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Ferric(III) Chloride Catalyzed Halogenation Reaction of Alcohols and Carboxylic Acids Using α,α-Dichlorodiphenylmethane

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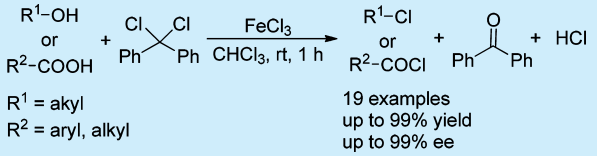
Supporting Information

ABSTRACT: A new method for chlorination of alcohols and carboxylic acids, using α,α-dichlorodiphenylmethane as the chlorinating agent and $FeCl_3$ as the catalyst, was developed. The method enables conversions of various alcohols and carboxylic acids to their corresponding alkyl and acyl chlorides in high yields under mild conditions. Particulary interesting is the observation that the respective alkyl bromides and iodides can be generated from alcohols when either LiBr or LiI are present in the reaction mixtures.



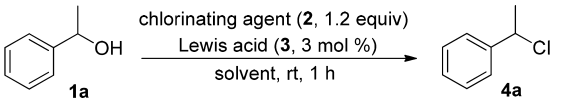
Halogenation of alcohols and carboxylic acids is an important and ubiquitous reaction in synthetic organic chemistry.[1] Conventional halogenating agents, such as hydrogen chloride,[2] thionyl chloride/DMF,[3] carbon tetrahalide/PPh_3[4] (Appel reaction), and phosphorus halides,[5] have been widely employed for this purpose. However, these methods often require the use of toxic reagents or harsh conditions. Among these processes, the Appel reaction is the most utilized method for halogenation, owing to its simplicity, mild conditions, and high stereoselectivity. However, this reaction not only forms triphenylphosphine oxide, a byproduct that is difficult to remove, but it also uses the toxic halogen source CCl_4. Therefore, investigations searching for new halogenation agents have been conducted in order to develop reactions that efficiently produce alkyl and acyl halides under mild and environmentally friendly conditions.[6]

In 2009, a novel method for chlorination of alcohols using dearomatization/rearomatization of 3,3-dichloro-1,2-diphenylcyclopropene as the chlorine source was described by Lambert and co-workers.[7] This novel aromatic activation/halogenation system enables chlorination reactions of alcohols to be conducted in a highly selective manner with good functional group tolerance. Based on the Lambert concept, other halogenating agents, such as 1,1-dichlorocycloheptatriene and dihaloimidazolidinedione, have been also explored by the Nguyen and Bielawski groups, respectively.[8] However, these processes add an additional step to the process, which is required for preparation of the unstable halogenation agents.

In the study described below, we developed the new, stable chlorinating agent, α,α-dichlorodiphenylmethane,[9] which is activated by the Lewis acid $FeCl_3$, for transforming alcohols and carboxylic acids to the corresponding alkyl and acyl chlorides. Moreover, the addition of lithium bromide or iodide to the reaction mixture containing an alcohol enables the process to be utilized to generate respective alkyl bromides or iodides.

In initial exploratory studies, chlorination reactions of 1-phenylethanol (**1a**) with α,α-dichlorodiphenylmethane (**2a**), giving (1-chloroethyl)benzene (**4a**), were performed at room temperature using various Lewis acid catalysts and solvents (Table 1). The results show that the reaction carried out in the presence of a catalytic amount of ferric chloride (**3a**, 3 mol % based on **1a**) produces **4a** in a 99% yield (entry 1). Other Lewis

Table 1. Chlorination of Alcohol 1a with Chlorinating Agent 2 Using Lewis Acids 3 and Various Solvents[a]



entry	Lewis acid	chlorinating agent	solvent	yield (%)[b]
1	$FeCl_3$ (**3a**)	 (**2a**)	$CHCl_3$	99
2	$Fe_2(SO_4)_3$ (**3b**)	**2a**	$CHCl_3$	86
3	$NiBr_2$ (**3c**)	**2a**	$CHCl_3$	16
4	$MnCl_2$ (**3d**)	**2a**	$CHCl_3$	31
5	$BF_3(OEt)_2$ (**3e**)	**2a**	$CHCl_3$	23
6	$AlCl_3$ (**3f**)	**2a**	$CHCl_3$	39
7	-	**2a**	$CHCl_3$	13
8	**3a**	 (**2b**)	$CHCl_3$	13
9	**3a**	 (**2c**)	$CHCl_3$	0
10	**3a**	 (**2d**)	$CHCl_3$	0
11	**3a**	**2a**	1,2-DCE	85
12	**3a**	**2a**	MeCN	25
13	**3a**	**2a**	DMF	0

[a]Unless otherwise noted, reactions were carried out with **1a** (0.2 mmol), **2** (0.24 mmol), and **3** (0.006 mmol) in 0.1 mL of solvent at room temperature. [b]Yield of **4a** was determined by using GC-MS analysis with hexadecane as the internal standard.

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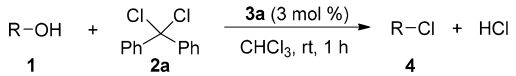
acids, including $Fe_2(SO_4)_3$ (**3b**, 86%), $NiBr_2$ (**3c**, 16%), $MnCl_2$ (**3d**, 31%), $BF_3(OEt)_2$ (**3e**, 23%), and $AlCl_3$ (**3f**, 39%) display reactivities lower than that of **3a** (entries 2−6) and in the absence of Lewis acids, **4a** is formed in only 13% yield (entry 7). The reactivities of other potential chlorinating agents were also explored (entries 8−10). We observed that chlorination of **1a** using *α*,*α*-dichlorophenylmethane (**2b**) forms **4a** in 13% yield (entry 8), and that no reaction takes place when *α*,*α*,*α*-trichlorophenylmethane (**2c**) and 2,2-dichloropropane (**2d**) are employed as chlorinating agents (entries 9 and 10). Finally, among the various solvents tested, $CHCl_3$ was found to be ideal for this reaction (entries 1 and 11−13).

The alcohol substrate scope of the chlorination reaction was investigated using **2a**, **3a**, and the optimized reaction conditions described above. Reactions of benzyl alcohols **1b−e**, regardless of whether they contain electron-donating or electron-withdrawing arene ring substituents, were found to produce the respective chlorinated products **4b−e** in modestly high yields (Table 2, entries 1−4). However, reaction of phenol (**1f**) does not take place under these conditions (entry 5). Heterocyclic alcohols such as furan-2-ylmethanol (**1g**) and thiophen-2-ylmethanol (**1h**) display reactivities lower than that of benzyl alcohol (**1b**), which is likely the result of binding of the Lewis acid $FeCl_3$ to oxygen or sulfur heteroatoms in these substances (entries 6 and 7). Moreover, we observed that reactions of aliphatic primary (**1i**), secondary (**1j**), and tertiary (**1k**) alcohols occur to generate the corresponding chlorides **4i−k** in 92, 78, and 94% respective yields (entries 8−10). The results suggest that steric hindrance does not affect this chlorination reaction. The reaction of the common aliphatic alcohol, octanol (**4l**), forms the desired octyl chloride (**4l**) in 86% yield (entry 11). The reaction of aliphatic alcohols containing carbonyl or olefinic functional group, **1m**,**n**, was found to produce the respective chlorinated products, **4m** and **4n**, in moderate yields (entries 12 and 13). It can be explained by the functional groups in **1m** and **1n** slightly deactivating the activity of the catalyst.

It is also possible to use this halogenation system to carry out bromination and iodination reactions of alcohols (Table 3). For example, reaction of benzyl alcohol (**1b**) with **2a** and **3a** in the presence of LiBr (**5a**) produces benzyl bromide (**4o**) in 98% yield. In this process, *α*,*α*-dibromodiphenylmethane (**6a**) likely serves as the actual bromination agent, a proposal that is supported by the observation that addition of LiBr (**5a**) to a $CDCl_3$ solution of **2a** generates **6a** (see the Supporting Information (SI)). Furthermore, addition of **1b** to a mixture of **6a** in $CDCl_3$ produces **4o** in 98% yield (Scheme 1). When LiI (**5b**) is present in the reaction mixture containing **2a** and **3a**, benzyl iodide (**4p**) is formed in 97% yield (Table 3, entry 2). Finally, reactions of octanol **1l** were also found to produce the respective halogenated products, **4q**,**r**, in good yields (Table 3, entries 3 and 4).

Several chiral secondary alcohols were employed to gain mechanistic insight into the new halogenation reaction (Scheme 2). As expected, reaction of racemic octan-2-ol (*rac*-**1o**), performed under standard reaction conditions, leads to formation of a racemic mixture of 2-chlorooctane (*rac*-**4s**) (Scheme 2a). Each enantiomer was identified by using gas chromatography equipped with a chiral column (see the SI). In contrast, under the same conditions, (*S*)-octan-2-ol ((*S*)-**1o**) and (*R*)-octan-2-ol ((*R*)-**1o**) individually react to generate (*R*)-2-chlorooctane ((*R*)-**4s**) and (*S*)-2-chloro-octane ((*S*)-**4s**) in 99% ee, respectively, through processes that occur with inversion stereochemistry at the stereogenic centers (Scheme 2b,c). However, reaction of (*R*)-1-phenylethanol ((*R*)-**1p**) takes

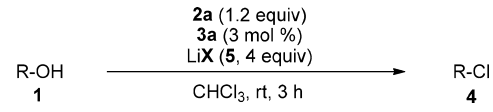
Table 2. $FeCl_3$-Catalyzed Chlorination of Various Alcohols Using 2a[a]



entry	R−OH	R−Cl	yield (%)[b]
1	R^1 = H (**1b**)		99 (**4b**)
2	OH Me (**1c**)	Cl	99 (**4c**)
3	R^1 CF_3 (**1d**)	R^1	90 (**4d**)
4	Cl (**1e**)		93 (**4e**)
5	Ph−OH (**1f**)	Ph−Cl	0 (**4f**)
6	OH (**1g**)	Cl	65 (**4g**)
7	OH (**1h**)	Cl	53 (**4h**)
8	Ph OH (**1i**)	Ph Cl	92 (**4i**)
9	Ph OH (**1j**)	Ph Cl	78 (**4j**)
10[c,d]	Ph OH (**1k**)	Ph Cl	94 (**4k**)
11	6 OH (**1l**)	6 Cl	86 (**4l**)
12	O OH (**1m**)	O Cl	69 (**4m**)
13	OH (**1n**)	Cl	71 (**4n**)

[a]Unless otherwise noted, reactions were carried out with **1** (0.2 mmol), **2a** (0.24 mmol), and **3a** (0.006 mmol) in 0.1 mL of solvent at room temperature. [b]Yield of **4** was determined by GC-MS analysis, and hexadecane was used as an internal standard. [c]The reaction was carried out for 6 h. [d]3% of (2-methylallyl)benzene and 3% of (2-methylprop-1-en-1-yl)benzene were formed.

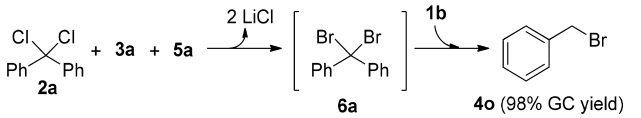
Table 3. $FeCl_3$-Catalyzed Halogenation of Benzyl Alcohol Using *α*,*α*-Dichlorodiphenylmethane with LiBr and LiI



entry	R-OH	LiX	product	yield (%)[b]
1	**1b**	LiBr (**5a**)	**4o** (X = Br)	98
2	**1b**	LiI (**5b**)	**4p** (X = I)	97
3	**1l**	LiBr (**5a**)	**4q** (X = Br)	85
4	**1l**	LiI (**5b**)	**4r** (X = I)	79

[a]Unless otherwise noted, reactions were carried out with **1** (0.2 mmol), **2a** (0.24 mmol), **3a** (0.006 mmol), and **5** (0.8 mmol) in 0.1 mL of $CHCl_3$ at room temperature. [b]Yields of **4** were determined by using GC-MS analysis, and hexadecane was used as the internal standard.

Scheme 1. Mechanistic Investigation of Bromination of Alcohol Using 2a with LiBr



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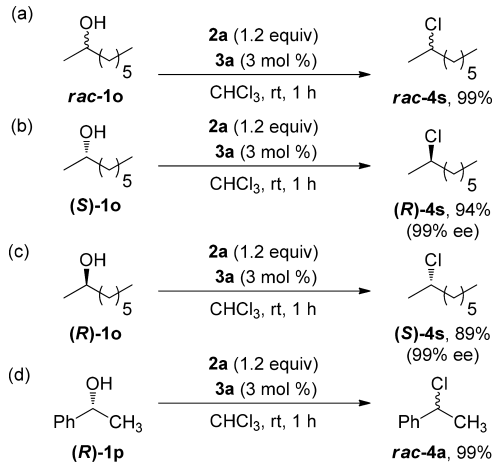
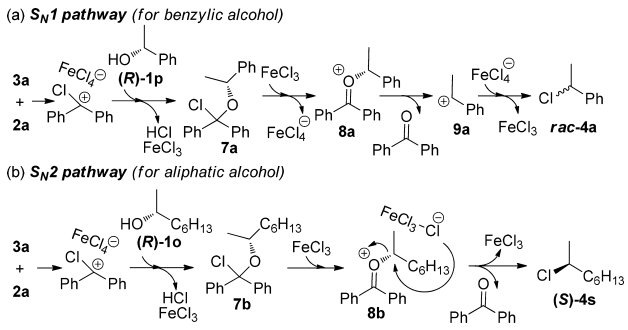
Scheme 2. Mechanistic Investigation of the Chlorination Reaction



place to give a racemic mixture of the chlorination product *rac*-**4a** in 99% yield (Scheme 2d).

These results indicate that chlorination reactions of aliphatic secondary alcohols take place by an S_N2 pathway, whereas an S_N1 pathway is followed in the cases of benzylic alcohols. Thus, it appears that two closely related mechanisms are responsible for this chlorination process, both being initiated by nucleophilic substitution of the alcohol (e.g., (*R*)-**1p**) with **2a** to generate intermediate α-chloroether **7a**, along with HCl. This step is followed by reaction of **7a** with $FeCl_3$ to produce the oxonium intermediate **8a**, along with $FeCl_4^-$. The pathway then diverges depending on the nature of the starting alcohol. Specifically, in the case of benzylic alcohols, **8a** readily loses benzophenone to form a stable benzylic carbocation **9a** that reacts with $FeCl_4^-$ to produce the catalyst $FeCl_3$ and chlorination product **4a** as a racemate (Scheme 3a). In the case of secondary aliphatic

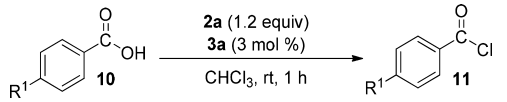
Scheme 3. Proposed Mechanism of Chlorination of Alcohols



alcohols, S_N2 reaction between **8b** and $FeCl_4^-$ takes place to form the corresponding nonracemic alkyl chloride (*S*)-**4s** together with $FeCl_3$ and benzophenone (Scheme 3b).

In the next phase of this effort, we extended the scope of the chlorination process to carboxylic acids (Table 4). We found that reaction of benzoic acid (**10a**) with **2a** at room temperature in $CHCl_3$ containing $FeCl_3$ (**3a**) forms benzoyl chloride (**11a**) in 95% yield (entry 1). The benzoic acid derivative **10b** possessing a *p*-methyl electron-donating group also displays similar reactivity to form the corresponding acid chloride (entry 2). However, in the cases of benzoic acids **10c,d**, which possess *p*-electron-withdrawing substituents (F, CF_3), the yields of the respective products **11c,d** are lower (78 and 57%) (entries 3 and 4). The

Table 4. Chlorination of Various Carboxylic Acids Using 2a[a]

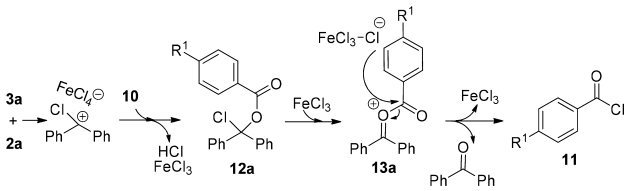


entry	carboxylic acid	product	yield (%)[b]
1	R^1 = H (**10a**)		95 (**11a**)
2	CH_3 (**10b**)		92 (**11b**)
3	F (**10c**)		78 (**11c**)
4	CF_3 (**10d**)		57 (**11d**)

[a]The reactions were carried out with **10** (2 mmol), **2a** (2.4 mmol), and **3a** (0.06 mmol) in 1.0 mL of $CHCl_3$ at room temperature. [b]Yield of **11** was determined by GC-MS analysis, and hexadecane was used as an internal standard.

lower reactivities of these substrates are likely a consequence of the lower nucleophilicities of carboxylic acid containing electron-withdrawing substituents that retard their reactions with **2a** to form **12a** (Scheme 4).

Scheme 4. Proposed Mechanism of Chlorination of Carboxylic Acids



The process can also be utilized for the one-pot synthesis of amides and esters from carboxylic acids. Specifically, reactions of carboxylic acids **10** with **2a** (1.2 equiv) at room temperature in $CHCl_3$ containing $FeCl_3$ (**3a**, 5 mol %) followed by addition of an amine or alcohol in the presence of triethylamine generate the corresponding amides or esters **13** (Table 5). For example, *N*-benzylbenzamide (**13a**) can be prepared in this manner in 92% isolated yield starting with benzoic acid (**10a**), **2a**, **3a**, and benzyl amine (entry 1). Reactions of benzoic acid derivatives possessing electron-donating and electron-withdrawing substituents, such as methyl (**10b**), fluoro (**10c**), trifluoromethyl (**10d**), and cyano (**10e**), produce the corresponding amides (**13b–e**) in good to moderate yields (entries 2–5). Reaction of naphthalenecarboxylic acid and benzyl amine under these conditions occurs to form *N*-benzyl-2-naphthamide (**13f**) in 83% yield (entry 6). Aliphatic carboxylic acids such as cyclohexanecarboxylic (**10g**) and octanoic (**10h**), 2-methylhexanoic (**10i**), and 2,2,2-trimethylethanoic acid (**10j**) also serve as viable substrates for this process (entries 7–10). Finally, reactions of benzoic acid (**10a**) with α,α-dichlorodiphenylmethane (**2a**) in the presence of **3a** followed by addition of nucleophiles such as cyclohexylamine and 1-heptanol lead to formation of the corresponding products, *N*-cyclohexylbenzamide (**13k**) and heptyl benzoate (**13l**) in 86 and 80% yields, respectively (entries 11 and 12).

4-(Hydroxymethyl)benzoic acid (**1q**) is a potentially interesting substrate for the chlorination reaction because it contains both a carboxylic acid and benzylic alcohol moiety (eq 1). We

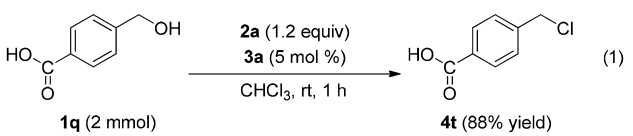


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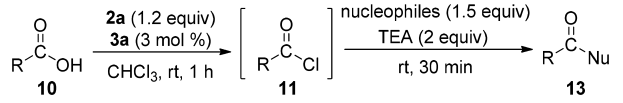
Table 5. $FeCl_3$-Catalyzed Halogenation Reactions of Carboxylic Acids To Produce Amides[a]



entry	carboxylic acid	nucleophiles	product	yield (%)[b]
1	R^1 = H (**10a**)	NH_2Bn (**14a**)		92 (**13a**)
2	CH_3 (**10b**)			80 (**13b**)
3	F (**10c**)			72 (**13c**)
4	CF_3 (**10d**)			53 (**13d**)
5	CN (**10e**)			56 (**13e**)
6	(**10f**)	**14a**		83 (**13f**)
7	(**10g**)	**14a**		86 (**13g**)
8	(**10h**)	**14a**		57 (**13h**)
9	(**10i**)	**14a**		79 (**13i**)
10	(**10j**)	**14a**		68 (**13j**)
11	**10a**			86 (**13k**)
12	**10a**			80 (**13l**)

[a]Reactions were carried out with **10** (2 mmol), **2a** (2.4 mmol), **3a** (0.06 mmol), TEA (4 mmol), and nucleophiles (3 mmol) in 1.0 mL of $CHCl_3$ at room temperature. [b]Isolated yield.

observed that reaction of **1q** with **2a** in the presence of **3a** under the standard reaction conditions generates the chloromethyl-substituted benzoic acid derivative **4t** in 88% isolated yield.[10] This result suggests that the benzylic alcohol moiety is more reactive with **2a** than is the carbxylic acid group.

In conclusion, this investigation led to the development of a simple, mild, and efficient method for halogenation of alcohols and carboxylic acid. The process utilizes commercially available α,α-dichlorodiphenylmethane as the halogenating agent and $FeCl_3$ as the catalyst. In addition, the conditions used for this process avoid the use of toxic starting materials and the formation of stoichiometric amounts of oxidized phosphine and noxious byproducts.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00831.

Compound characterization data, ^1H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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(9) α,α-Dichlorodiphenylmethane (**2a**) is a colorless and odorless oil. Because this compound is generally stable but reacts with water to generate HCl, be sure to handle with care.

(10) The reaction of **1q** (2 mmol) with **2a** (3 equiv) was carried out in the presence of **3a** (5 mol %) for 3 h to produce 4-(chloromethyl) benzoyl chloride in 73% GC yield.

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