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Tetrahedron Letters 45 (2004) 9617–9621

Tetrahedron Letters

A catalytic amount of nickel(II) chloride hexahydrate and 1,2-ethanedithiol is a good combination for the cleavage of tetrahydropyranyl (THP) and *tert*-butyldimethylsilyl (TBS) ethers

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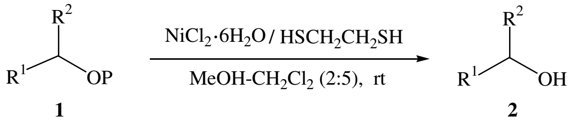
Received 27 August 2004; revised 26 October 2004; accepted 2 November 2004

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

Abstract—Various THP and TBS ethers can be unmasked easily to the corresponding hydroxyl compounds in good yields by using a combination of a catalytic amount of nickel(II) chloride hexahydrate and 1,2-ethanedithiol at room temperature. In addition, alkyl TBS ethers can be hydrolyzed chemoselectively in the presence of aryl TBS ethers. Moreover, alkyl TBS ethers can be cleaved easily in the presence of alkyl or aryl THP ethers using the same conditions.

Tetrahydropyranyl (THP)[1a] and *tert*-butyldimethylsilyl (TBS) groups[1b] are frequently employed as protecting groups for hydroxyl functionalities in multi-step synthesis due to their ease of preparation and stability under a wide variety of reaction conditions as well as their subsequent ease of removal. Recently new synthetic methods have been developed for both tetrahydropyranylation and depyranylation employing the following reagents: tetrabutylammonium tribromide,[2] aluminium chloride hexahydrate,[3] In(OTf)$_3$,[4] dialkylimidazolium tetrachloroaluminates,[5] InCl$_3$ immobilized in ionic liquids[6] and bromodimethylsulfonium bromide.[7] Similarly, a large number of methods have been developed for the cleavage of TBS ethers using various chloride, bromide and fluoride based reagents as well as other reagents, which have been reviewed recently.[8] However, some of the reported methods have drawbacks such as the requirement for long reaction times and harsh reaction conditions, and some of the reagents have to be prepared prior to use and involve expensive reagents. Although numerous synthetic methods have been developed for deprotection of THP ethers[9] and TBS ethers in recent years,[10] there is still a need for a catalytically efficient method, which needs only mild reaction conditions. Recently, we have shown[11] that anhydrous nickel(II) chloride is an efficient catalyst for thioacetalization of aldehydes. During this investigation, we noticed that THP ethers did not survive. At the same time, we learnt from the literature that nickel(II) chloride hexahydrate reacts with 1,2-ethanedithiol to provide a polymeric nickel complex.[12] From these results, we wondered whether a combination of a catalytic amount of nickel(II) chloride hexahydrate and 1,2-ethanedithiol, which might generate hydrochloric acid on complexation with the nickel, can be used for cleavage of THP and TBS ethers. In this paper, we disclose our results on the deprotection of tetrahydropyranyl and *tert*-butyldimethylsilyl ethers using a catalytic amount of nickel(II) chloride hexahydrate and 1,2-ethanedithiol (see Scheme 1).



R^1 = alkyl /aryl / sugar residue / nucleoside residue;
R^2 = H, alkyl; P = THP /TBS

Scheme 1.

Keywords: Deprotection of TBS and THP ethers.

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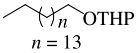
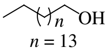
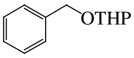
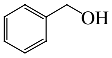
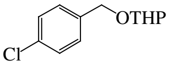
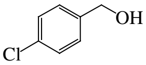
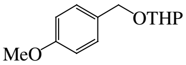
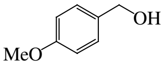
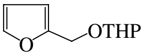
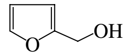
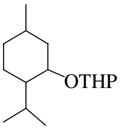
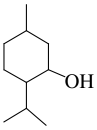
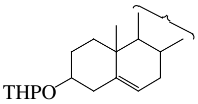
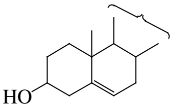
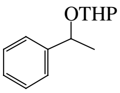
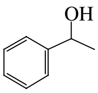
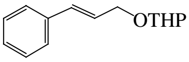
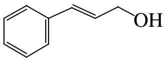
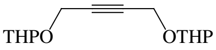
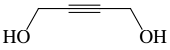
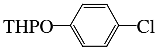
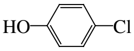
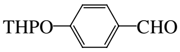
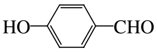
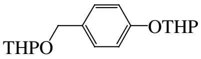
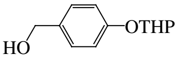
0040-4039/$ - see front matter © 2004 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2004.11.011

We prepared a wide variety of structurally different tetrahydropyranyl (THP)[7] and *tert*-butyldimethylsilyl (TBS)[13] ethers by following standard literature procedures. We attempted to optimize the conditions for cleavage of the THP and TBS ethers to obtain the parent hydroxyl compounds. It was observed that a mixture of substrate/nickel(II) chloride hexahydrate/1,2-ethanedithiol (1:0.2:0.2) in methanol–dichloromethane (2:5, 5 mL/mmol of the substrate) provided the best results,[14] for example, the THP ether of cetyl alcohol (run 1) was cleaved to give cetyl alcohol in a 90% yield within 40 min. The product cetyl alcohol was characterized by comparison of its IR and ^{1}H NMR spectra with those of an authentic sample. Similarly, several THP ethers of primary and secondary alcohols (runs 2–8) were converted into the parent hydroxyl compounds in good yields. THP ethers containing a double or triple bond (runs 9 and 10) were also hydrolyzed to the parent hydroxyl compounds. Moreover, aryl THP ethers (runs 11 and 12) could also be cleaved without thioacetalization of the aldehyde group. It is worth mentioning that no chlorination of the double or triple bond took place. These results are summarized in Table 1. The products were characterized by recording IR, ^{1}H NMR spectra and elemental analyses. We observed that the THP ether of 4-tetrahydropyranyloxybenzyl alcohol (run 13, Table 1) was converted chemoselectively into the 4-tetrahydropyranyloxybenzyl alcohol (65%) along with 20% of the aryl deprotected THP ether.

We considered whether the same reagent would be useful for deprotection of TBS ethers. When the TBS ether of 1-octadecanol (run 1, Table 2) was treated with 0.2 equiv of nickel(II) chloride hexahydrate and 0.2 equiv of 1,2-ethanedithiol in dichloromethane–methanol (5:2), it was converted into 1-octadecanol in a 90% yield within 10 min. Similarly, primary and secondary TBS ethers (runs 2 and 3) were hydrolyzed to the corresponding hydroxyl compounds as shown in Table 2. We noticed that phenolic TBS ethers (runs 5 and 6) could

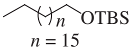
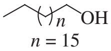
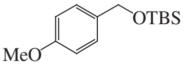
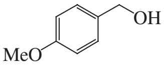
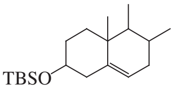
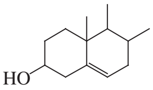
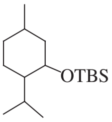
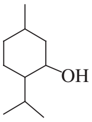
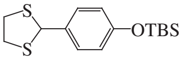
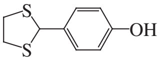
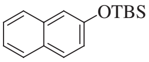
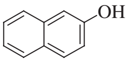
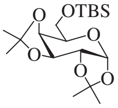
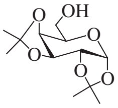
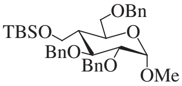
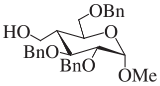
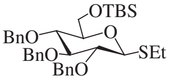
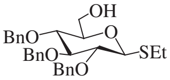
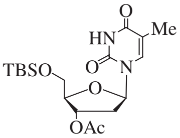
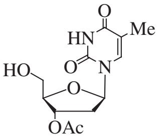
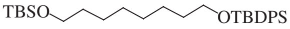
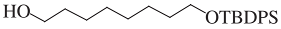
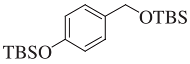
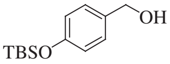
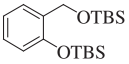
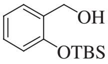
Table 1. Deprotection of various tetrahydropyranyl ethers giving the corresponding hydroxyl compounds using a catalytic amount of nickel(II) chloride hexahydrate (0.2 equiv) and 1,2-ethanedithiol (0.2 equiv) in dry dichloromethane–methanol

Run	Substrate **1**	Time (min/[h])	Product[a] **2**	Yield[b] (%)
1		45		90
2		40		80
3		50		84
4		40		80
5		50		91
6		75		83
7		90		95
8		40		84
9		[2]		85
10		40		76
11		72		90
12		90		86
13		20		65

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

[b] Isolated yield.

Table 2. Deprotection of various TBS ethers (**1**) to the parent hydroxyl compounds (**2**) using a catalytic amount of nickel(II) chloride hexahydrate and 1,2-ethanedithiol

Run	Substrate **1**	Time (min/[h])	Product[a] **2**	Yield[b] (%)
1		10		90
2		5		95
3		30		99
4		25		89
5		[4.5]		70
6		[12]		86
7		45		93
8		[2]		81
9		45		86
10		40		75
11		15		83
12		20		80
13		20		75

[a] All starting materials and final products were characterized by IR, ^{1}H NMR, ^{13}C NMR and elemental analysis.

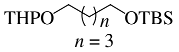
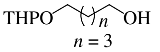
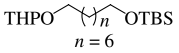
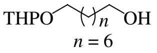
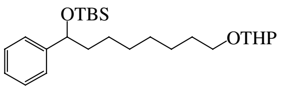
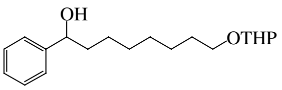
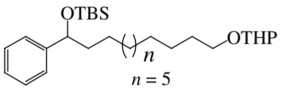
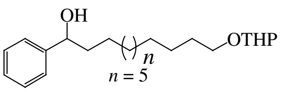
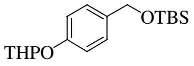
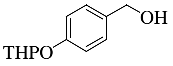
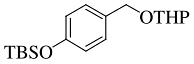
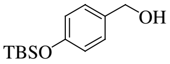
[b] Isolated yield.

also be unmasked in a similar manner. Various substrates containing other functional groups such as an isopropylidene protected sugar (run 7), a benzyl protected sugar (run 8), a benzyl protected sugar having an SEt group in the anomeric position (run 9) and an acetyl protected nucleoside (run 10) were cleaved to the corresponding sugars and nucleoside in good yields. By using our protocol, a TBS ether was chemoselectively deprotected in the presence of TBDPS ether (run 11). Furthermore, alkyl TBS ethers can be cleaved chemoselectively in the presence of aryl TBS ethers (runs 12 and 13). The reaction times and yields of the hydrolyzed products are shown in Table 2.

We have shown[15] that acetyl chloride and methanol provide dry HCl, which can be used for the deprotection of TBS ethers, although THP ethers do not survive during these experimental conditions. We prepared several TBS ethers containing THP ethers and found that by following the present protocol, the TBS ethers could be cleaved to the corresponding hydroxyl compounds in fairly good yields without affecting the THP groups (runs 1–5, Table 3).[16] By repeating our acetyl chloride method,[15] we confirmed that both the THP and TBS groups were hydrolyzed simultaneously. However, it is difficult to cleave selectively aryl TBS ethers in the presence of alkyl THP ethers (run 6) because aryl TBS ethers take longer to react as compared to alkyl TBS ethers. The reaction times and yields of the products are shown in Table 3.

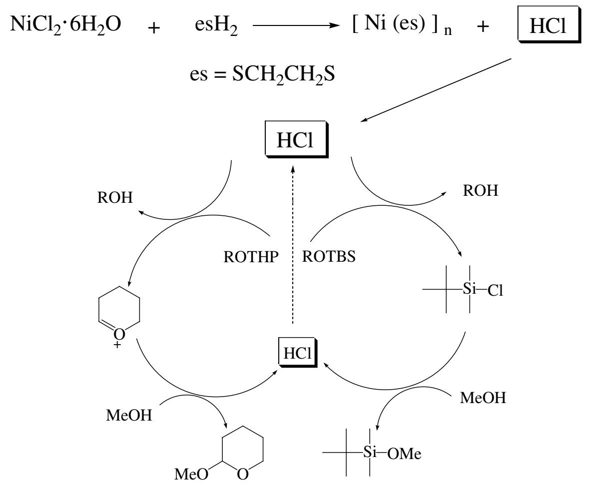
The formation of the product can be explained as outlined in Scheme 2. It may be that nickel(II) chloride

Table 3. Chemoselective cleavage of TBS ethers in presence of a THP ether

Run	Substrate	Time (min)	Product[a]	Yield[b] (%)
1		12		64
2		12		65
3		20		62
4		20		65
5		10		63
6		30		70

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

[b] Isolated yield.



Scheme 2. Proposed mechanism for the deprotection of THP and TBS ethers.

hexahydrate can form hydrochloric acid and a polymeric nickel complex, on reaction with 1,2-ethanedithiol (esH_2). We believe that the in situ generated hydrochloric acid catalyzes the deprotection of both the THP and TBS ethers. Following the nickel chloride method, the pH of the solution was 2.7, whereas during the acetyl chloride method it was 1.5.

We also established that both transformations can be achieved by employing nickel(II) chloride hexahydrate (0.2 equiv) and either ethanethiol or 1,3-propanedithiol. When the TBS ether of 1-octadecanol was treated with either ethanethiol or 1,3-propanedithiol in the presence of nickel(II) chloride hexahydrate, it was converted to 1-octadecanol in 90% yield. The reaction took 50 min in the case of ethanethiol and 75 min in the case of 1,3-propanedithiol. It is quite clear that the reaction is faster with 1,2-ethanedithiol because of the ease of formation of the polymeric $[Ni(es)]_n$ complex. However, the same reaction was unsuccessful when it was carried out with 2-aminothiophenol and nickel(II) chloride hexahydrate using the same solvent. From the chemoselectivity study mentioned in Table 3, it appears that the catalytic cycle for the cleavage of a TBS ether is faster compared to that of cleavage of THP ethers.

We have demonstrated a simple and useful method for deprotection of THP and TBS ethers to the corresponding hydroxyl compounds using a combination of nickel(II) chloride hexahydrate and 1,2-ethanedithiol. It is noteworthy that no chlorination takes place at double or triple bonds. In addition, alkyl TBS ethers can be cleaved chemoselectively in the presence of aryl TBS ethers. Moreover, alkyl TBS ethers can be hydrolyzed in the presence of alkyl THP ethers.

Acknowledgements

A.T.K. acknowledges the Department of Science and Technology (DST), New Delhi for financial grant (Grant No. SP/S1/G-35/98). L.H.C. and S.G. are grateful to the IITG for their research fellowships. We are grateful to Professor M. K. Chaudhuri for some helpful discussion on the mechanistic aspects. We are thankful for the referee's valuable comments and suggestions.

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14. General procedure for deprotection of TBS/THP ethers: To a stirred solution of the TBS or THP ether (1 mmol) in 5 mL of dichloromethane–methanol (5:2) were added nickel(II) chloride hexahydrate (0.2 mmol, 0.047 g) and 1,2-ethanedithiol (0.2 mmol, 17 μL) and the mixture stirred at room temperature. When the reaction was over, the mixture was passed through a silica gel column to obtain the product. In the cases of substrates containing both TBS and THP ethers (Table 3), the reactions were quenched by adding saturated aqueous sodium bicarbonate as soon as the starting material had disappeared.
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16. Spectroscopic data for the THP ether of 4-*tert*-butyldimethylsilyloxybenzyl alcohol: ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.19 (s, 6H, $–Si(CH_3)_2$), 0.98 (s, 9H, $–SiC(CH_3)_3$), 1.51–1.87 (m, 6H, $–CH_2–$), 3.54 (m, 1H, $–OCH_2–$), 3.93 (m, 1H, $–OCH_2–$), 4.44 (d, 1H, $J = 11.2$ Hz, $–OCH_2–$), 4.69 (m, 2H, –OCHO–, $–OCH_2–$), 6.81 (d, 2H, $J = 8.4$ Hz, ArH), 7.23 (d, 2H, $J = 8.4$ Hz, ArH). Anal. Calcd for $C_{18}H_{30}O_3Si$: C, 67.03; H, 9.38%. Found: C, 67.30; H, 9.40%. For 4-*tert*-butyldimethylsilyloxybenzyl alcohol: ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.19 (s, 6H, $–Si(CH_3)_2$), 0.98 (s, 9H, $–SiC(CH_3)_3$), 1.64 (br s, 1H, –OH), 4.6 (s, 2H, $–OCH_2–$), 6.83 (d, 2H, $J = 8.4$ Hz, ArH), 7.23 (d, 2H, $J = 8.4$ Hz, ArH). Anal. Calcd for $C_{13}H_{22}O_2Si$: C, 65.50; H, 9.30%. Found: C, 65.68; H, 9.25%.