucial role that the iron catalyst plays in the described condensation reaction, as the reaction did not occur. It is also important to note that the esters are not obtained as a result of the oxidation of the aldehydes to carboxylic acids followed by Fischer-type esterification of the acid in alcoholic solvents. Incubation of benzoic acid in ethanol in the presence of a catalytic amount of Fe(ClO₄)₃·xH₂O for a prolonged period of time did not lead to ethyl benzoate, and the starting acid was recovered unchanged.

The success of this iron-catalyzed methodology was further demonstrated by oxidative esterification of 4-methoxybenzaldehyde (**1b**) with simple alcohols. In general, the iron-catalyzed oxidative esterification occurs smoothly to provide the desired ester in good yields. When the reaction was performed in methanol, the methyl ester was obtained in 84% isolated yield. As can be seen from Table 2, with classical primary alcohols such as ethanol, 1-butanol, and 1-pentanol, the corresponding *p*-methoxybenzoates were isolated in good to excellent yields (87–99%; Table 2, Entries 2–4). Noteworthy, *i*PrOH can also lead to isopropyl *p*-methoxybenzoate with an isolated yield of 71% (Table 2, Entry 5). It must be pointed out that in this case, a larger quantity of hydroperoxide was used (10 equiv. instead of 4 equiv.) to obtain good conversion. However, more sterically hindered alcohols diminish the effectiveness of the reaction. In the case of *s*BuOH, the yield decreased and the corresponding *sec*-butyl ester was obtained with 30% yield (Table 2, Entry 6). Furthermore, the oxidative addition of *tert*-butyl alcohol did not lead to the corresponding *tert*-butyl ester, even when the reaction was conducted at 80 °C (Table 2,

Entry 9) In this last case, only oxidation of aldehyde into carboxylic acid was observed by GC analysis. The result was probably due to the steric effect of the bulky alcohol. More interestingly, the reaction can be extended to functional alcohols such as allylic alcohols or propargylic alcohols (Table 2, Entries 7 and 8).

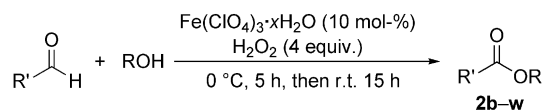
Table 2. Alcohol screening for the oxidative addition to 4-methoxybenzaldehyde (**1b**).^[a]

Entry	ROH	Equiv. of H ₂ O ₂	Ester	Yield ^[b] [%]
1	MeOH	4		2b 84
2	EtOH	4		2c 99
3	<i>n</i> BuOH	4		2d 87
3	1-Pentanol	4		2e 90
5	<i>i</i> PrOH	10		2f 71
6	2-Butanol	10		2g 30
7	CH ₂ =CH-CH ₂ OH	4		2h 75
8	Propargylic alcohol	10		2i 21
9	<i>t</i> BuOH	10	–	– 0

[a] Reaction conditions: 4-methoxybenzaldehyde (1 mmol), Fe(ClO₄)₃·xH₂O (35 mg, 10 mol-%), alcohol (3 mL), H₂O₂ (33% in water, 4 mmol, 0.43 mL), 0 °C, 5 h then room temp. 15 h. [b] Isolated yield.

Next, the scope of this iron-catalyzed oxidative esterification of different aldehydes was evaluated (Scheme 2, Table 3). In general, all reactions were clean, and esters **2** were obtained in good yields. It turned out that this iron-catalyzed oxidative esterification could be adapted for various aldehydes. The oxidative esterification reaction was amenable to both electron-rich and electron-poor aromatic aldehydes such as benzaldehydes or substituted (Me, Br, OMe, OH, CN) benzaldehydes, and the reaction gave the corresponding aromatic ester compounds **2** in good to excellent yields (70–99%; Table 3, Entries 1–7). Noteworthy, the deactivated nitro-substituted benzaldehydes gave moderate yields (45–67%) of the corresponding esters **2p–r** with concomitant formation of the corresponding carboxylic acids if the nitro substitution was in the *para* or *ortho* position (Table 3, Entries 8–10). Principles of oxidative transformation can also be extended to heterocyclic aldehydes as well. Thus, 2-furaldehyde was smoothly converted into methyl 2-furoate (**2u**) in 85% isolated yield (Table 3, Entry 13). When thiophene-2-carbaldehyde and 4-methylthiophene-2-carbal-

dehyde were used, corresponding esters **2s** and **2t** were isolated in 80 and 73% yield, respectively (Table 3, Entries 11 and 12).



Scheme 2. Iron-catalyzed oxidative esterification of aldehydes.

Table 3. Scope of the iron-catalyzed oxidative esterification.^[a]

Entry	RCHO	ROH	Equiv. of H ₂ O ₂	Ester	Yield ^[b] [%]
1		MeOH	4		2b 84
2		MeOH	4		2j 82
3		MeOH	4		2k 91
4		MeOH	4		2l 86
5		MeOH	4		2m 70
6		EtOH	9		2n 85
7		EtOH	5		2o 99
8		EtOH	4		2p 50
9		MeOH	4		2q 67
10		MeOH	4		2r 45
11		EtOH	4		2s 80
12		MeOH	4		2t 73
13		EtOH	4		2u 85
14		MeOH	4		2v 70
15	Ph-(CH ₂) ₂ -CHO	MeOH	4	Ph-CH ₂ -CH ₂ -CO ₂ Me	2w 80

[a] Reaction conditions: aldehyde (1 mmol), Fe(ClO₄)₃·xH₂O (35 mg, 10 mol-%), alcohol (3 mL), H₂O₂ (33% in water, 4 mmol, 0.43 mL), 0 °C, 5 h then room temp. 15 h. [b] Isolated yield.

More gratifying was the compatibility of the reaction to proceed successfully with primary and secondary aliphatic aldehydes as substrates (Table 3, Entries 14 and 15).

Although any mechanistic discussion is speculative at this point, we believe that the oxidative esterification proceeds through iron Lewis acid activation of the aldehyde moiety followed by the addition of the alcohol on the electrophilic carbonyl group to lead, after oxidation of the resulting hemiacetal intermediate, to the desired ester. Furthermore, in this iron-catalyzed reaction, Fe(ClO₄)₃·xH₂O is more effective than other FeX_n (X = Cl, Br) salts. Indeed, in the case of the Fe(ClO₄)₃, the heterolysis is more facile due to the lower charge density and coordination ability of the perchlorate counterion. Thus, the metal part of Fe(ClO₄)₃ is more cationic and more Lewis acidic.^[17]

Conclusions

In summary, we have developed an iron-based catalyst system for efficient oxidative esterification of aldehydes with alcohol as solvent and H₂O₂ (4 equiv.) under mild conditions, which represents an excellent complement to the previously established protocols. Both aliphatic and aromatic aldehydes are compatible with this reaction. Although the literature enumerates a number of procedures for conversion of aldehydes into esters, the simplicity, environmental acceptability, and inexpensiveness of our procedure makes it a practical alternative. As a result of its manipulation ease, low-cost, and benign character, the new iron catalyst described appears promising for large-scale applications. It must be pointed out that perchlorate salts are stable under ordinary conditions of use.^[18] Furthermore, the use of hydrogen peroxide as oxidant is quite attractive, because it generates water as the only byproduct. Studies to improve the catalyst performance and to expand the substrate scope of the method are currently in progress in our laboratories.

Experimental Section

Representative Procedure: Commercially available Fe(ClO₄)₃·xH₂O (35 mg, 10 mol-%) was added to a solution of benzaldehyde (106 mg, 1 mmol) in ethanol (3 mL). The mixture was cooled to 0 °C, and H₂O₂ (33% aqueous, 0.43 mL, 4 mmol) was slowly added over 4 h with the use of a syringe pump. One hour after the injection of H₂O₂, the ice bath was removed, and the reaction was stirred at room temperature for another 15 h. The reaction progress was monitored by GC. Then, the solvent was removed in vacuo, and the residue was purified by flash column (petroleum ether/ethyl acetate, 9:1). Ethyl benzoate was obtained as a colorless oil (105 mg, 70%).

Supporting Information (see footnote on the first page of this article): Experimental procedures and compound characterization, including NMR spectra.

Acknowledgments

The authors acknowledge the CNRS and the Ministère de l'Enseignement Supérieur et de la Recherche for financial support.

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Received: November 26, 2008

Published Online: January 28, 2009