9-18-2007

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Reduction of Esters to Ethers Utilizing the Powerful Lewis Acid $BF_2OTf•OEt_2$

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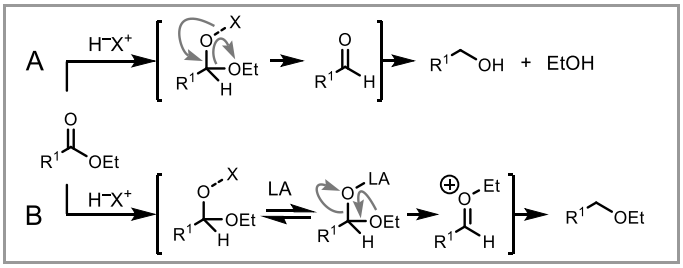
Received: The date will be inserted once the manuscript is accepted.

Abstract: The direct reduction of esters to their corresponding ethers has been achieved using the Lewis acid $BF_2OTf•OEt_2$ generated via anionic redistribution between TMSOTf and $BF_3•OEt_2$ with triethyl silane acting as the reducing agent. Isolated yields of up to 71% have been obtained with the corresponding alcohol as the only side product.

Key words: boron, esters, ethers, Lewis acid, reductions

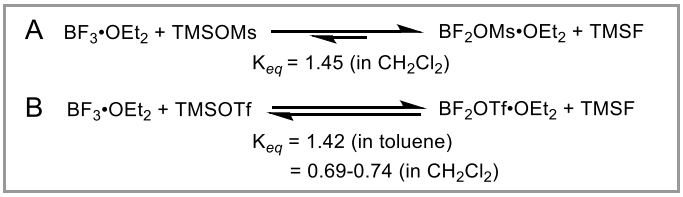
Lewis acids have played a fundamental role in the advancement of organic chemistry by improving reaction yields, increasing selectivity or mediating otherwise difficult reactions.[1] Carbonyl Lewis acid complexes in particular have generated a great deal of attention and have been thoroughly studied in the carbonyl ene reaction,[2] addition of allyl silanes or stannanes to aldehydes and conjugated enones,[3] as well as Diels-Alder[4] and aldol reactions.[5] In these examples, coordination of the Lewis acid to the carbonyl oxygen results in increased reactivity at the carbonyl carbon.

The reduction of esters to alcohols is a commonplace synthetic transformation that can be accomplished with a variety of hydride sources (Scheme 1A), but the direct reduction of esters to ethers is less well known (Scheme 1B). Such ester to ether reductions have been observed in the presence of strongly electron withdrawing Lewis acids.[6] For example, in work on the reductive cleavage of polysaccharides Gray noted the inadvertent reduction of a C2 propionate ester side chain to its corresponding propyl ether.[7] The system employed consisted of a 5:1 mixture of TMSOMs:$BF_3•OEt_2$ in CH_2Cl_2 with Et_3SiH serving as the hydride source. These results clearly showed that with the right Lewis acid it is possible to coax the collapse of the tetrahedral intermediate through a different reaction manifold thereby leading directly to ether formation. A general method for the direct formation of ethers from esters would provide a highly desirable alternative to the classical Williamson ether synthesis.[8]



Scheme 1 The well-known reduction of esters to alcohols (A), and an alternative pathway to ether formation (B)

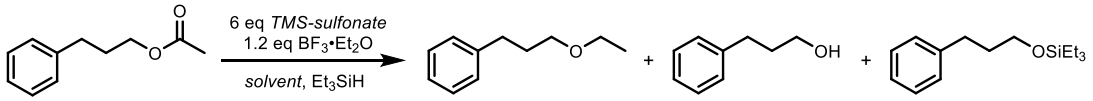
We sought to build on this early observation by confirming the nature of the Lewis acid responsible for ether formation, and by exploring the potential generality of this reduction. In the initial literature report it was proposed that the mixture of TMSOMs and $BF_3•OEt_2$ underwent anionic redistribution to form the active species of either $BF_2OMs•OEt_2$ or $BF(OMs)_2•OEt_2$.[9] In order for us to further clarify the nature of the anionic redistribution, no-D ^{11}B and ^{19}F NMR were taken of solutions of TMSOMs and $BF_3•OEt_2$ in 1:1, 5:1, and 10:1 ratios.[10] It was found that the parent Lewis acids underwent a single anionic redistribution only, to produce $BF_2OMs•OEt_2$ and TMSF. The reaction was very rapid at room temperature, and had reached equilibrium (K_{eq} = 1.45) within a few minutes (Scheme 2A).



Scheme 2 In situ generation of $BF_2OMs•OEt_2$ and $BF_2OTf•OEt_2$

Initial reductions of model ester hydrocinnamyl acetate using the original system[7] of TMSOMs and $BF_3•OEt_2$ with Et_3SiH as a reducing agent gave a modest 25% isolated yield of hydrocinnamyl ethyl ether (Table 1, entry 1). The normal reduction product, hydrocinnamyl alcohol, predominated at 66% yield along with 7% of the triethyl silyl ether. No reduction occurs in the absence of either TMSOMs or $BF_3•OEt_2$ which further supports the idea that $BF_2OMs•OEt_2$ was responsible for moderating the ester to ether reduction. We speculated that enhancing the Lewis acidity of the active species might lead to more ether formation, and therefore the mesylate was replaced with a triflate. The $BF_2OTf•OEt_2$ was prepared in a manner analogous to that of $BF_2OMs•OEt_2$, that is, simply by mixing TMSOTf and $BF_3•OEt_2$ in a 5:1 ratio, and as with $BF_2OMs•OEt_2$, the redistribution was complete within minutes. ^{19}F NMR studies of the reaction between TMSOTf and $BF_3•OEt_2$ in toluene gave an equilibrium constant of 1.42, compared to 0.69-0.74 in CH_2Cl_2 (Scheme 2B).[11]

Table 1 Comparison of reductions with $BF_2OMs•OEt_2$ or $BF_2OTf•OEt_2$

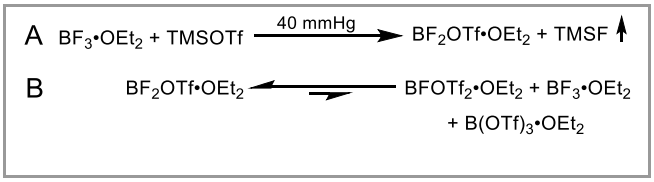


Entry	TMS-sulfonate	Solvent	Ether (%)[a]	Alcohol (%)[a]	Silyl Ether (%)[a]
1	TMSOMs	CH_2Cl_2	25	66	7
2	TMSOTf	CH_2Cl_2	45	46	7
3	TMSOTf	Toluene	51	40	7

[a] Isolated Yields

The use of $BF_2OTf•OEt_2$ in the reduction resulted in an improvement in ether formation to 45% (Table 1, entry 2), along with the alcohol (46%) and silyl ether (7%). A screening of various solvents found reactions in toluene gave a higher yield (Table 1, entry 3). Recently, Aggarwal and co workers described the in situ formation of $BF_2OTf•OEt_2$ and its use in Morita–Baylis–Hillman-type reactions.[11,12]

In an attempt to reduce the amount of TMSOTf used to generate the active Lewis acid, a 1:1 mixture of the parent Lewis acids in toluene was placed under reduced pressure (40 mmHg, rt) for two hours to remove the volatile TMSF and push the equilibrium further towards $BF_2OTf•OEt_2$ formation (Scheme 3A). A persistent white suspension immediately began to form upon evacuation and NMR analysis of the mixture suggested that approximately 15% of the $BF_2OTf•OEt_2$ underwent further anionic redistribution to produce $BF_3•OEt_2$, $BF(OTf)_2•OEt_2$, and $B(OTf)_3•OEt_2$ (Scheme 3B).[13]

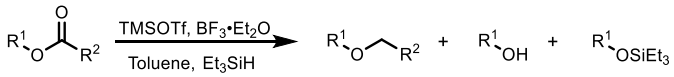


Scheme 3 Competing reactions in the formation of $BF_2OTf•OEt_2$

Use of the mixture containing di and tri triflate species was found to be disadvantageous in reduction reactions, and, in this regard, it was found that their production could be decreased to undetectable levels by adding an excess of $BF_3•OEt_2$ to the system prior to placing it under reduced pressure. In doing so, we successfully generated $BF_2OTf•OEt_2$ in situ free of TMSF, TMSOTf, $BF(OTf)_2•OEt_2$ and $B(OTf)_3•OEt_2$.

Additional reductions of aliphatic esters were performed with the new TMSF-free Lewis acid system, and not only was a marked improvement in the yields observed, but the undesired silyl ether was no longer produced[14] (Table 2). This reaction was found to be successful with esters of varying steric hindrance, including hydrocinnamyl acetate (entry 1, 62%), isobutrate (entry 2, 58%), pivalate (entry 3, 57%) and formate (entry 4, 62%). Other esters include methyl hydrocinnamate (entry 5, 70%) and hydrocinnamyl hydrocinnamate (entry 6, 71%). Complete conversion required up to 5 days at room temperature for the bulky pivalate ester (entry 3), and attempts to shorten reaction times by heating above 25 °C resulted in significantly lower yields.

Table 2 Reductions of esters with varying steric hindrance



Entry	R^1	R^2	Time (h)	Conditions[a]	Ether (%)[b]	Alcohol (%)[b]	Silyl Ether (%)[b]
1	$Ph(CH_2)_3$-	Me	28	A	50	41	8
				B	62	36	0
2	$Ph(CH_2)_3$-	iPr	72	A	47	44	6
				B	58	40	0
3	$Ph(CH_2)_3$-	tBu	120	A	47	47	4
				B	57	42	0
4	$Ph(CH_2)_3$-	H	24	A	46	48	3
				B	62	36	0

5	Me	$Ph(CH_2)_2$-	48	A	52	-	-
				B	70	-	-
6	$Ph(CH_2)_3$-	$Ph(CH_2)_2$-	72	A	67	20	9
				B	71	26	0

[a] Reaction conditions: A = 6 eq TMSOTf, 1.2 eq BF_3•OEt_2 ; B = 1.2 eq TMSOTf, 1.8 eq BF_3•OEt_2, reduced pressure (40 mmHg, 2 hours)

[b] Isolated Yields

Several other reducing agents were examined including triphenylsilane, catecholborane, tributyl tin hydride, triacetoxy borohydride and poly(methylhydrosiloxane).[15] Unfortunately, none of these hydride sources resulted in any reduction of the starting esters in the presence of TMSF-free BF_2OTf•OEt_2. Reactions in CH_2Cl_2 or toluene of aromatic esters, including electron rich and electron deficient examples, lead to complex reaction mixtures presumably due to Friedel-Crafts type processes.

In summary, the direct reduction of esters to ethers has been achieved using triethyl silane in the presence of BF_2OTf•OEt_2 generated in situ from BF_3•OEt_2 and TMSOTf. One noteworthy aspect of this reduction method is the nearly quantitative mass recovery, which in all cases examined was over 96%, and in the crude ^1H NMR spectra of these reactions no unassignable extraneous peaks were observed. While these preliminary results are encouraging, the highly reactive nature of the BF_2OTf•OEt_2 Lewis acid may limit this technique to relatively simple aliphatic esters. Other uses for BF_2OTf•OEt_2 are under investigation, and it is hoped that further optimization of this reduction reaction will lead to a practical method in organic chemistry for ether synthesis.

The analytical data for most of the reported compounds has been reported elsewhere.[16] TMSOMs and TMSOTf were made according to published procedures.[17] Dry solvents were obtained from a solvent dispensing system. ^1H, ^{11}B, ^{13}C, and ^{19}F NMR spectra were obtained on a Varian Inova 400 MHz spectrometer. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane and are, in all cases, referenced to the residual proton resonance peak δ 7.25 for $CDCl_3$. Column chromatography was preformed with Sorbent Technologies 32-63 μm silica gel.

General procedure for reduction of esters:

A solution of BF_3•OEt_2 (1.8 mmol, 1.8 eq) and TMSOTf (1.2 mmol, 1.2 eq) were combined with dry toluene (3 mL) and held under reduced pressure (40 mmHg, rt) for 2 hours. After the vacuum was released and the vessel was back filled with argon, ester (1 mmol, 1 eq), and Et_3SiH (5.0 mmol, 5 eq) were added sequentially. The reaction mixture was monitored by TLC and upon completion (2-5 days, depending upon steric bulk) was poured into 20 mL methanol and 20 mL of water, and diluted with 20 mL CH_2Cl_2. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 x 5 mL). The combined organic layers were washed with water (20 mL), brine (20 mL), dried over $MgSO_4$, filtered through a thin pad of celite, and excess solvent was removed by rotary evaporation. The crude product was purified by flash chromatography (hexanes:EtOAc, 9:1).

BF_2OMs•OEt_2 - Boron difluoride mesylate diethyl etherate

^1H NMR previously reported.[16a]

^{19}F NMR (375 MHz, $CDCl_3$) δ -148.26 (m, 2F).

^{11}B NMR (125 MHz, $CDCl_3$) δ -0.45 (broad s).

BF_2OTf•OEt_2 - Boron difluoride triflate diethyl etherate

^1H NMR (400 MHz, $CDCl_3$) δ 4.43 (q, *J* = 7.0 Hz, 4H), 1.51 (t, *J* = 7.0 Hz, 6H).

^{19}F NMR (375 MHz, $CDCl_3$) δ -77.24 (s, 3F), -146.92 (m, 2F).

^{11}B NMR (125 MHz, $CDCl_3$) δ -0.5 (broad s).

(3-Isobutoxy-propyl)-benzene (Table 2, Entry 2)[16j]

Yellow oil; R_f 0.69 (20% EtOAc/hexanes).

^1H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.29 (m, 2H), 7.23 – 7.19 (m, 3H), 3.44 (q, *J* = 6.9 Hz, 2H), 3.20 (d, *J* = 6.9 Hz, 2H), 2.73 (t, *J* = 6.9 Hz, 2H), 1.96 – 1.87 (m, 2H), 0.96 (s, 3H), 0.94 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 142.1, 128.5, 128.2, 125.7, 77.8, 69.9, 32.3, 31.3, 28.4, 19.4.

[3-(2,2-Dimethyl-propoxy)-propyl]-benzene (Table 2, Entry 3)[16h]

Yellow oil; R_f 0.70 (20% EtOAc/hexanes).

^1H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.26 (m, 2H), 7.21 – 7.16 (m, 3H), 3.42 (t, *J* = 6.9 Hz, 2H), 3.06 (s, 2H), 2.70 (t, *J* = 6.9 Hz, 2H), 1.92 – 1.85 (m, 2H), 0.93 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 142.2, 128.5, 128.2, 125.6, 81.3, 70.4, 32.3, 32.1, 31.3, 26.8.

Bis(3-phenylpropyl) ether (Table 2, Entry 6)[16i]

Pale yellow liquid; R_f 0.43 (20% EtOAc/hexanes).

^1H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.27 (m, 2H), 7.22 – 7.15 (m, 3H), 4.09 (t, *J* = 6.5 Hz, 2H), 2.96 (t, *J* = 7.8 Hz, 2H), 2.64 (t, *J* = 6.5 Hz, 4H), 1.97 – 1.90 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 142.0, 128.4, 128.3, 152.7, 69.9, 32.4, 31.3.

Acknowledgment

We thank NSERC and The University of Western Ontario for financial support of this work.

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(13) NMR analysis of the mixture showed the regeneration of BF_3•OEt_2 as well as peaks tentatively assigned to $BF(OTf)_2$•OEt_2, and $B(OTf)_3$•OEt_2:
^1H NMR showed two new etherate peaks downfield of BF_2OTf•OEt_2 [4.74 (q, *J* = 7.0 Hz, 4H), 1.65 (t, *J* = 7.0 Hz, 6H) and 4.61 (q, *J* = 6.9 Hz, 4H), 1.60 (t, *J* = 6.9 Hz, 6H)].
^{11}B NMR showed two new singlets upfield of the BF_2OTf•OEt_2 (-1.54, -2.28).
^{19}F NMR showed two new singlets in the triflate region (-75.47, -77.40).
(14) The ^{29}F NMR of a reaction run under Conditions A (see footnote Table 2) showed the presence of a peak at -178 ppm suggesting the formation of triethylsilyl fluoride, which is likely responsible for the formation of the triethylsilyl ether product. The signal at -178 ppm was absent under Conditions B.
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Graphical Abstract: