A Mild and Efficient Chemoselective Protection of Primary Alcohols as Pivaloyl Esters Using $La(NO_3)_3 \cdot 6H_2O$ as a Catalyst under Solvent-free Conditions

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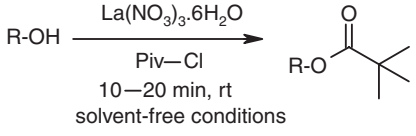
Primary alcohols are selectively and efficiently protected as their pivaloyl esters with pivaloyl chloride in the presence of catalytic amounts of $La(NO_3)_3 \cdot 6H_2O$ at room temperature under solvent-free conditions in excellent yields.

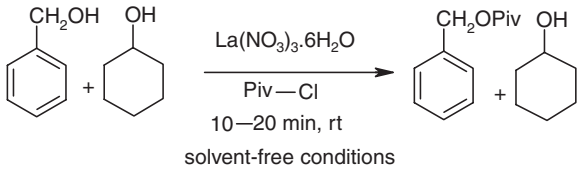
Functional group protection strategies are central to target molecule synthesis. The protection of alcohols is an important and useful transformation in organic synthesis.[1,2] Among the many protecting groups for alcohols, pivaloyl esters are important and common intermediates in natural product synthesis due to their stability and accessibility for easy interconversion. In addition, they also serve as stable protecting groups in the synthesis of nucleoside and carbohydrate chemistry.[3–5] The traditional methods involve reaction of alcohols with pivaloyl chloride in the presence of Lewis base,[6] and using of carboxylic acid and alcohol in the presence of mineral acids,[7–9] which are corrosive in nature and susceptible for acid labile protecting groups. Further, modifications of methods have been made with alcohols and acid chlorides in the presence of Lewis acids such as zinc chloride,[10] magnesium,[11] alumina,[12] and clay.[13] However, the use of either strongly acidic or basic conditions frequently leads to the formation of undesirable side products competing the reactions, hence a mild and chemoselective protection of alcohols is highly desirable.

Recently, we explored $La(NO_3)_3 \cdot 6H_2O$ as a mild and efficient chemoselective catalyst in various organic transformations,[14] such as tetrahydropyranylation of primary alcohols, deprotection of acetonides, synthesis of quinazolinones, acetylation of alcohols and phenols, amines synthesis of α-amino nitriles and benzodiazepines, and *N-tert*-butoxycarbonylation of amines. In the above transformations, it has been observed that the substrates containing other acid labile functional groups such as TBDMS ethers, some isopropylidene-protected diols and *N-t*-Boc-protected amines were intact in the presence of $La(NO_3)_3 \cdot 6H_2O$. Herein, we wish to report the $La(NO_3)_3 \cdot 6H_2O$-catalyzed chemoselective protection of primary alcohols as their pivaloyl esters under solvent-free conditions.

In this report (Scheme 1), we describe an efficient and chemoselective method for protection of primary alcohols. The reaction proceeded efficiently and smoothly at room temperature and the products are obtained in excellent yields. Furthermore, the reaction conditions are very mild, no by-products were observed. We first examined the reaction of 2-phenylethanol (1 mmol) with pivaloyl chloride (1.1 mmol) using $La(NO_3)_3 \cdot 6H_2O$ (5 mol %) at room temperature to form rapidly the corresponding pivaloyl ester in 96% yield (Table 1, Entry 1). This success has encouraged us to extend the generality of the reaction. In order to establish the validity of the catalytic activity of the $La(NO_3)_3 \cdot 6H_2O$, we carried out the reaction of various primary alcohols (Table 1) with pivaloyl chloride to give the corresponding pivaloyl esters in excellent yields. Moreover, the acid labile-protected functional groups such as TBDMS ethers and some acetonide-protected diols were intact under reaction conditions (Table 1, Entries 2, 3, and 21). The substrates contain both primary and secondary hydroxy groups; only primary hydroxy group was protected with pivaloyl chloride to yield the corresponding pivaloyl esters (Table 1 Entries 16 and 22). In a separate experiment a mixture of cyclohexanol and benzyl alcohol (1:1) was taken and reacted with pivaloyl chloride in the presence of $La(NO_3)_3 \cdot 6H_2O$ to form exclusively pivaloyl ester of benzyl alcohol (Scheme 2). This demonstrated the chemo-selectivity catalyst.



Scheme 1.



Scheme 2.

In conclusion, we described a mild and efficient method for protection of primary alcohols as pivaloyl esters under solvent-free conditions using $La(NO_3)_3 \cdot 6H_2O$ as a catalyst.

Typical experimental procedure: to a mixture of alcohol (1 mmol) and pivaloyl chloride (1.1 mmol) was added $La(NO_3)_3 \cdot 6H_2O$ (5 mol %) and the reaction was stirred under solvent-free conditions at room temperature for an appropriate time (Table 1). After completion of the reaction as monitored by TLC, the reaction mass was quenched with saturated $NaHCO_3$ solution (10 mL) and the product was extracted into ethyl acetate (3×20 mL). The combined organic layer was washed with a brine solution, dried over anhydrous sodium sulphate and concentrated under reduced pressure to give the crude product, which was purified over silica-gel column chromatography to afford the corresponding pivaloyl ester.[15]

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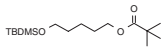
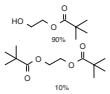
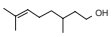
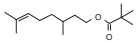
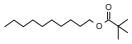
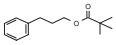
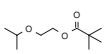
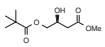
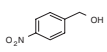
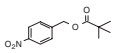
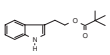
Table 1. Protection of primary alcohols as pivaloyl esters[15]

Entry	Substrate	Product[a]	Time /min	Yield /%[b]
1			10	96
2			20	90
3			20	90
4			20	93
5			20	92
6			30	95
7			20	94
8			30	92
9			20	94
10			20	95
11			20	90
12			20	92
13			20	92
14			30	93
15			20	91
16			20	92
17			10	90
18			20	90
19			20	88
20			20	95
21			20	90
22			20	92
23			15	93
24			20	89
25			20	95
26			20	95

[a]Products were characterized by ^{1}H NMR and EI-MS spectral data. [b]Isolated yields after column chromatography.

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