

PROTECTION OF HYDROXYL- AND THIOL GROUPS AS 2'-O-TETRAHYDROFURANYL-(THF-)ETHERS.

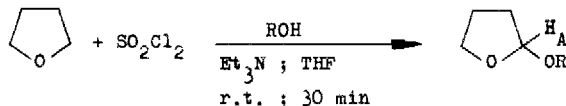
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An extensively used method for the protection of alcohols consists of their conversion into 2'-O-tetrahydropyranyl-(THP-)ethers<sup>1</sup>. Reaction with an excess of 2,3-dihydro-4H-pyran in the presence of trace amounts of (p-toluenesulfonic) acid affords the corresponding THP-ethers in good yields. This protecting group combines stability under a wide range of conditions with susceptibility to facile removal under relatively mild acidic conditions<sup>2,3</sup>.

Since tetrahydrofuran (THF) is known to be more basic than tetrahydropyran<sup>4,5</sup>, hydrolysis of tetrahydrofuran-yl-(THF-)ethers should occur under still milder acidic conditions, while the relative stability towards nucleophilic reagents is expected to be essentially unaffected. Although several THF-ethers, prepared by different methods, have been described<sup>5,6</sup>, application of the tetrahydrofuran-yl group for the protection of alcohols has hitherto been prevented by lack of a general method for the preparation of THF-ethers in high yield from the corresponding alcohols. In this communication we report such a method.

Upon dissolving sulfuryl chloride in THF at room temperature, an exothermic reaction starts after a short induction period (10-30 sec). Addition of the resulting mixture in two portions (see exp. procedure) to a solution of an alcohol in the presence of triethylamine in THF-solution provides, after work-up, the corresponding THF-ethers in excellent yields.

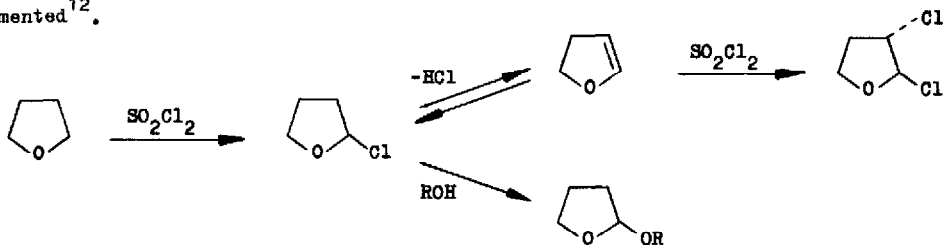


Thus, applying readily available and inexpensive chemicals, this reaction provides a fast and simple procedure for converting alcohols into their THF-ethers. Thiols, phenols, azoles and acids give a similar reaction. The results are summarized in the table. In those cases where literature data of the prepared compounds were available, good agreement is found. The table also gives the chemical shift of H<sub>A</sub>, which appears as a multiplet. The properties of these THF-ethers are currently being investigated. So far we have found that the THF-group is very

stable to base (unaffected by 1N KOH/THF (1/1) at reflux temperature) and to the conditions employed in Grignard, Wittig and lithium aluminum hydride reactions.



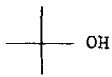
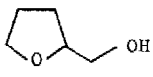
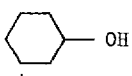
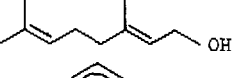
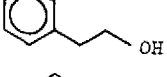
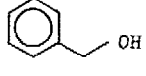
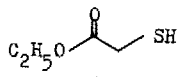
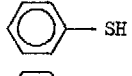
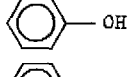
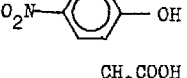

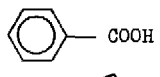
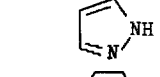


The THF-group can be quantitatively removed by hydrolysis under very mild acidic conditions. Under standard conditions<sup>2,3</sup>, the THF-ether of cyclohexanol was hydrolysed appreciably faster than the corresponding THP-ether. In acetic acid-water-THF (3:1:1)<sup>2</sup> - mixtures at 25°C, hydrolysis proceeded to 90% completion in 30 min for the THF-ether and in 160 min for the THP-ether (0.1 M each). In 0.01 N HCl - THF<sup>3</sup> (1:1 - two layers!), at 25°C, the half-time for hydrolysis is 10 min for the THF-ether and 75 min for the THP-ether (0.1 M each). Using milder acidic conditions (stirring at room temperature for 3 hrs in equal amounts of THF and demineralized water at pH 5) the THF-ether was 90% hydrolysed, while the THP-ether remained virtually unaffected, thus demonstrating the possibility of selective removal.

The mechanism of the exothermic reaction of sulfuryl chloride with THF may well involve  $\alpha$ -chlorination by a radical pathway as the first step. Vilsmeier et al. have reported the preparation of 2-chloro-THF in moderate yields by reaction of THF with either iodobenzene dichloride<sup>8a</sup> or sulfuryl chloride<sup>8b</sup> under irradiation in the presence of a radical initiator. Middelbos<sup>9</sup> however has reported an ionic reaction of THF with sulfuryl chloride in the presence of cyclohexene. NMR-spectra taken from dilute sulfuryl chloride/THF reaction mixtures reveal the presence of both 2-chloro-THF ( $\delta H_A = 6.40$  (multiplet)) and trans-2,3-dichloro-THF ( $\delta H_A = 6.25$  (singlet))<sup>10,11</sup>. When equal amounts of THF and sulfuryl chloride are allowed to react, only the 2,3-dichloro product is found. Under the conditions employed, the primary monochloro compound apparently loses hydrogen chloride to form 2,3-dihydrofuran. The formation of vicinal dichlorides from the reaction of olefins with sulfuryl chloride is well documented<sup>12</sup>.



We found that trans-2,3-dichloro-THF is unreactive towards alcohols under the conditions employed. Its formation therefore does not affect the conversion of alcohols with the monochloro compound. It only necessitates the use of more than one equivalent of sulfuryl chloride. The remarkable reactivity of 2-chloro-THF and the application of the sulfuryl

**TABLE**  
Conversion of substrates RX-H into 2'-tetrahydrofuranyl derivatives.

SUBSTRATE	YIELD (%)	$\delta H_A$	$n_D$
1. 	98	5.08	$n_D^{24} = 1.4408$
2. 	96 <sup>1)</sup>	5.22	$n_D^{24} = 1.4123$ <sup>2)</sup>
3. 	98 <sup>1)</sup>	5.40	$n_D^{24} = 1.4180$ <sup>3)</sup>
4. 	93	5.13	$n_D^{21} = 1.4562$
5. 	98	5.28	$n_D^{24} = 1.4580$ <sup>4)</sup>
6. 	96	5.08	$n_D^{22} = 1.4698$
7. 	98	5.06	$n_D^{21} = 1.5007$
8. 	96	5.18	$n_D^{22} = 1.5062$
9. 	90	5.50	$n_D^{20} = 1.4829$
10. 	95	5.58	$n_D^{24} = 1.5491$
11. 	82	5.74	$n_D^{22} = 1.5112$
12. 	86	5.84	m.p. = 75.5-76°C
13. 	85	6.24	$n_D^{21} = 1.4323$
14. 	90	6.39	m.p. = 76-77°C <sup>5)</sup>
15. 	94	6.51	$n_D^{23} = 1.5197$ <sup>6)</sup>
16. 	87	5.94	$n_D^{23} = 1.4911$ <sup>7)</sup>
17. 	97	6.20	$n_D^{24} = 1.5532$

1) from GLC; 2) lit. <sup>6b</sup>  $n_D^{20} = 1.4147$ ; 3) lit. <sup>6b</sup>  $n_D^{20} = 1.4193$ ; 4) b.p.<sub>0.5</sub> : 46°C, lit. <sup>5</sup>: b.p.<sub>10</sub> : 90-2°C; 5) lit. <sup>8b</sup> m.p.: 76-77°C; 6) b.p.<sub>0.04</sub> : 86°C; lit. <sup>6c</sup> : b.p.<sub>0.2</sub> : 96-100°C, 7) 1,2,4-triazole afforded a lower yield (71%), probably because of its higher basicity.  $n_D^{23} = 1.4882$ ;  $\delta H_A = 6.06$ ; imidazole does not react at all.

chloride reaction to other (thio)ethers with the aim of introducing other potentially useful protecting groups<sup>2,6,7</sup> are the subject of further study.

#### General Procedure:

The alcohol (10 mMole) and triethylamine (distilled from KOH; 45 mMole) are dissolved in 20 ml of THF (freshly distilled from  $\text{LiAlH}_4$ ) in a nitrogen atmosphere<sup>13</sup>. Sulfuryl chloride (freshly distilled; 10 mMole) is dissolved in THF (10 ml). A yellow green colour develops. An exothermic reaction starts after 10-30 sec. The colour gradually disappears. After allowing the mixture to cool to about 30°C, it is added rapidly to the stirred solution of the alcohol. Triethylamine.HCl precipitates instantly. The temperature of the reaction mixture rises initially to 40-50°C, but drops quickly to room temperature. After 15 min, another 10 mmoles of the sulfuryl chloride/THF reagent is added. Stirring for another 15 min results in quantitative conversion of the alcohol (GLC). The reaction mixture is cooled to 0°C and the precipitated triethylamine.HCl is removed by filtration. Evaporation of the filtrate gives a yellow oil, which is extracted twice with petroleum ether (b.p. 60-80°C) or ether. Drying ( $\text{MgSO}_4$ ) of the decanted ethereal layers and evaporation of the solvent affords the THF-ethers, as compounds of better than 95% purity (GLC)<sup>14</sup>. The yields are listed in the Table.

#### References and Notes

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11. This also holds for mixtures obtained by reaction of THF with high concentrations of iodobenzene dichloride (0°, 1/2 h). This deviation from the results obtained by Vilsmeier et al.<sup>8a,b</sup>, who state that neither sulfuryl chloride nor iodobenzene dichloride engages in secondary reactions with 2-chloro-THF, may well be the result of the strong concentration dependence of this secondary reaction.
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13. Alternatively, acetonitrile may be used as a solvent.
14. Satisfactory analyses (GLC, IR, NMR, MS) were obtained for all compounds described.