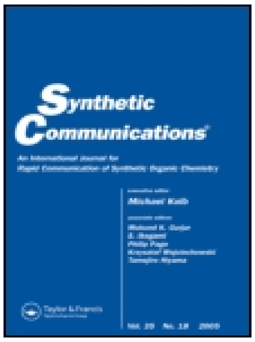

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Synthetic Communications

An International Journal for Rapid Communication of Synthetic Organic Chemistry

ISSN: 0039-7911 (Print) 1532-2432 (Online) Journal homepage: http://www.tandfonline.com/loi/lsyc20

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To cite this article: F. Kazemi , A. R. Kiasat & S. Ebrahimi (2002) $LiBF_4$: A MILD AND EFFICIENT CATALYST FOR THE TETRAHYDROPYRANYLATION OF ALCOHOLS AND THEIR DETETRAHYDROPYRANYLATION, Synthetic Communications, 32:16, 2483-2487, DOI: 10.1081/SCC-120003397

To link to this article: http://dx.doi.org/10.1081/SCC-120003397

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SYNTHETIC COMMUNICATIONS
Vol. 32, No. 16, pp. 2483–2487, 2002

$LiBF_4$: A MILD AND EFFICIENT CATALYST FOR THE TETRAHYDROPYRANYLATION OF ALCOHOLS AND THEIR DETETRAHYDROPYRANYLATION

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ABSTRACT

Catalytic amount of lithium tetrafluoroborate in dry acetonitrile catalyzes an efficient tetrahydropyranylation of different types of alcohols to afford the corresponding tetrahydropyranyl ethers in high yields. Deprotection of tetrahydropyranyl ethers can also be achieved efficiently in the presence of lithium tetrafluoroborate in methanol. The chemoselectivity was observed in the protection of alcoholic function in the presence of phenolic function.

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DOI: 10.1081/SCC-120003397
0039-7911 (Print); 1532-2432 (Online)

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Tetrahydropyranylation of hydroxyl groups has been recognized as the useful and representative method for the protection of a great number of alcohols and phenols.[1] Due to its low cost, its general stability in a variety of reactions under neutral and basic conditions, and the ease with which it can be removed under mild H^+ conditions, THP ether is often the protective group of choice in the synthesis of peptides, nucleotides, carbohydrates, and steroids.[2] Numerous methods have been reported for the tetrahydropyranylation of alcohol functionality.[3–5] However, some of them have limitations such as, expensive reagents, use in strongly acidic media, tedious and time consuming work up procedures, high temperatures, and long reaction times.

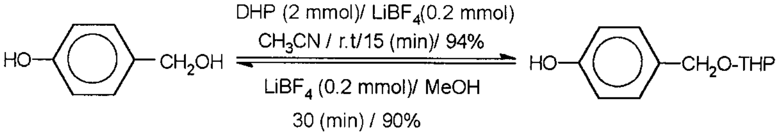
Similar to protection, deprotection of the tetrahydropyranyl ethers constitutes important processes in the synthetic chemistry of polyfunctional molecules including the total synthesis of natural products. Although, many catalysts[4–6] have been proposed for this carbon–oxygen bond cleavage, but there are few examples which make use of non-aqueous neutral reaction conditions.[7] Therefore, it is still of considerable interest to develop new efficient catalysts which can be easily prepared, handled, and used under neutral conditions for the protection as well as deprotection.

The successful applications of $LiBF_4$, as a slow BF_3 releasing source, in organic synthesis,[8–11] prompted us to explore the potential of this lithium salt as catalyst for tetrahydropyranylation of hydroxyl groups and the cleavage of tetrahydropyranyl ethers to the parent alcohols.

The catalyst, $LiBF_4$, can be easily prepared from tetrafluoroboric acid and LiOH and in comparison with $BF_3{\cdot}OEt_2$ is solid and stable. We examined the catalytic ability of $LiBF_4$ for tetrahydropyranylation of alcohols with 3,4-dihydro-2H-pyran, DHP, in CH_3CN at room temperature. This catalyst acted very efficiently and it was observed that only 0.2 molar equivalent of the catalyst is enough to protect alcoholic functions in high to excellent yields within 10–150 min. It is worthy to mention that lower quantities of $LiBF_4$ (i.e. 0.1 mol%) also gave satisfactory results at longer reaction time.

The effects of other solvents such as CCl_4, $CHCl_3$, petroleum ether, acetone, CH_2Cl_2, and *n*-hexane were also studied, but in comparison with CH_3CN the reactions times were longer and the yields were found to be considerably lower.

The procedure turned out to be general for range of structurally diverse alcohols. Primary, secondary, tertiary, allylic and benzylic alcohols as well as phenol were easily and efficiently protected and afforded the corresponding THP ethers as the exclusive products in high to excellent yield. They were of high purity as determined by TLC and ^1H NMR spectroscopy. Table 1 includes representative examples.



Scheme 1.

Tetrahydropyranylation of tertiary alcohols[12] are difficult and only a few reports are available in the literature for this transformation. Contrary to the previous reports, as shown in Table 1, our procedure provides excellent yield of tetrahydropyranyl ether of these classes of compounds.

The removal of the protective tetrahydropyranyl group can be carried out in methanol under similar mild reaction conditions and with the same ease the protection process. The results collected in Table 1, indicate that the efficiency of the LiBF$_4$ catalyzed deprotection is also high satisfactory.

The chemoselectivity in the protection of alcoholic function in the presence of phenolic function was definitely confirmed by the reaction of *p*-hydroxy benzyl alcohol with DHP (Scheme 1).

In conclusion, this catalytic method provides a convenient procedure for mild and efficient protection of different classes of alcohols and also for deprotection of THP ethers with excellent yields and could serve as a useful addition to available methods.

EXPERIMENTAL

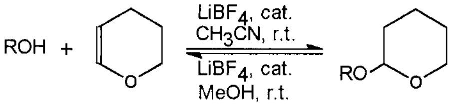
General

Products were isolated and their physical properties, i.e., n.m.r and mass spectral data were compared with those of known samples which are prepared according to literature procedures.

General Procedure for the Protection of Alcohols

LiBF$_4$ (2 mmol) was added to a solution of alcohol (10 mmol) and DHP (20 mmol) in dry acetonitrile (15 mL). The mixture was stirred at room temperature for the specified period of time (Table 1). The progress of reaction was monitored by TLC or GC. After the disappearance of starting material, solvent was evaporated, NaHCO$_3$ 10%(80 mL) was added and extracted with diethyl ether (3×50 mL). The organic layer was

Table 1. Protection and Deprotection of Alcohols Catalyzed with $LiBF_4$ at Room Temperature



	Protection with DHP		Deprotection	
Alcohol	Time (min)	Yield (%)	Time (min)	Yield (%)
Cyclohexanol	45	82	20	85
Cyclooctanol	150	88[a,b]	90	85
1-octanol	60	92	45	93
2-octanol	60	90	45	91
1-phenylethanol	45	92	60	88
2-phenylethanol	20	96	20	94
3-phenylpropanol	20	96	25	95
benzyl alcohol	25	98	25	97
p-chlorobenzyl alcohol	10	95	25	96
p-nitrobenzyl alcohol	10	95	330	79
Menthol	90	92[b]	75	84
Cinnamyl alcohol	50	96[c]	25	96
Allyl alcohol	30	93	60	77
t-butanol	60	95	25	98[d]
Phenol	180	91	60	80

[a] molar ratio of DHP to alcohol was 4 : 1.
[b] 0.4 molar equivalent $LiBF_4$ was used.
[c] reflux conditions were used.
[d] GC yield.

washed with water, brine and dried over $CaCl_2$ successively. Evaporation of solvent, followed by chromatography (ethyl acetate/petroleum ether) furnished the desired THP ether in 82–96% yields.

General Procedure for the Deprotection of Alcohols

THP ether (10 mmol) was stirred at room temperature in methanol (15 mL) in the presence of 2 mmol of $LiBF_4$. After completion of the reaction, methanol was evaporated in vacuum and the crude product was taken in ether. The organic layer was washed with water, brine, and dried (anhydrous $CaCl_2$). Solvent removal and purification over silica gel gave pure alcohol in 77–97% yields.

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Received in Japan May 23, 2001

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