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Cerium(III) Chloride, a Novel Reagent for Nonaqueous Selective Conversion of Dioxolanes to Carbonyl Compounds

Enrico Marcantoni* and Francesco Nobili

Dipartimento di Scienze Chimiche, via S. Agostino 1,
I-62032 Camerino (MC), Italy

Giuseppe Bartoli,* Marcella Bosco, and Letizia Sambri

Dipartimento di Chimica Organica "A. Mangini",
v. le Risorgimento 4, I-40136 Bologna, Italy

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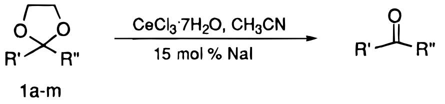
Introduction

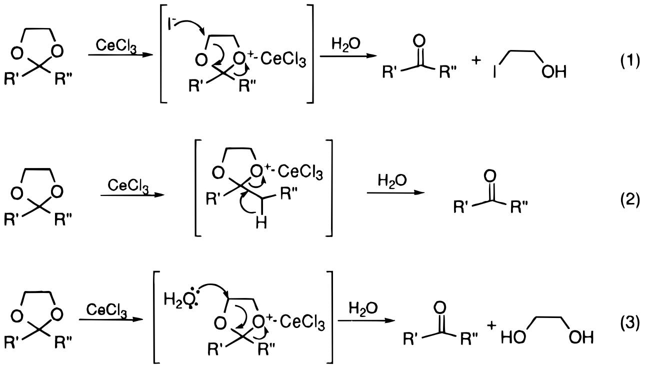
The electrophilicity of the carbonyl group is a dominant feature of its extensive chemistry. A major challenge in a multistep synthesis is to shield a carbonyl from nucleophilic attack until its electrophilic properties can be exploited. For this reason, the protection and deprotection of the carbonyl functional group remain crucial challenges to organic chemists. Experience shows that the critical parameters are generally the stability and the cleavage of the protecting group rather than its introduction. As with most protecting groups, then, many methods are available for the deprotection of acetals and ketals. Generally, this transformation is carried out by acid-catalyzed aqueous hydrolysis.[1] However, very often this method is incompatible with the presence of some other functional group in the molecule like, e.g., a protected hydroxyl group. To overcome the problem, several nonacidic cleaving methods of acetals have been employed, such as wet silica gel[2] or lithium tetrafluoroborate in wet acetonitrile.[3] A few nonaqueous methods utilizing phosphorous triiodide and diphosphorous tetraiodide,[4] iodotrimethylsilane,[5] chlorotrimethylsilane−sodium iodide,[6] chlorotrimethylsilane−samarium trichloride,[7] titanium(IV) chloride,[8] and boron trifluoride−iodide ion[9] have also been reported for deprotection of acetals to carbonyl compounds, although the first four reagents failed to deprotect the dioxolane moiety. Many of these procedures suffer from one or more drawbacks: lack of selectivity, unsatisfactory yields, cost or toxicity of the reagent, or necessity of anhydrous conditions. These limitations prompted us to further investigate a new reagent, which is able to carry out the selective cleavage of acetals and ketals with good yields.

Recently, several synthetically useful organic reactions using trivalent lanthanide salts have been reported,[10] and the use of $CeCl_3$ in methanol is a well-known method for the acetalization of aldehydes.[11] Now we wish to describe here that the deprotection of 1,3-dioxolanes, which remains the most usual protecting group for the ketone functionality, can be effectively realized under mild conditions by cerium(III) chloride hydrate in acetonitrile (Scheme 1).

Scheme 1



Scheme 2



Results and Discussion

The 1,3-dioxolane **1a** is transformed to cyclohexanone at room temperature after 3 days by treatment with 1.5 molar equiv of $CeCl_3 \cdot 7H_2O$. The rate of this reaction is greatly improved by adding a catalytic amount (15 mol %) of sodium iodide, and the parent ketone is then obtained with good yield (entry 1, Table 1). However, the same conditions are inoperant with dioxolane **1c**, where after 48 h at room temperature only 3% deprotection is observed. To obtain high yields of the corresponding ketone (entry 3, Table 1), refluxing of the reaction mixture for only a few hours is sufficient.

The deprotection of dioxolane **1a** is studied in different solvents such as acetonitrile, THF, and dichloromethane. Acetonitrile turned out to be a suitable solvent for the reaction. We have also investigated the possibility that $CeCl_3 \cdot 7H_2O$ could function catalytically or, at least, in less than stoichiometric amounts. But high yields of deprotected carbonyl compounds are found only for $[CeCl_3 \cdot 7H_2O]/[substrate]$ ratios larger than 1.5.

The cleavage of 1,3-dioxolanes in conjugated enone systems is faster than in saturated dioxolanes (entry 2, Table 1). Thus, selective deacetalization is possible using cerium(III) chloride hydrate reagent (entry 9, Table 1). Transformation of acetals to aldehydes is known to be slower than that to ketones; therefore, chemoselective

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(1) For general methods see: (a) Green, T. W. *Protective Group in Organic Synthesis*; Wiley: New York, 1991. (b) Kocienski, P. J. *Protecting Groups*; Thieme: New York, 1994.

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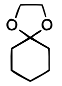
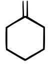
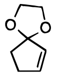
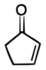
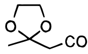
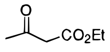
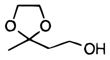
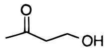
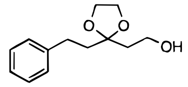
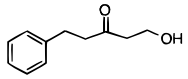
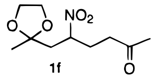
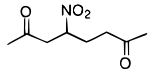
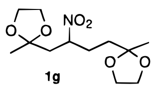
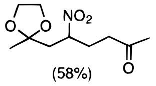
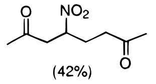
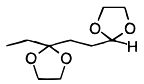
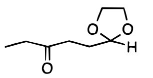
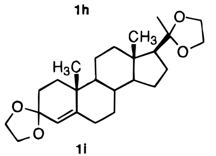
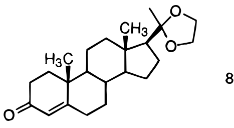
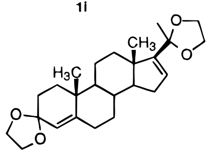
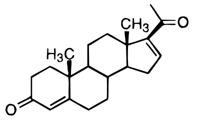
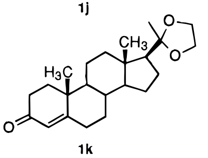
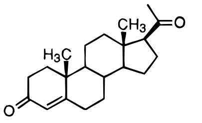
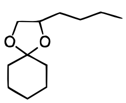
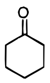
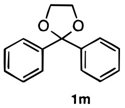
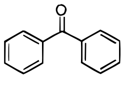
Table 1. Cleavage of 1,3-Dioxolanes by Cerium(III) Chloride Hydrate

Entry	Starting material[a]	Conditions[d]	Product[b]	Yield, %[c]
1	 **1a**	rt, 12 h		85
2	 **1b**	rt, 30 min		90
3	 **1c**	reflux, 1.5 h		96
4	 **1d**	rt, 21 h		91
5	 **1e**	rt, 18 h		92
6	 **1f**	reflux, 3.5 h		87
7	 **1g**	reflux, 3 h	 (58%)  (42%)	84
8	 **1h**	reflux, 3 h		94
9	 **1i**	rt, 2 h		88
10	 **1j**	rt, 2 h		94
11	 **1k**	rt, 15 h		89
12	 **1l**	reflux, 3 h		86
13	 **1m**	reflux, 5 h		91

[a] Dioxolanes were prepared by conventional methods.[12] [b] All products were identified by their IR, NMR, and GC/MS spectra. [c] Yields of products isolated by column chromatography. [d] rt = room temperature.

deprotection of dioxolanes to ketones is achieved by treatment with dioxolanes of ketones and aldehyde (entry 8, Table 1). Other functional groups, such as nitro and ester functions, are stable under our reaction conditions (entries 3, 6, and 7, Table 1). Also, the examples of **1d** and **1e** are representative for the chemoselectivity of the reagent since the deprotection−dehydration process[8] is not observed by conditions that remove completely the ethylene ketal group (entries 4, and 5, Table 1).

The mechanism for these transformations of 1,3-dioxolanes to carbonyl compounds is unclear. Some reaction mechanisms have been proposed[13] for other reactions of dioxolanes initiated by titanium tetrachloride, trimethylsilyl iodide, or boron trifluoride etherate, which would require the formation of 2-iodoethanol as a byproduct (eq 1, Scheme 2). However, these mechanisms are not supported by our experimental data, since it was not possible to detect the presence of a β-iodoalkanol in the reaction mixture. On the other hand, in the case of substrate **1m**, the lack of hydrogens in the α-position to the C-2 atom of the 1,3-dioxolane ring suggests that the deprotection does not proceed exclusively by formation of the enol intermediate (eq 2, Scheme 2). A reasonable explanation may be that the combination[14] of a Lewis acid-like species that polarizes the dioxolane oxygen and the presencs of water effects easily the deprotection (eq 3, Scheme 2). Indeed, in the case of dioxolane **1l** (entry 12, Table 1), we have isolated the 1,2-hexanediol from the reaction mixture. On the other hand, the deprotection did not proceed by treatment of 1,3-dioxolanes with anhydrous cerium(III) chloride in dry acetonitrile at reflux temperature.

It is clear that the simplicity of this approach, the low cost of reagents, the ease of use, and the high yields of the cleavage products display the attractiveness of the reagent system described here. Various aspects of the process of deprotection using cerium(III) chloride are currently under investigation in this laboratory.

Experimental Section

Flash chromatography[15] was performed on Merck silica gel (0.040−0.063 mm).

The procedure used in the case of dioxolane **1e** is given as an example. To a stirred suspension of 1-hydroxy-5-phenylpentan-3-one ethylene acetal (**1e**; 0.11 g, 0.5 mmol) and sodium iodide (11.2 mg, 0.075 mmol) in acetonitrile (5 mL) was added $CeCl_3 \cdot 7H_2O$ (0.28 g, 0.75 mmol), and the resulting mixture was stirred for 15 h at room temperature. The reaction mixture was diluted with ether and treated with 0.5 N HCl (10 mL). The organic layer was separated, and the aqueous layer was extracted with ether (3 × 25 mL). The combined organic layers were washed twice with aqueous saturated sodium bicarbonate solution and saturated brine solution and dried over anhydrous sodium sulfate. The extracts were then concentrated under reduced pressure and the residue chromatographed on a silica gel column (eluent: hexane−ethyl acetate, 7:3) to give 81 mg (92%) of the corresponding hydroxy ketone as an oil.

The conditions for the other reactions were given in Table 1.

During the deprotection of dioxolanes, one can note the formation of a precipitae, which is solubilized in aqueous solution during the hydrolysis.

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