Pergamon

Tetrahedron Letters, Vol. 38, No. 26, pp. 4679-4682, 1997
© 1997 Elsevier Science Ltd
All rights reserved. Printed in Great Britain
0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00965-9

An Improved Williamson Etherification of Hindered Alcohols Promoted by 15-Crown-5 and Sodium Hydride

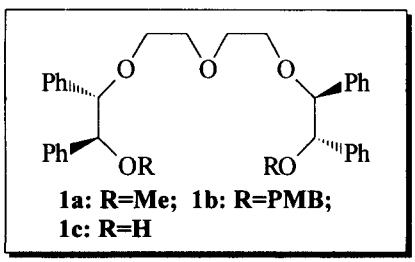
Helen C. Aspinall, Nicholas Greeves*, Wai-Man Lee,
Edward G. McIver, Peter M. Smith

Department of Chemistry, Robert Robinson Laboratories, University of Liverpool,
PO Box 147, Liverpool L69 7ZD, United Kingdom.

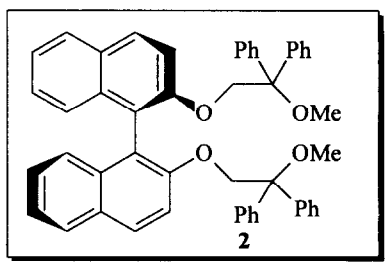
Abstract: 15-crown-5 greatly facilitates Williamson ether synthesis when sodium hydride base is used in THF solvent. This mild yet versatile procedure has been employed in the synthesis of new homochiral polyether ligands and bis-allylic ethers which are inaccessible by conventional methods.
© 1997 Elsevier Science Ltd.

One of the most common procedures for the synthesis of unsymmetrical ethers was originally introduced by Williamson,[1] and involves the reaction of alkoxides with alkyl halides. Although this method has been known for nearly 150 years, there are few variants which allow secondary-primary or tertiary-primary ether combinations to be prepared easily in high yields. A variety of bases have been employed for generation of the metal alkoxides, including alkali metals, sodamide, and alkali metal hydrides.[2] When sodium hydride is used, reaction times and yields are often unacceptable and usually require the use of dipolar aprotic solvents, DMSO and DMF,[3] sometimes with the aid of phase-transfer catalysts.[4,5] Owing to their toxicity and difficulty of removal, the use of these solvents is best avoided if possible. We report that the use of 15-crown-5 greatly facilitates the preparation of hindered ethers in THF which are inaccessible using traditional techniques.

We are interested in the convenient preparation of new homochiral lanthanide polyether complexes for use in asymmetric versions of reactions catalytic in lanthanide triflates, notably our carbonyl allylation with allyltributyltin.[6] Target ligands include **1** and **2**, derived from optically pure hydrobenzoin and binaphthol respectively. Both of these targets require a routine preparation of hindered ethers in high yields.



1a: R=Me; 1b: R=PMB;
1c: R=H

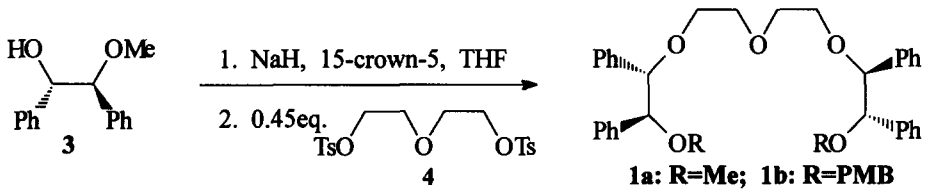


2

Our strategy for chiral polyether ligand **1a** required the double coupling of the chiral α–hydroxymethyl ether **3** to diethyleneglycol ditosylate **4**. Numerous sets of conditions were employed, ranging from the use of aprotic dipolar solvents to iodide catalysts, all with little or no success. This lack of reactivity was attributed to the strong association of the sodium cation with the alkoxide anion. We believed that the nucleophilicity could by increased by solvation of the ion pair with 15-crown-5, since it has been successfully utilised in the preparation of vinyl oxiranes through intramolecular cyclisation.[7] Modified 15-crown-5 has been employed in phase-transfer catalysed Michael additions.[8]

When **3** was treated with a small excess of sodium hydride in THF followed by subsequent addition of **4**, no reaction was observed after refluxing for 6 days. However on addition of 1 equivalent of 15-crown-5, the desired product **1a** was isolated in 71% yield after only 5 hours at room temperature (scheme 1):[9]

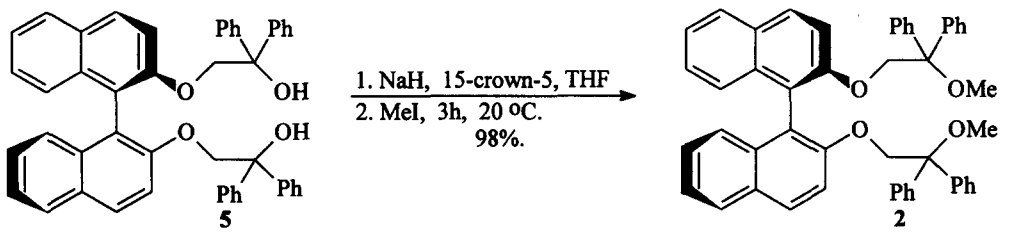
Scheme 1



Similar problems were encountered in attempts to synthesise the *p*-methoxybenzyl (PMB) analogue **1b**, which is the precursor to the chiral polyethylene glycol **1c**. Use of our 15-crown-5 procedure overcame these difficulties and furnished **1b** in 67% yield.

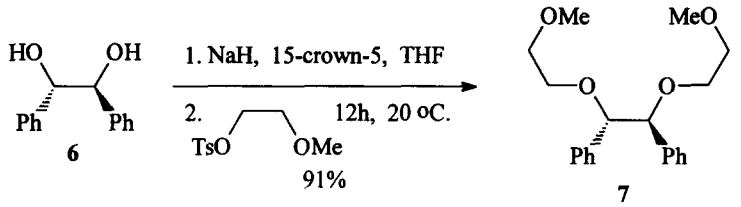
The successful synthesis of the highly hindered binaphthol derived polyether ligand **2** also resulted from this new procedure. We were encountering serious difficulties in methylating the hindered tertiary diol **5** using conventional procedures. However on treatment of diol **5** with sodium hydride and 15-crown-5 followed by subsequent addition of methyl iodide, excellent yields were obtained after only 3.5 hours stirring at room temperature in THF (scheme 2):

Scheme 2



Scheme 3 illustrates the synthesis of chiral triglyme analogue **7** in high yield:

Scheme 3



The results for the polyether synthesis are summarised in table 1:

Table 1. Preparation of Homochiral Polyether Ligands.

Entry	Reagent	Product	Solvent	Temp. / °C	Additive	Time / h	Yield / %
1	3a	1a	DMF	20-100	KI	26	<10%
2	3a	1a	THF	80	none	150	0
3	3a	1a	THF	20	15-crown-5	5	71
4	3b	1b	THF	20	none	16	0
5	3b	1b	THF	20	15-crown-5	6	67
6	5	2	THF	0-20	none	10	0
7	5	2	THF	0-20	15-crown-5	3.5	98
8	6	7	THF	20	15-crown-5	6	91

This methodology was extended into the synthesis of a series of bis-allylic ether substrates (scheme 4) for our tandem-[2,3]-Wittig-anionic oxy-Cope rearrangements.[10] Table 2 summarises the results which clearly illustrate the generality of this reaction.

Scheme 4

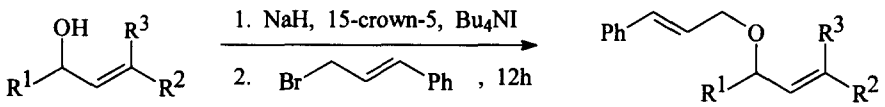


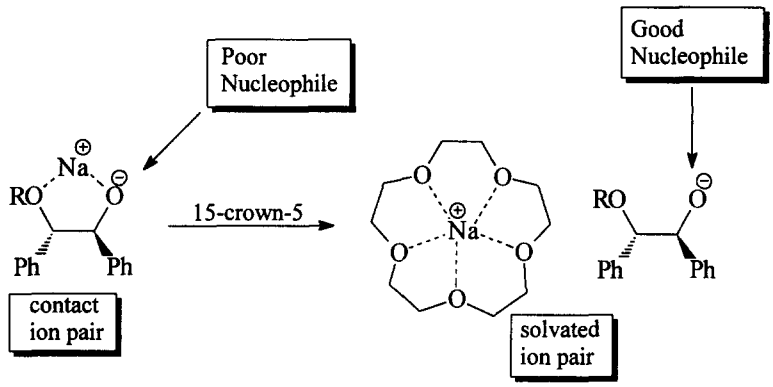
Table 2. Preparation of Bis-Allylic Ethers.

Entry	R^1	R^2	R^3	Temp. / °C	Additive	Yield / %
1	^{t}Pr	^{t}Bu	H	20	none	0
2	^{i}Pr	^{t}Bu	H	40	none	16
3	^{i}Pr	^{t}Bu	H	20	15-crown-5	89
4	^{i}Pr	H	^{t}Bu	20	15-crown-5	72
5	^{i}Pr	Me	Me	20	15-crown-5	78
6	^{i}Pr	n-Bu	H	20	15-crown-5	87
7	^{i}Pr	H	H	20	15-crown-5	66
8	Cyclohexyl	H	H	20	15-crown-5	98

As bromide is an inferior leaving group to tosylate, a catalytic quantity of tetrabutylammonium iodide was used to generate a more reactive allyl iodide intermediate. The benefit of 15-crown-5 becomes obvious by comparing the low yields of entries 1 and 2 with the excellent yield of entry 3.

The role of the crown ether is almost certainly to activate the sodium alkoxide intermediate. In absence of the 15-crown-5 the metal ion will be strongly associated with the alkoxide resulting in a greatly reduced nucleophilicity. Addition of crown ether should solvate the ion pair resulting in a rapid increase in the rate of nucleophilic attack on tosylates or alkyl halides (scheme 5):

Scheme 5



Investigation into the use of sub-stoichiometric quantities of crown ether is currently underway.

Acknowledgements

We would like to thank EPSRC, ORS, DTI and United Phosphorus for their financial support under the Asymmetric Synthesis LINK Scheme.

References and Notes

1. Williamson, W., *J. Chem. Soc.*, **1852**, *4*, 106, 229.
2. For a comprehensive review of etherification techniques: Baggett, N., *Comprehensive Organic Chemistry*, Pergamon Press, New York 1979, Volume 1, pp. 799-850.
3. Diner, U. E., Sweet, F., Brown, R. K., *Canad. J. Chem.*, **1966**, *4*, 1591-1592.
4. Schlosser, M., Strunk, S., *Tetrahedron*, **1989**, *45*, 2649-2664.
5. Patel, S. T., Percy, J. M., Wilkes, R. D., *J. Org. Chem.*, **1996**, *61*, 166-173.
6. Aspinall, H. C., Browning, A. F., Greeves N., Ravenscroft, P., *Tetrahedron Lett.*, **1994**, *35*, 4639-4640.
7. Cookson, R., Crumbie, R. L., *Tetrahedron Lett.*, **1985**, *26*, 3377-3380.
8. Dehmlow, E. V., Knufinke, V., *Liebigs Ann. Chem.*, **1992**, *3*, 283-285.
9. *Typical procedure:* A solution of **3** (6.58 mmol) in anhydrous THF (2 ml) was added to NaH (9.00 mmol) in THF (10 ml). 15-Crown-5 (1.52 ml, 7.5 mmol) was carefully added to the mixture. Diethyleneglycol ditosylate (2.96 mmol) in THF (5 ml) was added and the reaction was stirred at room temperature for a further 5 hours. The reaction was quenched with brine (10 ml) and extracted with diethyl ether (3x 25 ml). The combined organic extracts were dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification by flash chromatography yielded product **1a** as a colourless syrup.
10. Greeves, N., Vines, K. J., *J. Chem. Soc., Chem. Commun.*, **1994**, 1469-1470.

(*Received in UK* 1 *May* 1997; *revised* 14 *May* 1997; *accepted* 15 *May* 1997)