Pergamon

Tetrahedron Letters 43 (2002) 5353–5355

TETRAHEDRON
LETTERS

Lithium triflate (LiOTf) catalyzed efficient and chemoselective tetrahydropyranylation of alcohols and phenols under mild and neutral reaction conditions

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Received 23 February 2002; revised 1 May 2002; accepted 10 May 2002

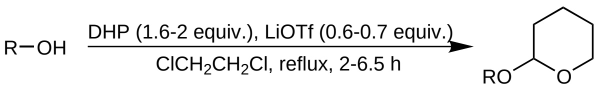
Abstract—Different types of alcohols and phenols were effectively converted to the corresponding THP ethers in the presence of DHP and a catalytic amount of lithium trifluoromethanesulfonate (LiOTf) in refluxing 1,2-dichloroethane under essentially neutral reaction conditions. The method also shows good chemoselectivity for mono-tetrahydropyranylation of symmetrical diols.

Protection of hydroxy groups by their conversion to the corresponding tetrahydropyranyl ethers (THP ethers) is a common and widely used transformation in organic synthesis.[1] This wide use is undoubtedly due to the stability of THP group against a wide range of strong nucleophilic and basic reagents.[2] THP groups are also the protective groups of choice in peptide, nucleotide, carbohydrate, and steroid chemistry.[3] A variety of protonic as well as Lewis acid catalysts have been developed for tetrahydropyranylation of hydroxy functions such as acidic Clay,[3] PTSA,[4] bis[trimethylsilyl]sulfate,[5] trimethyliodosilane,[6] $CuCl_2$,[7] DDQ,[8] $BF_3{\cdot}OEt_2$,[9] triphenylphosphine hydrobromide,[10] $Ru(CH_3)_3$-(triphos)]$(OTf)_2$,[11] I_2,[12] and silica chloride,[13] some supported reagents such as $BF_3{\cdot}OEt_2$ and $Al_2(SO_4)_3$ on silica gel[14] and ionic liquids.[15] However, many of these methods have drawbacks such as harsh and acidic conditions. In our development of new methods for functional group transformations we are especially interested in developing the potential uses of various types of neutral catalysts.[16] Along this line, very recently we have found that LiOTf is a good catalyst for highly chemoselective dithioacetalization of carbonyl compounds[16g] and transdithioacetalization of acetals and 1,1-diacetate[16k] under neutral reaction conditions. LiOTf has also been shown to be a catalyst for the chemoselective aminolysis of oxiranes[17] and glycosylation of nucleophiles[18] under neutral conditions. Herein, we disclose a new mild and efficient protocol for tetrahydropyranylation of a variety of alcohols and phenols using dihydro-4*H*-pyran in the presence of a catalytic amount of lithium triflate (LiOTf) under neutral reaction conditions (Scheme 1).[19]

In a typical procedure,[20] when the alcohols or phenols were treated with DHP (1.2–1.7 equiv.) in the presence of LiOTf (0.6–0.7 equiv.) in refluxing 1,2-dichloroethane, the corresponding THP-ethers were obtained in good to excellent yields (Table 1).

The present protocol is quite general as a wide range of structurally varied alcohols such as primary, secondary, tertiary, benzylic, and allylic underwent tetrahydropyranylation in good to excellent yields. The method was also found to be highly selective for mono-tetrahydropyranylation of symmetrical diols (Table 2).

In conclusion, the present procedure of tetrahydropyranylation demonstrates the potential of LiOTf as a neutral catalyst in organic synthesis. Mild and neutral reaction conditions, simplicity of the procedure, general applicability for primary through tertiary alcohols, and selective mono-tetrahydropyranylation of diols offer significant improvements over many existing procedures.



Scheme 1.

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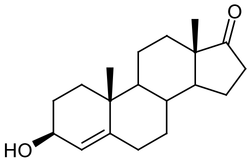
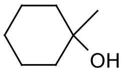
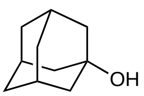
PII: S0040-4039(02)00892-4

Table 1. Tetrahydropyranylation of alcohols and phenols using DHP in the presence of LiOTf in refluxing 1,2-dichloroethane

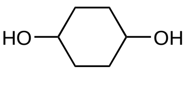
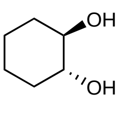
Entry	Alcohol	Subst/DHP/ LiOTf	Time (h)	Yield[a] (%)
1	$PhCH_2OH$	1:1.6:0.6	2.5	96
2	$4\text{-}BrC_6H_4CH_2OH$	1:1.6:0.7	2.5	90
3	$4\text{-}NO_2C_6H_4CH_2OH$	1:1.6:0.6	3	92
4	4-i-$PrC_6H_4CH_2OH$	1:2:0.6	2	91
5	$4\text{-}ClC_6H_4CH_2OH$	1:1.6:0.6	2.25	95
6	$Ph(CH_2)_2OH$	1:1.7:0.6	2.5	94
7	$Ph(CH_2)_3OH$	1:1.7:0.7	2.5	96
8	Ph_2CHOH	1:2:0.7	4	95
9		1:3:0.7	4	86[b]
10		1:1.7:0.7	4	84
11		1:2:0.7	6	89[c]
12		1:1.6:0.6	5	89
13	$4\text{-}BrC_6H_4OH$	1:1.6:0.6	5	96
14	$4\text{-}FC_6H_4OH$	1:1.7:0.6	6	93
15	$4\text{-}MeC_6H_4OH$	1:1.7:0.6	5.5	94
16	$4\text{-}OHC_6H_4CHO$	1:1.7:0.6	6.5	91
17	1-Naphthol	1:1.7:0.6	6	91
18	2-Naphthol	1:1.6:0.6	6	92

[a] Isolated yield.

[b] Yield refers to isolated pure bis-THP ether.

[c] No elimination products were observed.

Table 2. Chemoselective mono-tetrahydropyranylation of symmetrical diols in the presence of LiOTf

Entry	Alcohol	Subst/DHP/ LiOTf	Time (h)	Yield[a,b] (%)
1		1:1:0.6	5.5	83 (93)
2		1:1:0.6	5.5	87 (95)

[a] Conversion based on NMR and GC.

[b] The numbers in parentheses refer to selective formation of mono-THP ethers evaluated from NMR spectra.

Acknowledgements

The authors acknowledge the Institute for Advanced Studies in Basic Sciences Research Council for support of this work.

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19. Lithium trifluoromethanesulfonate was purchased from Aldrich. A 0.1 M solution of the salt in deionized water showed a pH of 6.6–6.8.
20. *A typical procedure is as follows:* To a stirred mixture of the alcohol (10 mmol) and 3,4-dihydro-2*H*-pyran (16–20 mmol) in dichloroethane (50 mL), anhydrous LiOTf (6–7 mmol) was added. The mixture was heated at reflux while stirring was continued, and the progress of the reaction

was followed by TLC. After completion of the reaction, $CHCl_3$ (100 mL) was added and the mixture was washed successively with 10% NaOH solution (2×25 mL), brine (15 mL), and water (15 mL). The organic layer was separated and dried over anhydrous Na_2SO_4. Evaporation of the solvent under reduced pressure gave almost pure product. Further purification was achieved by vacuum distillation (Table 1). All of the products are known and gave satisfactory physical data compared with those of authentic samples.