# Acetyl Chloride-mediated Mild and Chemoselective Attachment and Removal of Tetrahydropyranyl (THP) Group

**Chang-Eun Yeom, Yong Je Shin, and B. Moon Kim***

*Department of Chemistry, College of Natural Sciences, Seoul National University, Seoul 151-747, Korea*
**E-mail: kimbm@snu.ac.kr*
*Received October 3, 2006*

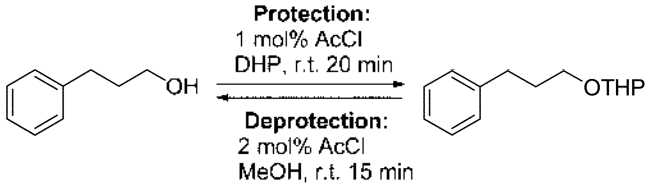
A mild, chemoselective and convenient method for the formation and deprotection of tetrahydropyranyl ethers is described. With 1-5 mol% of acetyl chloride and slightly excess dihydropyran in methylene chloride or in neat dihydropyran, the formation of THP ethers from the corresponding alcohols was accomplished in the presence of many acid-sensitive functional groups. Efficient cleavage of THP ethers was also accomplished with the same reagent by switching the solvent to methanol.

**Key Words :** THP ether, Protecting group, Chemoselective, Tetrahydropyranylation, Detetrahydropyranylation

## Introduction

Mild and chemoselective protection and deprotection of hydroxyl functionality are essential parts in the synthetic operation of polyfunctional organic compounds,[1] especially in the context of natural product and carbohydrate chemistry. Among numerous protecting groups of alcohols, tetrahydropyranyl (THP) group is one of the most frequently employed protecting groups due to its stability towards most nonacidic reaction conditions, ease of preparation, and facile removal under mild acidic conditions. Furthermore, its precursor, 3,4-dihydro-2*H*-pyran (DHP) is relatively inexpensive, rendering the process amenable to large-scale processes.[2]

There are a number of protocols for introduction and cleavage of the THP group and most common reagents include *p*-toluenesulfonic acid (*p*-TsOH)[3] and pyridinium *p*-toluenesulfonate (PPTS).[4] Recently, various other catalysts have been actively investigated, *e.g.* LiBr,[5a] $LiBF_4$,[5b] $LiClO_4$,[5c] $In(OTf)_3$,[5d] $CuSO_4 \cdot 5H_2O$,[5e] CuCl,[5f] $ZrCl_4$,[5g] $LaCl_3$,[5h] CAN,[5i] $AlCl_3 \cdot 6H_2O$,[5j] dialkylimidazolium tetrachloroaluminates,[5k] $TaCl_5$,[5l] $Fe(ClO_4)_3$,[5m] $NiCl_2 \cdot 6H_2O$,[5n] $Bi(OTf)_3$,[5o] and $K_5CoW_{12}O_{40} \cdot 3H_2O$.[5p] Other reagents include $BF_3 \cdot OEt_2$,[6a] DDQ,[6b] $I_2$,[6c] Pd/C,[6d] TBATB,[6e] IBX and $\beta$-cyclodextrin,[6f] heteropoly acids,[6g] acetonyl triphenylphosphonium bromide,[6h,i] bromodimethylsulfonium bromide,[6j] $NH_4Cl$,[6k] $PPh_3 \cdot Br_2$,[6l] microwave,[6m] ion-exchange resins,[6n] protic acid in ionic liquid,[6o] and clay materials.[6p] Though some protocols exhibit impressive results employing simplified operations, most of them are still associated with some limitations such as high loadings of the reagents/catalysts, long reaction time, incompatibility with other acid-sensitive functional groups, and scarcity of the reagents. From our continuing effort in developing efficient protocols for protecting group chemistry,[7] we have encountered facile "on" and "off" reactions of THP ether through the use of a catalytic amount of acetyl chloride, which is one of the most readily available organic chemicals. With only 1-5 mol% of acetyl chloride in an aprotic solvent such as methylene chloride or under solvent-free conditions, various alkyl and aryl THP ethers were prepared from the corresponding alcohols in excellent yields. Initial reaction of the reactant alcohol with a catalytic amount of acetyl chloride generates anhydrous HCl, which acts as the active catalyst for the reaction (forward reaction in Scheme 1). Moreover, when a protic solvent such as methanol was employed, the reverse process, *i.e.* the rapid cleavage of THP ether was observed, which was mediated by anhydrous HCl catalyzed methanolysis (reverse reaction in Scheme 1). Herein we report on the extended scope of this simple and convenient protocol.

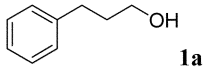
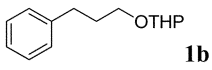
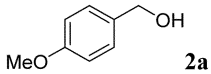
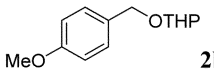
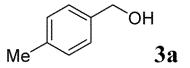
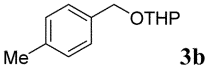
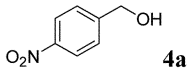
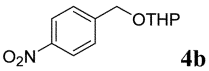
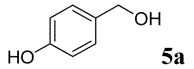
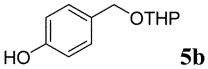
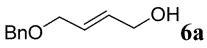
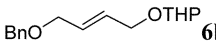
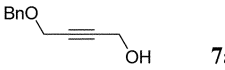
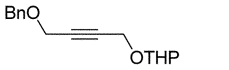
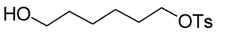
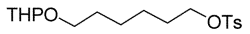
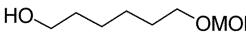
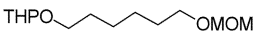
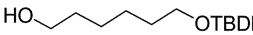
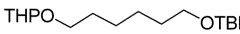
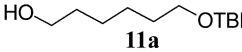
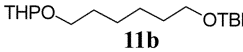
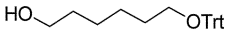
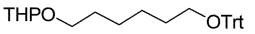
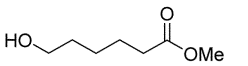
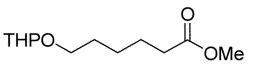
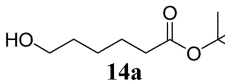
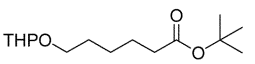
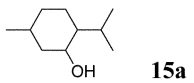
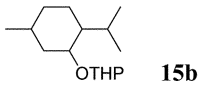
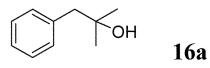
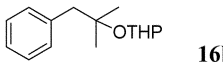
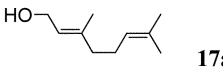
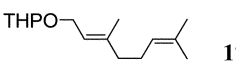
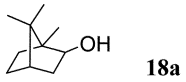
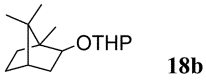
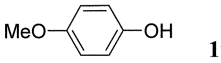
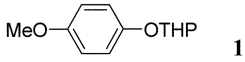
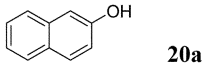
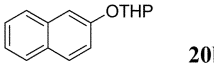



**Scheme 1**

## Results and Discussion

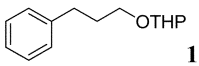
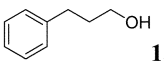
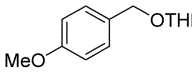
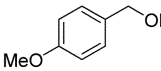
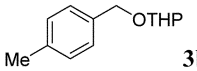
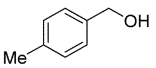
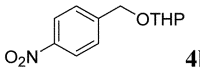
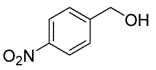
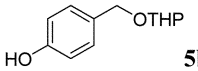
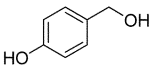
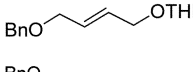
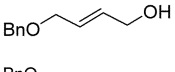
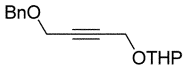
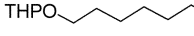
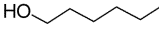
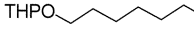
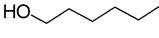
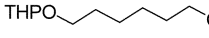
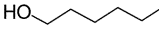
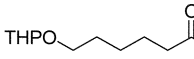
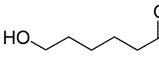
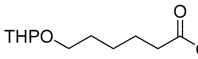
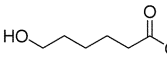
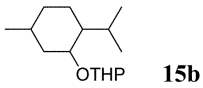
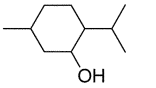
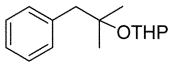
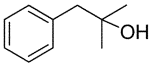
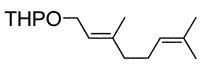
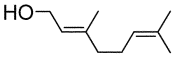
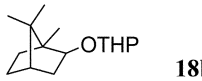
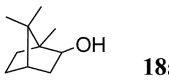
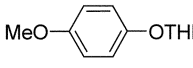
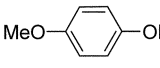
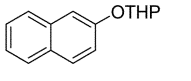
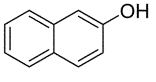
For the installation of the THP ether, employment of a catalytic amount of AcCl on a number of primary, secondary, tertiary, benzylic, and phenolic alcohols provided successful etherification and the results are summarized in Table 1. In general, the reactions were carried out with 1.2 equiv of DHP under solvent-free conditions. The amount of AcCl was appropriated according to the steric environment of the alcohol. Unhindered primary alcohols and phenols were smoothly converted to the corresponding THP ethers with only 1-2 mol% of AcCl within 30 min (entries 1-3, and 5-14). Unfortunately, several substrates did not provide satisfactory results in neat DHP, presumably due to solubility problem (entries 4, 5, 11, 12, 18, 20, and 21). In those cases, employment of methylene chloride as a solvent provided desired THP ethers in good to excellent yields. It is noteworthy that acid-sensitive groups such as MOM (entry

**Table 1.** Preparation of THP ethers using catalytic amount of acetyl chloride and 1.2 equiv DHP at rt

| Entry | Alcohol | THP ether | Amount of AcCl | Solvent | Time | Yield (%)[a,b] |
|---|---|---|---|---|---|---|
| 1 |  **1a** |  **1b** | 1 mol% | neat | 20 min | 86. |
| 2 |  **2a** |  **2b** | 1 mol% | neat | 30 min | 88 |
| 3 |  **3a** |  **3b** | 1 mol% | neat | 30 min | 94 |
| 4 |  **4a** |  **4b** | 1 mol% | $CH_2Cl_2$ | 1 h | 96 |
| 5 |  **5a** |  **5b** | 1 mol% | $CH_2Cl_2$ | 30 min | 75 |
| 6 |  **6a** |  **6b** | 1 mol% | neat | 30 min | 95 |
| 7 |  **7a** |  **7b** | 1 mol% | neat | 30 min | 92 |
| 8 |  **8a** |  **8b** | 1 mol% | neat | 30 min | 94 |
| 9 |  **9a** |  **9b** | 1 mol% | neat | 30 min | 93 |
| 10 |  **10a** |  **10b** | 1 mol% | neat | 30 min | 87 |
| 11 |  **11a** |  **11b** | 1 mol% | $CH_2Cl_2$ | 30 min | 93 |
| 12 |  **12a** |  **12b** | 1 mol% | $CH_2Cl_2$ | 30 min | 97 |
| 13 |  **13a** |  **13b** | 1 mol% | neat | 30 min | 94 |
| 14 |  **14a** |  **14b** | 1 mol% | neat | 30 min | 90 |
| 15 |  **15a** |  **15b** | 5 mol% | neat | 3 h | 90 |
| 16 |  **16a** |  **16b** | 5 mol% | neat | 3 h | 87 |
| 17 |  **17a** |  **17b** | 5 mol% | neat | 3 h | 93 |
| 18 |  **18a** |  **18b** | 5 mol% | $CH_2Cl_2$ | 3 h | 93 |
| 19 |  **19a** |  **19b** | 1 mol% | neat | 30 min | 93 |
| 20 |  **20a** |  **20b** | 1 mol% | $CH_2Cl_2$ | 30 min | 90 |
| 21 | Cholesterol - OH **21a** | Cholesterol-OTHP **21b** | 5 mol% | $CH_2Cl_2$ | 3 h | 91 |

[a]All products were identified from $^1H$ NMR spectral analyses. [b]Yields of isolated products.

**Table 2.** Cleavage of THP ether using catalytic amount of acetyl chloride at rt

| Entry | THP ether | Alcohol | Amount of AcCl | Time | Yield (%)[a,b] |
|---|---|---|---|---|---|
| 1 |  **1b** |  **1a** | 2 mol% | 20 min | 98 |
| 2 |  **2b** |  **2a** | 2 mol% | 30 min | 96 |
| 3 |  **3b** |  **3a** | 2 mol% | 30 min | 98 |
| 4 |  **4b** |  **4a** | 2 mol% | 1 h | 98 |
| 5 |  **5b** |  **5a** | 2 mol% | 30 min | 85 |
| 6 |  **6b** |  **6a** | 2 mol% | 30 min | 97 |
| 7 |  **7b** |  **7a** | 2 mol% | 30 min | 94 |
| 8 |  **8b** |  **8a** | 2 mol% | 30 min | 91 |
| 9 |  **9b** |  **9a** | 2 mol% | 30 min | 93 |
| 10 |  **11b** |  **11a** | 2 mol% | 30 min | 88 |
| 11 |  **13b** |  **13a** | 2 mol% | 30 min | 98 |
| 12 |  **14b** |  **14a** | 2 mol% | 30 min | 95 |
| 13 |  **15b** |  **15a** | 3 mol% | 30 min | 97 |
| 14 |  **16b** |  **16a** | 3 mol% | 30 min | 98 |
| 15 |  **17b** |  **17a** | 2 mol% | 30 min | 94 |
| 16 |  **18b** |  **18a** | 3 mol% | 1 h | 98 |
| 17 |  **19b** |  **19a** | 5 mol% | 40 min | 97 |
| 18 |  **20b** |  **20a** | 5 mol% | 1 h | 97 |
| 19 | Cholesterol-OTHP **21b** | Cholesterol-OH **21a** | 5 mol% | 2 h | 86 |

[a]All products were identified from $^1$H NMR spectral analyses. [b]Yields of isolated product.

9), TBDMS (entry 10), TBDPS (entry 11), trityl (entry 12), and *t*-butyl ester (entry 14) remained unaffected under these conditions. In addition, other acid-labile functional groups such as benzyl (entries 6 and 7), allylic (entry 6 and 17), propargylic (entry 7), and *p*-toluenesulfonyl (entry 8) groups survived the acetyl chloride-mediated tetrahydropyranylation conditions. Alcohols with moderate steric bulkiness were also transformed into the desired THP ethers with increased amount of AcCl in prolonged reaction times (entries 15, 16, 18 and 21). Another remarkable aspect of

this protocol is that a tertiary alcohol, which is difficult to be converted to THP ether under normal conditions, also went through tetrahydropyranylation cleanly (entry 16).[8]

Deprotection of the THP ethers using the same catalyst was also smoothly accomplished when the solvent was switched to methanol. For the deprotection, typically 2~3 mol% of acetyl chloride was introduced to a methanol solution of THP ether, and reactions were complete within 1 h providing 85-98% yields of the desired alcohols (Table 2). Only for sterically hindered cholesterol THP ether and phenolic ethers, 5 mol% acetyl chloride was required (entries 17-19). Similar to tetrahydropyranylation reaction, the deprotection conditions also allowed completely chemoselective cleavage of THP ethers. Deprotection in the presence of benzyl, *p*-toluenesulfonyl, MOM, TBDPS, and *t*-butyl ester groups (entries 6-15) was clean and sterically hindered THP ethers were readily cleaved under these conditions (entries 13, 14 and 16). To our disappointment, in the case of TBDMS and trityl protected alcohols, the removal of these protecting groups were competitively occurred with that of THP group.

## Conclusion

A simple and efficient tetrahydropyranylation and deprotection methods were established using a catalytic amount of acetyl chloride as an acid promoter. This method is operationally straightforward, mild and chemoselective, utilizing a minute amount of the reagent. Simple basic quenching and purification through a pad of silica gel are sufficient to provide the desired THP ethers and alcohols in a pure form.

## Experimental Section

All reactions were carried out in dried solvents. Methylene chloride ($CH_2Cl_2$) was dried from refluxing over $CaH_2$. Methanol (MeOH), 3,4-dihydro-2*H*-pyran (DHP) and alcohols (**1a**, **2a**, **3a**, **4a**, **5a**, **15a**, **16a**, **17a**, **18a**, **19a**, **20a** and **21a**) were purchased from commercial supplier such as Aldrich and used without further purification. $^1H$ and $^{13}C$ NMR spectra were recorded in $CDCl_3$ on Bruker AM-300 instruments with $Me_4Si$ (TMS) or residual $CHCl_3$ as internal standards. High-resolution mass (HRMS) data were obtained on JEOL JMS 600 mass spectrometer. All reactions as well as column chromatography were monitored routinely by thin layer chromatography, which is performed with aluminum backed silica gel plates coated with a 0.2 mm thickness of silica gel 60 F254 (Merck). Column chromatography was performed on silica gel (Merck 7734 or 9385 Kiesel gel 60) using indicated eluting conditions.

**Representative procedure for tetrahydropyranylation (1b, Solvent-free conditions).** To a magnetically stirred solution of 3-phenyl-1-propanol (0.50 g, 3.67 mmol) and 3,4-dihydro-2H-pyran (0.401 mL, 4.40 mmol, 1.2 equiv), was added acetyl chloride (2.61 μL, 0.0367 mmol, 0.01 equiv) at rt. The mixture was stirred for 20 min and the reaction was quenched upon addition of triethylamine (1.00 mL). The mixture was concentrated and the resulting residue was purified through silica gel column chromatography (*n*-hexane/ethyl acetate = 10 : 1) to provide the desired tetrahydropyranyl ether (0.695 g, 86% yield).

**Representative procedure for tetrahydropyranylation (18b, in methylene chloride).** To a magnetically stirred solution of isoborneol (0.50 g, 3.24 mmol) were added 3,4-dihydro-2H-pyran (0.355 mL, 3.89 mmol, 1.2 equiv) and acetyl chloride (11.5 μL, 0.162 mmol, 0.050 equiv) in methylene chloride (3.24 mL) at rt. The mixture was stirred for 20 min and the reaction was quenched upon addition of triethylamine (2.0 mL). The mixture was concentrated and the resulting residue was purified through silica gel column chromatography (*n*-hexane/ethyl acetate = 10 : 1) to provide the desired tetrahydropyranyl ether (0.717 g, 93% yield).

**Representative procedure for depyranylation.** To a magnetically stirred solution of 3-phenyl-1-propyl tetrahydropyranyl ether (**1b**, 0.42 g, 1.91 mmol) in methanol (1.91 mL), was added acetyl chloride (2.72 μL, 0.0382 mmol, 0.020 equiv) at rt. The mixture was stirred for 20 min and the reaction was quenched upon addition of triethylamine (1.00 mL). The mixture was concentrated and the resulting residue was purified through silica gel column chromatography (*n*-hexane/ethyl acetate = 5 : 1) to provide the desired alcohol (0.255 g, 98% yield).

**Spectroscopic Data for New Compounds**

**Compound 4b** yellowish oil (eluted with *n*-hexane : EtOAc = 6 : 1) $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 8.22-8.19 (m, 2H), 7.54-7.52 (m, 2H), 4.94-4.86 (m, 2H), 4.74-4.72 (m, 1H), 4.66-4.59 (m, 2H), 3.92-3.85 (m, 2H), 3.58-3.54 (m, 2H), 1.87-1.58 (m, 6H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 147.6, 146.6, 128.1, 123.9, 98.7, 68.0, 62.6, 30.8, 25.7, 19.6; HRMS (EI) Calcd. for $C_{12}H_{15}O_4N$ $[M]^-$, 237.1001. Found 237.1003.

**Compound 7b** colorless oil (eluted with *n*-hexane : EtOAc = 8 : 1); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.35 (m, 5H), 4.83 (m, 1H), 4.59 (s, 2H), 4.40-4.22 (m, 4H), 3.87-3.84 (m, 1H), 3.55 (m, 1H), 1.82-1.56 (m, 6H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 137.39, 128.45, 128.10, 127.89, 96.84, 82.58, 81.89, 71.59, 62.02, 57.48, 54.31, 30.25, 25.36, 19.07; HRMS (CI) Calcd. for $C_{16}H_{21}O_3$ $[M+H]^+$, 273.2066, Found 273.2067.

**Compound 14b** colorless oil (eluted with *n*-hexane : EtOAc = 8 : 1); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 4.58-4.56 (m, 1H), 3.86 (m, 1H), 3.75-3.70 (m, 1H), 3.52 (m, 1H), 3.42-3.37 (m, 1H), 2.22 (t, $J$ = 7.4 Hz, 2H), 1.44 (s, 9H), 1.70-1.35 (m, 12H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 173.5, 98.8, 67.4, 62.3, 35.5, 30.8, 29.4, 28.1, 25.8, 25.5, 25.0, 19.7; HRMS (CI) Calcd. for $C_{15}H_{29}O_4$ $[M+H]^+$, 261.1491. Found 261.1491.

**Acknowledgment.** This work was supported by the Korea Research Foundation Grant funded by the Korean Government (MOEHRD) (KRF-2005-041-C00247).

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10. Spectroscopic data of alcohols except commercially available ones have been reported in our previous paper, ref. 7b.