Pergamon

Tetrahedron Letters 41 (2000) 6249–6252

TETRAHEDRON
LETTERS

An efficient and extremely mild method for protecting alcohols as 2-tetrahydrofuranyl ethers

Jenny M. Barks,[a] Bruce C. Gilbert,[b] Andrew F. Parsons[b,]* and Bala Upeandran[b]

[a]*Zeneca Agrochemicals, Process Technology Department, Leeds Road, Huddersfield HD2 1FF, UK*
[b]*Department of Chemistry, University of York, Heslington, York YO10 5DD, UK*

Received 25 May 2000; accepted 20 June 2000

Abstract

Reaction of primary or secondary alcohols with $BrCCl_3$ and tetrahydrofuran, usually in the presence of 2,4,6-collidine, leads to the formation of 2-tetrahydrofuranyl ethers in good to excellent yield (56–92%). The reaction mechanism is believed to involve a free-radical chain reaction. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: acetals; protecting groups; radicals and radical reactions; oxygen heterocycles.

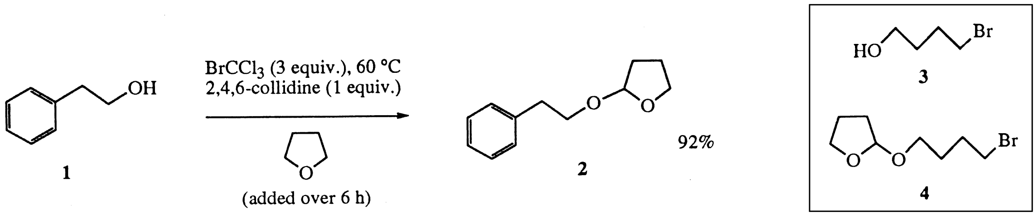
A very important method for protecting alcohol functional groups in synthesis involves their conversion to acetals.[1] Conversion to tetrahydropyranyl (THP) ethers is very common and these are generally prepared from an acid-catalysed addition of the alcohol to dihydropyran (DHP). The resultant THP ethers are stable to strongly alkaline conditions, Lewis acids or organometallic reagents (although low temperatures are often required), and can be hydrolysed back to the alcohol using mild acid. In comparison, the related tetrahydrofuranyl (THF) ethers offer the same stability to a variety of alkaline and organometallic conditions, but have the advantage that they can be hydrolysed under even milder acidic conditions. Indeed, THF ethers can be selectively cleaved in the presence of THP ethers. Although a number of methods have been reported for the synthesis of THF ethers (using, for example, THF in combination with SO_2Cl_2,[2] CAN,[3] TsCl/NaH[4] or $CrCl_2/CCl_4$[5]) this paper reports a new approach to these derivatives using THF and $BrCCl_3$, usually in the presence of 2,4,6-collidine. This method allows the efficient protection of a variety of primary and secondary alcohols under very mild reaction conditions. The reagents are inexpensive and also less toxic than those previously employed to make THF ethers.

Our initial experiments involved the reaction of 2-phenylethanol **1** with $BrCCl_3$ and THF under a variety of conditions (Scheme 1). For example, when alcohol **1**(10 mmol, 1 equiv.) was added to $BrCCl_3$ (3 equiv.) in (degassed) THF (15 cm^3) and the solution stirred overnight at reflux (under

---

* Corresponding author. Tel: +44 1904 432608; fax: +44 1904 432516; e-mail: afp2@york.ac.uk

0040-4039/00/$ - see front matter © 2000 Elsevier Science Ltd. All rights reserved.
PII: S0040-4039(00)01045-5



Scheme 1.

an atmosphere of nitrogen), the desired THF ether **2** was formed in only 8% yield.[6] TLC analysis indicated the remaining starting material and the formation of bromoalcohol **3**, but the major by-product was bromoacetal **4**, which proved difficult to separate from **2** on column chromatography. The use of dry (degassed) THF, or the addition of AIBN, had little effect on the reaction and **2** was isolated in similar yield (9–16%). However, when THF was added slowly to alcohol **1** and $BrCCl_3$ (at 60°C) over 6 h, in the presence of 2,4,6-collidine (1 equiv.), then the yield of **2** improved to an excellent 92% (after column chromatography).[7]

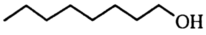
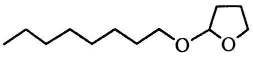
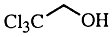
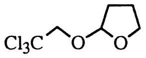
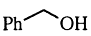
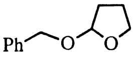
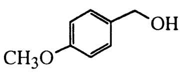
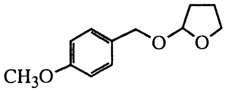
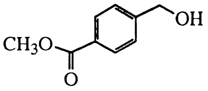
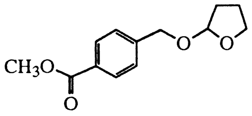
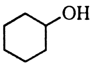
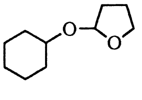
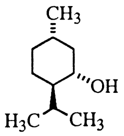
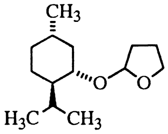
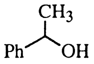
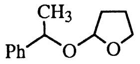
The protection of alternative alcohols, under similar reaction conditions, was then investigated as shown in Table 1. Hence the reaction of 1-octanol gave the desired THF ether in 88% yield, in the absence of 2,4,6-collidine (entry 1). Whereas 1-octanol was efficiently protected in the absence of base, for most alcohols, a good yield of the THF ether was only realised when 2,4,6-collidine was added to the reaction mixture. The addition of 2,4,6-collidine also minimised the formation of the by-product bromoalcohol **3**, which simplified product purification and therefore subsequent reactions (entries 2–8) were carried out in the presence of 2,4,6-collidine. The protection of primary benzylic alcohols is also possible (entries 3–5) although for these reactions, competitive (alcohol to aldehyde) oxidation was observed and benzaldehyde derivatives were isolated in 3–21% yield. Secondary alcohols can be protected as shown by the reactions of cyclohexanol, (1*S*,2*R*,5*S*)-menthol and 1-phenylethanol (entries 6–8). For these reactions, the presence of 2,4,6-collidine proved crucial. For example, the reaction of cyclohexanol in the presence of alternative nitrogen bases (e.g. DBU, Et_3N or DMAP), or the reaction of (1*S*,2*R*,5*S*)-menthol in the absence of 2,4,6-collidine, gave the corresponding THF ethers in 17–37% yield.

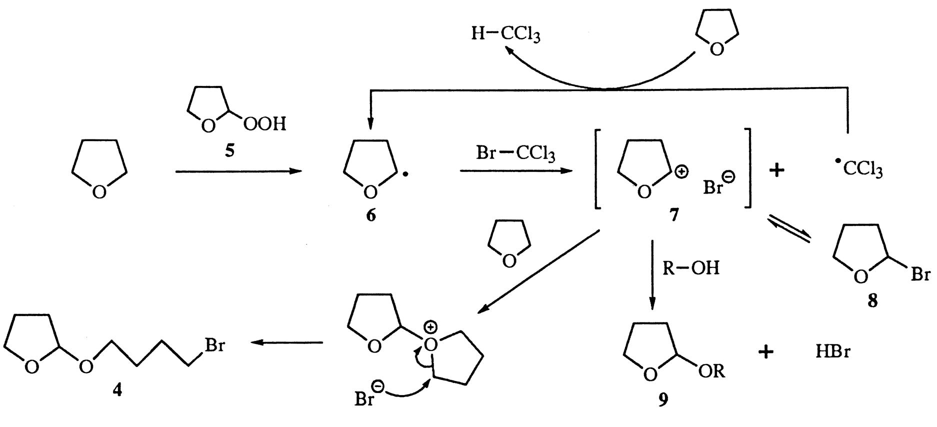
Although both primary and secondary alcohols were efficiently protected, reaction of tertiary alcohols [such as $PhC(OH)Me_2$] was more problematic. The reactions proved to be very slow and yields of the THF ethers were, at best, modest. Low yields were also observed when using allylic alcohols and reaction with cinnamyl alcohol, for example, gave the corresponding THF ether in only 20% yield.

The proposed mechanism for the formation of the THF ethers is outlined in Scheme 2. It is anticipated that autoxidation of THF generates a small quantity of hydroperoxide **5** which produces oxygen-centred radicals (on homolysis of the weak oxygen—oxygen bond) which react with THF to generate radical **6**. This radical could react with $BrCCl_3$ to give bromide **8** in one of two ways. Firstly, by abstraction of a bromine atom from $BrCCl_3$ or, alternatively, radical **6** could be oxidised by $BrCCl_3$ (in a single electron transfer process) to produce carbocation **7** which subsequently reacts with the bromide anion. The resulting bromide **8** can then react with the alcohol, presumably via the intermediate carbocation **7**, to generate the desired THF ether **9**. Alternatively, carbocation **7** could react with THF to give the byproduct bromoacetal **4**. Slow addition of THF (to the alcohol and $BrCCl_3$) therefore increases the yield of **9** because a low

Table 1

Protection of alcohols as tetrahydrofuranyl ethers. [a]Carried out in the absence of 2,4,6-collidine. [b]Yield based on recovered starting material. [c]Benzaldehyde was also isolated in 3% yield. [d]4-Methoxybenzaldehyde was also isolated in 21% yield. [e]Methyl 4-formylbenzoate was also isolated in 11% yield. [f]Carried out in the presence of DBU rather than 2,4,6-collidine. [g]Isolated as a mixture of diastereomers. [h]Acetophenone was also isolated in 11% yield.

Entry	Alcohol	THF Ether	Yield (%)
1			88[a]
2			56 (88[b])
3			87[c]
4			71[d]
5			71[e]
6			87 (33[f])
7			60[g] (37[a])
8			57[g,h] (70[b])



Scheme 2.

concentration of THF minimises the competing pathway (leading to **4**). The formation of **9** results in the formation of HBr which can be quenched by reaction with 2,4,6-collidine, and this reduces the (acidic) ring-opening of THF, leading to byproduct **3**. It should also be noted that the trichloromethyl radical is formed during the reaction and it is likely that this abstracts an α-hydrogen atom from THF so as to regenerate radical **6**.

The formation of THF ethers derived from both primary and secondary alcohols can therefore be carried out efficiently by reaction with $BrCCl_3$ and THF, generally in the presence of 2,4,6-collidine. For efficient conversions, the reaction is limited to primary and secondary alcohols. Reactions of tertiary alcohols are much slower and lower yielding, presumably due to steric effects, while competitive hydrogen-atom abstraction and/or radical addition (to the alkene double bond) may explain the low yields observed when using allylic alcohols. This extremely mild and simple method of alcohol protection has the advantage of using readily available and economical reagents. The method works extremely well when using THF; attempts at forming THP ethers, by reaction of alcohols with THP, were considerably lower yielding.[8] This is presumably due to the slower rate of autoxidation of THP compared to THF.[9]

Acknowledgements

We would like to thank the EPSRC and Zeneca Agrochemicals for a CASE award (to B.U.).

References

1. Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Chemistry*; Wiley: New York, 1999; Chapter 2.
2. Kruse, C. G.; Broekhof, N. L. J. M.; van der Gen, A. *Tetrahedron Lett.* **1976**, 1725–1728.
3. Maione, A. M.; Romeo, A. *Synthesis*, **1987**, 250–251.
4. Yu, B.; Hui, Y. *Synth. Commun.* **1995**, *25*, 2037–2042.
5. Baati, R.; Valleix, A.; Mioskowski, C.; Barma, D. K.; Falck, J. R. *Org. Lett.* **2000**, *2*, 485–487.
6. All new compounds exhibited satisfactory spectral and analytical (high resolution mass) data.
7. *Typical procedure*. To a stirred solution of the alcohol (5 mmol, 1 equiv.), 2,4,6-collidine (1 equiv.) and $BrCCl_3$ (3–3.75 equiv.) was added degassed THF (HPLC grade, 15–35 cm^3) over 6 h while the mixture was heated at 60°C (under an atmosphere of nitrogen). After 8–15 h, sat. aq. ammonium chloride (20 cm^3) was added and the mixture extracted three times with diethyl ether (3×20 cm^3). The (combined) organic layer was washed with water, followed by brine, dried ($MgSO_4$) and evaporated under reduced pressure. Purification by column chromatography afforded the THF ethers as oils (56–92%).
8. Reaction of 1-octanol with THP, under the same reaction conditions as for the THF reaction, gave the corresponding THP ether in 6% yield.
9. Howard, J. A.; Ingold, K. U. *Can. J. Chem.* **1969**, *47*, 3809–3815.