A Facile Procedure for Acetalization of Aldehydes and Ketones Catalyzed by Cerium(III) Trifluoromethanesulfonate

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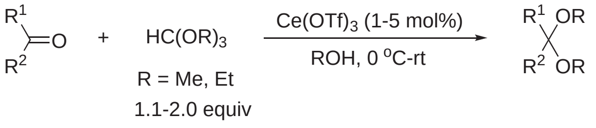
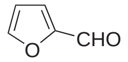
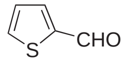
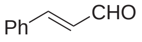
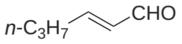
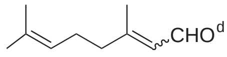
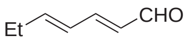
Aldehydes and ketones are readily protected in the presence of trialkyl orthoformate and a catalytic amount of cerium(III) trifluoromethanesulfonate under mild conditions to give the corresponding acetals in good to excellent yields. Due to the mild reaction conditions, this method is compatible with acid-sensitive substrates.

The protection of carbonyl groups as acetals is now commonly used as an important synthetic technique in the course of preparation of many organic compounds.[1] The introduction of new methods and modification of existing methodology for making acetals is thus an important challenge. Among acetalization methods,[2] Luche's procedure[3] with trimethyl orthoformate and cerium(III) chloride hexahydrate as Lewis acid is useful for the synthesis of acetals under almost neutral conditions and has been widely used during the synthesis of many biologically important compounds.[4] However, a stoichiometric amount of $CeCl_3 \cdot 6H_2O$ and excessive amounts of $HC(OMe)_3$ (7 equiv) are required to accomplish the reaction completely and this method is applied only to aldehydes.[3] Recently, Okano et al. reported the dimethyl acetalization of carbonyl compounds with trimethyl orthoformate in methanol catalyzed by ytterbium(III) trifluoromethanesulfonate.[5] Cerium(III) trifluoromethanesulfonate has been often used as a mild and efficient Lewis acid to catalyze acylation,[6] cyclization,[7] or deprotection[8] of organic compounds. In this paper, we wish to report a facile procedure for the synthesis of acetals from the parent ketones and aldehydes using a slight excess of trialkyl orthoformates and a catalytic amount of $Ce(OTf)_3$ under mild conditions (Scheme 1).



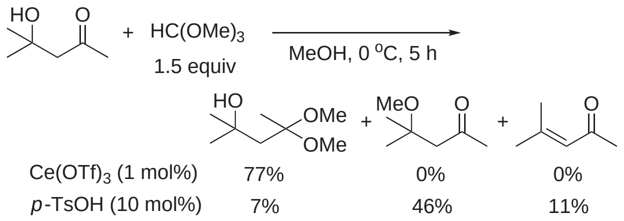
Scheme 1.

Table 1. $Ce(OTf)_3$-catalyzed dimethyl acetalization of aldehydes and ketones using $HC(OMe)_3$[a]

Entry	$R^1R^2C{=}O$	Time /min	Yield /%[b]
1	PhCHO	1	99 (90)
2	p-BrC_6H_4CHO	1	96 (80)
3	p-$MeOC_6H_4CHO$	1	97 (70)
4		2	99 (90)
5		1	92 (60)
6		1	99 (75)
7[c]		5	90
8		5	99[d] (95)
9[c]		5	99
10	n-$C_7H_{15}CHO$	1	95 (100)
11	*cyclo*-$C_6H_{11}CHO$	1	98 (95)
12	$(CH_2)_4C{=}O$	45	90
13	$(CH_2)_5C{=}O$	20	93
14	n-$C_6H_{13}(Me)C{=}O$	30	99
15	$Ph(Me)C{=}O$	30	98
16[e]	$Ph_2C{=}O$	300	98

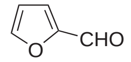
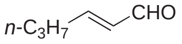
[a]Conditions: $R^1R^2C{=}O$ (3.0 mmol), $HC(OMe)_3$ (3.3 mmol), $Ce(OTf)_3$ (0.03 mmol), MeOH (3 mL), rt, unless otherwise noted. [b]Isolated yield. The yield reported by Luche and Gemal[3a] is given in parenthesis to compare with our result. [c]At 0 °C. [d]E/Z = 55/45. [e]$Ce(OTf)_3$ (0.15 mmol) and $HC(OMe)_3$ (6.0 mmol) were used.

First, we undertook examination of the conversion of a series of aldehydes and ketones to the corresponding dimethyl acetals. The reaction was carried out by stirring the carbonyl compounds and trimethyl orthoformate (1.1–2.0 equiv) in methanol with 1–5 mol % of $Ce(OTf)_3$. The results that we have obtained are summarized in Table 1.[9] Both activated and deactivated aldehydes including acid-sensitive furfural and 2-thiophenecarboxaldehyde (Entries 1–5) and α,β-unsaturated aldehydes (Entries 6–9) underwent smooth acetalization without any trace of by-products to give the corresponding acetals in excellent yields and in very short reaction times. Aliphatic aldehydes worked equally well (Entries 10 and 11). Application of this method was then extended to the protection of different types of cyclic (Entries 12 and 13) and acyclic (Entry 14) ketones. The corresponding acetals were formed in high yields. Similarly, acetophenone gave the desired acetal in 98% yield (Entry 15). Diaryl ketones such as benzophenone are quite resistant to standard conditions for acetalization.[10] However, with the present method, benzophenone could easily be converted to its dimethyl acetal in 98% yield (Entry 16).[11] The most valuable result was found in the acetalization of 4-hydroxy-4-methyl-2-pentanone, a typical tertiary aldol, utilizing our protocol (Scheme 2). When the aldol was allowed to react with $HC(OMe)_3/Ce(OTf)_3$ under usual conditions, only the desired acetal was obtained in 77% yield. ^1H NMR analysis of the crude product showed that neither substitution by-product nor dehydration by-product was produced at all under the reaction conditions. In contrast to this result, when acetalization was carried



Scheme 2. Acetalization of 4-hydroxy-4-methyl-2-pentanone.

Table 2. Diethyl acetalization of aldehydes and ketones catalyzed by $Ce(OTf)_3$ [a]

Entry	$R^1R^2C{=}O$	Time /min	Yield /% [b]
1	PhCHO	2	97
2		10	94
3 [c]		5	95
4	n-$C_7H_{15}CHO$	1	96
5	$(CH_2)_4C{=}O$	90	92
6	$(CH_2)_5C{=}O$	30	95
7	n-$C_6H_{13}(Me)C{=}O$	30	89
8	Ph(Me)C=O	60	97
9 [d]	$Ph_2C{=}O$	660	97

[a] Conditions: $R^1R^2C{=}O$ (3.0 mmol), $HC(OEt)_3$ (3.3 mmol), $Ce(OTf)_3$ (0.03 mmol), EtOH (3 mL), rt, unless otherwise noted. [b] Isolated yield. [c] At 0 °C. [d] $Ce(OTf)_3$ (0.15 mmol) and $HC(OEt)_3$ (6.0 mmol) were used.

out by using *p*-TsOH, a considerable amount of both by-products was formed. Because of the mild Lewis acidity of $Ce(OTf)_3$, the substitution and the dehydration were completely suppressed and only the acetalization proceeded.

Our method is also effective for the preparation of diethyl acetal in a variety of structurally different aldehydes and ketones (Table 2). Even in the case of benzophenone, the desired product was obtained in 97% yield (Entry 9).

In conclusion, we have presented a highly efficient and powerful method for the acetalization of aldehydes and ketones catalyzed by $Ce(OTf)_3$. This reaction took place smoothly using only 1–5 mol % of $Ce(OTf)_3$ and could be applied to a broad range of ketones including acid-sensitive 4-hydroxy-4-methyl-2-pentanone.

Dedicated to Professor Ryoji Noyori on the occasion of his 70th birthday.

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9 Typical procedure (Table 1, Entry 1): Trimethyl orthoformate (351 mg, 3.3 mmol) was added dropwise to a stirred mixture of benzaldehyde (319 mg, 3.0 mmol) and $Ce(OTf)_3$ (Alfa Aesar, 17.7 mg, 0.03 mmol) in MeOH (3 mL) at room temperature. After the mixture was kept stirring at the same temperature for 1 min, it was quenched by adding Et_3N (101 mg, 1.0 mmol). The resulting mixture was poured into sat. $NaHCO_3$ (15 mL) and extracted with ether (30 mL × 2). The combined extracts were washed with sat. NaCl (15 mL). The organic layer was dried (Na_2SO_4) and evaporated. Column chromatography of the residue on silica gel (1% EtOAc–hexane containing 0.1% Et_3N) afforded benzaldehyde dimethyl acetal (453 mg, 99%).

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11 Other lanthanoid trifluoromethanesulfonates are less effective than $Ce(OTf)_3$ in our reaction system. The reaction of benzophenone under identical conditions are as follows: $La(OTf)_3$ (1%), $Sm(OTf)_3$ (0%), $Gd(OTf)_3$ (1%), $Er(OTf)_3$ (2%), and $Yb(OTf)_3$ (4%).

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