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Lanthanum trichloride: An efficient catalyst for the silylation of hydroxyl groups by activating hexamethyldisilazane (HMDS)

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Abstract

A variety of hydroxy functional groups was protected as their corresponding trimethylsilyl ethers using HMDS in the presence of lanthanum trichloride. The catalyst $LaCl_3$ activates the HMDS and accelerates the reaction under mild reaction conditions at room temperature to afford the corresponding silylated products in excellent yields.

Keywords: $LaCl_3$; Hexamethyldisilazane; Protection of hydroxy group; Silylation ethers

1. Introduction

Trimethylsilylation of hydroxy functional groups is a frequently used protection method in several chemical transformations involving the synthesis of natural and unnatural molecules [1]. Generally, the formation of silyl ethers was carried out by the treatment of alcohols with silyl chlorides or silyl triflates under the influence of basic conditions [2]. However, some of these methods frequently suffered from drawbacks such as the lack of reactivity or the difficulty in removal of amine salts derived from the reaction of by-product acids and co-bases during the silylation reaction. In the course of decades, a wide variety of methods using 1,1,1,3,3,3-hexamethyldisilazane (HMDS), a silylating agent have been developed [3]. Because, the hexamethyldisilazane is a stable, commercially available and cheap reagent for trimethylsilylation of hydrogen-labile substrates, giving ammonia as the only by-product. On the other hand, silylation using this silazane type reagent is nearly neutral and does not need special precautions. Even though the handling of this reagent is easy, its main drawback is its poor silylating power, which needs forceful conditions and long reaction times [4]. Therefore, in sequential developments, to circumvent these problems, considerable attention has been focused on activation of hexamethyldisilazane by using a variety of catalysts [5]. Subsequently, Lewis acids are found to catalyze this reaction under mild reaction conditions [6]. Recently, lanthanum chloride emerged as an efficient Lewis acid catalyst for various organic transformations [7]. We are especially interested in exploring the potential use of lanthanum chloride due to its mild and neutral nature.

2. Results and discussion

Herein, we wish to report an efficient procedure for the rapid trimethylsilylation of a wide variety of alcohols using hexamethyldisilazane and a catalytic amount of lanthanum chloride as shown in the Scheme 1. For instance, the treatment of glucose diacetonide with hexamethyldisilazane in the presence of lanthanum chloride (10 mol%) at room temperature to afford the corresponding trimethylsilyl ether (entry t) in 80% yield without affecting the acetonide groups.

The reaction was completed within 4.0 h of reaction time. The obtained product was very clean by ^1H NMR and did not require further purification. In a similar

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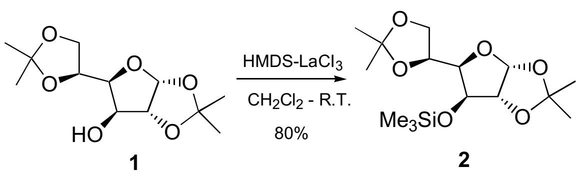
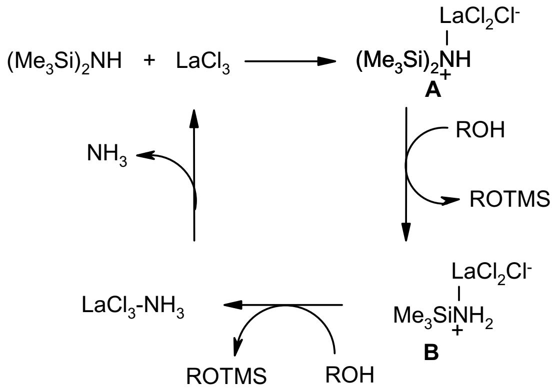


Scheme 1.



Scheme 2.

fashion, a wide range of structurally diverse and functionalized alcohols, such as primary, secondary, benzylic, phenolic, allylic and tertiary alcohols were underwent smooth reaction to give the corresponding silyl ether derivatives in excellent yields. Phenolic and benzylic alcohols were reacted little faster than aliphatic alcohols (entry a, e, f, h, n, o). The acid sensitive Baylis–Hillman alcohol (entry q) was converted to the corresponding TMS–ether derivative without forming any side products. This protocol has been used successfully where the acid sensitive protecting groups like THP–ether and Boc-esters were present (entry j, k, r). In such cases also the reactions were very clean and did not yield any other products like deprotection of the existing groups.

Sterically hindered alcohols (entry g, h, p, t) also reacted very smoothly while giving the products in very good yields. In the case of *N*-Boc amino alcohol (entry k) the reaction is comparatively faster (3.5 h) and gave the corresponding product in very good yield. The substrates like cinnamyl alcohol (entry d) and octanyl (entry s) alcohols also underwent smooth conversion. In general, the reactions were carried out at room temperature and the solvent used was methylenedichloride. All the reactions were completed within 3–5 h of reaction time and the obtained yields were in 79–95%.

The above probable mechanism shows that the lanthanum chloride initially makes a complex with hexamethyldisilazane. The complex **A** will polarize the Si–N bond to produce the reactive silylating agent, which on reaction with one mole of alcohol gives the corresponding silyl ether derivative. In a similar manner, another silyl portion of the hexamethyldisilazane again forms a complex **B** with the catalyst. This complex **B** on reaction with another mole of alcohol gives the corresponding silyl ether derivative. The mechanism clearly shows that one mole of HMDS molecule reacting with two moles of alcohols. Finally, the Cl$_3$La–NH$_3$ complex, which ends up with the evolution of gaseous ammonia and the recycling of LaCl$_3$ (Scheme 2).

The selectivity and versatility of the reaction was further confirmed by application of the general procedure for various examples (Table 2) in which, a mixture of phenyl propanol (1 mmol) and menthol (1 mmol) was treated with hexamethyldisilazane (0.7 mmol) in presence of the catalyst. After stirring the reaction mixture for a period of 5 h, found that 88% of phenyl propanol and 12% of menthol were converted to their respective silyl ether derivatives. In the second experiment, a mixture of benzyl alcohol (1 mmol) and diphenyl methanol (1 mmol) was treated with hexamethyldisilazane (0.7 mmol), in the presence of catalyst, for a period of 3.0 h. The observation shows that benzyl alcohol 85% and the diphenylmethanol 15% converted to their respective silylether derivatives. In the third experiment, the equimolar mixture of menthol and *tert*-amyl alcohol was treated with HMDS (0.7 mmol) and the catalyst for a period of 5.0 h. Only menthol was protected as silylether but *tert*-amyl alcohol was unaffected. The above selectivity study shows that the reactivity order of benzylic > primary alcohol > tertiary alcohol.

In summary, we have demonstrated that lanthanum chloride as mild and efficient catalyst for the activation of hexamethyldisilazane to silylate hydroxy functional groups. This method is applicable to a wide range of alcohols having multi-functionalities. The experimental conditions are very simple and the isolation of products also very easy. The highly catalytic nature of lanthanum chloride and its wide applicability should make this protocol an attractive alternative over existing methods.

3. General procedure for the silylation reaction

To a mixture of menthol (312 mg, 2 mmol) and hexamethyldisilazane (225 mg, 1.4 mmol) in methylenedichloride (10 mL) was added the catalyst lanthanumtrichloride (0.2 mmol). The resulting reaction mixture was stirred at room temperature for a specified period (Table 1). The progress of the reaction was monitored by thin layer chromatography (TLC). After complete conversion of the starting material as confirmed by TLC, the reaction mixture was diluted by adding methylenedichloride (20 mL). The organic layer was washed with water and brine then dried over Na$_2$SO$_4$ and concentrated under reduced pressure to afford the crude product, which was conformed by its spectral data of ^{1}H NMR, IR and mass spectroscopy.

Spectral data for selected compounds. Compound **2g**: ^{1}H NMR (200 MHz, CDCl$_3$): δ 0.50 (s, 9H), 0.65 (s, 3H), 0.93