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A mild method for the deprotection of tetrahydropyranyl (THP) ethers catalyzed by iron(III) tosylate

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ABSTRACT

A mild method for the deprotection of THP ethers catalyzed by iron(III) tosylate (2.0 mol %) in CH_3OH has been developed. Iron(III) tosylate, $Fe(OTs)_3 \cdot 6H_2O$, is a commercially available solid that is inexpensive, noncorrosive, and easy to handle. The room temperature reaction conditions make this method attractive for deprotection of a range of THP ethers.

Tetrahydropyranyl (THP) ethers are frequently used to protect alcohols and phenols in the course of a total synthesis.[1] Hence, mild methods for their deprotection are especially desirable and as a result, several methods have been developed for this purpose. Some recent catalysts used for the deprotection of THP ethers include $NO^+BF_4^-$,[2] $[PCl_{3-n}(SiO_2)_n]$ (SILPHOS),[3] $TBPA^+ \cdot SbCl_6^-$,[4] H_2O_2/Mn(II) Schiff-base complex,[5] activated carbon supported sulfuric acid,[6] ionene supported peroxodisulfates,[7] P_2O_5/SiO_2,[8] CH_3COCl,[9] DABCO-Bromine complex,[10] ceric ammonium nitrate,[11] $Fe(ClO_4)_3$,[12] bromodimethylsulfonium bromide $(CH_3)_2S^+Br\ Br^-$,[13] natural kaolinitic clay,[14] bismuth(III) salts,[15] CrO_3/zeolite,[16] *n*-butyltriphenylphosphonium peroxodisulfate $(n\text{-}BuPPh_3)_2S_2O_8$,[17] $AlCl_3 \cdot 6H_2O$,[18] and pyridinium *p*-toluenesulfonate.[19] Several methods for the selective deprotection of THP ethers involve aqueous acid and careful pH control.[20]

Our continued interest in developing environmentally friendly synthetic methodology prompted us to investigate a mild and catalytic method for the deprotection of acetals utilizing inexpensive, commercially available reagents. Herein we wish to report that iron(III) tosylate[21] (2.0 mol %) in CH_3OH is an efficient catalyst for the deprotection of THP ethers at room temperature (Table 1). The mild conditions make this method attractive for the deprotection of THP ethers, especially on a large scale. As can be seen from Table 1, the reaction worked with a range of THP ethers including those derived from 1° alcohols (entries 1–3), allylic alcohols (entries 4 and 5), 2° alcohols (entries 6–8), 3° alcohols (entry 9), propargylic alcohol (entry 10), benzylic alcohol (entry 11), and phenols (entries 12 and 13). Two methods were developed to work-up the reaction. In one, the crude product was isolated via an aqueous work-up (Method A). When purification was deemed necessary, the crude product was filtered through a short column of silica gel. Alternatively, the product (entries 2 and 10) could also be isolated directly by evaporation of methanol followed by filtration of the crude reaction material through a silica column (Method B). The latter method is especially attractive because it avoids an aqueous waste stream. When product purification was necessary, the direct column work-up (Method B) gave better yields (entries 2 and 10). In contrast to simple acetals, no deprotection was observed in H_2O (entry 2, 24 h, rt).[21d] Unfortunately, deprotection was sluggish in the safer solvent, ethanol. Even after 24 h, a small amount (5%) of the starting material was present when the deprotection of the THP ether of 4-hydroxyacetophenone (entry 13) was carried out in ethanol. In contrast to the reaction in CH_3OH, the deprotection of the THP ether of isoeugenol (entry 12) in ethanol was not complete in 2 h.

As stated earlier, we have previously developed a $Bi(OTf)_3$-catalyzed deprotection of THP ethers in DMF/CH_3OH. In contrast to the drastic conditions used in that method, the present methodology utilizes mild reaction conditions, and a less expensive and less moisture sensitive catalyst. In conclusion, a mild and efficient method for the deprotection of THP ethers using an inexpensive, commercially available catalyst, $Fe(OTs)_3 \cdot 6H_2O$, has been developed.

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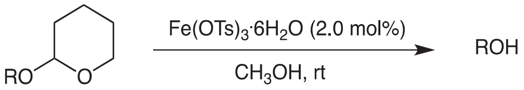
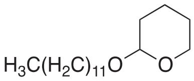
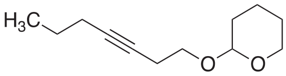
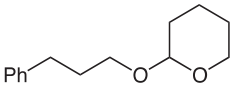
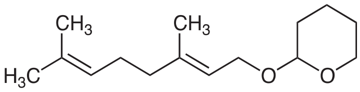
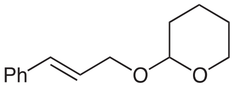
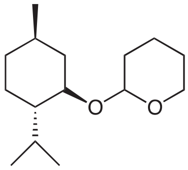
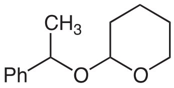
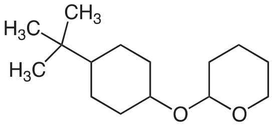
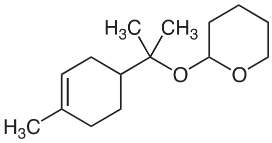
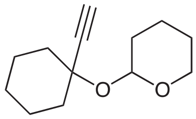
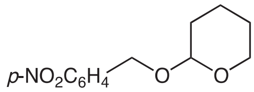
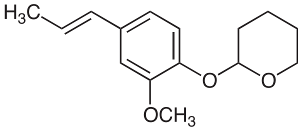
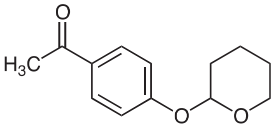
Table 1
Deprotection of THP ethers catalyzed by $Fe(OTs)_3 \cdot 6H_2O$



Entry	Substrate[a]	Time[b]	Yield[c] (%)
1		3 h	78[d]
2		3 h 45 min	72[e]
3		2 h 45 min	84[d]
4		3 h	75[d]
5		4 h 30 min	80[d]
6		4 h	82[d]
7		4 h 30 min	86[f]
8		3 h	97[d]
9		1 h 15 min	77[f]
10		2 h	77[e]
11		2 h 25 min	91[d]
12		2 h	76[f]
13		1 h 50 min	89[f]

[a] THP ethers were synthesized by previously reported literature methods.[15b] THP ether in entry 13 was synthesized using pyridinium *p*-toluenesulfonate (PPTS).[22]
[b] Reaction progress was monitored by TLC.
[c] Refers to yield of isolated product that is ⩾98% pure by ^1H and ^{13}C NMR spectroscopy.
[d] Yield after chromatographic purification of crude material obtained by aqueous workup (Method A).
[e] Isolated by evaporation of CH_3OH followed by direct filtration of the residue (Method B).
[f] Crude product, isolated by Method A, was found to be >98% by ^1H and ^{13}C NMR spectroscopy and hence further purification was deemed unnecessary.

Representative procedures

Method A: A solution of the THP ether of cinnamyl alcohol (entry 5) (1.00 g, 4.58 mmol) in CH_3OH (10 mL) was stirred at room temperature as $Fe(OTs)_3 \cdot 6H_2O$ (0.0621 g, 0.0916 mmol, 2.0 mol %) was added. The reaction progress was monitored by TLC (EtOAc/heptane, 30/70). After 4 h 30 min, water (15 mL) was added and methanol was removed on a rotary evaporator. The resulting mixture was extracted with EtOAc (2 × 20 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ (15 mL), saturated aqueous NaCl (15 mL), dried (Na_2SO_4), and concentrated on a rotary evaporator to yield 0.59 g of the crude product. The crude product was purified by flash chromatography (35 g silica gel, EtOAc/heptane, 30/70) to yield 0.49 g (80%) of a white solid that was identified to be cinnamyl alcohol. The purity was estimated to be >98% by ^1H and ^{13}C NMR spectroscopy, and GC analysis. ^1H NMR: δ 2.56 (s, 1H), 4.29 (dd, J = 1.5, 5.7 Hz, 2H), 6.35 (doublet of triplets, J = 5.7, 16.8 Hz, 1H), 6.60 (apparent doublet, J = 16.8 Hz, 1H), 7.31 (m, 5H); ^{13}C NMR (7 peaks): 63.4, 126.3, 127.5, 128.43, 128.47, 130.8, 136.6

Method B: A solution of the THP ether of 1-ethynyl-1-cyclohexanol (entry 10) (0.50 g, 2.40 mmol) in CH_3OH (5 mL) was stirred at room temperature as $Fe(OTs)_3 \cdot 6H_2O$ (0.0325 g, 0.0480 mmol, 2.0 mol %) was added. The reaction progress was monitored by TLC (EtOAc/heptane, 30/70). After 2 h, CH_3OH was removed on a rotary evaporator and the residue was purified by flash chromatography (35 g silica gel, EtOAc/pentane, 30/70) to yield 0.23 g (77%) of a colorless liquid that was identified to be 1-ethynyl-1-cyclohexanol. The purity was estimated to be >98% by ^1H and ^{13}C NMR spectroscopy, and GC analysis. ^1H NMR: δ 1.55 (d, 10H), 2.4 (s, 1H), 2.7 (s, 1H); ^{13}C NMR (6 peaks) 23.0, 24.9. 39.6, 68.4, 72.0, 87.7.

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