Iron(III) Chloride-catalyzed Reductive Etherification of Carbonyl Compounds with Alcohols

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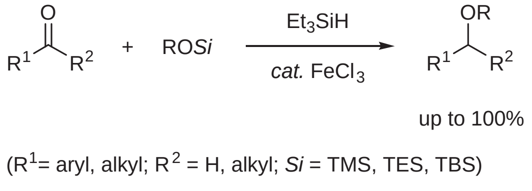
A facile reductive etherification of carbonyl compounds can be performed by the reaction with alcohols and triethylsilane catalyzed by iron(III) chloride. The corresponding alkyl ethers are obtained in good to excellent yields under mild reaction conditions.

Alkyl ether is one of the most important functional groups for organic synthesis, because it is included in many organic chemicals, and also it is widely used as a protective group of the hydroxy function.[1] Reductive etherification of carbonyl compounds is known as an alternative method of the Williamson ether synthesis. In 1972, Doyle et al. reported the synthesis of ethers by the reduction of carbonyl compounds with triethylsilane in alcohol in the presence of excess amounts of sulfuric acid or trifluoroacetic acid.[2] Nicolaou et al. demonstrated the formation of the oxepane ring from hydroxy ketone using 10 equiv. of triethylsilane and a stoichiometric amount of TMSOTf.[3] Very recently, Izumi and Fukase described a reductive benzylation of hydroxy functions by using the combination of benzaldehyde, triethylsilane, and quite an excess molar TMSCl.[4] On the other hand, some methods have been reported for reductive etherification of carbonyl compounds with triethylsilane and alkoxytrimethylsilane under the influence of Lewis acids.[5] However, these reactions require an annoying step-by-step procedure or a longer reaction time. Although Wada et al. reported a reductive etherification of carbonyl compounds with alcohols promoted by bismuth(III) chloride under mild reaction conditions,[6] this involves some substrate limitation; the yields of the ether products from aliphatic aldehydes and ketones are unsatisfactory.

In the course of our exploration of the usefulness of the reactions promoted by iron(III) chloride,[7] quite recently, we have developed a highly efficient reductive etherification of carbonyl compounds with alkoxytrialkylsilane and triethylsilane catalyzed by iron(III) chloride (Scheme 1).[8] This includes some striking features: 1) extremely short reaction time is needed in contrast to the known methods, 2) not only trimethylsilyl (TMS) ether but also triethylsilyl (TES) and *t*-butyldimethylsilyl (TBS) ethers can be used as the parent silyl ether, 3) various ethers are obtained from a wide range of aldehydes and ketones, and 4) high-yielding process. Etherification of carbonyl compounds with the parent alcohol, not alkoxytrialkylsilane, is more straightforward and promising. Therefore, we applied this reductive etherification into the naked and unmodified alcohols.



Scheme 1. Iron(III) chloride-catalyzed reductive etherification of carbonyl compounds with alkoxytrialkylsilane.

In the first place, we undertook to examine the reductive etherification of aldehyde with alcohol and triethylsilane according to the procedure reported in a previous paper.[8a] To a mixture of benzaldehyde and 1.2 equiv. of 3-phenylpropanol in the presence of 5 mol % of iron(III) chloride was added 1.2 equiv. of triethylsilane at 0 °C and stirred at room temperature for 1 h. The usual work-up of the reaction mixture afforded the desired product, 1-benzyloxy-3-phenylpropane, in 90% yield (Table 1, Run 1). On the other hand, when triethylsilane was added at room temperature, the yield was improved to 97% (Run 2). In addition, we found that the usage of alcohol needed slightly longer reaction time compared with the corresponding silyl ether.[8b] These results show that the reactivity of unmodified alcohol is lower than that of silyl ether. A screening of solvents revealed that nitromethane as a solvent gave the best result.[9] Next, the reaction was conducted using various alcohols. Benzyl alcohol, acyclic and cyclic secondary alcohols also gave the desired product in excellent yields (Runs 3–5). In the case of chiral secondary alcohol, (*S*)-2-octanol (>99% ee), the corresponding (*S*)-ether (>99% ee) was obtained with complete retention of stereochemistry (Run 6).[10] On the other hand, tertiary alcohol gave the product in only 25% yield (Run 7). In the case of phenol, the expected reaction did not proceed at all (Run 8).

The reaction was carried out with various representative aromatic and aliphatic aldehydes as summarized in Table 2.[13] Using this method, all aldehydes tested were uniformly transformed into the corresponding dialkyl ethers in good to excellent

Table 1. Reductive etherification of benzaldehyde with various alcohols[a]

$$\mathrm{PhCHO} \quad + \quad \mathrm{ROH} \quad \xrightarrow[\mathrm{FeCl_3}]{\mathrm{Et_3SiH}} \quad \mathrm{PhCH_2OR}$$

CH_3NO_2, rt, 1 h

Run	Alcohol	Yield/%[b]
1[c]	$PhCH_2CH_2CH_2OH$	90
2	$PhCH_2CH_2CH_2OH$	97
3	BnOH	96
4	$PhCH_2CH_2CH(CH_3)OH$	95
5	Cyclohexanol	97
6	(*S*)-2-Octanol	81[d]
7	$PhCH_2CH_2C(CH_3)_2OH$	25
8	Phenol	0[e]

[a] Molar ratio of PhCHO:alcohol:Et_3SiH:$FeCl_3$ = 1:1.2:1.2:0.05. [b] Isolated yield of purified product. [c] Triethylsilane was added at 0 °C. [d] >99% ee (Determined by HPLC with chiral column analysis; Daicel Chiralpak IA, *t*-butyl methyl ether/hexane = 1/1000, 0.1 mL/min). [e] Dibenzyl ether was obtained in 92% yield.

Table 2. Reductive etherification of various aldehydes with alcohols[a]

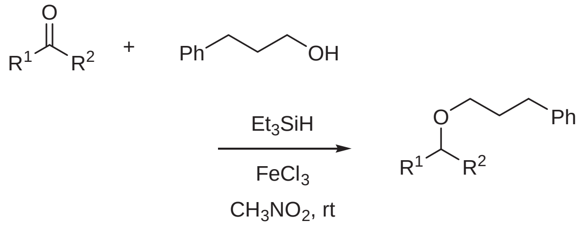
$$\mathrm{RCHO} \quad + \quad \mathrm{R'OH} \xrightarrow[\mathrm{FeCl_3}]{\mathrm{Et_3SiH}} \mathrm{RCH_2OR'}$$

CH_3NO_2, rt, 1 h

Run	Aldehyde	Alcohol	Yield /%[b]
1	PhCHO	$PhCH_2CH_2CH_2OH$	97
2	2-MeC_6H_4CHO		85
3	3-MeC_6H_4CHO		82
4	4-MeC_6H_4CHO		90
5	2-$MeOC_6H_4CHO$		54
6[c]	2-$MeOC_6H_4CHO$		77
7	3-$MeOC_6H_4CHO$		92
8	4-$MeOC_6H_4CHO$		22
9[c]	4-$MeOC_6H_4CHO$		43
10	4-BrC_6H_4CHO		92
11	4-AcC_6H_4CHO		73
12	4-$AcOC_6H_4CHO$		87
13	4-$MeO_2CC_6H_4CHO$		89
14	1-Naphthaldehyde		82
15	2-Naphthaldehyde		90
16	(*E*)-PhCH=CHCHO		0
17[c]	(*E*)-PhCH=CHCHO		40
18	$PhCH_2CH_2CHO$		87
19	$PhCH_2CH_2CHO$	BnOH	78
20	$PhCH_2CH_2CHO$	$PhCH_2CH_2CH(CH_3)OH$	79
21	*n*-BuCHO	$PhCH_2CH_2CH_2OH$	84
22	$PhCH_2CH(CH_3)CHO$[d]		86
23	*cyclo*-$C_6H_{11}CHO$		91
24	$BnOCH_2C(CH_3)_2CHO$[e]		86
25	*t*-BuCHO		71

[a] Molar ratio of aldehyde:alcohol:Et_3SiH:$FeCl_3$ = 1:1.2:1.2:0.05. [b] Isolated yield of purified product. [c] CH_3CN was used as a solvent. When nitromethane was used as a solvent, the reaction mixture became complicated. [d] For the preparation of this compound.[11] [e] For the preparation of this compound.[12]

Table 3. Reductive etherification of ketones with 3-phenylpropanol[a]



Run	Ketone	Time/h	Yield/%[b]
1	Benzylacetone	6	76
2	Cyclohexanone	6	76
3	Acetophenone	24	36

[a] Molar ratio of aldehyde:alcohol:Et_3SiH:$FeCl_3$ = 1:1.2:1.2:0.05. [b] Isolated yield of purified product.

yields. Especially, the protective groups, such as acetate and methyl ester function were tolerated under these reaction conditions (Runs 12 and 13). Even in the case of sterically hindered aldehydes, the desired product was obtained in 86 and 71% yields, respectively (Runs 24 and 25).

Furthermore, we have found that this reaction is similarly effective for aliphatic and alicyclic ketones to yield the corresponding ethers in good yields (Table 3, Runs 1 and 2). On the other hand, aromatic ketone gave the desired ether in only 36% yield (Run 3).

In conclusion, the present reaction has the following synthetic advantages: 1) in contrast to the known procedure of catalytic reductive etherification, this procedure can use free alcohol; 2) various ethers are obtained from a wide range of aromatic and aliphatic aldehydes and aliphatic ketones; 3) extremely mild reaction conditions under the influence of a catalytic amount of iron(III) chloride; and 4) experimental convenience. Further investigations to broaden the scope and synthetic applications of this valuable etherification are under way in our laboratory.

This paper is dedicated to Professor Teruaki Mukaiyama on the occasion of his 80th birthday, and for his outstanding contributions to synthetic organic chemistry.

References and Notes

1 T. W. Greene, P. G. M. Wuts, in *Protective Groups in Organic Synthesis*, 3rd ed., Wiley-Interscience, New York, **1999**, Chap. 2.

2 M. P. Doyle, D. J. DeBruyn, D. A. Kooistra, *J. Am. Chem. Soc.* **1972**, *94*, 3659.

3 K. C. Nicolaou, C.-K. Hwang, D. A. Nugiel, *J. Am. Chem. Soc.* **1989**, *111*, 4136.

4 M. Izumi, K. Fukase, *Chem. Lett.* **2005**, *34*, 594.

5 a) J.-I. Kato, N. Iwasawa, T. Mukaiyama, *Chem. Lett.* **1985**, 743. b) M. B. Sassaman, K. D. Kotian, G. K. S. Prakash, G. A. Olah, *J. Org. Chem.* **1987**, *52*, 4314. c) S. Hatakeyama, H. Mori, K. Kitano, H. Yamada, M. Nishizawa, *Tetrahedron Lett.* **1994**, *35*, 4367. d) N. Komatsu, J. Ishida, H. Suzuki, *Tetrahedron Lett.* **1997**, *38*, 7219. e) J. S. Bajwa, X. Jiang, J. Slade, K. Prasad, O. Repič, T. J. Blacklock, *Tetrahedron Lett.* **2002**, *43*, 6709. f) W.-C. Yang, X.-A. Lu, S. S. Kulkarni, S.-C. Hung, *Tetrahedron Lett.* **2003**, *44*, 7837. g) S. Chandrasekhar, G. Chandrashekar, B. Nagendra Babu, K. Vijeender, K. Venkatram Reddy, *Tetrahedron Lett.* **2004**, *45*, 5497.

6 M. Wada, S. Nagayama, K. Mizutani, R. Hiroi, N. Miyoshi, *Chem. Lett.* **2002**, 248.

7 a) T. Watahiki, T. Oriyama, *Tetrahedron Lett.* **2002**, *43*, 8959. b) T. Watahiki, Y. Akabane, S. Mori, T. Oriyama, *Org. Lett.* **2003**, *5*, 3045. c) K. Iwanami, T. Oriyama, *Chem. Lett.* **2004**, *33*, 1324. d) K. Iwanami, M. Aoyagi, T. Oriyama, *Tetrahedron Lett.* **2005**, *46*, 7487. e) K. Iwanami, M. Aoyagi, T. Oriyama, *Tetrahedron Lett.* **2006**, *47*, 4741.

8 a) K. Iwanami, H. Seo, Y. Tobita, T. Oriyama, *Synthesis* **2005**, 183. b) K. Iwanami, K. Yano, T. Oriyama, *Synthesis* **2005**, 2669.

9 CH_3NO_2 (97%), CH_3CN (49%), CH_2Cl_2 (56%), THF (0%).

10 $[\alpha]_D = +17.1$ (*c* 1.00, $CHCl_3$). (lit. $[\alpha]_D = +16.5$ (*c* 0.47, $CHCl_3$): M. Node, K. Nishide, Y. Shigeta, K. Obata, H. Shiraki, H. Kunishige, *Tetrahedron* **1997**, *53*, 12883.)

11 H. Akita, C. Y. Chen, K. Kato, *Tetrahedron* **1998**, *54*, 11011.

12 M. C. Stumpp, R. R. Schmidt, *Tetrahedron* **1986**, *42*, 5941.

13 Typical procedure: To a suspension of anhydrous iron(III) chloride (2.4 mg, 0.015 mmol) and benzaldehyde (30 µL, 0.30 mmol) in nitromethane (1.5 mL) was added 3-phenylpropanol (49.1 mg, 0.36 mmol) and triethylsilane (58 µL, 0.36 mmol) successively at room temperature under an argon atmosphere. After stirring for 1 h, the reaction mixture was quenched with a phosphate buffer (pH 7, 20 mL). The organic materials were extracted with dichloromethane, washed with brine, and dried over sodium sulfate. 1-Benzyloxy-3-phenylpropane (64.9 mg, 97%) was isolated by thin-layer chromatography on silica gel.