An Efficient and Versatile Procedure for the Synthesis of Acetals from Aldehydes and Ketones Catalyzed by Lithium Tetrafluoroborate

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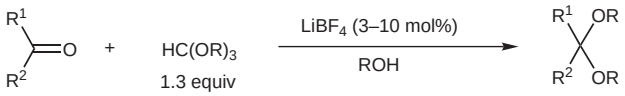
Abstract: Acetals are obtained in good to excellent yields by treatment of aldehydes and ketones with trialkyl orthoformate and the corresponding alcohol in the presence of a catalytic amount of lithium tetrafluoroborate. Due to the mild reaction conditions, this method is compatible with acid-sensitive substrates.

Key words: acetals, carbonyl compounds, Lewis acids, lithium tetrafluoroborate, protecting groups

The protection of aldehydes and ketones as acetals is one of the most widely used methods in organic chemistry.[1] In addition, acetals can be converted to a variety of other functional groups and hence serve as useful intermediates in organic synthesis.[2] A variety of reagents have been developed for the acetalization of carbonyl compounds which include mainly protic acids and Lewis acids, as well as other miscellaneous catalysts.[3] Although these methods are suitable for many synthetic conditions, they can have limitations when applied to acid-sensitive substrates. Thus, the development of more efficient catalysts for this reaction is still actively pursued by synthetic chemists. Lithium tetrafluoroborate ($LiBF_4$) is a new type of mild Lewis acid, and many useful reactions using $LiBF_4$ have been developed.[4] Our previous report has also documented that $LiBF_4$ is a very effective catalyst for the conversion of aldehydes into the corresponding acylals.[5] In this paper, we wish to report an efficient and convenient procedure for the synthesis of acetals from the parent aldehydes and ketones using a catalytic amount of $LiBF_4$ (Scheme 1).



Scheme 1

We first examined the dimethyl acetalization of a series of simple aldehydes and ketones. The reaction was carried out by stirring the carbonyl compounds and trimethyl orthoformate (1.3 equiv) in anhydrous methanol (0.5 cm^3 per mmol of substrate) with 3–10 mol% of $LiBF_4$ at reflux temperature. The results that we have obtained are summarized in Table 1. Aromatic aldehydes with both activating and deactivating groups underwent smooth transformation to the corresponding acetals in excellent yields (entries 1–3).[6] Acid-sensitive substrate such as furfural was efficiently protected as dimethyl acetal without any accompanying self-condensation or ring cleavage (entry 4).[7] Notably, α,β-unsaturated aldehydes were facilely acetalized without concomitant double-bond isomerization (entries 5–7). Aliphatic aldehydes including citronellal[8] worked equally well (entries 8–11). Application of this method was then extended for the protection of different types of aliphatic (entry 12), cyclic (entries 13 and 14), and aromatic ketones (entries 15 and 16). The corresponding acetals were formed in good to excellent yields. Diaryl ketones such as benzophenone are quite resistant to the standard conditions for acetalization.[3b,9] However, with the present method, benzophenone could easily be converted to its dimethyl acetal in 72% yield (entry 16).[10]

We next examined the same reaction using the carbonyl compounds carrying an additional *O*-functional group in their molecules (Table 2). Acetalization of hydroxybenzaldehydes such as *o*-hydroxy- and *p*-hydroxybenzaldehyde under acid-catalyzed conditions is a very difficult process and is usually accompanied with low yields of the products.[11] Nevertheless, this reaction using our methodology proceeded efficiently and gave the desired products in quantitative yields (entries 1 and 2). A variety of functional groups such as methylenedioxy (entry 3), acetoxy (entry 4), *p*-methoxybenzyloxy (entry 5), *tert*-butyldiphenylsiloxy (entry 6), methoxymethoxy (entry 7), (2-methoxyethoxy)methoxy (entry 8), tetrahydropyranyloxy (entry 9),[12] and 2,2-dimethyltrimethylene acetal (entry 10) remained intact under our reaction conditions. Interestingly, methyl acetoacetate, a typical β-keto ester, acetalized smoothly in 83% yield without significant formation of a vinyl ether.[13] These results clearly indicate the mildness and the versatility of this method.

While a large number of methods exist for the synthesis of dimethyl acetals, fewer methods are available for the synthesis of diethyl acetals.[14] To study the versatility of lithium tetrafluoroborate, the diethyl acetalization of a variety of structurally different aldehydes and ketones was finally investigated (Table 3). It can be clearly seen that acetalization of carbonyl compounds was achieved in the presence of triethyl orthoformate (1.3 equiv), anhydrous ethanol (0.5 cm^3 per mmol of substrate), and $LiBF_4$

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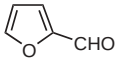
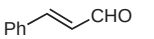
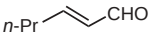
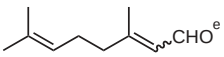
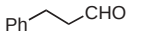
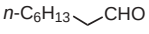
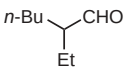
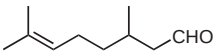
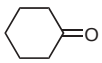
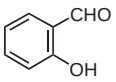
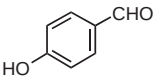
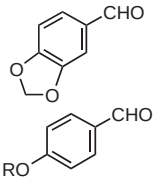
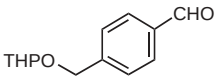
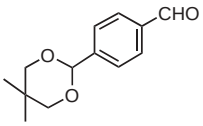
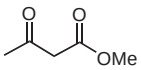
Table 1 Dimethyl Acetalization of Simple Carbonyl Compounds Catalyzed by $LiBF_4$[a]

Entry	$R^1R^2C=O$	Time	Yield (%)[b]
1	PhCHO	30 min	100
2	*p*-ClC_6H_4CHO	1.7 h	98
3	*p*-MeC_6H_4CHO	40 min	95
4		45 min	85
5		15 min	95[c]
6[d]		3 h	100[c]
7		20 min	100[e]
8		1.5 h	93
9		30 min	100
10		2 h	89
11		2 h	100
12[f]		2 h	95
13[f]		40 min	78
14		20 min	98
15[f]		5 h	99
16		24 h	72[g]

[a] Reaction conditions: $R^1R^2C=O$ (5 mmol), $HC(OMe)_3$ (6.5 mmol), $LiBF_4$ (0.15 mmol), dry MeOH (2.5 cm^3), reflux temperature, unless otherwise mentioned.
[b] Refers to the yield of crude product unless otherwise mentioned. Purity of the crude product was estimated to be ≥98% by GC and ^1H and ^{13}C NMR spectroscopy.
[c] *Z*/*E* = 0:100.
[d] At 50 °C.
[e] *Z*/*E* = 45:55.
[f] $LiBF_4$ (10 mol%) was used.
[g] Purified by column chromatography.

Table 2 Dimethyl Acetalization of Functionalized Carbonyl Compounds Using $LiBF_4$[a]

Entry	$R^1R^2C=O$	Time	Yield (%)[b]
1		40 min	100
2		20 min	100
3		50 min	100
4[c]	R = COMe	30 min	96
5[c]	R = $CH_2C_6H_4$-*p*-OMe	60 min	88
6[c]	R = $SiPh_2$-*t*-Bu	30 min	92
7[c]	R = CH_2OMe	5 h	81
8[c]	R = $CH_2OCH_2CH_2OMe$	5 h	83
9[c,d]		2 h	81[e]
10[c,f]		9 h	85[g]
11[c,h]		9 h	83

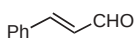
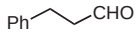
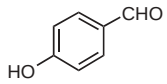
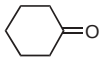
[a] Reaction conditions: see footnote a in Table 1.
[b] See footnote b in Table 1.
[c] $LiBF_4$ (10 mol%) was used.
[d] At 40 °C.
[e] *p*-$HOCH_2C_6H_4CH(OMe)_2$ (5%) was formed.
[f] At 25 °C.
[g] *p*-$(MeO)_2CHC_6H_4CH(OMe)_2$ (3%) and terephthaldehyde bis(2,2-dimethyltrimethylene acetal) (2%) were formed.
[h] At 65 °C.

(3–10 mol%) in good to excellent yields at 40 °C (except for benzophenone). Of particular note, benzophenone was again smoothly acetalized in 71% yield (entry 8).

A typical procedure is as follows (Table 1, entry 1): To a solution of benzaldehyde (531 mg, 5 mmol) and $LiBF_4$ (14.1 mg, 0.15 mmol) in anhydrous methanol (2.5 cm^3) trimethyl orthoformate (690 mg, 6.5 mmol) was added. After the mixture was kept stirring at reflux for 30 minutes, it was quenched by adding saturated $NaHCO_3$ (10 cm^3). The resulting mixture was extracted with EtOAc (30 cm^3, 10 $cm^3 \times 2$). The combined extracts were washed with saturated NaCl (10 cm^3). The organic layer was dried (Na_2SO_4), and concentrated to give 761 mg (100%) of benzaldehyde dimethyl acetal (>99% pure by GC and ^1H and ^{13}C NMR).[15]

In conclusion, we have demonstrated an efficient and versatile method for the acetalization of aldehydes and ketones catalyzed by $LiBF_4$. Works on other reactions catalyzed by $LiBF_4$ and related compounds are currently underway in our laboratory.

Table 3 $LiBF_4$-Catalyzed Diethyl Acetalization of Carbonyl Compounds[a]

Entry	$R^1R^2C=O$	Time (h)	Yield (%)[b]
1	PhCHO	1	92[c]
2		2	100[c,d]
3		5	83[e]
4		1	79[e]
5[f]		4	74[c]
6		0.5	77[c]
7[f]		4	81[c]
8[f,g]		6	71[e]

[a] Reaction conditions: $R^1R^2C=O$ (5 mmol), $HC(OEt)_3$ (6.5 mmol), $LiBF_4$ (0.15 mmol), anhyd EtOH (2.5 cm^3), 40 °C, unless otherwise mentioned.
[b] Isolated yields.
[c] Purified by kugelrohr distillation.
[d] *Z*/*E* = 0:100.
[e] Purified by column chromatography.
[f] $LiBF_4$ (10 mol%) was used.
[g] At reflux temperature.

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(6) Other lithium salts and alkali metal tetrafluoroborates are less effective than $LiBF_4$ in our reaction system. The reaction of benzaldehyde under the identical conditions is as follows: LiCl (19%), LiBr (15%), $LiClO_4$ (36%), LiOTf (35%), $NaBF_4$ (8%), KBF_4 (3%).

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(10) Both methanol and trimethyl orthformate were necessary in order to obtain the products in satisfactory yields. On the reaction of benzophenone (3 mmol) using $LiBF_4$ (0.3 mmol): $HC(OMe)_3$ (3.9 mmol) alone (90 °C, 19 h, 15%); MeOH (1.5 cm^3) alone (reflux, 19 h, 2%).

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(15) The spectroscopic data of new compounds are shown as follows.
4-(Methoxymethoxy)benzaldehyde Dimethyl Acetal: ^1H NMR ($CDCl_3$): δ = 3.32 (s, 6 H), 3.48 (s, 3 H), 5.18 (s, 2 H), 5.35 (s, 1 H), 7.03 (d, *J* = 8.85 Hz, 2 H), 7.36 (d, *J* = 8.85 Hz, 2 H). ^{13}C NMR ($CDCl_3$): δ = 52.6, 56.0, 94.4, 103.0, 115.9, 127.9, 131.6, 157.3.
4-(2-Methoxyethoxy)benzaldehyde Dimethyl Acetal: ^1H NMR ($CDCl_3$): δ = 3.32 (s, 6 H), 3.37 (s, 3 H), 3.53–3.57 (m, 2 H), 3.80–3.84 (m, 2 H), 5.27 (s, 2 H), 5.34 (s, 1 H), 7.05 (d, *J* = 8.70 Hz, 2 H), 7.36 (d, *J* = 8.70 Hz, 2 H). ^{13}C NMR ($CDCl_3$): δ = 52.6, 59.0, 67.6, 71.6, 93.4, 103.0, 115.9, 127.9, 131.6, 157.3.
4-(Perhydro-2*H*-pyran-2-yloxymethyl)benzaldehyde Dimethyl Acetal: ^1H NMR ($CDCl_3$): δ = 1.49–1.92 (m, 6 H), 3.33 (s, 6 H), 3.52–3.56 (m, 1 H), 3.89–3.95 (m, 1 H), 4.51 (d, *J* = 12.2 Hz, 1 H), 4.70 (t, *J* = 3.35 Hz, 1 H), 4.79 (d, *J* = 12.2 Hz, 1 H), 5.39 (s, 1 H), 7.37 (d, *J* = 7.95 Hz, 2 H), 7.43 (d, *J* = 7.95 Hz, 2 H). ^{13}C NMR ($CDCl_3$): δ = 19.4, 25.5, 30.6, 52.7, 62.1, 68.5, 97.8, 103.1, 126.7, 127.6, 137.3, 138.6.
4-(5,5-Dimethyl-1,3-dioxan-2-yl)benzaldehyde Dimethyl Acetal: ^1H NMR ($CDCl_3$): δ = 0.80 (s, 3 H), 1.30 (s, 3 H), 3.29 (s, 6 H), 3.65 (d, *J* = 10.9 Hz, 2 H), 3.77 (d, *J* = 10.9 Hz, 2 H), 5.40 (s, 1 H), 5.41 (s, 1 H), 7.46 (d, *J* = 8.25 Hz, 2 H), 7.51 (d, *J* = 8.25 Hz, 2 H). ^{13}C NMR ($CDCl_3$): δ = 21.9, 23.0, 30.2, 52.4, 77.7, 101.5, 102.6, 126.0, 126.7, 138.6.