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An efficient $FeCl_3$-promoted *O*-alkyl cleavage of esters to carboxylic acids

Xiaoyan Lian, Shaomin Fu, Tongmei Ma, Shunbin Li and Wei Zeng*

A reliable and practical procedure for $FeCl_3$-promoted ester cleavage has been developed. Lewis acids including $TiCl_4$, ZnO and $FeCl_3$ etc. were investigated as promoters for *O*-alkyl cleavage of carboxylic acid ester. Under optimal reaction conditions, $FeCl_3$ (1.5 equiv.) was found to possess the highest activity and efficiently enhanced dealkylation of aryl esters, alkyl esters and aromatic heterocyclic esters to give their corresponding carboxylic acids in 54–98% yield, the method provides a complementary access to dealkylation of ester under neutral condition.

Supporting information may be found in the online version of this article.

Keywords: ferric chloride; *O*-alkyl cleavage; carboxylic acid ester

Introduction

The protection and de-protection of carboxylic acids is a widely used transformation in highly selective organic synthesis.[1,2] Most moderately stable carboxylic acid esters can be used to protect carboxylic acids since they can be hydrolyzed using various methods. Traditionally, the cleavage of carboxylic acid esters to afford the corresponding acids is carried out in aqueous acid or base;[3–5] however, many substrates containing either acid or base labile groups limit this approach, so some efficient neutral reagents, such as NaHTe, Na_2Te and Na_2Te_2,[6] Dowex-50,[7] NaHSe,[8] PhSH/KF,[9] Al_2O_3/KF,[10] $I_2/Me_3SiSiMe_3$,[11] $AlCl_3.6H_2O$/KI/CH_3CN/H_2O [12] and Ln(II) or Sc(III) complexes,[13] have been developed for ester cleavage under mild conditions. Even so, considering that a single reagent cannot catalyze hydrolysis efficiently for various kinds of esters, further search for a universal catalyst for *O*-alkyl cleavage of ester is necessary. Recently, we found that $TiCl_4$ could efficiently enhance the direct *N*-acylation of sulfonamide using carboxylic esters as acylating agents, and further studies on the reaction mechanism indicated that carboxylic esters were first transformed to their corresponding acids via *O*-alkyl cleavage and then condensed with sulfonamide to form *N*-acylated sulfonamide.[14] Therefore, we present an alternative ester cleavage method using Lewis acids as promoters under mild conditions.

Experimental

Materials and Techniques

All reactions were carried out in an oven-dried sealed tube with stirring under an Ar atmosphere. Dioxane, THF and toluene were distilled after being dried with Na; DMF and DMSO were used after being dried with CaH_2; CCl_4, 1,1,2,2-tetrachloroethane (TCE), CH_2Cl_2 and acetonitrile were used after being dried with molecular sieves. All other commericially available reagents were purchased from Across or TCI and used directly. Purification of reaction products was carried out by flash chromatography using Qingdao Haiyang Chemical Co. Ltd silica gel (40–63 mm). The melting point was measured on Büchi Melting Point B-545 and are uncorrected. Infrared spectra (IR) were recorded on a Brucker Tensor 27 FTIR spectrophotometer in the range of 4000–400 cm^{-1}, and are reported as wavelength numbers (cm^{-1}). Infrared spectra were recorded by preparing a KBr pellet containing the title compound. ^1H NMR spectra were recorded with tetramethylsilane as internal standard at ambient temperature unless otherwise indicated, on a Bruker Avance DPX 400 Fourier transform spectrometer operating at 400 or 600 MHz. Chemical shifts are reported in parts per million (ppm) and coupling constants are reported as Hertz (Hz). Splitting patterns are designated as singlet (s), broad singlet (bs), doublet (d) or triplet (t). Splitting patterns that could not be interpreted or easily visualized are designated as multiplet (m). Low-resolution mass spectra were recorded using a Waters HPLC/ZQ4000 mass spectrometer, and low-molecular-weight chlorohydrocarbons were detected by a Shimadzu GCMS-QP5050A gas chromatograph mass spectrometer.

General Experimental Procedure for $FeCl_3$-promoted Ester Cleavage

Carboxylic acid ester (1 mmol), Lewis acid (1.5 equiv.) and solvent (2.5 ml) were combined in a pressure tube equipped with a stir bar under Ar atmosphere. The mixture was stirred at given temperature for 24 h (see Table 1) until nearly all the carboxylic acid ester had disappeared (monitored by thin-layer chromatography). The reaction mixture was cooled down, diluted with 10 ml of H_2O, and acidified with 3 N of aqueous HCl to pH 4–6. The corresponding mixture was extracted with ethyl acetate (3 × 10 ml), and the combined organic layers were dried over anhydrous Na_2SO_4; then the solvent was evaporated in

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Table 1. Lewis acid screening for *O*-alkyl cleavage of ethyl benzoate[a]

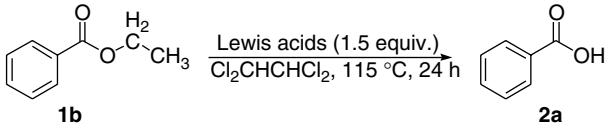
Entry	Lewis acid	Temperature (°C)	Yield (%)[b]
1	$AlCl_3$	115	29
2	ZnO	115	14
3	$TiCl_4$	115	71
4	$FeCl_3$	115	88
5	$Co(OAc)_2.4H_2O$	115	No reaction
6	$Cu(OAc)_2.2H_2O$	115	No reaction
7	Fe_2O_3	115	No reaction
8	$ZnCl_2$	115	No reaction
9	$CdCl_2$	115	No reaction
10	$MnCl_2$	115	No reaction
11	$NiCl_2$	115	No reaction
12	$ZrCl_4$	115	18
13	$FeCl_2$	115	33

[a] Reaction conditions: ethyl benzoate, 1 mmol; TCE, 2.5 ml; Lewis acid promoter, 1.5 equiv. The reaction was carried out at 115 °C for 24 h in a sealed tube. [b] Isolated yield after purification.

vacuo and the crude compound was purified by flash column chromatography (silica gel, petroleum/ethyl acetate) to afford the corresponding carboxylic acid. All the products are known compounds and were identified using ^1H NMR, LRMS, IR and melt point by comparison with previously reported data (see Supporting Information).

Optimization of Reaction Conditions for $FeCl_3$-promoted *O*-alkyl Cleavage of Ethyl Benzoate

Optimal conditions for dealkylation of esters were first determined by systematically investigating Lewis acid promoters, reaction solvents, reaction time, reaction temperature and catalyst/substrate ratio. Initially, the ester cleavage of readily available ethyl benzoate **1b** (1 mmol) was carried out in TCE (2.5 ml) using different kinds of Lewis acid (1.5 equiv., 1.5 mmol), such as $Cu(OAC)_2$ and $FeCl_3$, etc. (Scheme 1) at 115 °C for 24 h in a sealed tube under an Ar atmosphere (Table 1). Gratifyingly, we quickly found that $FeCl_3$ possesses the highest activity and could efficiently promote *O*-alkyl cleavage of ester (**1b**) to form the corresponding acid in 88% yield (Table 1, entry 4), and basically other Lewis acid promoters produced poor results except for $TiCl_4$ (Table 1, entry 3).



Scheme 1. Lewis acid screening for *O*-alkyl cleavage of ethyl benzoate.

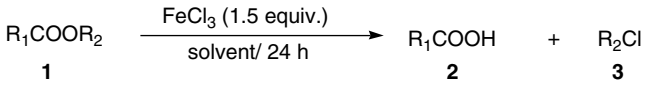
We further investigated other reaction conditions to define the reaction parameters (Scheme 1, Table 2). To find the best solvent, the dealkylation of ethyl benzoate (**1b**) was carried out for 24 h in different solvents such as THF and methylene chloride. We found that the nonpolar solvent CCl_4 or $Cl_2CHCHCl_2$ was superior to polar solvent THF or DMSO (Table 2, entries 1, 2, 9 and 10). It is worthy of note that the $FeCl_3/H_2O$ (1.5/1.0 equiv.) system inhibited the *O*-alkyl cleavage of ethyl benzoate to some extent, and the dealkylation using concentrated HCl (37 wt%/H_2O, 0.20 g) instead of $FeCl_3$ as promoter provided only a very low yield of benzoic acid (Table 2, entry 10).

Based on the above-mentioned positive results, we further investigated the effect of the amount of Lewis acid, reaction temperature and reaction time on the transformation. Dealkylation of ethyl benzoate in CCl_4 at 85 °C provided the desired carboxylic acid in up to 92% yield (Table 2, entry 10). Shortening the reaction time (from 24 to 18 h) decreased the yield from 92

Table 2. Optimization of reaction conditions for $FeCl_3$-promoted *O*-alkyl cleavage of ethyl benzoate[a]

Entry	Reaction time (h)	Temperature (°C)	Solvent	Equivalents ($FeCl_3$)	Yield (%)[b]
1	24	110	THF	1.5	15
2	24	110	DMSO	1.5	7
3	24	110	1,4-Dioxane	1.5	Trace
4	24	110	DMF	1.5	Trace
5	24	115	Toluene	1.5	Decomposition
6	24	85	Acetonitrile	1.5	No reaction
7	24	45	CH_2Cl_2	1.5	No reaction
8	24	135	Chlorobenzene	1.5	65
9	24	115	TCE[c]	1.5	88
10	24	85	CCl_4	1.5	92 (72[d], 10[e])
11	24	80	CCl_4	1.5	67
12	24	90	CCl_4	1.5	86
13	18	85	CCl_4	1.5	78
14	36	85	CCl_4	1.5	93
15	48	85	CCl_4	1.5	74
16	24	85	CCl_4	0.5	10
17	24	85	CCl_4	1.0	76
18	24	85	CCl_4	2.5	91

[a] Reaction conditions: ethyl benzoate, 1 mmol; solvent, 2.5 ml. The reaction was carried out at the given temperature in a sealed tube. [b] Isolated yield after purification. [c] TCE: 1,1,2,2-tetrachloroethane. [d] One equivalent of H_2O (1 mmol) was added. [e] 0.2 g of conc. HCl (37 wt%/H_2O) was used as the promoter instead of $FeCl_3$.



Scheme 2. $FeCl_3$ -promoted dealkylation of carboxylic ester.

to 78%; in addition, a longer reaction time (48 h) or higher reaction temperature (90 °C) led to tedious workup and lower yields (Table 2, entries 12 and 15). Increasing the amount of promoter loading from 1.0 to 1.5 equiv. resulted in higher conversions and yields (from 76 to 92%; Table 2, entries 10, 16 and 17). On the other hand, a Lewis acid loading of 2.5 equiv. did not bring improved yields (see Table 2, entries 10 and 18).

Results and Discussion

Under optimized reaction conditions, a variety of substrates were surveyed to explore the scope of the reaction. The results (Scheme 2, Table 3) showed that all the esters of aryl carboxylic acid, alkyl carboxylic acid and aromatic heterocyclic carboxylic acid underwent clean *O*-cleavage to give the corresponding carboxylic acids in good to excellent yields (54–98%). We made no attempt to isolate the low-boiling-point chlorohydrocarbon co-product **3** listed in Scheme 2, although GC-MS analyses of the reaction mixture indicated essentially quantitative yields of chlorohydrocarbon. Analysis of the efficiency with which our substrates are tested indicated that steric and electronic effects govern the dealkylated system to some extent.

Increasing the steric hindrance of alkoxy (-OR_2) led to a moderate decrease in product yield (Table 3, entries 2–4). Electronic effects also play a key role in this reaction system: compared with the results from dealkylation of the ester with an electronic-donating group (Table 3, entries 9–11), the ester with an electronic-withdrawing group on aromatic ring led to improved product yield (Table 3, entries 6–8).

Clearly, $FeCl_3$ could also promote efficiently *O*-cleavage of alkyl carboxylic ester to give the corresponding acid with good yield (Table 3, entries 12, 13 and 16), but for furan-2-carboxylic acid ethyl ester (**1n**) and pyridine-2-carboxylic acid ethyl ester (**1o**), a higher reaction temperature in excess of 115 °C is necessary to achieve good yield (Table 3, entries 14 and 15).

The possible mechanism about this transformation is that carboxylic acid ester (**4**) and Fe (III) first form an adduct (**5**), then a Cl^- from the Fe-complexes (**5**) attack the adjacent carbon atom of alkoxy group via S_N2 dealkylation, [15] and result to the formation of R_1COO^- (**6**) and R_2CH_2Cl (**7**) (see Scheme 3), then the protonation of R_1COO^- in the workup stage afford the corresponding carboxylic acid. The formation of the desired 6-chrolo-hexanoic acid (**2m**) from dealkylation of oxepan-2-one (**1p**) under Ar atmosphere fur-

Table 3. $FeCl_3$-promoted *O*-alkyl cleavage of ester to carboxylic acid[a]

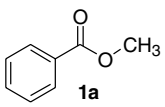
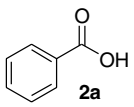
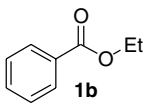
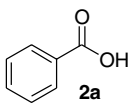
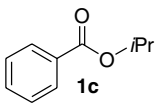
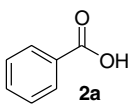
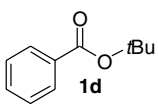
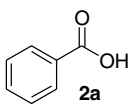
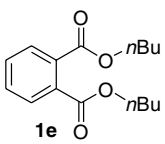
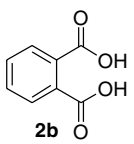
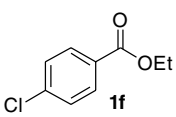
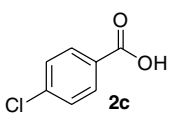
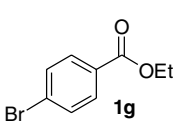
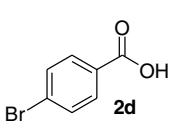
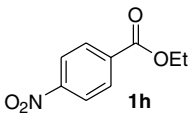
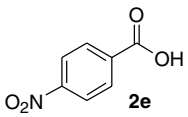
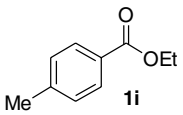
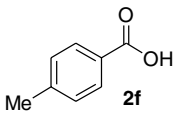
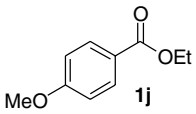
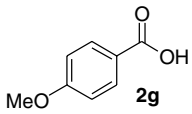
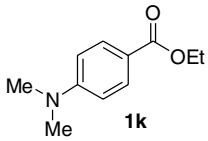
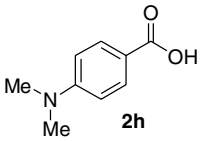
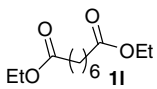
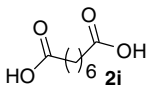
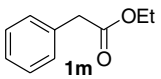
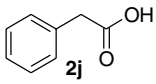
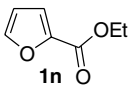
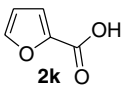
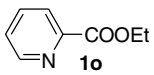
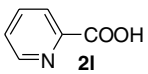
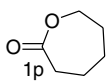
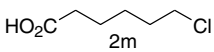
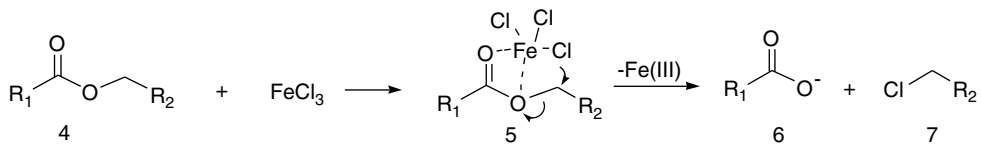
Entry	Carboxylic ester	Solvent	Temperature (°C)	Product	Yield (%)[b]
1	 **1a**	CCl_4	85	 **2a**	80
2	 **1b**	CCl_4	85	 **2a**	93
3	 **1c**	CCl_4	85	 **2a**	78
4	 **1d**	CCl_4	85	 **2a**	75
5	 **1e**	CCl_4	85	 **2b**	85[c]
6	 **1f**	CCl_4	85	 **2c**	98
7	 **1g**	CCl_4	85	 **2d**	92

Table 3. (*Continued*)

Entry	Carboxylic ester	Solvent	Temperature (°C)	Product	Yield (%)[b]
8	 **1h**	CCl_4	85	 **2e**	96
9	 **1i**	CCl_4	85	 **2f**	82
10	 **1j**	TCE [e]	115	 **2g**	80
11	 **1k**	CCl_4	85	 **2h**	77
12	 **1l**	CCl_4	85	 **2i**	88[c]
13	 **1m**	TCE	115	 **2j**	70[d]
14	 **1n**	TCE	115	 **2k**	54
15	 **1o**	TCE	150	 **2l**	75
16	 1p	TCE	85	 2m	92

[a] Reaction conditions: the reaction was performed using carboxylic acid ester (**1**, 1.0 mmol) and $FeCl_3$ (1.5 equiv.) in 2.5 ml of solvent (CCl_4 or TCE) at the given temperature for 24 h in a sealed tube under an Ar atmosphere. [b] Isolated yields, average of two runs, and their standard deviations ≤3. [c] Addition of 3.0 equiv $FeCl_3$. [d] Use of 1.5 equiv. $TiCl_4$. [e] TCE, 1, 1, 2, 2 - tetrachloroethane.



Scheme 3. The possible reaction mechanism for $FeCl_3$-promoted *O*-alkyl cleavage of ester.

ther identified this reasonable reaction pathway (Table 3, entry 16).

Conclusion

In summary, a reliable and practical procedure for $FeCl_3$-promoted ester cleavage has been developed; the substrates including aryl ester, alkyl carboxylic ester and aromatic heterocyclic ester were easily cleavaged to corresponding acids with good to excellent yields. Thus, the method provides a complementary means of dealkylation of ester under neutral conditions.

Supporting information

Supporting information may be found in the online version of this article.

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