Vanadium(III) Chloride (VCl_3): Efficient Reagent for the Introduction of Tetrahydrofuran-Based Acetal Protecting Groups for Alcohols[1])

by **Biswanath Das***, **Maddeboina Krishnaiah**, **Vtukuri Saidi Reddy**, and **Keetha Laxminarayana**

Organic Chemistry Division-I, Indian Institute of Chemical Technology, Hyderabad-500007, India (phone: +91-40-7193434; fax: +91-40-7160512; e-mail: biswanathdas@yahoo.com)

Treatment of different types of alcohols with tetrahydrofuran (THF) in the presence of VCl_3 and CCl_4 smoothly afforded the corresponding THF-based acetals in excellent yields. The reaction is fast at room temperature, and several functional groups are tolerated, with no racemization being observed. A radical mechanism, based on $Cl_3C^{\bullet}$ as the active species, is proposed for this novel kind of transformation, which complements the classical tetrahydro-2*H*-pyran-2-yl (THP) protocol.

Introduction. – The protection of hydroxy (OH) functions as tetrahydrofuran-2-yl (THF) ethers is an important strategy in organic synthesis [1]. THF Ethers are acid labile and are preferred sometimes in the synthetic sequence over the more commonly used tetrahydro-2*H*-pyran-2-yl (THP) ethers [1]. Different methods are available for the introduction of the THF moiety [2]. However, the reagents used in many of these methods are often commercially not available, expensive, and toxic, or their introduction may effect other functionalities.

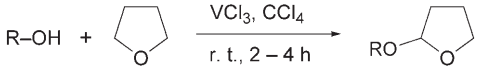
In continuation of our work on the development of useful synthetic methodologies [3], we herein report a novel method for the introduction of the THF (protective) group by C–O bond-formation with a broad variety of alcohols in the presence of VCl_3.

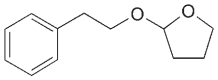
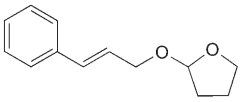
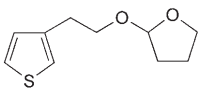
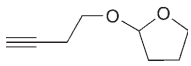
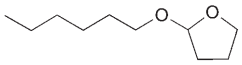
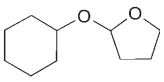
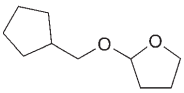
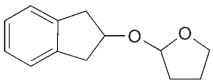
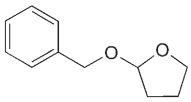
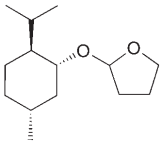
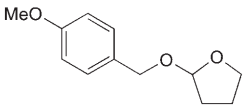
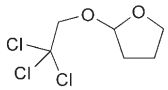
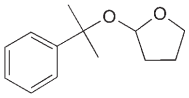
Results and Discussion. – We observed that alcohols can efficiently be protected with the tetrahydrofuranyl group by employing a mixture of VCl_3 and CCl_4 in THF proper. As can be seen from the results presented in the *Table*, primary, secondary, tertiary, allylic, and benzylic alcohols were smoothly converted into the corresponding tetrahydrofuran-2-yl ethers at room temperature. The conversion was complete within 2 to 4 h in all cases, and good-to-excellent yields (75–90%) of the acetals were obtained. Our results demonstrate that even acid-sensitive and oxidation-labile OH groups can conveniently be tetrahydrofuranylated.

A further advantage is the observation that C=C and C≡C bonds (*Table*, *Entries 8* and *9*, resp.) are unaffected, and that ether linkages (*Entry 6*) also remain intact. Further, there was no racemization of a chiral secondary alcohol, *i.e.*, menthol (*Entry 12*). However, we found that acetals do not tolerate the reaction conditions. An

[1]) Part 134 in the series 'Studies on Novel Synthetic Methodologies'.

Table. *Tetrahydrofuranylation of Alcohols.* For details, see *Exper. Part.*



Entry	Product	Yield [%][a])	Entry	Product	Yield [%][a])
1		84	*8*		82
2		78	*9*		70
3		82	*10*		72
4		80	*11*		78
5		85	*12*		90[b])
6		86	*13*		78
7		75			

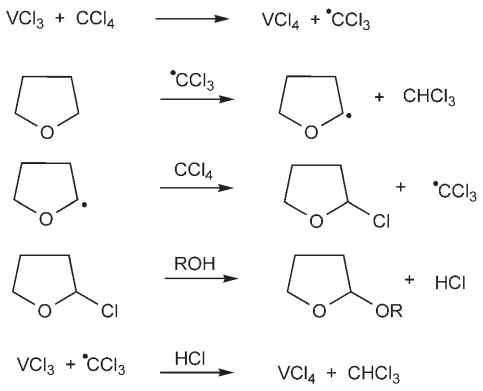
[a]) After chromatographic purification. [b]) 1 : 1 Diastereoisomer mixture.

alcohol containing an acetal, when subjected to the above procedure, gave rise to a mixture of products due to deprotection and re-protection *in situ*.

VCl_3 as a reagent in organic synthesis [4] is relatively unexplored, although it is commercially available and not too expensive. The mechanism of the above conversion possibly involves single electron transfer [2h] from VCl_3 to CCl_4 to form a trichloromethyl radical ($Cl_3C^{\bullet}$; *Scheme*). The latter then abstracts a H-atom from the α-CH_2 group of THF to form $CHCl_3$ and a heteroatom-stabilized radical, which, in turn, may react with another molecule of CCl_4 to form 2-chlorotetrahydrofuran and a new $Cl_3C^{\bullet}$ species. Finally, 2-chlorotetrahydrofuran, on reaction with an alcohol, produces the desired THF ethers. The newly formed $Cl_3C^{\bullet}$ may again propagate the reaction, or it

is reduced to $CHCl_3$ by VCl_3 in the presence of HCl generated during etherification. Notably, when the THF protection of menthol (*Table*, *Entry 12*) was carried out as above, but in the presence of *styrene*, a mixture of the expected THF adduct and (3,3,3-trichloropropyl)benzene was found, indicating the formation of $Cl_3C^{\bullet}$ during the reaction.

Scheme. *Proposed Mechanism for the Formation of THF-Based Acetals from Alcohols in the Presence of VCl_3 and CCl_4*



In conclusion, we have developed a simple, mild, and efficient protocol for the tetrahydrofuranylation of alcohols using the poorly explored reagent VCl_3.

We wish to thank *CSIR* and *UGC* (New Delhi, India) for financial assistance.

Experimental Part

General. ^{1}H-NMR Chemical shifts δ (at 200 MHz in $CDCl_3$) and coupling constants J are provided in ppm (rel. to Me_4Si) and in Hz, resp. Mass-spectrometric (MS) data are reported in m/z.

General Procedure. To a mixture of an alcohol (1 mmol) and CCl_4 (1.5 mmol) in anh. THF (5 ml) was added VCl_3 (1.5 mmol), and the mixture was stirred at r.t. After completion of the reaction (TLC control), H_2O (10 ml) was added, and the mixture was extracted with AcOEt (3×10 ml). The combined org. extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2; hexane/AcOEt) to afford the pure THF ether. The ^{1}H-NMR and MS data of some representatives are given below (see *Table* entries).

2-[2-(Thiophen-3-yl)ethoxy]tetrahydrofuran (see *Entry 2*). ^{1}H-NMR: 7.08 (*d*, $J = 4.5$, 1 H); 6.89 (*dd*, $J = 4.5$, 2.0, 1 H); 6.80 (*d*, $J = 2.0$, 1 H); 5.10 (*m*, 1 H); 3.92–3.80 (*m*, 3 H); 3.60–3.52 (*m*, 1 H); 3.30 (*t*, $J = 7.0$, 2 H); 2.06–1.75 (*m*, 4 H). FAB-MS: 199 ($[M + 1]^+$).

2-(Cyclopentylmethoxy)tetrahydrofuran (see *Entry 4*). ^{1}H-NMR: 5.04 (*m*, 1 H); 3.91–3.76 (*m*, 2 H); 3.48 (*m*, 1 H); 3.19 (*m*, 1 H); 2.18–1.43 (*m*, 11 H); 1.31–1.09 (*m*, 2 H). FAB-MS: 171 ($[M + 1]^+$).

2-[(4-Methoxybenzyl)oxy]tetrahydrofuran (see *Entry 6*). ^{1}H-NMR: 7.21 (*d*, $J = 8.0$, 2 H); 6.90 (*d*, $J = 8.0$, 2 H); 5.11 (*m*, 1 H); 4.59 (*d*, $J = 12.0$, 1 H); 4.36 (*d*, $J = 12.0$, 1 H); 3.95–3.81 (*m*, 2 H); 3.77 (*s*, 3 H); 2.05–1.76 (*m*, 4 H). FAB-MS: 209 ($[M + 1]^+$).

2-(2,3-Dihydro-1H-inden-2-yloxy)tetrahydrofuran (see *Entry 11*). ^{1}H-NMR: 7.19–7.04 (*m*, 4 H); 5.25 (*m*, 1 H); 4.55 (*m*, 1 H); 3.92–3.81 (*m*, 2 H); 3.24–3.10 (*m*, 2 H); 2.99–2.87 (*m*, 2 H); 2.06–1.74 (*m*, 4 H). FAB-MS: 205 ($[M + 1]^+$).

REFERENCES

[1] T. W. Greene, P. G. M. Wuts, 'Protecting Groups in Organic Chemistry', 3rd edn., J. Wiley & Sons, New York, 1999, Chapt. 2, pp. 57 – 58.

[2] a) C. G. Kruse, N. L. J. M. Broekhof, A. Van der Gen, *Tetrahedron Lett.* **1976**, *17*, 1725; b) C. G. Kruse, E. K. Poels, F. L. Jonkers, A. Van der Gen, *J. Org. Chem.* **1978**, *43*, 3548; c) A. M. Maione, A. Romeo, *Synthesis* **1987**, 250; d) J. C. Jung, H. C. Choi, Y. H. Kim, *Tetrahedron Lett.* **1993**, *34*, 3581; e) B. Yu, Y. Hui, *Synth. Commun.* **1995**, *25*, 2037; f) Y. S. Hon, C. F. Lee, *Tetrahedron Lett.* **1999**, *40*, 2389; g) J. M. Barks, B. C. Gilbert, A. F. Parsons, B. Upeandran, *Tetrahedron Lett.* **2000**, *41*, 6249; h) R. Baati, A. Valleix, C. Mioskowski, D. K. Barma, J. R. Falck, *Org. Lett.* **2000**, *2*, 485; i) M. Ochiai, T. Sueda, *Tetrahedron Lett.* **2004**, *45*, 3557; j) J. R. Falck, D. R. Li, R. Bejot, C. Mioskowski, *Tetrahedron Lett.* **2006**, *47*, 5111.

[3] B. Das, R. Ramu, B. Ravikanth, K. R. Reddy, *Tetrahedron Lett.* **2006**, *47*, 779; B. Das, K. R. Reddy, R. Ramu, P. Thirupathi, B. Ravikanth, *Synlett* **2006**, 1756; B. Das, K. Venkateswarlu, H. Holla, M. Krishnaiah, *J. Mol. Catal., Sect. A* **2006**, *253*, 107; B. Das, N. Chowdhury, J. Banerjee, A. Majhi, G. Mahender, *Chem. Lett.* **2006**, *35*, 358.

[4] T. Inokuchi, H. Kawafuchi, S. Torii, *Synlett* **1992**, 510; G. Sabitha, G. S. K. K. Reddy, K. B. Reddy, J. S. Yadav, *Tetrahedron Lett.* **2003**, *44*, 6497.

Received June 29, 2007