Tetrahedron Letters, Vol. 33, No 25, pp 3607-3610, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .00
Pergamon Press Ltd

Stereocontrolled Formation of Polysubstituted Tetrahydrofurans by Debenzylating Cycloetherification

Henrietta Dehmlow *, Johann Mulzer, Carsten Seilz, Achim R. Strecker, Andreas Kohlmann

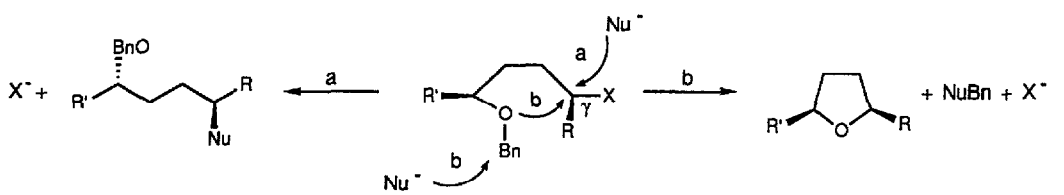
Institut für Organische Chemie der Freien Universität Berlin
Takustrasse 3, W-1000 Berlin 33, FRG

Keywords. tetrahydrofuran; neighboring group participation of benzyl ethers; Mitsunobu conditions; small rings; mesylates.

Abstract: Benzyl ethers with S_N2 active sites in γ-position undergo spontaneous regio- and stereocontrolled tetrahydrofuran cyclization with concomitant debenzylation even under mildly acidic or neutral conditions.

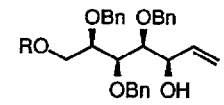
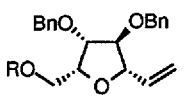
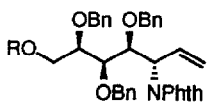
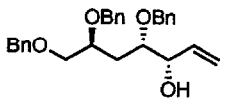
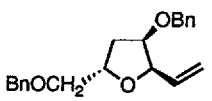
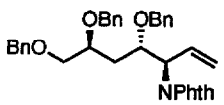
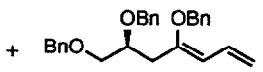
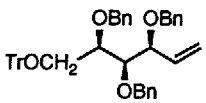
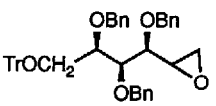
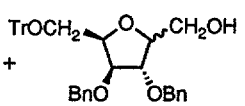
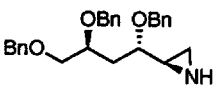
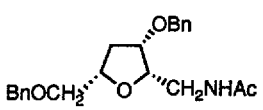
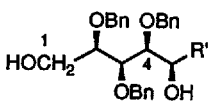
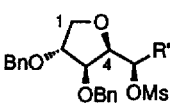
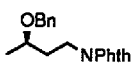
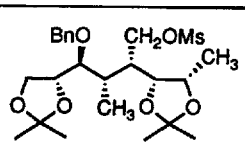
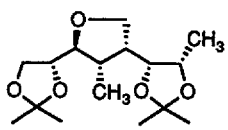
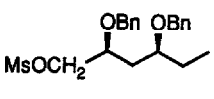
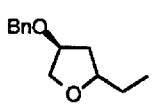
Benzyl ethers are considered to be stable O-protective groups over a wide pH-range, even towards mineral acids at room temperature. In the course of some natural product syntheses we observed however, that spontaneous debenzylation occurs under mildly acidic or even neutral conditions if a S_N2 type leaving group is present in γ-position to the benzyl ether. This is indicated by pathway **b** in Scheme 1, which competes with the direct S_N2 attack (pathway **a**). Apart from the familiar iodoetherification[1] (mercuricyclisation, heteroselenylation etc.) of γ-hydroxy- or γ-benzyloxy-alkenes a similar dealkylative tetrahydrofuran cyclization has only been observed for solvolytic nucleophilic substitution reactions[2] of 4-methoxy-butyl-1-O-tosylates, reductions with lithium aluminium hydride[3] of 4-methoxy-pentyl- and 5-methoxy-pentyl-1-O-brosylates and for reactions of 4-alkoxyalcohols with thionylchloride[4] in low yields.

Scheme 1.



For the preparation of some intermediates in the synthesis of the glucosidase inhibitors castanospermine[5] and N-acetyl-4-deoxy-mannosamine[6] the Mitsunobu reaction[7] was chosen to introduce the N-function. Treating **1** (Entry 1) with Ph_3P, phthalimide and diethylazodicarboxylate (DEAD) for 16 h in THF gave a mixture of the acyclic product **3** and tetrahydrofuran **2** in 45 and 24% yield, respectively. The stereochemistry of **2** was determined by NOE difference spectroscopy clearly showing a 2,4,5 cis relationship of the hydrogen atoms. Similar treatment of **4** (Entry 2) gave 43.3% of the expected product **6**, 23.8% of the dehydrated substance **7**

Table I.

Entry	Educt	Products	Conditions
1	 R = *t*BuPh$_2$Si **1**	 **2** (24%) +  **3** (45%)	1.2 eq PPh_3,1 2 eq Phth, 1.2 eq DEAD, THF, -20°C → rt.
2	 **4**	 **5** (14.3%) +  **6** (43.3%) +  + BnNPhth (16%) **7** (23.8%)	2 eq PPh_3, 2 eq Phth, THF, 2 eq DEAD, -20°C → rt
3	 **8**	 **9** (20%) +  **10a/b** (3:2, 43%)	1.25 eq m-CPBA, CH_2Cl_2, rt → Δ.
4	 **11**	 **12** (67%)	acetic acid, 1h, Δ.
5	 **13**	 **14** (89%) R' = 	2.7 eq MsCl, 2.9 eq DMAP, pyridine, 0°C → rt.
6	 **15**	 **16** (75%)	a) MeOH, p-TsOH; b) CH_2Cl_2, DMAP, p-TsOH.
7	 **17**	 **18** (78%)	NaCN, EtOH / H_2O (vv 9/1), Δ.

and 14.3% of 2,3-cis-substituted tetrahydrofuran **5**. The simultaneous formation of benzylphthalimide (=NuBn) in 16% yield further supports the validity of Scheme 1

Tetrahydrofuran cyclizations were observed also if the benzyloxy group was in γ-position to an epoxide or aziridine ring. Oxidation of alkene **8** (Entry 3) with m-chloroperbenzoic acid (m-CPBA) gave a mixture of the epoxide epimers **9** and hydroxymethyl compounds **10a/b** (ratio 3:1) in 20 and 43% yield, respectively. **9** is an intermediate in the formation of **10a/b** from **8**. This can be shown by isolating and converting **9** into **10a/b** under the epoxidation conditions applied. Even if buffered systems or other epoxidation conditions[8] are used, **10a/b** are still the main products. Heating the aziridine derivative **11**[6c] (Entry 4) in anhydrous acetic acid to 100°C for 1 h led to the N-acetyl protected all-cis substituted tetrahydrofuran **12** in 67% yield. Notably no tetrahydropyran isomers of **10a/b** and **12** were isolated indicating that the S_N2-reaction occurs at the secondary C-atom of the small ring only. This corresponds to the observation[9] that oxiranes are opened by O-nucleophiles rather in an exo- than in endo fashion. Furthermore, in the reaction of compound **11** pathway **b** affects the 4-O-benzyl- and not the 5-O-benzyl-function.

Diol **13** was prepared as an intermediate in the synthesis of castanospermine[5]. With mesylchloride in pyridine **13** (Entry 5) gave none of the expected di-mesylate. Instead, tetrahydrofuran **14** was formed in 89% yield. Variation of the reaction temperature and base as well as the use of either mesyl anhydride or tosylchloride did not change the outcome of the reaction. Quite obviously, the 1-OMs leaving group has invoked a neighboring group participation of the 4-OBn moiety, resulting in S_N2-type cyclization and debenzylation.

Treatment of **15** (Entry 6) with p-TsOH in methanol or with DMAP and p-TsOH in CH_2Cl_2 furnished tetrahydrofuran **16** in 75% yield, whose stereochemistry was secured by single-crystal X-ray analysis[10]. Finally, mesylate **17** (Entry 7) cyclized to tetrahydrofuran **18** on stirring with sodium cyanide in hot ethanol/water. This example shows that the debenzylation proceeds even under basic conditions in contrast to the familiar stability of 'normal' O-benzyl protective groups towards bases.

In conclusion, our findings have a threefold consequence: 1. on planning total syntheses which involve S_N2 type processes O-benzyl protective groups in γ-position should be avoided. 2. By virtue of the spontaneous tetrahydofuran formation benzyl ethers are sensitives probes for S_N2 active centers in γ- position. In a certain sense this is an S_N2 analogue to the familiar cyclization of 5-hexenyl radicals[11]. 3. From the point of synthetic utility the debenzylating cyclization affords an easy access to stereochemically pure highly substituted tetrahydrofurans from readily available acyclic starting materials (Entries 4-7 in Table 1). Tetrahydrofuran subunits are characteristic features of many important natural products (e.g. lasalocid[12], monensin[13] and citreoviral[1c]).

Acknowledgment. This work was generously supported by the Schering AG, Berlin-Bergkamen, the Fonds der Chemischen Industrie and the Graduiertenkolleg "Synthese und Strukturaufklärung niedermolekularer Verbindungen". We also thank Dr. B. Kirste and W. Münch for the NOE measurements.

References and Notes.

1. (a) Rychnovsky, S. D.; Bartlett, P. A. *J. Am. Chem. Soc.* **1981**, 103, 3963; (b) Williams, D. R.; White, F. H. *Tetrahedon Lett.***1985**, 26, 2529; (c) Williams, D. R.; White, F. H. *Tetrahedon Lett.***1986**, 27, 2195; (d) Reitz, A. B.; Nortey, S. O.; Maryanoff, B. E.; Liotta, D.; Monahan, R., III *J. Org. Chem.*

1987, 52, 4191; (e) Bartlett, P. A. Cyclization Forming Carbon-Heteroatom Bonds. in *Asymmetric Syntheses* , Morrison, J. D.; Acedemic Press, Orlanda **1984**, Vol. 3, pp. 411; (f) *Syntheses of Natural Products, Problems of Stereoselectivity*, Kočovský, P.; Tureček, F.; Hájíček, J.; Vol I,II CRC Press, Inc. Boca Raton, Florida **1986** and literature cited therein.

2. (a) Winstein, S.; Allred, E.; Heck, R.; Glick, R. *Tetrahedron* **1958**, 3, 1; (b) Allred, E. L.; Winstein, S. *J. Am. Chem. Soc.* **1967**, 89, 4012; (c) Novak, E. R.; Tarbell, D. S. *J. Am. Chem. Soc.* **1967**, 89, 73; (d) Perst, H. in *Oxonium Ions in Organic Chemistry*, Verlag Chemie, Weinheim **1971**, pp. 100.
3. Allred, E. L.; Winstein, S. *J. Am. Chem. Soc.* **1967**, 89, 4008.
4. Kirrmann, A.; Wartski, L. *Compt. rend.* **1960**, 250, 3492.
5. Mulzer, J.; Dehmlow, H. submitted.
6. (a) Mulzer, J.; Seilz, C.; Luger, P.; Weber, M.; Reutter, W. *Liebigs Ann. Chem.* **1991**, 947.(b) Mulzer, J.; Seilz, C.; Reutter, W. *Liebigs Ann. Chem.* **1991**, 957. (c) Seilz, C. *PhD Thesis*, FU Berlin **1990.**
7. Mitsunobu, O. *Synthesis* **1981**,1.
8. (a) Camp, F.; Coll, J.; Messeguer, A.; Pujol, F. *J. Org. Chem.* **1982**, 47, 5402; (b) Imuta, M.; Ziffer,.H. *J. Org. Chem.* **1979**, 44, 1351.
9. Masamune, T.; Ono, M.; Sato, S.; Murai, A. *Tetrahedon Lett.* **1985**, 4, 371.
10. Mulzer, J.; Kattner, L.; Strecker, A. R.; Schröder, Ch.; Buschmann, J.; Lehmann, Ch.; Luger, P. *J. Am. Chem. Soc.* **1991**, 113, 4218.
11. (a) Griller, D.; Ingold, K. U. *Acc. Chem. Res.* **1980**, 13, 317; (b) Beckwith, A. L. J.; Ingold, K. U. in *Rearrangements in Ground and Excited States;* de Mayo, P. Ed., Academic Press, New York **1980.**
12. Nakata, T.; Schmid, G.; Vranesic, B.; Okigawa, M.; Smith-Palmer, T.; Kishi, Y. *J. Am. Chem. Soc.* **1978**, 100, 2933.
13. (a) Fukuyama, T.; Wang, C.-L. J.; Kishi, Y.*J. Am. Chem. Soc.* **1979**, 101, 260; (b) Schmid, G:; Fukuyama, T.; Kishi, Y. *J. Am. Chem. Soc.* **1979**, 101, 260.
14. ^{1}H-NMR (250/270 MHz, $CDCl_3$, TMS): (**2**): δ 7.66 (m, 4 H), 7.44-7.21 (m, 16 H), 5.93 (ddd, 1 H, J = 6.3, 8.8, 13.8 Hz), 5.29 (dt, 1 H, J = 1.3, 14 Hz), 5.12 (dt, 1 H, J = 1.3, 8.8 Hz), 2 AB systems: (δ_{A1} = 4.61, δ_{B1} = 4.55, δ_{A2} = 4.57, δ_{B2} = 4.51, 4 H, J = 10 Hz), 4.3 (dd, 1 H, J = 3, 6.3 Hz), 4.22 (m, 1 H), 4.10 (dd, 1 H, J = 2, 3 Hz), 4.02 (dd, 1 H, J = 5.5, 8.7 Hz), 3.88 (m, 1 H), 3.86 (dd, 1 H, J = 4.5, 8 Hz), 1.04 (s, 9 H); (**5**): 7.40-7.20 (m, 10 H), 5.80 (ddd, 1 H, J = 5.5, 10, 17 Hz), 5.34, 5.14 (each dt, 1 H, J = 2, 10.5/17 Hz), AB-system: (δ_A = 4.62, δ_B = 4.54, 2 H, J = 12 Hz), 4.48 (s, 2 H), 4.54-4.46, 4.38-4.28, 3.95-3.86 (each m, 1 H), 3.63 (dd, 1 H, J = 6, 10 Hz), 3.49 (dd, 1 H, J = 5, 10 Hz), 2.22 (ddd, 1 H, J = 6.5 , 7.5, 13 Hz), 1.86 (dt, 1 H, J = 5.5, 13 Hz); (**10a**): 7.52-7.08 (25 H), 2 AB-systems: (δ_A = 4.34, 4.3; δ_B = 4.5, 4.5; 4 H; J = 12 Hz), 3.7, 3.58 (each dd, 1 H, J = 3.75, 10 Hz), 3.54, 3.32 (each dd, 1 H, J = 5, 10 Hz), 2.42 (s, 1H); (**10b**): 7.5-7.08 (25 H), 2 AB-systems: (δ_A = 4.43, 4.36; δ_B = 4.58, 4.45; 4 H; J = 12.5 Hz), 4.45, 4.18-4.08 (m, 4 H), 3.86, 3.76 (dd, 1 H, J = 5, 10 Hz), 3.48 (dd, 1 H, J = 5, 10 Hz), 3.28 (dd, 1 H, J = 6, 10 Hz), 2.5 (s, 1H); (**12**): 7.40-7.24 (m, 10 H), 6.02 (s, 1 H), 2 AB-systems: (δ_A = 4.61, 4.54, δ_B =4.54, 4.37, 4 H, J = 10.5 Hz), 4.19-4.08 (m, 2 H), 3.95 (dt, 1 H, J = 4.4, 7.8 Hz), 3.79 (ddd, 1 H, J = 4.4, 7.3, 14.2 Hz), 3.60 (dd, 1 H, J = 5.9, 9.8 Hz), 3.54 (dd, 1 H, J = 4.9, 9.5 Hz), 3.35 (ddd, 1 H, J = 3.9, 7.8, 14.2 Hz), 2.18 (ddd, 1 H, J = 6.4, 7.8, 13.2 Hz), 1.89 (ddd, 1 H, J = 3.9, 6.8, 13.2 Hz),1.87 (s, 3 H); (**14**): 7.8 (m, 2 H), 7.64 (m, 2H), 7.26 (mc,15 H), 5.0 (dd, 1 H, J = 2, 8 Hz), 2 AB-systems: (δ_A = 4.6, 4.38; δ_B = 4.38, 4.2; 4 H; J = 11 Hz), 4.46 (s, 2 H), 4.4 (t, 1 H, J = 5.5 Hz), 4.12 (dd, 1 H, J = 4, 9.5 Hz), 4.04 (d, 1 H, J = 4 Hz), 3.82 (m, 2 H), 3.68 (m, 3 H), 3.1 (s, 3 H), 2.12 (m, 2 H); (**18**): 7.44-7.22 (m, 5 H), AB-system: (δ_A = 4.53, δ_B = 4.48, 2 H, J = 13.7 Hz), 4.08-3.92 (m, 2 H), 3.83 (dd, 1 H, J = 3.8, 12.5 Hz), 2.25 (ddd, 1 H, J = 1.3, 7.5, 13 Hz), 1.75-1.35 (m, 3 H), 0.95 (t, 3 H, J = 7.5 Hz).

(Received in Germany 20 January 1992)