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A mild and efficient chemoselective tetrahydropyranylation of primary alcohols using $La(NO_3)_3 \cdot 6H_2O$ as a catalyst under solvent-free conditions[☆,☆☆]

T. Srikanth Reddy, K. Ravinder, N. Suryakiran, M. Narasimhulu, K. Chinni Mahesh and Y. Venkateswarlu*

Natural Products Laboratory, Organic Chemistry Division-I, Indian Institute of Chemical Technology, Hyderabad 500 007, India

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Abstract—Primary alcohols undergo selective and efficient tetrahydropyranylation in the presence of a catalytic amount of $La(NO_3)_3 \cdot 6H_2O$ under solvent-free conditions.

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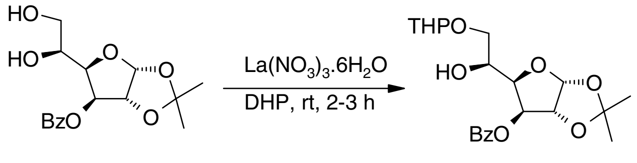
1. Introduction

The tetrahydropyranyl (THP) group is frequently used for the protection of alcohols and phenols due to the ease of preparation of the corresponding THP-ethers and their stability under a wide variety of reaction conditions, such as with hydrides, alkylating reagents, Grignard reagents and organometallic reagents.[1] In addition, it also serves as a stable protecting group in peptide, nucleoside and nucleotide, carbohydrate and steroid chemistry. THP is a general and important protecting group for hydroxy groups in multi-step organic transformations.[2] There are several reagents available for the tetrahydropyranylation of alcohols, which include the use of protic[3] and Lewis acids,[4] Amberlyst,[5] Nafion-H,[6] zeolites,[7] montmorillonite K-10,[8] sulfuric acid on silica gel,[9] $ZnCl_2$,[10] $AlPO_4$ on alumina,[11] tetrabutylammonium bromide,[12] PTSA,[13] PPTS,[14] $BF_3 \cdot Et_2O$,[15] $ZrCl_4$,[16] $In(OTf)_3$,[17] iodine,[18] LiBr[19] and lithium perchlorate-diethyl ether.[20] However, several of the reported methods are associated with drawbacks, which include long reaction times under reflux and incompatibility with other functionalities. Thus, there is a need for a suitable, mild, selective and efficient alternative for the protection of alcohols as THP-ethers. As a part of our ongoing exploration of the acidic catalytic activity of lanthanum(III) nitrate hexahydrate,[21] we envisaged the chemoselective THP-protection of primary alcohols in the presence of secondary alcohols using $La(NO_3)_3 \cdot 6H_2O$ (Scheme 1).

In order to establish the scope of $La(NO_3)_3 \cdot 6H_2O$ in the chemoselective THP-protection of primary alcohols in the presence of secondary alcohols, we reacted 3,4-dihydro-2*H*-pyran with the furan from entry 9 (Table 1) at room temperature using 0.1 equiv of $La(NO_3)_3 \cdot 6H_2O$ to produce the corresponding tetrahydropyranyl ether in 92% yield. Encouraged by the success of this reaction, various alcohols were subjected to the tetrahydropyranylation with excellent yields (Table 1). Substrates containing other acid labile functional groups such as acetonide, TBDMS and isopropylidene protected diols remained intact during the tetrahydropyranylation



Scheme 1.

Keywords: Lanthanum nitrate hexahydrate; Primary alcohols; Tetrahydropyranylation; Solvent-free.

[☆] Reactions using lanthanum(III) nitrate hexahydrate paper 2; for paper 1 refer to Ref. 21.

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[*] Corresponding author. Tel.: +91 40 27193167; fax: +91 40 27160512; e-mail: luchem@iict.res.in

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Table 1. Lanthanum(III) nitrate hexahydrate catalyzed tetrahydropyranylation of primary alcohols

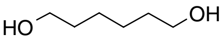
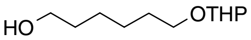
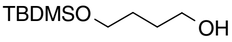
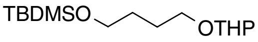
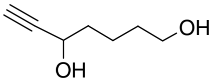
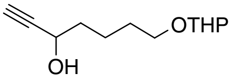
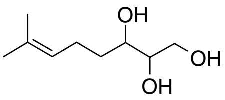
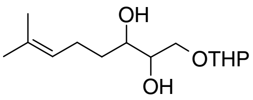
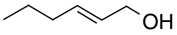
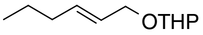
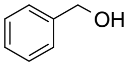
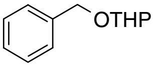
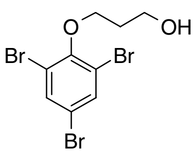
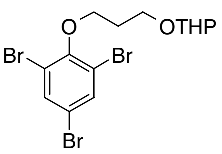
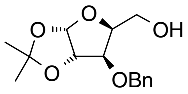
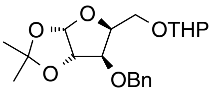
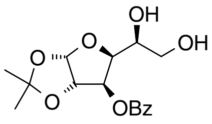
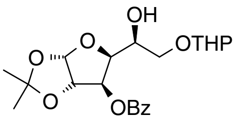
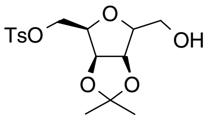
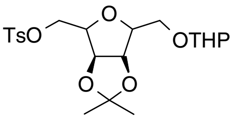
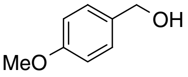
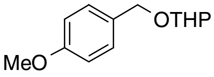
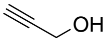
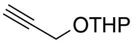
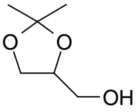
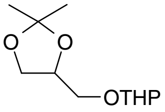
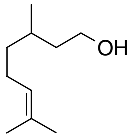
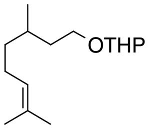
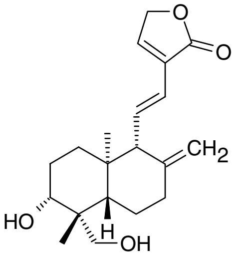
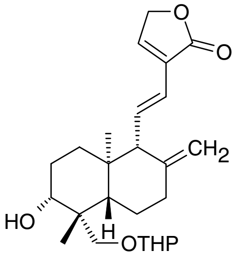
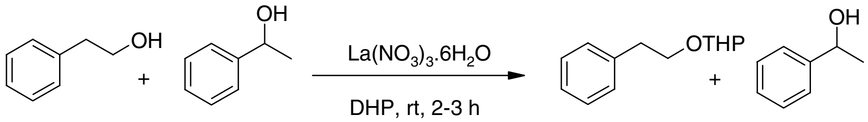
Entry	Substrate	Product	Time (h)	Yield (%)[a]
1			3.0	96
2			2.5	98
3			2.5	92
4			2.5	90
5			3.0	98
6			2.5	93
7			3.0	86
8			3.0	88
9			2.5	92
10			3.0	96
11			2.5	95
12			2.5	92
13			3.0	88

Table 1 (*continued*)

Entry	Substrate	Product	Time (h)	Yield (%)[a]
14			2.5	90
15			3.0	85

[a] Isolated yield after column chromatography. All compounds gave satisfactory analytical data.



Scheme 2.

(Table 1). In order to check the versatility of $La(NO_3)_3 \cdot 6H_2O$, a mixture of 2-phenylethanol and 1-phenylethanol was reacted with dihydropyran in the presence of lanthanum(III) nitrate hexahydrate to give exclusively, THP-protected 2-phenylethanol (Scheme 2). Further, when the diterpene andrographolide (entry 15), which contains a lactone ring and primary and secondary alcohol groups, was reacted with DHP, only the primary alcohol group was THP-protected in 85% yield (Table 1).

In conclusion, we have developed a simple, efficient, mild and highly selective process for tetrahydropyranylation of alcohols using lanthanum nitrate as a catalyst. The mild, environmentally clean reaction conditions and short reaction times with high yields are advantages of the present method.

We believe that the present protocol will find useful application for the protection of alcohols in modern synthetic methodology.

2. Typical experimental procedure

To a solution of benzyl alcohol (108 mg, 1 mmol) and 3,4 dihydro-2*H*-pyran (84 mg, 1 mmol), $La(NO_3)_3 \cdot 6H_2O$ (10 mol %) was added and the reaction was stirred at room temperature. After completion of the reaction as monitored by TLC, water was added and the organics extracted into ethyl acetate. The organic layer was washed with brine and concentrated in vacuum to give a crude mass, which was purified over silica gel to afford the desired THP-ether of benzyl alcohol.

Acknowledgements

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