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Tetrahedron Letters 47 (2006) 5111–5113

Tetrahedron
Letters

An economic and practical synthesis of the 2-tetrahydrofuranyl ether protective group

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Received 26 April 2006; revised 11 May 2006; accepted 12 May 2006

Abstract—Primary, secondary, and tertiary alcohols as well as phenols and carbohydrates are efficiently transformed into the corresponding 2-tetrahydrofuranyl ethers by a combination of Mn(0) powder and CCl_4 in tetrahydrofuran.

Despite its well-established reputation[1] as a versatile, orthogonal[2] protecting group, the 2-tetrahydrofuranyl (THF) ether is often disregarded in favor of its homologous relative, the tetrahydropyranyl (THP) ether. This is due, in large measure, to limitations in the extant procedures for its introduction, that is, the required reagents not commercially available, corrosive, incompatible with sensitive functionality, and/or unstable.[2–11] To address these issues, we introduced a convenient protocol utilizing $CrCl_2$ and CCl_4 in tetrahydrofuran.[12] However, the high costs of $CrCl_2$, the need for a large excess of reagent, and chromium's toxicity spurred us to seek a more economic and environmentally benign alternative.

Initially, a panel of readily available, eco-friendly metals was evaluated for their ability to promote the 2-tetrahydrofuranylation of *n*-octanol (**1**) under a standard set of reaction conditions (0.4 M in THF, 65 °C, 15 h, 1.5 equiv of CCl_4). Fe(0) and Zn(0) furnished only modest yields of **2**[13] (73% and 63%, respectively). Mg(0), with the largest reduction potential of all the metals tested, gave rise to a disappointing 5% of the desired THF ether. The most consistent results were obtained with Mn(0) powder.[14] Just 1.5 equiv of Mn(0) provided an excellent yield of **2** (Table 1, entry 1); fewer equivalents of Mn(0) led to proportionately lower yields of **2**.

Likewise, secondary[12] (entry 2), allylic[15] (entry 3), and benzylic[12] (entry 4) THF ethers were easily obtained from alcohols **3**, **5**, and **7**, respectively. Less reactive hydroxyls such as phenol (**9**) and the highly hindered dimethylphenylcarbinol **11** were transformed without complication into their THF derivatives **10**[12] (entry 5) and **12**[12] (entry 6), respectively. Importantly, a variety of common functionality proved compatible with the standard reaction conditions. For instance, methylenedioxy (entry 7), acetonide (entry 8), and silyl (entry 9) groups were all well tolerated and accordingly led to THF ethers **14**,[12] **16**,[15] and **18**.[15] The successful protection of labile 1,1,1-trichloride **19**,[12] acid sensitive epoxide **21**, and α,β-unsaturated steroidal ketone **23**, all in excellent yields, are especially notable.[15]

The mechanism of the tetrahydrofuranylation like most parallels as that of the $CrCl_2$-mediated reaction,[12] that is, single electron transfer from Mn(0)[16] to CCl_4 during the initiation phase generates the well-known trichloromethyl radical (Scheme 1). This radical subsequently abstracts a hydrogen atom from the tetrahydrofuran methylene adjacent to oxygen in the first step of the propagation phase forming chloroform and a heteroatom stabilized radical that is chlorinated by a second molecule of CCl_4. The newly evolved trichloromethyl radical can either propagate the reaction via hydrogen atom abstraction from another equivalent of tetrahydrofuran or is further reduced and in the process consumes the HCl produced during the etherification step.

Keywords: Protecting group; Manganese; Radical reaction; Tetrahydrofuran.

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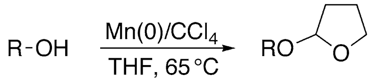
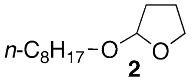
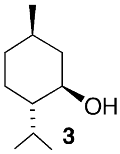
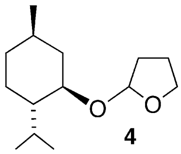
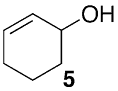
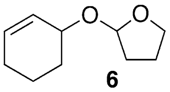
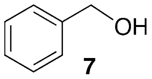
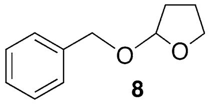
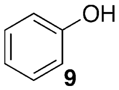
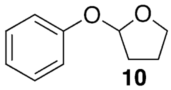
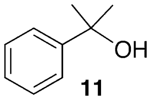
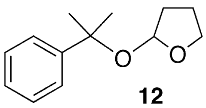
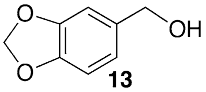
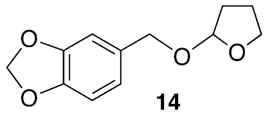
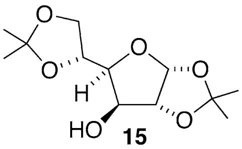
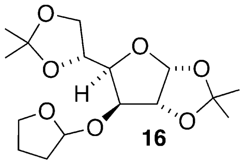
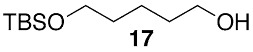
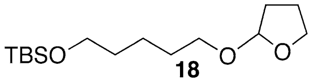
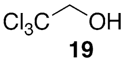
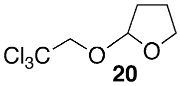
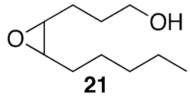
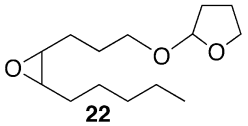
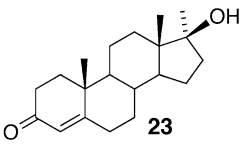
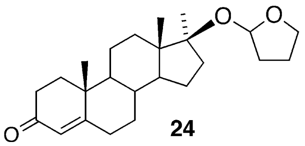
doi:10.1016/j.tetlet.2006.05.081

Table 1. Preparation of THF ethers



Entry	Alcohol	THF ether	Time (h)	Yield (%)
1	n-C_8H_{17}-OH **1**	 **2**	15	96
2	 **3**	 **4**	15	99[a]
3	 **5**	 **6**	7	85[a]
4	 **7**	 **8**	4	93
5	 **9**	 **10**	6	91
6	 **11**	 **12**	6	88[a]
7	 **13**	 **14**	14	90
8	 **15**	 **16**	6	99[a,b]
9	 **17**	 **18**	3	96
10	 **19**	 **20**	4	88[a]
11	 **21**	 **22**	13	85[a]
12	 **23**	 **24**	8	91[a,b]

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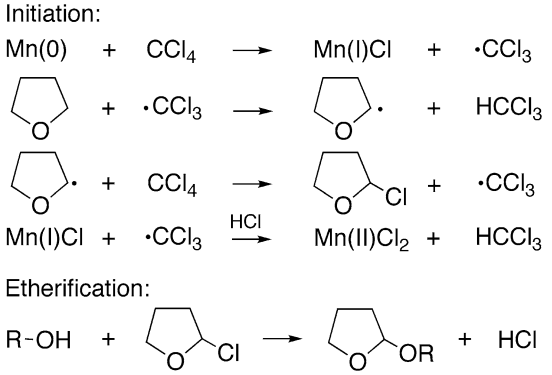
[a] ~1:1 Diastereomeric mixture by NMR analysis.

[b] 2 equiv each of Mn(0) and CCl_4 were used.



Scheme 1.

General Procedure: CCl_4 (0.145 mL, 1.5 mmol, 1.5 equiv) was added via syringe to a stirring suspension of alcohol (1 mmol, 1.0 equiv) and Mn(0) powder[14] (83 mg, 1.5 mmol, 1.5 equiv) in anhydrous THF (3 mL) under an argon atmosphere and then warmed to 65 °C. A white precipitate of $MnCl_2$ accumulated during the course of the reaction. After the time periods indicated in Table 1, the reaction mixture was cooled to room temperature, diluted with ether (20 mL), filtered through a pad of silica gel, and the filter cake was washed with ether. In most cases, the residue after concentration in vacuo required no further purification, but if necessary, was passed over a SiO_2 column to give the corresponding THF ether in indicated yields (Table 1).

In summary, an operationally simple, inexpensive, and efficient method to make THF ethers has been developed. Its mild reaction conditions and general tolerance of most functional groups make it widely applicable in the synthesis of complex molecules.

Acknowledgments

Financial support was provided by the Robert A. Welch Foundation, NIH (GM31278, DK38226), and Ministère délégué à l'Enseignement supérieur et à la Recherche.

References and notes

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14. Mn(0) powder was purchased from Aldrich Chem. (99%, −325 mesh). While it could be weighed and handled without special precautions, it was stored under an inert atmosphere to help retain its full reactivity.
15. Spectral data for **6** (~1:1 diastereomeric mixture): ^1H NMR (300 MHz, $CDCl_3$) δ 5.86–5.68 (m, 4H), 5.32 (dd, $J = 4.2$, 2.1 Hz, 1H), 5.29 (dd, $J = 4.2$, 1.8 Hz, 1H), 4.18–4.11 (m, 2H), 3.94–3.82 (m, 4H), 2.02–1.84 (m, 20H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 131.0, 130.6, 129.2, 127.9, 103.3, 102.0, 70.9, 69.7, 66.8 (2C), 32.9, 32.7, 30.5, 28.4, 25.3, 25.2, 23.7 (2C), 19.6, 19.4; HRMS (CI, CH_4) calcd for $C_{10}H_{17}O_2$ (M+1) *m/e* 169.1228, found 169.1230. Compound **16** (~1:1 diastereomeric mixture): ^1H NMR (400 MHz, $CDCl_3$) δ 5.87 (d, $J = 4.0$ Hz, 1H), 5.84 (d, $J = 3.2$ Hz, 1H), 5.31 (t, $J = 2.8$ Hz, 1H), 5.24 (br s, 1H), 4.60 (d, $J = 3.2$ Hz, 1H), 4.51 (d, $J = 3.6$ Hz, 1H), 4.31 (d, $J = 3.6$ Hz, 1H), 4.26–4.16 (m, 4H), 4.11–3.99 (m, 2H), 3.98–3.86 (m, 6H), 1.99–1.83 (m, 8H), 1.49 (s, 6H), 1.42 (s, 6H), 1.34 (s, 6H), 1.31 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 111.8, 109.0, 108.8, 105.3, 101.2, 84.2, 82.4, 81.1, 80.2, 76.4, 72.8, 72.7, 67.4, 67.20, 67.16, 67.1, 32.4, 27.0, 26.9, 26.7, 26.3, 25.5, 23.4, 23.0. Compound **18** (~1:1 diastereomeric mixture): ^1H NMR (400 MHz, $CDCl_3$) δ 5.09 (d, $J = 3.2$ Hz, 1H), 3.88–3.81 (m, 2H), 3.68–3.60 (m, 3H), 3.40–3.34 (m, 1H), 2.01–1.79 (m, 4H), 1.61–1.54 (m, 4H), 0.91 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 103.9, 67.1, 66.8, 63.1, 32.4, 29.7, 26.3, 26.1 (3C), 23.6, 18.5, −5.1 (2C); HRMS (CI, CH_4) calcd for $C_{15}H_{33}O_3Si$ (M+1) *m/e* 289.2199, found 289.2198. Compound **22**: 1:1 diastereo mixture; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 5.38$ (dd, $J = 4.2$, 1.8 Hz, 1H), 5.13 (dd, $J = 4.2$, 1.8 Hz, 1H), 3.89–3.59 (m, 10H), 3.50–3.41 (m, 2H), 1.84–1.71 (m, 16H), 1.58–1.20 (m, 18H), 0.81–0.77 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 104.0$, 103.0, 82.6, 80.0, 78.1, 77.8, 77.7, 68.5, 68.0, 67.0, 66.8, 32.6, 32.5, 32.2, 32.1, 32.0, 30.8, 28.5, 27.3, 26.2, 26.0, 25.6, 25.2, 23.7, 22.8, 22.7, 14.1 (2C); HRMS (CI, CH_4) calcd for $C_{14}H_{27}O_3$ (M+1) *m/e* 243.1960, found 243.1960. Compound **24** (~1:1 diastereomeric mixture): ^1H NMR (300 MHz, $CDCl_3$) δ 5.72 (s, 2H), 5.39–5.37 (m, 1H), 5.34–5.32 (m, 1H), 3.94–3.88 (m, 2H), 3.79–3.74 (m, 2H), 2.50–2.22 (m, 8H), 2.19–1.24 (m, 26H), 1.24 (s, 3H), 1.22 (s, 3H), 1.21 (s, 3H), 1.19 (s, 3H), 1.02–0.86 (m, 4H), 0.85 (s, 3H), 0.84 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.8 (2C), 171.1, 171.6, 124.0 (2C), 100.0, 99.6, 86.2, 85.8, 66.9, 66.7, 54.0 (2C), 49.9, 49.8 (2C), 46.6, 46.1, 38.8, 36.6, 36.5, 36.4, 36.1, 35.9 (2C), 34.1 (2C), 33.6, 33.5, 33.0 (2C), 32.6, 32.0 (2C), 31.7, 24.1 (2C), 23.7, 23.3, 23.2, 22.5, 20.9, 20.8, 17.6 (2C), 14.4, 14.2; HRMS (CI, CH_4) calcd for $C_{24}H_{37}O_3$ (M+1) *m/e* 373.2743, found 373.2740.
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