



A fast and practical approach to tetrahydropyranylation and depyranylation of alcohols using indium triflate

Tomoko Mineno*

Department of Medicinal Chemistry, School of Pharmacy, University of Mississippi, PO Box 1848, University, MS 38677-1848, USA

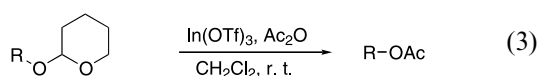
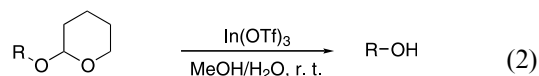
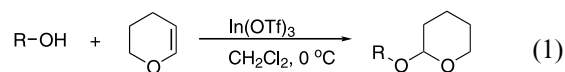
Received 31 July 2002; accepted 26 August 2002

Abstract—Indium triflate-mediated tetrahydropyranylation of alcohols in dichloromethane and depyranylation of these products in aqueous methanol utilizing the same reagent but different molar ratio is described. In addition, indium triflate-promoted conversion of tetrahydropyran ethers to their corresponding acetates has also been described. © 2002 Elsevier Science Ltd. All rights reserved.

The choice of the protection and deprotection strategy in a synthetic sequence is inevitable, owing to chemoselective transformations in the presence of various functional groups.^{1,2} Tetrahydropyran (THP) is an attractive protecting group that is often used for protection of alcohol moieties due to its stability and compatibility under various reaction conditions and reagents, such as metal hydrides, alkylolithiums, Grignard reagents, and catalytic hydrogenation. There are several known methods for the tetrahydropyranylation and depyranylation of alcohols.³ The most commonly used reagents that can catalyze both transformations are *p*-toluenesulfonic acid (PTSA),^{4,5} pyridinium *p*-toluenesulfonate (PPTS),⁶ NH₄Cl,⁷ ZrCl₄,⁸ I₂,^{9,10} potassium dodecatangestocobaltate trihydrate,¹¹ LiBr,¹² acetyltriphenylphosphonium bromide,¹³ and tetrabutylammonium tribromide.¹⁴ However, these procedures have several drawbacks including elevated reaction temperatures, longer reaction times, expensive reagents. Despite a number of precedents, an efficient and practical method for these transformations is desired. During our endeavors to explore the utility of indium and its salt, we have earlier reported a new, mild, and chemoselective method for deprotection of trichloroethoxycarbonyl and trichloroacetyl groups using indium powder and aqueous NH₄Cl in methanol,¹⁵ as well as a mild method for deprotecting

trichloroethyl carbamates.¹⁶ In further extension to our work, we have discovered that indium triflate (In(OTf)₃), which acts as Lewis acid catalyst for various synthetic transformations,¹⁷ can affect the tetrahydropyranylation and depyranylation of alcohols under different reaction conditions. The details of our studies are presented herein.

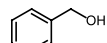
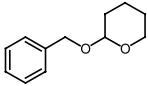
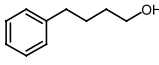
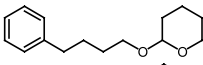
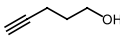
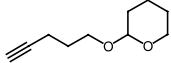
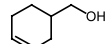
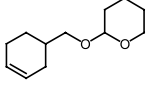
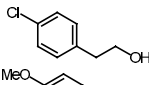
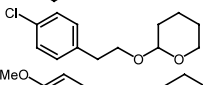
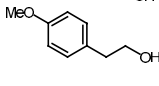
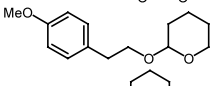

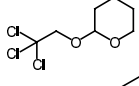
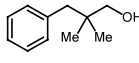
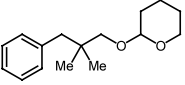

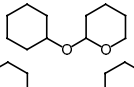
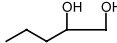
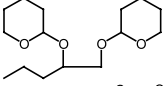
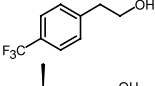
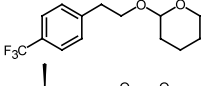
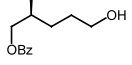
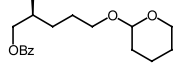
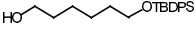
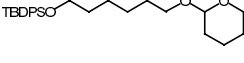
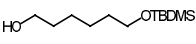
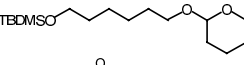
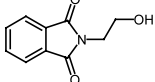
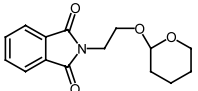
The tetrahydropyranylation of various alcohols was carried out using 0.005 equiv. of In(OTf)₃ in dichloromethane at 0°C (Eq. (1) and Table 1).¹⁸ As evident from Table 1 the protection methodology was successful over a range of functional groups furnishing the protected alcohols in good yields. However, the trichloroethanol derivative (entry 7) yielded the product in only 33% yield. The possible reason ascribed to this observation could be the inductive electron-withdrawing effect of the trichloromethyl moiety. We extended our method to investigate the protection of alcohols that also possess silyl-protected alcohol moieties, such as *t*-butyldiphenylsilyl (TBDPS) and *t*-butyldimethylsilyl (TBDMS) groups (entries 13 and 14). In both cases, the THP protection was successful and gave satisfactory yields without affecting silyloxy-protected moieties.



Keywords: indium triflate; tetrahydropyranylation; depyranylation; alcohols; acetylation.

* Present address: University of Notre Dame, Dept. of Chemistry and Biochemistry, 251 Nieuwland Science Hall, Notre Dame, IN 46556, USA. Tel: 1-574-631-5606; fax: 1-574-631-6652; e-mail: tmineno@nd.edu

Table 1. Indium triflate-catalyzed tetrahydropyranylation of alcohols^a

Entry	Starting Material	Product	Time (min.)	Yield ^b (%)
1			30	85
2			30	76
3			50	68
4			30	80
5			30	87
6			30	85
7			50	33
8			50	75
9			30	85
10			50	75
11			30	80
12			30	65
13			30	82
14			30	78
15			30	64

^aAll reactions were performed at 0 °C using 0.005 equiv. of In(OTf)₃. ^bIsolated yields.

Subsequently, we discovered that depyranylation of the THP ethers can be carried out to obtain the corresponding alcohols in good to excellent yields, using the same catalyst but different molar ratio in aqueous methanol at room temperature (Eq. (2) and Table 2).¹⁹ Compared to the protection, deprotection reactions required 10 folds, or 0.05 equiv. of In(OTf)₃ and extended reaction time for completion. Selective deprotection was observed in entry 9, in which the deprotection reaction proceeded without cleaving TBDPS-protected alcohol unit. However, the TBDMS-protected compound in entry 10 did not undergo chemoselective deprotection. In general, the TBDMS group is not as stable as the TBDPS in this reaction condition. Selection of a TBDPS group

would be favored when there are more than one alcohol unit to manipulate by protection and deprotection.

In addition to these results, during our studies, we also observed that In(OTf)₃ promotes the acetylation of THP ethers (Eq. (3) and Table 3).²⁰ Earlier to this report, the direct methods known to convert THP ethers into acetate,^{21,22} generally require air sensitive reagents and longer reaction periods. In contrast, the method reported herein is fast and does not involve any special reaction conditions or modifications. Besides, this one step transformation can probably confer a change of acid labile protecting group into a base labile protecting group.

Table 2. Indium triflate-catalyzed depyranylation of THP ethers^a

Entry	Starting Material	Product	Time (h)	Yield ^b (%)
1			6	91
2			6	92
3			10	82
4			10	60
5			10	95
6			10	94
7			10	90
8			6	85
9			12	81
10		N. R.	-	-
11			7	81

^aAll reactions were performed at r. t. using 0.05 equiv. of In(OTf)₃. ^bIsolated yields.

Table 3. Indium triflate-catalyzed acetylation of THP ethers^a

Entry	Starting Material	Product	Time (h)	Yield ^b (%)
1			1	93
2			1	88
3			2	90
4			2	90
5			2	83
6			1	85
7			2	85

^aAll reactions were performed at r. t. using 0.05 equiv. of In(OTf)₃ catalyst. ^bIsolated yields.

In conclusion, we have established a simple and efficient method for tetrahydropyranylation and depyranylation of alcohols, as well as acetylation of THP ethers, using catalytic amount of $\text{In}(\text{OTf})_3$. Since the reactions described here are fast and practical, these methodologies will be highly useful in the total synthesis of natural products.

Acknowledgements

The author is grateful to Professor Mitchell A. Avery for his profound support and suggestions.

References

- Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley & Sons: New York, 1999.
- Kocienski, P. J. *Protecting Groups*; Georg Thieme Verlag: New York, 2000.
- (a) Deka, N.; Sarma, J. C. *J. Org. Chem.* **2001**, *66*, 1947–1948; (b) Branco, L. C.; Afonso, C. A. M. *Tetrahedron* **2001**, *57*, 4405–4410; (c) Babu, B. S.; Balasubramanian, K. K. *Synlett* **1999**, 1261–1262; (d) Nishiguchi, T.; Hayakawa, S.; Hirasaka, Y.; Saitoh, M. *Tetrahedron Lett.* **2000**, *41*, 9843–9846; (e) Curini, M.; Epifano, F.; Marcotullio, M. C.; Rosati, O.; Costantino, U. *Tetrahedron Lett.* **1998**, *39*, 8159–8162; (f) Babu, B. S.; Balasubramanian, K. K. *Tetrahedron Lett.* **1998**, *39*, 9287–9288; (g) Davis, K. J.; Bhalerao, U. T.; Rao, B. V. *Synth. Commun.* **2000**, *30*, 2301–2308; (h) Marko, I. E.; Ates, A.; Augustyns, B.; Gautier, A.; Quesnel, Y.; Turet, L.; Wiaux, M. *Tetrahedron Lett.* **1999**, *40*, 5613–5616; (i) Ramasamy, K. S.; Bandaru, R.; Averett, D. *Synth. Commun.* **1999**, *29*, 2881–2894.
- Bernady, K. F.; Floyd, M. B.; Poletto, J. F.; Weiss, M. J. *J. Org. Chem.* **1979**, *44*, 1438–1446.
- Corey, E. J.; Niwa, H.; Knolle, J. *J. Am. Chem. Soc.* **1978**, *100*, 1942–1943.
- Miyashita, M.; Yoshikoshi, A.; Grieco, P. A. *J. Org. Chem.* **1977**, *42*, 3772–3774.
- Yadav, J. S.; Srinivas, D.; Reddy, G. S. *Synth. Commun.* **1998**, *28*, 1399–1404.
- Rezai, N.; Meybodi, F. A.; Salehi, P. *Synth. Commun.* **2000**, *30*, 1799–1805.
- Deka, N.; Sarma, J. C. *Synth. Commun.* **2000**, *30*, 4435–4441.
- Kumar, H. M. S.; Reddy, B. V. S.; Reddy, E. J.; Yadav, J. S. *Chem. Lett.* **1999**, 857–858.
- Habibi, M. H.; Tangestaninejad, S.; Mohammadpoor-Baltork, I.; Mirkhani, V.; Yadollahi, B. *Tetrahedron Lett.* **2001**, *42*, 2851–2853.
- Reddy, M. A.; Reddy, L. R.; Bhanumathi, N.; Rao, K. R. *Synth. Commun.* **2000**, *30*, 4323–4328.
- Hon, Y.-S.; Lee, C.-F. *Tetrahedron Lett.* **1999**, *40*, 2389–2392.
- Naik, S.; Gopinath, R.; Patel, B. K. *Tetrahedron Lett.* **2001**, *42*, 7679–7681.
- Valluri, M.; Mineno, T.; Hindupur, R. M.; Avery, M. A. *Tetrahedron Lett.* **2001**, *42*, 7153–7154.
- Mineno, T.; Choi, S.-R.; Avery, M. A. *Synlett* **2002**, 883–886.
- (a) Yadav, J. S.; Subba Reddy, B. V.; Srinivasa Rao, R.; Veerendhar, G.; Nagaiah, K. *Tetrahedron Lett.* **2001**, *42*, 8067–8070; (b) Loh, T.-P.; Hu, Q.-Y.; Tan, K.-T.; Cheng, H.-S. *Org. Lett.* **2001**, *3*, 2669–2672; (c) Prajapati, D.; Laskar, D. D.; Sandhu, J. S. *Tetrahedron Lett.* **2000**, *41*, 8639–8643; (d) Gadhwal, S.; Sandhu, J. S. *J. Chem. Soc., Perkin 1* **2000**, 2827–2829; (e) Chauhan, K. K.; Frost, C. G.; Love, I.; Waite, D. *Synlett* **1999**, 1743–1744; (f) Trost, B. M.; Portnoy, M.; Kurihara, H. *J. Am. Chem. Soc.* **1997**, *119*, 836–837.
- General procedure for tetrahydropyranylation:** Benzyl alcohol (100 mg, 0.925 mmol, entry 1, Table 1) was dissolved in dry CH_2Cl_2 (5 mL) under an argon atmosphere at 0°C. Dihydropyran (92 mg, 1.11 mmol) and $\text{In}(\text{OTf})_3$ (2.6 mg, 0.005 mmol) were added and stirred at the same temperature for 30 min. The reaction mixture was diluted with water and extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4 . The mixture was filtered and then concentrated by rotary evaporation. Purification by flash chromatography using hexanes/ethyl acetate (9:1) furnished the THP ether of benzyl alcohol (151 mg, 85% yield).
- General procedure for depyranylation:** Benzyl THP ether (100 mg, 0.52 mmol, entry 1, Table 2) was dissolved in aqueous methanol (5 mL, 2:1 MeOH/ H_2O) at 0°C. $\text{In}(\text{OTf})_3$ (15 mg, 0.026 mmol) was added and stirred at the same temperature for 10 min. and then at rt for 6 h. Methanol was removed by rotary evaporation. The residue was extracted with ethyl acetate (3×10 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4 . The mixture was filtered and concentrated by rotary evaporation. Purification by flash chromatography using hexanes/ethyl acetate (8:2) yielded the corresponding alcohol (52 mg, 93% yield).
- General procedure for acetylation of THP ethers:** Benzyl THP ether (100 mg, 0.52 mmol, entry 1, Table 3) was taken in dry CH_2Cl_2 (5 mL) under argon atmosphere at 0°C, to which Ac_2O (63 mg, 0.62 mmol) and $\text{In}(\text{OTf})_3$ (15 mg, 0.026 mmol) were added and stirred at the same temperature for 10 min and then at rt for 1 h. The reaction mixture was diluted with water and extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4 . The mixture was filtered and concentrated by rotary evaporation. Purification by flash chromatography using hexanes/ethyl acetate (8:2) furnished benzyl acetate (73 mg, 94% yield).
- Ranu, B. C.; Hajra, A. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2262–2265.
- Chandra, K. L.; Saravanan, P.; Singh, V. K. *Tetrahedron Lett.* **2001**, *42*, 5309–5311.