

## Simple and Efficient Chemoselective Mild **Deprotection of Acetals and Ketals Using Cerium(III)** Triflate

Renato Dalpozzo,<sup>†</sup> Antonio De Nino,<sup>†</sup> Loredana Maiuolo,<sup>†</sup> Antonio Procopio,\*,† Antonio Tagarelli,† Giovanni Sindona,<sup>†</sup> and Giuseppe Bartoli<sup>‡</sup>

Dipartimento di Chimica, Università della Calabria, I-87030 Arcavacata di Rende (CS), Italy, and Dipartimento di Chimica Organica "A. Mangini", viale Risorgimento 4, I-40136 Bologna, Italy

procopio@unical.it

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Abstract: A new and chemoselective method for the cleavage of alkyl and cyclic acetals and ketals at room temperature in wet nitromethane by using catalytic cerium(III) trifluoromethane sulfonate is presented. The high yields, the observed selectivity, the very gentle reaction conditions, and the almost neutral pH make this procedure particularly attractive for multistep synthesis.

Chemoselective transformation of polyfunctional molecules is a challenging problem in organic syntheses. The selective protection/deprotection of carbonyl groups occupies a fundamental role in the multistep synthesis. There are tens of protective groups that can be introduced and removed by a variety of methods,<sup>1</sup> but considerable efforts are still directed toward developing efficient, selective, and mild systems for both the introduction and cleavage of many existing protective groups.<sup>2</sup> Acetals and ketals are frequently used to protect carbonyl compounds and hence several reagents have been developed for their deprotection in very smoothly conditions: CAN in neutral or mildly conditions,3 thiourea in EtOH/H2O,4 SmCl3/ TMSCL<sup>5</sup>

In recent years, metal triflate mediated Lewis acid catalysis has attracted enormous interest throughout the scientific community.<sup>6</sup> Bismuth triflate, for example, was reported to be a highly efficient Lewis catalyst for deprotection of acetals and ketals in aqueous tetrahydrofuran.<sup>7</sup> A suspension of Bi(OTf)<sub>3</sub>· $xH_2O$  in water is acidic, and the aqueous layer from the workup was also found to be acidic (pH = 2). Moreover, the method

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 TABLE 1. Deprotection of 2-Phenyl-1,3-dioxolane by
 Using Ce(OTf)<sub>3</sub> in Various Experimental Conditions

	Ph	catalyst solvent Ph	- Konton and Andrewski And				
entry	Ce(OTf) <sub>3</sub> (mol %)	solvent	<i>t</i> (h)	yield (%)			
1	30	THF <sup>a</sup>	15	60			
2	30	CHCl <sub>3</sub> <sup>a</sup>	15	25			
3	30	CH <sub>3</sub> CN <sup>a</sup>	6	80			
4	30	CH <sub>3</sub> NO <sub>2</sub> <sup>a</sup>	6	98			
5	30	CH <sub>3</sub> NO <sub>2</sub> <sup>b</sup>	6	17			
6	15	CH <sub>3</sub> NO <sub>2</sub> <sup>a</sup>	6	73			
<sup>a</sup> Saturated with water. <sup>b</sup> Dry solvent.							

reported needs to reflux the reaction mixture for several hours to deprotect the most resistant acetals and ketals as 1,3-dioxolanes.

Herein, we reported a new mild efficient method for the selective deprotection of acetal and ketal groups in the presence of other protective groups by using cerium(III) trifluoromethane sulfonate hydrate as a Lewis acid catalyst.

The deprotection of cyclic acetals and ketals as 1,3dioxolane was already described by using cerium(III) chloride heptahydrate in acetonitrile,<sup>8</sup> a system previously used for cleavage of different protective groups.<sup>9</sup> The method does not use CeCl<sub>3</sub>·7H<sub>2</sub>O as catalyst, but as reagent in 1.5 molar equiv, and it does not work properly for acetals and ketals different from 1,3-dioxolane. Metal parts of metal triflates are more cationic than those of metal chlorides,<sup>10</sup> and thus, we expected that cerium(III) triflate was more Lewis acidic than cerium(III) chloride.

We tested cerium(III) triflate as Lewis acid for deprotection of acetals and ketals because the reagent is known to fulfill the requirements of  $pK_h$  values ( $K_h$  = hydrolysis constant) of 4.3-10.08 and WERK (water exchange rate constant) greater than  $3.2 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$  for obtaining sufficient activity as Lewis acid catalyst according to Kobayashi et al. [Ce(OTf)<sub>3</sub>:  $pK_h = 8.3$ ; WERK = 2.7 × 10<sup>8</sup>].<sup>10</sup>

Ce(OTf)<sub>3</sub> is not easily commercially available, but it can be prepared in the laboratory in a straightforward manner.<sup>11</sup> Cerium(III) trifluoromethane sulfonate is a noncorrosive white solid, and it can be stored under dry

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<sup>\*</sup> To whom correspondence should be addressed. Tel: +39 984 492077. Fax: +39 984 492055.

Università della Calabria.

<sup>&</sup>lt;sup>‡</sup> Dipartimento di Chimica Organica "A. Mangini".

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TABLE 2.	Cleavage	of Acetals ar	nd Ketals in	Wet CH <sub>3</sub> NO <sub>2</sub>	Using Ce(OTf) <sub>3</sub>
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Entry	Starting material	Ce(OTf), (mol %)	t (h)	Yield (%)	Entry	Starting material	Ce(OTf), (mol %)	t (h)	Yield (%)
1	ОСН3	5	1	>99	16		30	0.5	>99
2	OCH <sub>2</sub> CH <sub>3</sub> OCH <sub>2</sub> CH <sub>3</sub>	5	1	>99		X°J			
	OCH <sub>3</sub>	5	48	70	17 <sup>b</sup>		30	3	>99
3	OCH3	30	7	79ª		OH TO Y			
4	OHC-C-CH2CH3 OCH2CH3	5	3	97	18	Ph O O O O O O O O O O O O O O O O O O O	30	240	< 5
5	CCH <sub>2</sub> CH <sub>3</sub>	5	12	92		но ссн,			
6	CCH3 OCH3	5	4	93	19		30	24	< 5
7	H <sub>3</sub> CO Ph Ph	5	1	>99	20	HO HO HO OCH.	30	24	< 5
8	$( ) \rightarrow )$	30	6	98	21		30	24	< 5
9	сн30-	30	1.5	>99	22	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	30	24	< 5
10	ci–	30	2	98	23 <sup>e,d</sup>	TBDPSOOTBDMS	30	24	< 5
11	0,N	30	168	25	24		5	1	>99
		50	168	25		OTBDMS			
12		30	8	93	25 <sup>4</sup>		5	1	91
13	H <sub>3</sub> CO	30	6	>99	26°	OBn OMe OMe	5	1	96
14		30	6	>99	27 <sup>r</sup>	OPMBn OMe OMe	5	1	90
		30	168	-	208	OAc	5	1	97
15	o <sub>2</sub> n-	50	168	-	20	ОМе	5	1	21

<sup>*a*</sup> After 24 h, the corresponding methyl ester (3.5%) and carboxylic acid were determined by GC–MS analysis. <sup>*b*</sup> After 4 days, the 1,2-*O*-isopropylidene-D-glucopyranoside is still the only one product formed. <sup>*c*</sup> Only a small percentage of TBDMS was cleaved. <sup>*d*</sup> Prepared according to literature methods.<sup>12</sup> <sup>*e*</sup> Prepared according to literature methods.<sup>13</sup> <sup>*f*</sup> Prepared according to literature methods.<sup>15</sup>

conditions for a long time. Any attempt to obtain dry product failed, and in addition, the Ce(OTf)<sub>3</sub> left at 110 °C under vacuum gave a characteristic broad band of water at 3300 cm<sup>-1</sup> on the IR spectrum.

We tested the catalytic activity of  $Ce(OTf)_3$  in the deprotection of acetals and ketals at room temperature. On the basis of our preliminary results, which are shown in Table 1, for 2-phenyl-1,3-dioxolane,  $Ce(OTf)_3$  acts more efficiently in polar solvents such as  $CH_3NO_2$  and  $CH_3$ -CN saturated with water. Less satisfactory results were obtained in aqueous THF, and in CHCl<sub>3</sub> saturated with water only 25% of deprotected product was collected. The water seems to be an essential element in the reaction pathway, and only very low yields of deprotected product were obtained when dry  $CH_3NO_2$  was used as solvent (entry 5, Table 1). The molecular percent of catalyst is also crucial and significantly lower yield of benzaldehyde was produced using only 15 mol % of Ce(OTf)<sub>3</sub> (entry 6, Table 1).

Based on the results reported in Table 1, we adopted a simple experimental procedure that involves stirring the solution of acetal or ketal substrates in  $CH_3NO_2$  saturated with water in the presence of cerium (III) triflate (Table 2).

Except for cyclic acetals and ketals, which require a 30 mol % amount of catalyst, dialkyl acetals and ketals derived from aromatic (entries 4, 6, and 7, Table 2) as well as aliphatic (entries 1, 2, and 5, Table 2) carbonyl compounds underwent smooth deprotection at room temperature using 5 mol % of catalyst only. No substantial differences in reactivity between dimethyl and diethyl ketals were registered.

When the dimethyl acetal of heptanal (entry 3, Table 2) was subjected to the reaction conditions, only 70% of heptanal formed and even after longer reaction time (48 h) and more catalyst addition (30 mol %) only 79% of heptanal was collected together with heptanoic acid and its methyl ester (3.5% and 13.5%, respectively, based on GC/MS analysis).

Cyclic ketals were more resistant to the reagent than the corresponding acetals (entries 8-11 and 12-15, Table 2), whereas the conjugated aliphatic cyclic acetals seems to be easier to remove (entry 16, Table 2).

The cleavage of cyclic acetals and ketals of aromatic carbonyl compounds was shown to be strongly dependent on the presence of electron-withdrawing groups on the aromatic ring. In fact, 2-(4-nitrophenyl)-1,3-dioxolane gave only a low percentage in deprotection also after a very long time and using a higher amount of catalyst (entry 11, Table 2). No cleavage was registered for 2-(4nitrophenyl)-2-methyl-1,3-dioxolane under the same reaction conditions (entry 15, Table 2).

Ce(OTf)<sub>3</sub> was revealed to be a very useful tool for the selective deprotection of isopropylidene ketals. Quantitative yields of 1,2-isopropylidene-D-glucose were obtained when the diacetone-D-glucose reacted with 30 mol % of catalyst for 3 h (entry 17, Table 2); no other products were recovered even after longer reaction time (48 h). Instead, it was impossible to remove the more resistant benzylidene acetal group from (4,6-O-benzylidene) methyl- $\alpha$ -D-glucopyranoside (entry 18, Table 2), and even after 10 days, the starting material was recovered intact from the reaction mixture. Moreover, this method might be used to selectively deprotect acetals in the presence of several protecting groups (THP, Tr, Bn, p-MBn, TBDMS, and TMDPS). Less than 5% of deprotected product was recovered when alcohols protected with these groups were subjected to the above-reported reaction conditions (entries 19-23, Table 2). In fact, we were able to remove chemoselectively the dimethyl acetal group in the presence of Ac, Bn, p-MBn, and TBDMS (entries 25-28, Table 2).

Several considerations can be studied in order to get some mechanism insights. It is possible to rule out that the triflic acid could be the active catalyst; in fact, a solution of  $Ce(OTf)_3$  in water is only weakly acidic (pH = 6.0), and the aqueous layer from the workup was also a weak acid (pH = 6.7). The presence of water is necessary to the reaction to proceed fully, and only low yields of carbonyl compounds were obtained in dry CH<sub>3</sub>-NO<sub>2</sub>.

In conclusion, we have described a new and chemoselective method for the cleavage of acetals and ketals at room temperature in wet nitromethane under mild and nearly neutral reaction conditions. The advantages of this method are the general applicability in cleavage of alkyl and cyclic acetals and ketals, the high yields of deprotected products, the observed selectivity, and a very gentle reaction conditions such as the use of catalytic amount of the reagent at room temperature and almost neutral pH.

## **Experimental Section**

All the chemicals were purchased from commercial sources besides the protected acetals **24–28**, which were synthesized according to trivial literature methods.

**Typical Procedure.** A solution of benzaldehyde dimethyl acetal (152.2 mg, 1.0 mmol) and Ce(OTf)<sub>3</sub>·xH<sub>2</sub>O (29.4 mg, 0.05 mmol) in CH<sub>3</sub>NO<sub>2</sub> saturated with water (2.0 mL) was stirred at room temperature. After 1 h, the CH<sub>3</sub>NO<sub>2</sub> was removed under reduced pressure, and the residue was extracted with diethyl ether. The organic layer was washed with a saturated brine solution and dried over anhydrous sodium sulfate. Benzaldehyde (93%) was determined by GC–MS using the standard addition method.

The solvent was removed on a rotary evaporator to yield 98.6 mg of benzaldehyde isolated by flash chromatography.

For all compounds reported in Table 2, full NMR and IR data were compared with those of pure sample.

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