A Highly Efficient Method for the Reductive Etherification of Carbonyl Compounds with Triethylsilane and Alkoxytrimethylsilane Catalyzed by Iron(III) Chloride

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Abstract: Facile reductive etherification of carbonyl compounds can be conveniently performed by reaction with triethylsilane and alkoxytrimethylsilane catalyzed by iron(III) chloride. The corresponding alkyl ethers, including benzyl and allyl ethers, of the reduced alcohols were obtained in good to excellent yields under mild reaction conditions.

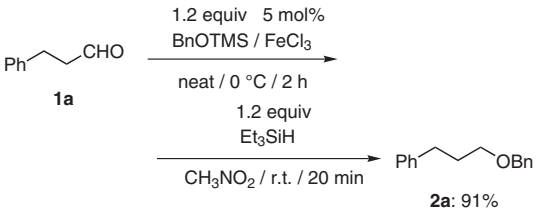
Key words: reductive etherification, iron(III) chloride, alkoxytrimethylsilane, triethylsilane, carbonyl compounds

Benzyl ethers are very important functional groups and have been extensively utilized mainly as a protecting group in multi-step synthesis.[1] Further development of efficient and convenient methods for protection of the hydroxyl function remains a significant objective. Two separate transformations including a protection process would combine to occur smoothly in one-pot to afford readily the valuable synthetic intermediates, because no protection procedure is required. On the basis of these considerations, we have recently demonstrated the iron(III) chloride-catalyzed novel one-pot synthesis of benzyl homoallyl ethers directly from aldehydes.[2] So we next considered that a combination of the reduction of carbonyl compounds and subsequent benzyl-etherification can be carried out to yield the corresponding benzyl ethers of the reduced alcohols.

Although some methods have been reported for reductive etherification of carbonyl compounds with alkoxysilane and triethylsilane promoted by Lewis acids, such as trityl perchlorate,[3] trimethylsilyl iodide,[4] trimethylsilyl triflate,[5] bismuth bromide,[6] copper triflate,[7] and tris(pentafluorophenyl)borane,[8] these reactions require a step-by-step procedure or a long reaction time.

In this communication, we wish to report that the reductive etherification of aldehydes and ketones proceeds smoothly with triethylsilane and alkoxytrimethylsilane catalyzed by iron(III) chloride.

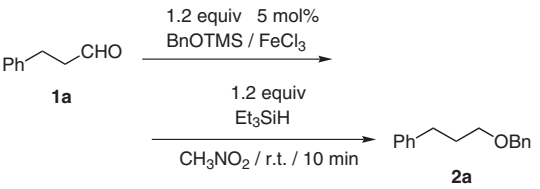
First, we examined the reductive etherification of 3-phenylpropanal with triethylsilane and benzyloxytrimethylsilane (BnOTMS) in the presence of a catalytic amount of iron(III) chloride according to the procedure reported in a previous paper.[2] Reductive benzyl-etherification has been achieved efficiently as shown in Scheme 1.



Scheme 1 Reductive etherification of 3-phenylpropionaldehyde

After screening of the reaction times, we found that the desired product, benzyl 3-phenylpropyl ether, was produced in 91% yield upon formation of the intermediate (Table 1, entry 4). Screening of solvents revealed that 5 mol% of iron(III) chloride as a catalyst and nitromethane as a solvent gave the best result (Table 2, entry 5).

Table 1 Optimization of Reaction Time in the First Step



Entry	Time (min)	Temp (°C)	Yield (%)[a]
1[b]	120	0	91
2	10	0	89
3	0	0	88
4[c]	0	0	91
5	0	r.t.	78

[a] Isolated yield of purified product.
[b] Reaction was performed in 20 min at the second step.
[c] Nitromethane was added in the first step.

The reaction was carried out under optimal conditions with various aromatic and aliphatic aldehydes and ketones as shown in Table 3. Using this method, all aldehydes tested were uniformly transformed into the corresponding benzyl ethers in good to excellent yields. Especially, sterically hindered aldehydes gave the corresponding ethers

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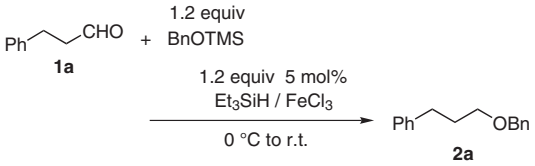
Table 2 Optimization of Solvent



Entry	Solvent	Time	Yield of **2a** (%)[a]
1	CH_2Cl_2	5 h	27
2	toluene	20 h	42
3	DMF	6 h	trace
4	THF	4 h	0
5	CH_3NO_2	10 min	91
6[b]	CH_3NO_2	10 min	84
7	CH_3CN	10 min	85
8	EtCN	10 min	82
9	*n*-PrCN	10 min	70

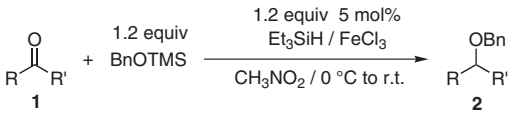
[a] Isolated yield of purified product.
[b] $FeCl_3$ (2 mol%) was used.

in high yields (entries 2 and 8), and the ester function is tolerated under these reaction conditions (entries 12 and 13). We have found that ketones also undergo this transformation to the benzyl ethers of secondary alcohols in good yields (entries 16 and 17). In the absence of BnOTMS, no reduction of ketones occurred under comparable reaction conditions, which suggests that a reactive species such as an oxonium ion was formed from ketone and BnOTMS in this reductive etherification. In the case of aromatic ketone, longer reaction time was needed (entry 18). Taking advantage of this feature, chemoselective conversion of formyl group into benzyl ether in the presence of the less reactive aroyl group was demonstrated successfully as shown in entry 14.

Next, to clarify the generalization of this useful reaction, we tried several alkoxysilanes instead of BnOTMS. As summarized in Table 4, various alkoxytrimethlysilanes are also similarly effective in this reaction to give the corresponding ethers. Particularly, allyloxytrimethylsilane gave allyl ether in 81% yield, which is one of the most significant protecting groups for the hydroxyl function (entry 1). On the other hand, silyl ethers of primary and cyclic secondary alcohols gave the corresponding ethers in 89% and 70% yields, respectively (entries 2 and 3). However, by using *t*-butoxytrimethylsilane as an alkyl silyl ether, the corresponding *t*-butyl ether could be obtained in only 33% yield (entry 4).

In conclusion, the present reductive etherification has the following synthetic advantages: 1) extremely short reaction time is needed in contrast to the known methods; 2) various ethers are obtained from a wide range of aldehydes and alkoxytrialkylsilanes; 3) extremely mild reaction conditions; and 4) experimental convenience.

Table 3 Reductive Etherification of Various Aldehydes and Ketones



Entry	Substrate		Time (min)	Product	Yield of **2** (%)[a]
1	$PhCH_2CH_2CHO$	**1a**	10	**2a**	91
2	$PhCH(CH_3)CHO$	**1b**	10	**2b**	91
3	(*E*)-PhCH=CHCHO	**1c**	30	**2c**	42[b]
4	PhCHO	**1d**	10	**2d**	98
5	2-MeC_6H_4CHO	**1e**	10	**2e**	88
6	3-MeC_6H_4CHO	**1f**	10	**2f**	82
7	4-MeC_6H_4CHO	**1g**	15	**2g**	96
8	2,4,6-$Me_3C_6H_2CHO$	**1h**	60	**2h**	82
9[c]	4-$MeOC_6H_4CHO$	**1i**	60	**2i**	77
10	4-BrC_6H_4CHO	**1j**	10	**2j**	99
11	4-$NO_2C_6H_4CHO$	**1k**	30	**2k**	87
12	4-$MeO_2CC_6H_4CHO$	**1l**	10	**2l**	95
13	4-$AcOC_6H_4CHO$	**1m**	10	**2m**	93
14	4-AcC_6H_4CHO	**1n**	60	**2n**	76
15	2-Naphthaldehyde	**1o**	10	**2o**	95
16	Cyclohexanone	**1p**	10	**2p**	78
17	Benzylacetone	**1q**	15	**2q**	80
18	Acetophenone	**1r**	1440	**2r**	72

[a] Isolated yield of purified product.
[b] The lower yield was due to a complicated reaction mixture.
[c] BnOTMS (150 mol%) was used and CH_3CN was used as a solvent.

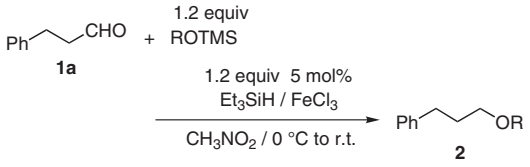
All reactions were carried out under an Ar atmosphere. ^1H and ^{13}C NMR spectra were recorded on a JEOL GSX-400 spectrometer at 400 MHz and 100 MHz, respectively. The chemical shifts are reported in ppm (δ) relative to TMS in $CDCl_3$. IR spectra were recorded in cm^{-1} on a JASCO FT/IR-300E spectrometer. Iron(III) chloride was purchased from Aldrich and used without further purification. Nitromethane was dried over MS 4A prior to use. TLC was performed on Wakogel B-5F silica gel with Et_2O and hexane as eluents.

Products **2a**,[9,10] **2c**,[11] **2d**,[9] **2g**,[12] **2i**,[13] **2p**,[14] **2q**,[10] **2r**,[14] **2s**,[15] **2t**,[16] and **2v**[17] had identical data to that reported in the literature.

1-Benzyloxy-3-phenylpropane (2a); Typical Procedure

To a suspension of anhyd iron(III) chloride (5.3 mg, 0.033 mmol) and 3-phenylpropionaldehyde (79 μL, 0.601 mmol) in nitromethane (2 mL) were added benzyloxytrimethylsilane (142 μL, 0.721 mmol)

Table 4 Synthesis of Various Ethers from 3-Phenylpropionaldehyde



Entry	ROTMS	Time (min)	Product	Yield of **2** (%)[a]
1	CH_2=$CHCH_2$OTMS	10	**2s**	81
2	*n*-BuOTMS	10	**2t**	89
3	*cyclo*-C_6H_{11}OTMS	15	**2u**	70
4	*t*-BuOTMS	30	**2v**	33[b]

[a] Isolated yield of purified product.
[b] The lower yield was due to a complicated reaction mixture.

and triethylsilane (116 μL, 0.727 mmol) successively at 0 °C under an Ar atmosphere. After stirring for 10 min at r.t., the reaction mixture was quenched with a phosphate buffer (pH 7, 20 mL). The organic materials were extracted with CH_2Cl_2, washed with brine, and dried over Na_2SO_4. 1-Benzyloxy-3-phenylpropane (**2a**; 123.3 mg, 91%) was isolated by TLC on silica gel.

1-Benzyloxy-2-phenylpropane (2b)
IR (neat): 3364, 1453, 1098, 698 cm^{-1}.

^{1}H NMR: δ = 1.31 (d, *J* = 7.0 Hz, 3 H), 3.07 (dqd, *J* = 7.7, 7.0, 6.2 Hz, 1 H), 3.50 (dd, *J* = 7.7, 9.2 Hz, 1 H), 3.59 (dd, *J* = 9.2, 6.2 Hz, 1 H), 4.50 (s, 2 H), 7.18–7.36 (m, 10 H).

^{13}C NMR: δ = 18.46, 40.10, 72.96, 76.11, 126.24, 127.29, 127.36, 127.43, 128.25, 138.46, 144.32.

1-Benzyloxymethyl-2-methylbenzene (2e)
IR (neat): 3029, 2857, 1496, 1454, 1359, 1072, 743, 697 cm^{-1}.

^{1}H NMR: δ = 2.33 (s, 3 H), 4.55 (s, 2 H), 4.57 (s, 2 H), 7.15–7.38 (m, 9 H).

^{13}C NMR: δ = 18.88, 70.58, 72.28, 125.68, 127.54, 127.71, 127.75, 128.30, 128.62, 130.15, 136.04, 136.67, 138.26.

1-Benzyloxymethyl-3-methylbenzene (2f)
IR (neat): 3029, 2856, 1454, 1356, 1157, 779, 737, 696 cm^{-1}.

^{1}H NMR: δ = 2.36 (s, 3 H), 4.52 (s, 2 H), 4.56 (s, 2 H), 7.09–7.39 (m, 9 H).

^{13}C NMR: δ = 21.44, 72.10, 72.13, 124.78, 127.51, 127.68, 128.20, 128.28, 128.44, 137.94, 138.07, 138.21.

1-Benzyloxymethyl-2,4,6-trimethylbenzene (2h)
IR (neat): 2917, 1453, 1070, 736, 697 cm^{-1}.

^{1}H NMR: δ = 2.24 (s, 3 H), 2.32 (s, 6 H), 4.52 (s, 2 H), 4.55 (s, 2 H), 6.84 (s, 2 H), 7.26–7.38 (m, 5 H).

^{13}C NMR: δ = 19.58, 21.04, 66.25, 72.36, 127.49, 127.81, 128.25, 128.84, 131.14, 137.48, 137.80, 138.49.

4-Benzyloxymethyl-1-bromobenzene (2j)
IR (neat): 3412, 1487, 1071, 1011 cm^{-1}.

^{1}H NMR: δ = 4.50 (s, 2 H), 4.55 (s, 2 H), 7.22–7.49 (m, 9 H).

^{13}C NMR: δ = 71.29, 72.24, 121.40, 127.70, 128.38, 129.28, 131.42, 137.23, 137.89.

4-Benzyloxymethyl-1-nitrobenzene (2k)
IR (neat): 2859, 1605, 1521, 1346, 1100, 739, 699, 661 cm^{-1}.

^{1}H NMR: δ = 4.62 (s, 2 H), 4.64 (s, 2 H), 7.31–7.39 (m, 5 H), 7.52 (d, *J* = 8.8 Hz, 2 H), 8.20 (d, *J* = 8.8 Hz, 2 H).

^{13}C NMR: δ = 70.77, 72.85, 123.54, 127.68, 127.71, 127.89, 128.47, 137.45, 145.86, 147.28.

Methyl 4-(Benzyloxymethyl)benzoate (2l)
IR (neat): 1721, 1436, 1281, 1109, 1019, 757 cm^{-1}.

^{1}H NMR: δ = 3.89 (s, 3 H), 4.57 (s, 2 H), 4.59 (s, 2 H), 7.26–7.38 (m, 5 H), 7.42 (d, *J* = 8.1 Hz, 2 H), 8.02 (d, *J* = 8.1 Hz, 2 H).

^{13}C NMR: δ = 52.00, 71.37, 72.42, 127.13, 127.65, 128.33, 129.22, 129.58, 129.63, 137.76, 143.47, 166.74.

4-(Benzyloxymethyl)phenyl acetate (2m)
IR (neat): 2858, 1759, 1508, 1368, 1195, 1092, 910 cm^{-1}.

^{1}H NMR: δ = 2.30 (s, 3 H), 4.54 (s, 2 H), 4.56 (s, 2 H), 7.07 (d, *J* = 8.4 Hz, 2 H), 7.28–7.39 (m, 7 H).

^{13}C NMR: δ = 21.20, 71.44, 72.17, 121.45, 127.60, 127.70, 128.35, 128.70, 136.85, 138.03, 149.97, 169.37.

1-Acetyl-4-(benzyloxymethyl)benzene (2n)
IR (neat): 2858, 1683, 1609, 1359, 1267, 1092, 698 cm^{-1}.

^{1}H NMR: δ = 2.60 (s, 3 H), 4.59 (s, 2 H), 4.61 (s, 2 H), 7.25–7.37 (m, 5 H), 7.46 (d, *J* = 8.2 Hz, 2 H), 7.95 (d, *J* = 8.2 Hz, 2 H).

^{13}C NMR: δ = 26.70, 71.40, 72.51, 127.36, 127.70, 127.73, 128.40, 128.42, 136.36, 137.80, 143.75, 197.65.

2-(Benzyloxymethyl)naphthalene (2o)
IR (neat): 3056, 1335, 1128, 818, 732 cm^{-1}.

^{1}H NMR: δ = 4.59 (s, 2 H), 4.71 (s, 2 H), 7.27–7.51 (m, 8 H), 7.79–7.85 (m, 4 H).

^{13}C NMR: δ = 72.10, 72.18, 125.72, 125.76, 126.00, 126.41, 127.59, 127.75, 127.78, 128.09, 128.33, 128.35, 132.90, 133.20, 135.66, 138.13.

1-Cyclohexyloxy-3-phenylpropane (2u)
IR (neat): 2931, 2855, 1451, 1108, 699 cm^{-1}.

^{1}H NMR: δ = 1.18–1.32 (m, 5 H), 1.49–1.55 (m, 1 H), 1.70–1.76 (m, 2 H), 1.84–1.92 (m, 4 H), 2.69 (t, *J* = 7.7 Hz, 2 H), 3.15–3.21 (m, 1 H), 3.44 (t, *J* = 6.4 Hz, 2 H), 7.13–7.28 (m, 5 H).

^{13}C NMR: δ = 24.26, 25.89, 31.74, 32.39, 32.44, 66.89, 77.44, 125.54, 128.13, 128.36, 142.03.

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