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Tetrahedron Letters 45 (2004) 7891–7894

Tetrahedron
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Cupric sulfate pentahydrate ($CuSO_4 \cdot 5H_2O$): a mild and efficient catalyst for tetrahydropyranylation/depyranylation of alcohols and phenols

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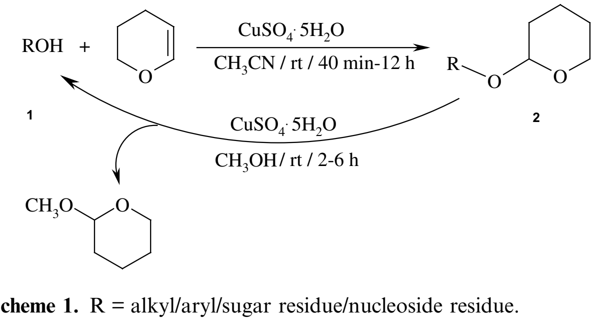
Received 22 July 2004; revised 15 August 2004; accepted 24 August 2004
Available online 11 September 2004

This paper is dedicated to Professor H. Ila on the occasion of her 60th birthday

Abstract—Various alcohols and phenols can be smoothly converted to the corresponding THP ethers using 20 mol% $CuSO_4 \cdot 5H_2O$ under mild reaction conditions at room temperature. Some of the major advantages of this procedure are nonaqueous work-up, very good yields, less expensive catalyst and compatibility with other protecting groups.

The tetrahydropyranyl (THP) group is frequently used for the protection of alcohols and phenols due to their ease of preparation and stability under a wide variety of reaction conditions such as with hydrides, alkylating reagents, Grignard reagents and organometallic reagents.[1] In addition, they also serve as stable protecting group in peptide, nucleoside and nucleotide, carbohydrate and steroid chemistry. Tetrahydropyranylation of alcohols can be accomplished by using *p*-TSA,[2] $BF_3 \cdot OEt_2$[3] and PPTS.[4] Some of the recently used reagents that can catalyze both tetrahydropyranylation and depyranylation are $ZrCl_4$,[5] I_2,[6] LiBr,[7] acetonyltriphenylphosphonium bromide (ATPB),[8] TBATB,[9] aluminium chloride hexahydrate,[10] $In(OTf)_3$,[11] dialkylimidazolium tetrachloroaluminates,[12] $InCl_3$ immobilized in ionic liquids[13] and bromodimethylsulfonium bromide.[14] On the other hand, many methods have also been developed by using heterogeneous catalysts, and these have been reviewed recently.[15] However, some of these procedures have some difficulties such as requirement of much longer reaction times, incompatibility with other acid-sensitive functional groups,[3,9,10,13] involvement of expensive and moisture sensitive catalysts and some of them have to be prepared prior to use.[4,8,9,14] There is a need for a greener catalytically efficient method, which might work under mild and economically cheaper conditions. As a part of our ongoing research program to develop new synthetic methodologies involving various new reagents,[16,17] we perceived that cupric sulfate pentahydrate, which is readily available, might be a useful catalyst for tetrahydropyranylation because of its mild Lewis acidity. In this paper we disclose that cupric sulfate pentahydrate can be used as an efficient catalyst for tetrahydropyranylation/depyranylation of alcohols and phenols as shown in Scheme 1.

When a mixture of 1-hexadecanol **1a** and 3,4-dihydro-2*H*-pyran was treated with 20 mol% of cupric sulfate pentahydrate in acetonitrile as solvent, it was smoothly converted to the corresponding THP ether **2a** within



Scheme 1. R = alkyl/aryl/sugar residue/nucleoside residue.

Keyword: Protection of hydroxyl compounds.

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doi:10.1016/j.tetlet.2004.08.141

40 min in 90% yield. Similarly, 4-methoxybenzyl alcohol **1b** was converted to the corresponding THP ether **2b** within 40 min under identical reaction conditions. Although dichloromethane can also be used, we employed acetonitrile as solvent because dichloromethane is a halogenated solvent and harmful. The tetrahydropyranylation could be achieved on a large scale between 10 and 100 mmol without any difficulty. Following the typical reaction procedure,[18] various benzylic, allylic and secondary alcohols **1c–i** as well as phenols **1j–k** were smoothly transformed to the corresponding THP ethers **2c–k**, respectively, in very good yields. Remarkably, various diols were transformed to mono THP ethers **2l–n** along with 5–8% di-THP ether by using 20 mol% catalyst instead of 40 mol% catalyst. The diols could be converted to the di-THP ethers **2o–p** in good yields in a similar manner. In various substrates containing other functional groups such as acetyl, TBDMS and TBDPS ethers, isopropylidene protected diols and benzyl ethers were smoothly converted to the desired THP ethers **2q–w** in good yields as shown in Table 1. All the products were fully

Table 1. Tetrahydropyranylation of alcohols and phenols in presence of a catalytic amount of $CuSO_4 \cdot 5H_2O$

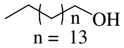
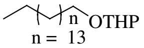
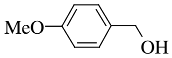
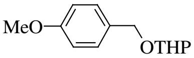
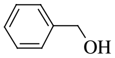
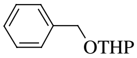
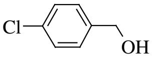
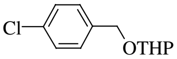
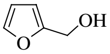
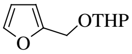
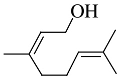
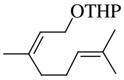
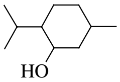
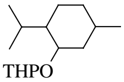
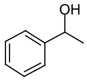
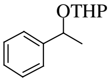
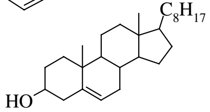
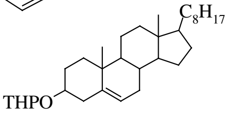
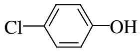
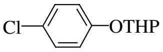
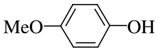
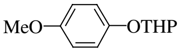
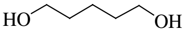
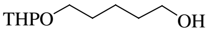
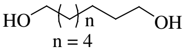
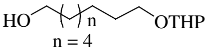
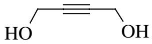
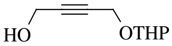
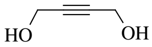
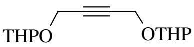
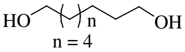
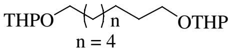
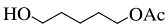
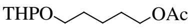
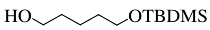
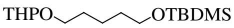
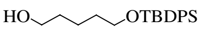
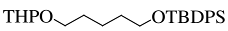
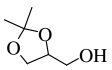
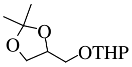
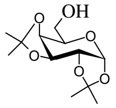
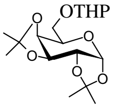
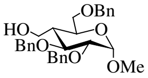
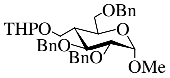
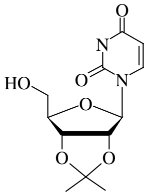
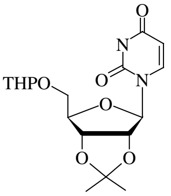
Entry	Substrate **1**	Time (min)	Product **2**[a]	Yield[b] (%)
a		40		90
b		40		89
c		40		91
d		45		92
e		40		90
f		55		87
g		60		89
h		55		91
i		80		85
j		95		87
k		90		89
l		45		70
m		12 h		83[c]
n		60		55
o		90		92
p		12 h		93
q		40		84
r		40		82
s		40		82

Table 1 (*continued*)

Entry	Substrate **1**	Time (min)	Product **2**[a]	Yield[b] (%)
t		50		85
u		85		83
v		90		81
w		45		90

[a] All products were characterized by IR, ^{1}H NMR and elemental analysis.

[b] Isolated yields.

[c] Yield based on starting material recovery.

Table 2. Tetrahydropyranylation of 4-methoxybenzyl alcohol **1b** using various forms of cupric sulfate[a]

Run	Catalyst	Conversion (%)	Time (min/[h])
1	$CuSO_4{\cdot}5H_2O$	100	45
2	$CuSO_4$	80	[3]
3	$CuSO_4{\cdot}SiO_2$	90	[2.5]
4	SiO_2	0	[3]

[a] Reactions were monitored by GC.

characterized by IR, ^{1}H NMR spectroscopy and by elemental analyses. The most interesting feature is that the THP ether **2a** undergoes cleavage within 5h using same catalyst (20mol%) in methanol in 85% yield.[19] Other THP ethers **2b**, **2c**, **2f** and **2k** were converted to the respective hydroxyl compounds **1b**, **1c**, **1f** and **1k** within 2–6h in 80–85% yields under identical reaction conditions.

The tetrahydropyranylation of 4-methoxybenzyl alcohol **1b** was investigated with the various forms of cupric sulfate to find out the relative efficiencies (Table 2). Cupric sulfate pentahydrate showed the highest catalytic activity in terms of reaction time and yield.

In summary, the present methodology demonstrates $CuSO_4{\cdot}5H_2O$ as an effective catalyst for tetrahydropyranylation/depyranylation of alcohols and phenols. The main advantages of our protocol are: mild, clean, environmentally benign reaction conditions as well as good yields. In addition, our methodology might be useful for the substrates containing acid-sensitive protecting groups because of the almost neutral reaction conditions. Furthermore, this method is also expected to have better applicability in organic synthesis due to the low cost of the reagent. We believe this protocol will be a useful addition to the modern synthetic methodologies.

Acknowledgements

A.T.K. thanks the DST, New Delhi for a financial grant (Grant No SP/S1/G-35/98), L.H.C. and S.G. are grateful to IITG for their research fellowships. The authors are also grateful to the referee for his valuable comments and suggestions.

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18. Typical procedure of protection: Into a mixture of 3,4-dihydro-2*H*-pyran (1.1 mmol) and alcohol or phenol (1 mmol) in acetonitrile (2 mL) was added cupric sulfate pentahydrate (0.05 g, 0.2 mmol) at room temperature and the mixture stirred until completion of the reaction was ascertained by the disappearance of the alcohol spot on TLC. The product was isolated in almost pure form from the reaction mixture by simply filtering through a Whatman 42 filter paper without aqueous work-up. The pure product was obtained from the reaction mixture by passing it through a short column of basic alumina. Compound **2a**: IR (Neat): 2919, 2854, 1469, 1354, 1228, 1122, 1071, 1037; ^{1}H NMR ($CDCl_3$): 0.85 (t, 3H, $J = 6.6$ Hz), 1.22–1.32 (m, 26H), 1.47–1.81 (m, 8H), 3.32–3.38 (m, 1H), 3.44–3.49 (m, 1H), 3.65–3.73 (m, 1H), 3.81–3.87 (m, 1H), 4.54 (m, 1H). Elemental analysis: calcd for, $C_{21}H_{42}O_2$ (326.56); C 77.24, H 12.96, found C 77.08, H 12.87.
19. Typical procedure of deprotection: To a solution of THP ether **2a** (0.325 g, 1 mmol) in methanol (5 mL) was added cupric sulfate pentahydrate (0.05 g, 0.2 mmol) and the mixture stirred at room temp. The reaction was completed within 5 h and the solid cupric sulfate was filtered off. The solid residue was washed with dry methanol (2×5 mL). After concentration of the combined filtrate, the crude residue was purified through a short silica gel column. The desired cetyl alcohol **1a** was obtained 0.206 g in 85% yield.