ORGANIC
LETTERS

2000
Vol. 2, No. 4
485−487

A Convenient Synthesis of 2-Tetrahydrofuranyl Ethers

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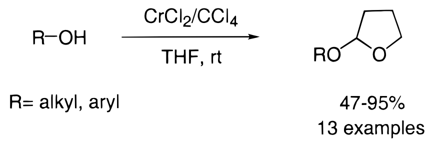
Received December 10, 1999

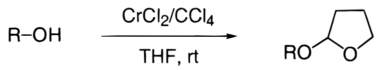
ABSTRACT



A wide spectrum of alcohols and phenols are readily transformed to the corresponding 2-tetrahydrofuranyl ethers in good to excellent yields using $CrCl_2$ and CCl_4 in THF under nearly neutral conditions at room temperature.

Tetrahydrofuranylation is a well-established tactic for the protection of hydroxyl and phenolic functions.[1] The resultant 2-tetrahydrofuranyl (THF) ethers are acid labile and can be selectively cleaved in the presence of the more commonly used tetrahydropyranyl (THP) ethers.[1,2] While a variety of methods[2−8] are available for the introduction of THF ethers, few are inexpensive, convenient, and use commercial reagents. We disclose herein a new and operationally simple procedure for the preparation of 2-tetrahydrofuranyl ethers from alcohols or phenols using $CrCl_2$ and CCl_4 in THF at room temperature under nearly neutral conditions (Scheme 1).

Scheme 1



The scope of the protection protocol was explored using a representative panel of alcohols (Table 1).

Simple, primary alcohols such as 2-phenylethanol (**1**) afforded excellent yields of the corresponding 2-tetrahydrofuranylated alcohol **2** (entry 1).[14] Likewise, secondary (entry 2), allylic (entry 3), benzylic (entry 4), and furfuryl (entry 5) THF ethers were obtained from alcohols **3**, **5**, **7**, and **9**, respectively, in good yields. Less reactive alcohols such as phenol (**11**) and the highly hindered dimethylphenylcarbinol (**13**) gave rise to their THF derivatives **12** (entry 6) and **14**

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(1) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Chemistry*, Wiley: New York, 1999; Chapter 2, pp 57−58.

(2) 2-Chlorotetrahydrofuran: Kruse, C. G.; Broekhof, N. L. J. M.; van der Gen, A.; *Tetrahedron Lett.* **1976**, *20*, 1725−1728.

(3) Dihydrofuran: Sosnovsky, G. *J. Org. Chem.* **1965**, *33*, 2441. Sosnovsky, G.; *Tetrahedron* **1961**, *13*, 241. Hon, Y. S.; Lee, C. F *Tetrahedron Lett.* **1999**, *40*, 2389−2392.

(4) 2-Chlorotetrahydrofuran: Kruse, C. G.; Jonkers, F. L.; Dert, V.; van der Gen, A. *Recl. Trav. Chim. Pays-Bas* **1979**, *424*, 371.

(5) Acetal exchange: Kruse, C. G.; Poels, E. K.; Jonkers, F. L.; van der Gen, A. *J. Org. Chem.* **1978**, *43*, 3548.

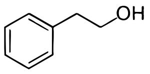
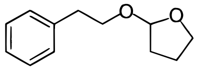
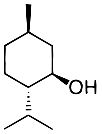
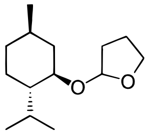
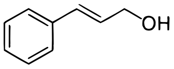
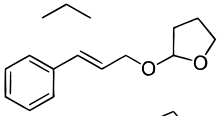
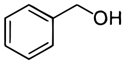
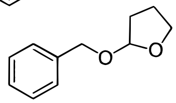
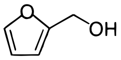
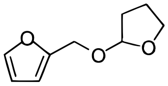
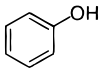
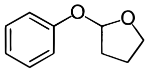
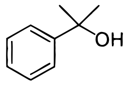
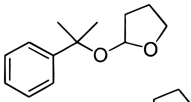
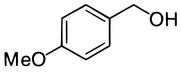
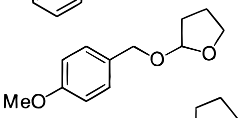
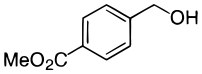
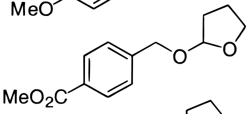
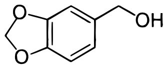
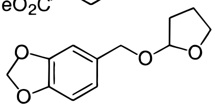
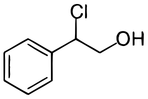
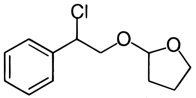
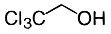
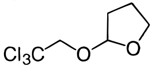
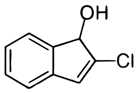
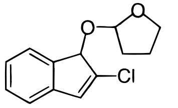
(6) THF/ceric ammonium nitrate: Maione, A. M.; Romeo, A. *Synthesis* **1987**, 250.

(7) THF/tetrabutylammonium peroxydisulfate: Jung, J. C.; Choi, H. C.; Kim, Y. H. *Tetrahedron Lett.* **1993**, *34*, 3581−3584.

(8) *p*-TsCl/NaH/THF: Yu, B.; Hui, Y. *Synth. Commun.* 1**995**, *25* (14), 2037−2042.

10.1021/ol991332f CCC: $19.00

Table 1. Tetrahydrofuranylation of Alcohols

Entry	Alcohol		THF ether		Yield^a %
1		**1**		**2**	90
2		**3**		**4**	85^b
3		**5**		**6**	92
4		**7**		**8**	95
5		**9**		**10**	91
6		**11**		**12**	58
7		**13**		**14**	47
8		**15**		**16**	95
9		**17**		**18**	91
10		**19**		**20**	84
11		**21**		**22**	82^b
12		**23**		**24**	87
13		**25**		**26**	90^b

a: Isolated yield, b: Diastereomeric mixture

(entry 7), respectively, but in more modest yields. For these examples, the unreacted starting alcohols could be easily recovered for recycling.

Importantly, the reaction conditions are compatible with many common functional groups. Indeed, substrates containing ether (entry 8), ester (entry 9), or acetal (entry 10) groups are suitable substrates and furnish THF ethers **16**, **18**,[9] and **20**, respectively. The smooth conversion of benzylic chlorohydrin **21**, trichloroethanol **23**, and vinyl chloride **25** to THF ethers **22**, **24**,[10] and **26**, respectively, is notable. Neither reduction nor transmetalation of the starting alcohols or products was detected. This suggests that there is initially a selective reaction between the CCl_4 and $CrCl_2$ reagents and that there is not a direct reaction with other reaction components.

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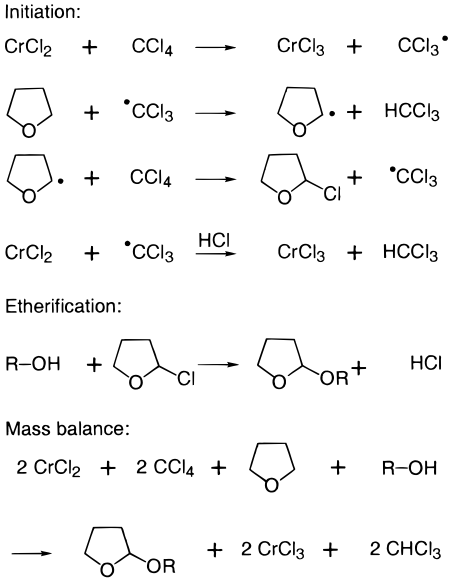
(9) NMR ^{1}H ($CDCl_3$, 300 MHz) of **18**: 1.70−2.20 (m, 4H), 3.70−4.10 (m, 5H), 4.54 (d, $J = 13$ Hz, 1H), 4.77 (d, $J = 13$ Hz, 1H), 5.23 (m, 1H), 7.41 (d, $J = 8$ Hz, 2H), 8.01 (d, $J = 8$ Hz, 2H). ^{13}C NMR ($CDCl_3$, 300 MHz): 23.4, 32.4, 52.1, 67.1, 68.1, 103.4 (acetal), 127.3, 129.2, 129.7, 143.8, 166.9. IR (neat, cm^{-1}): 2995, 1730, 1643, 932.

(10) NMR ^{1}H ($CDCl_3$, 300 MHz) of **24**: 1.70−2.30 (m, 4H), 3.95 (m, 2H), 4.10 (d, $J = 11$ Hz, 1H), 4.25, (d, $J = 11$ Hz, 1H), 5.39 (d, $J = 7$ Hz, 1H). ^{13}C NMR ($CDCl_3$, 300 MHz): 23.1, 32.3, 67.6, 78.7, 97.2 (CCl_3) 104.4 (acetal). IR (neat, cm^{-1}): 2987, 920.

A mechanism consistent with the above observations and stoichiometry is outlined in Scheme 2. Single electron transfer[11] from Cr(II)Cl_2 to CCl_4 during the initiation phase generates the well-known trichloromethyl radical and Cr(III)Cl_3. 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 it is reduced by $CrCl_2$ and in the process consumes the HCl produced during the etherification step.

Scheme 2



Attempts to recycle the Cr(II) utilizing mild reducing agents,[12] thus rendering the tetrahydrofuranylation catalytic in this reagent, have proven somewhat disappointing to date. Etherification of **7** using 10% $CrCl_2$ and manganese[13] (2 equiv) afforded **8** (30%), unreacted **7** (40%), and an unidentified product (30%). Zinc was ineffective and resulted in no THF ether.

We also evaluated the alternative of initially generating the proposed 2-chlorotetrahydrofuran intermediate in situ using a catalytic amount of $CrCl_2$ and excess CCl_4 and then adding the alcohol in the presence of an acid scavenger in a second step. Chlorinations at room temperature with 10% $CrCl_2$ and CCl_4 (4 equiv) for 6 h followed by addition of **7** (1 equiv) and Et_3N (1 equiv) gave mixtures of **8** (25−64%) and recovered starting alcohol.

It appears that both catalytic approaches are limited by competing side reactions such as dimerization of the trichloromethyl radical or decompostion to the well-known dichlorocarbene. We are currently intensively working to improve these crucial processes in order to reduce the quantity of $CrCl_2$ and to further explore the scope of the reaction.

Acknowledgment. Financial support from Instituts de Recherche Pierre Fabre and the CNRS (to R.B.), the Robert A. Welch Foundation, and NIH (GM31278) is gratefully acknowledged.

Supporting Information Available: Experimental procedures and characterization data for the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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[11] Kochi, J. K.; Davis, D. D. *J. Am. Chem. Soc.* **1964**, *86*, 5264. Kochi, J. K.; Singleton, D. M. *J. Am. Chem. Soc.* **1968**, *90*, 1582. Fürstner, A. *Chem. Rev.* **1999**, *99*, 991−1045.

[12] Fürstner, A.; Shi, N. *J. Am. Chem. Soc.* **1996**, *118*, 2533−2534 and references therein.

[13] Fürstner, A.; Shi, N. *J. Am. Chem. Soc.* **1996**, *118*, 12349−12357.

[14] **General Procedure:** A mixture of alcohol **1** (511 mg, 4.18 mmol, 1 equiv) and CCl_4 (1.01 mL, 10.45 mmol, 2.5 equiv) in THF (10 mL) is added via syringe to a room-temperature suspension of $CrCl_2$ (1.285 g, 10.45 mmol, 2.5 equiv) in THF (50 mL), under an argon atmosphere. The resulting brownish mixture gradually develops a reddish coloration characteristic of Cr(III)Cl_3. After 4−6 h at ambient temperature, the reaction is quenched with saturated aqueous NH_4Cl (40 mL) and extracted twice with Et_2O (40 mL). The combined ethereal extracts are washed with brine (60 mL), dried over $MgSO_4$, and concentrated in vacuo. Purification by SiO_2 chromatography (eluent 98/2 hexane/diethyl ether, $R_f = 0.25$) afforded the THF ether **2** (722 mg) in 90% yield.