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# Mild and Efficient Chemoselective Synthesis of Acetals and Geminal Diacetates (Acylals) from Aldehydes using Lanthanum(III) Nitrate Hexahydrate

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# Mild and Efficient Chemoselective Synthesis of Acetals and Geminal Diacetates (Acylals) from Aldehydes using Lanthanum(III) Nitrate Hexahydrate

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**Abstract:** A mild and efficient chemoselective method has been developed for the preparation of acetals and gem-diacetates in good to excellent yields through a reaction of aldehydes with ethlyleneglycol or acetic anhydride using catalytic amounts of lanthanum(III) nitrate hexahydrate as a catalyst under solvent-free conditions.

Keywords: Acetals, aldehydes, gem-diacetates, lanthanum(III) nitrate hexahydrate

### INTRODUCTION

Selective protection and deprotection of carbonyl compounds plays an important role in the multistep organic synthesis of complex natural products. Acetals are among the most popular protecting groups for carbonyl compounds.<sup>[1]</sup> Acetals, as a functional group that is stable under neutral and basic conditions, are not only the most widely used protecting groups but are also efficient chiral auxiliary groups for enantioselective synthesis.<sup>[2]</sup> Numerous procedures have described the formation of acetals under acidic conditions. These include different acid catalysts such as SbCl<sub>3</sub>;<sup>[3]</sup> WCl<sub>6</sub>;<sup>[4]</sup> ZrCl<sub>4</sub>;<sup>[5]</sup> PTSA;<sup>[6]</sup> InCl<sub>3</sub>;<sup>[7]</sup> FeCl<sub>3</sub>;<sup>[8]</sup> I<sub>2</sub>;<sup>[9]</sup> CAN;<sup>[10]</sup> ZnCl<sub>2</sub>;<sup>[11]</sup> anhydrous

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ferroussulphate;<sup>[12]</sup> triflates;<sup>[13]</sup> oxidizing agents such as NBS,<sup>[14]</sup> SeO<sub>2</sub>,<sup>[15]</sup> and DDQ;<sup>[16]</sup> and solid-supported reagents such as silica-bound  $H_2SO_4^{[17]}$  and silica-supported perchloric acid.<sup>[18]</sup> However, several of these reported methods are associated with drawbacks involving low chemo selectivity, incompatibility with other protecting groups, strong acidic conditions, long reaction times, and tedious procedure for the preparation of catalyst, and most of the methods demand dry reaction media. All the Lewis acids require dry media and large amounts of reagent if the substrate contains nitrogen, as Lewis acids are trapped by the nitrogen. Thus there is a need for suitable, mild, and selective alternative for the synthesis of acetals.

Recently, we reported  $La(NO_3)_3 \cdot 6H_2O$  as a mild and efficient catalyst for various organic transformations<sup>[19]</sup> such as chemoselective deprotection of primary acetonides; tetrahydropyranylation of primary alcohols; acetylation of alcohols, phenols, and amines; mild and efficient *Ntert*-butoxycabonylation; and *N*-bezoyloxycarbonylation of amines; synthesis of  $\alpha$ -amino nitriles, 4(3H)-quinazolinones, and benzodiazepines. In the course of study of these reactions, it has been observed that the substrates containing other acid labile functional groups such as tert-butyldimethylsilyl (TBDMS) ethers, some isopropylidene protected diols, and *Ntert*-Boc protected amines were intact in the presence of  $La(NO_3)_3 \cdot 6H_2O$ . In continuation of our work using mild and efficient chemoselective Levis acid catalyst in the multistep synthesis of the natural product, we envisaged the synthesis of acetals and acylals in the presence of a catalytic amount of  $La(NO_3)_3 \cdot 6H_2O$  under solvent-free conditions.

#### **RESULTS AND DISCUSSION**

In this article, we have described an efficient chemoselective method for the synthesis of acetals and acylals (Schemes 1 and 2) using catalytic amounts of commercially available inexpensive lanthanum(III) nitrate hexahydrate under solvent-free conditions. This method does not require expensive reagents or special care to exclude moisture from the reaction medium. Initially, we have reacted benzaldehyde with ethylene glycol in the resence of catalytic amounts (5 mol%) of lanthanum nitrate hexahydrate to yield corresponding acetal in excellent yields (90%) at room temperature under solvent-free conditions. Encouraged by the results obtained for the protection of aldehydes as their corresponding acetals, we turned our attention to another important protection of aldehydes as their geminal acetates (acylals). Acylals



Scheme 1.

**Acetals and Geminal Diacetates** 



Scheme 2.

are also one of the useful protecting groups for carbonyls compounds because of their stability under neutral and basic media as well as aqueous acids.<sup>[20]</sup> Moreover, the diacetates of  $\alpha,\beta$ -unsaturated aldehydes serve as an important precursors for Diels–Alder reactions, and some industrial uses of these compounds also have been reported.<sup>[21,22]</sup> Usually the acylals are prepared from the reaction of aldehydes and acetic anhydride using strong protic acids or Lewis acids, which include H<sub>2</sub>SO<sub>4</sub>, trifficacid, PCl<sub>3</sub>, ZnCl<sub>2</sub>, FeCl<sub>3</sub>, I<sub>2</sub>, Sc(OTf)<sub>3</sub>, Cu(OTf)<sub>2</sub>, Bi(OTf)<sub>3</sub> · xH<sub>2</sub>O, AlPN<sub>12</sub>O<sub>40</sub>, and Zn(BF<sub>4</sub>)<sub>2</sub>. The successes of the two reactions led us to test the veracity of the method on various substrates to give corresponding acetals (Scheme 1, Table 1) and acylals (Scheme 2, Table 2) in excellent yields respectively.

It is also evident from Tables 1 and 2 that a large number of acid-sensitive groups remain intact during the protection as acetals and acylals. Only

Entry	Substrate	Product <sup>a</sup>	Time (h)	Yield (%) <sup>b</sup>
	R CHO			
1	R = H	1a	1.5	90
2	R = Me	1b	1.2	92
3	R = Cl	1c	1.4	86
4	$R = NO_2$	1d	2	84
5	R = Ome	1e	1.5	90
6	R = OTBDMS	1f	1.2	92
	H C C C C C C C C C C C C C C C C C C C			
7	R = Bn	2a	1.5	80
8	R = Bz	2b	1.5	82
		3a	1	95
9	тнро сно сно	4a	1.2	92

*Table 1.* Protection of aldehydes as acetals using lanthanum(III) nitrate hexahydrate as a catalyst under solvent-free conditions

<sup>*a*</sup>All compounds were characterized by <sup>1</sup>H NMR and EIMS spectral data.

<sup>b</sup>Isolated yields after column chromatography.

Table 2. Protection of aldehydes as geminal acetates using lanthanum(III) nitrate hexahydrate as a catalyst under solvent free conditions

Entry	Substrate	Product <sup>a</sup>	Time (h)	Yield $(\%)^b$
1	$RO \qquad \lor \ $ R - TRDMS	19	2	02
2	$R = B_7$	1a 1b	25	86
3	R = BZ R = Bn	10 10	2.5	90
4	R = Me	1d	2.5	92
5	R = Ac	1e	2	90
	H O NOR			
6	R = Bn	2a	3	85
7	R = Bz	2b	3	82
8	R = Ac	2c	3.5	90
9	R = Me	2d	3	92
	R			
10	R = H	3a	2	95
11	R = Me	3b	2.5	92
12	R = Cl	3c	2.5	86
13	$R = NO_2$	3d	3	90
14	R = OMe	3e	3	92
15	R = OTBDMS	3f	2	86
16	R = OTHP	3g	2.5	88
17	R = OCH2CH = CH2	3h	3	90
18	R = O-Propargyl	3i	3	80
19	R = O-Prenyl	3ј	2.5	80
	СНО	4a	2.5	85
20	тнро	5a	2	88
21		6a	2.5	86
22		7a	2	92
	<i>К</i> о,,,сно			
23	Benzophenone	—	24	No product
24	Acetophenone	—	24	No product

<sup>*a*</sup>All compounds were characterized by <sup>1</sup>H NMR and EIMS spectral data. <sup>*b*</sup>Isolated yields after column chromatography.

#### **Acetals and Geminal Diacetates**

aldehydes underwent protection as acetals and acylals under these reaction conditions, whereas ketones were not protected in similar reaction conditions even after 24 h (Table 2, entries 8 and 9).

### CONCLUSION

In conclusion, we have developed a mild and efficient reagent, lanthanum(III) nitrate hexahydrate, for protection of aldehydes as acetals and acylals using ethylene glycol and acetic anhydride under solvent-free condition at room temperature. The reaction conditions do not require dry conditions.

#### **EXPERIMENTAL SECTION**

#### **Typical Experimental Procedure**

Finely powdered La(NO3) $3 \cdot 6$ H2O (5 mol%) was added to a mixture of aldehyde (1 mmol) and acetic anhydride (2.2 mmol) or ethylene glycol (1.1 mmol), and the reaction was stirred under solvent-free conditions at room temperature for an appropriate time (Tables 1 and 2). After completion of the reaction as monitored by thin-layer chromatography (TLC), water (10 mL) was added to the reaction mixture, and the product was extracted into ethyl acetate (3 × 20 mL). The combined organic layer was washed with brine solution, dried over anhydrous sodium sulphate, and concentrated under reduced pressure to give the crude product, which was purified over a silica-gel column to afford corresponding acylals or acetals respectively.

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