Pergamon

Tetrahedron Letters 39 (1998) 787–790

TETRAHEDRON LETTERS

Opening of Levoglucosane Derived Epoxides with Oxygen, Nitrogen and Sulfur Nucleophiles

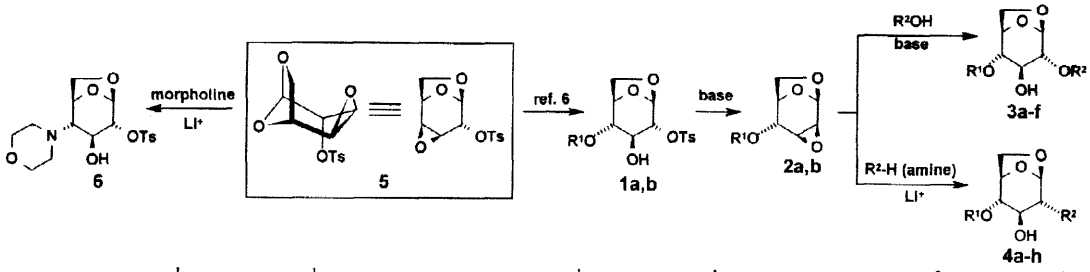
Wolfgang K.-D. Brill*, Dominique Tirefort

Combinatorial Chemistry, Novartis Pharma AG, R-1060.3.42, CH-4002-Basle

Received 17 September 1997; revised 20 November 1997; accepted 22 November 1997

Abstract: A variety of nucleophiles were employed to open levoglucosane derived epoxides.

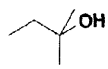
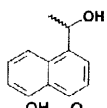
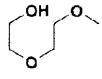
Levoglucosane has frequently been used as building block in the *de novo* synthesis of natural products[1], their analogs[2] and polymers.[3] Its 6,8-dioxa-bicyclo[3.2.1]octane skeleton has potential for diverse derivatization via regio and stereoselective epoxide opening reactions, which follow the *Fürst-Plattner* rule.[4] A large set of structurally very diverse carbohydrate structures could be obtained without lengthy protective schemes. This study intended to find general methods to achieve this goal using basic or only mildly acidic reaction media. We based our studies on some 4-alkyl or aryl 2-toluenesulfonyl levoglucosanes **1a-b**, readily obtained from 1,6:3,4-dianhydro-2-O-p-toluenesulfonyl-β-D-galactopyranose (**5**)[5] upon BF_3-catalyzed epoxide opening.[6]



Scheme: 1

1a: R^1=4-methoxyphenyl; **1b:** R^1=allyl; **2a:** R^1=4-methoxyphenyl; **2b:** R^1=allyl; **3a:** R^1=4-methoxyphenyl, R^2=Bn; **3b:** R^1=allyl, R^2=Bn; **3c:** R^1=1-propenyl, R^2=Bn; **3d:** R^1=allyl, R^2=1-(α-naphtyl)ethyl; **3e:** R^1=allyl, R^2=methoxyethoxy ethyl; **3f:** R^1=1-Z-propenyl, R^2=methoxyethoxy ethyl; **4a:** R^1=allyl, R^2=NBu_2; **4b:** R^1=4-methoxyphenyl, R^2=NBu_2; **4c:** R^1=4-methoxyphenyl, R_2=NPh_2; **4d:** R^1=4-methoxyphenyl, R^2=morpholinyl; **4e:** R^1=4-methoxyphenyl, R^2=piperidinyl; **4f:** R^1=4-methoxyphenyl, R_2=NHtBu; **4g:** R^1= 4-methoxyphenyl, R^2=$NHCH_2CH_2OH$; **4h:** R^1=4-methoxyphenyl, R^2=imidazolyl.

Table 1: Epoxide Opening with Alkoxides

Entry	Starting Material	R^2-OH	Solvent	Base	T[°C]	Reaction Time [h]	Product No.	Yield[a][%]
1	**1a**	BnOH	DMF	NaH	100	0.1	**3a**	27[b]
2	**1a**	BnOH	dioxane	NaH	100	2	**3a**	44
3	**1b**	BnOH	DMA	NaH	100	0.3	**3b**	38
4	**1b**	BnOH		KO tBu	100	18	**3c**	66[c]
5	**1b**	BnOH	dioxane	NaH, 15-crown-5	100	2	**3b**	80
6	**1b**		dioxane	NaH, 15-crown-5	100	2	**3d**	67
7	**1b**		dioxane	NaH, 15-crown-5	100	12	**3e,f**	69[c,d]
8	**1b**	BnOH	dioxane	LiOBu	100	24	epoxide formation	n.d.
9	**1b**	BnOH	dioxane/ n-hexane 1/1 (V/V)	{(Me₂N)₃P=N}₃-P=N-(tBu)	reflux	0.75	**3c**	68[c]

[a]) Isolated yields after extractions and chromatography; [b])Many side products; [c]) Allyl isomerization; [d])Isomerization caused by excess of alcohol over NaH leading to a protic medium.

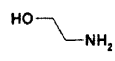
0040-4039/98/$19.00
PII: S0040-4039(97)10715-8

The compounds **1a-b** gave the 1,6:2,3-dianhydro-4-O-alkyl or aryl-β-D-mannopyranoses **2a-b**, if the reaction conditions were sufficiently basic[7] (Scheme 1).

Our first task was the opening of these stable 2,3-epoxides with alkoxides[3b,8](Table 1). Levoglucosane derived epoxides could be opened by alkoxides with bulky counterions, such as protonated "*Schwesinger base*" P<t/4>-t-Bu, K^+ and crown ether complexed Na^+.[9,10] Lithium alkoxides were ineffective. Reversible bases like KOtBu (entry 4) or P<t/4>-t-Bu[10,11] (entry 9) lead to the isomerization of the allyl group affording only the Z-enol ether. Allyl isomerization was suppressed in aprotic media (entry 2, 3, 5, 6). The reaction (entry 9) employing the "*Schwesinger base*" was free of precipitates, which occur with other bases upon absorption of even traces of water or CO_2. Polymerizations were not observed.

Subsequently, we investigated the epoxide opening of **2a** and **2b** with amines[12](Table 2). Lithium or sodium amides[13] gave no or little conversion due to their poor solubility and uncatalyzed epoxide openings are sluggish (entry 2). Catalysis by Li^+-ions[14] was successful in a number of solvents. 2,6-Lutidine was our favored choice, because it allows solubilization of organic compounds and Li salts without strong coordination of the Li^+-ion.

Table 2[15]: Epoxide Opening with Nitrogen Nucleophiles

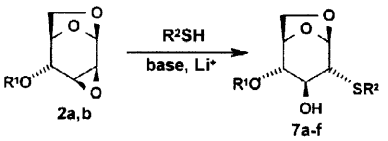
Entry	Starting Material	Nucleophile	Solvent	Conditions	T[°C]	Reaction Time [h]	Product	Yield[a][%]
1	**1b**	Bu_2NH	neat	0.1eq. $LiClO_4$	150	3	**4a**	84
2	**1a**	Bu_2NH	2,6-lutidine/ Bu_2NH 4/1 (V/V)	no catalyst	100	44	**2a**	traces
3	**2a**	Bu_2NH	dioxane/ Bu_2NH 4/1 (V/V)	$LiClO_4$: 0.1 eq., 5mM	100	9	**4b**	87
4	**2a**	Bu_2NH	2,6-lutidine/ Bu_2NH 4/1 (V/V)	$LiClO_4$: 0.1 eq., 30mM	100	7	**4b**	quant.
5	**2a**	Ph_2NH	xylenes	Li ClO_4slurry	100-150[b]	17[b]	**4c**	8[c]
6	**2a**		2,6-lutidine/ morpholine 4/1 (V/V)	$LiPF_6$ 0.1eq., 6.7mM	100	3	**4d**	quant.
7	**2a**		2,6-lutidine/ morpholine 4/1 (V/V)	$LiClO_4$, 0.1eq., 5mM	100	1.5	**4d**	quant.
8	**1a**		2,6-lutidine/ morpholine 4/1 (V/V)	$LiClO_4$, 0.1eq., 5mM	100	24	**4d**	trace[f]
9	**1a**		2,6-lutidine/ piperidine 4/1 (V/V)	$LiClO_4$, 0.1eq., 5mM	100	48	**4e**	37
10	**1a**		2,6-lutidine/ tert.$BuNH_2$ 4/1 (V/V)	$LiClO_4$, 0.1eq., 5mM	reflux	48	**4f**	53[d]
11	**1a**		2,6-lutidine/ ethanolamie 4/1 (V/V)	$LiClO_4$, 0.1eq., 3.3mM	100	24	**4g**	47[e]
12	**2a**		2,6-lutidine/ imidazole 4/1 (V/V)	$LiClO_4$, 0.1eq., 5mM	100	9	**4h**	quant.
13	**5**		0.2M morpholine in 2,6-lutidine	$LiClO_4$, 1.1eq., 51mM	100	3	**6**	quant.

[a]) Isolated yields after extractions and chromatography; [b]) 12 hours at 100°C (little conversion) then 5 hours at 150°C; [c])decomposition;[d]) rest is **1a**; [e]) Trace of O-alkylation product; [f])not sufficiently basic to form required intermediate **2a**.

Analogous experiments in this series revealed the influence of the counterion on the activity of the Li salt in the order: $LiClO_4$>$LiNTf_2$>$LiPF_6$. Substantial side reactions were only observed with Ph_2NH (Table 2, entry 5), probably due to oxidative and photochemical degradation.

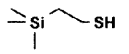
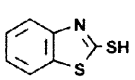
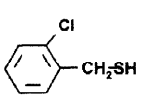
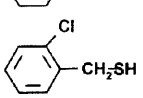
The opening of levoglucosane epoxides with several thiols (Table 3, Scheme 2) required concerted action of thiolate anion and a suitable *Lewis acid*. Thus, the reaction of **2b** with ethyldiisopropylammonium thiophenolate only proceeds, when $LiPF_6$ is sufficiently solubilized by 2,6-lutidine (entry 2, 3). Favorable is the use of $LiN(SiCH_3)_2$ as reaction promotor, since it deprotonates thiols efficiently and provides Li^+ for *Lewis acid* cocatalysis.[16]

Scheme 2:



7a: R^1=allyl, R^2=Ph; **7b:** R^1=4-methoxyphenyl, R^2=trimethylsilyl ethyl; **7c:** R^1=allyl, R_2=benzothiazol-2-yl; **7d:** R^1=allyl, R^2=2-chlorobenzyl; **7e:** R^1=allyl, R^2=n-docecyl; **7f:** R^1=allyl, R^2=tert. butyl.

Table 3: Epoxide Opening with Sulfur Nucleophiles

Entry	Starting Material	R_2SH	Solvent	Conditions	Reaction Time [h]	Product	Yield[a] [%]
1	**2b**	PhSH	dioxane	no catalyst	84	no reaction	-
2	**2b**	PhSH	DIPEA	$LiPF_6$	84	no reaction	-
3	**2b**	PhSH	2,6-lutidine/ DIPEA 9/1 (V/V)	$LiPF_6$	72	**7a**[b]	26
4	**2a**		2,6-lutidine	$LiClO_4$	24	**7b**	61
5	**2b**	PhSH	2,6-lutidine/ DBU 9/1 (V/V)	$LiPF_6$	1	**7a**	89
6	**2b**		2,6-lutidine/ DBU 9/1 (V/V)	$LiPF_6$	24	**7c**	69
7	**2b**		2,6-lutidine/ DBU 9/1 (V/V)	$LiPF_6$	25	decom-position	-
8	**2b**		dioxane	$LiN(SiMe_3)_2$	1	**7d**	88
9	**2b**	n-$C_{12}H_{25}SH$	dioxane	$LiN(SiMe_3)_2$	1	**7e**	quant.
10	**2b**	tBuSH	dioxane	$LiN(SiMe_3)_2$	1	**7f**	95

[a]) All reactions were performed at 100°C, isolated yields after extractions and chromatography are reported;
[b]) 38% recovered **2b**.

In conclusion, very stable levoglucosane derived epoxides were opened with a variety of nucleophiles under an improved set of conditions. Due to their structure based reactivity, levoglucosane based epoxides allow stereo and regioselective introduction of a many functionalities via S_N2 displacements without side reactions and lengthy protection schemes.

Acknowledgments: We wish to thank Josette Schaub for technical assistance, Dr. Tammo Winkler for NMR and the Central Analytical Laboratories for mass spectroscopy.

References:

1. Among many examples: a) K. Takatori, M. Kajiwara, *Synlett* **1995**, 280-282; b) Y. Ichikawa, R. Mondan, H. Kuzuhara, *Tetrahedron Lett.* **1986**, 27, 611-614; c) B. Frazer-Reid, L. Magdzinski, B. Molino, *J. Am. Chem. Soc.* **1984**, 106, 731-734; d) T. Ogawa, T. Kawano, M. Matsui, *Carbohydrate Research* **1977**, 57, C31-35; e) A. F. Sviridov, N. S. Ermolenko, D. V. Yashunsky, V. S. Borodkin, N. K. Kochetkov, *Tetrahedron Lett.* **1987**, 28, 3835-3818.

2. For instance: H. Paulsen, M. Schüller, *Liebigs Ann. Chem.* **1987**, 249-258.
3. For instance: a) H. R. Kriecheldorf, U. Delius, *Makromol. Chem.* **1989**, 190, 1289-1301; b) A. A. Gorkovenko, E. L. Berman, V. A. Ponomarenko, *Bioorg. Khim.* **1987**, 13, 218-222; (English translation: 126-129); c) T. Uryu, K. Hatanaka, K. Matsuzaki, H. Kuzuhara, *Macromolecules* **1983**, 16, 853-858.
4. A. Fürst, Pl. A. Plattner, *Helv. Chim. Acta* **1949**, 32, 275-283.
5. a) M. Cerny, V. Gut, J. Pacak, *Collect. Czech. Chem. Commun.* **1961**, 26, 2542-2550; b) W. Szeja, *Carbohydrate Res.* **1988**, 183, 135-139; M. Cerney, J. Stanek Jr., J. Pacak, *Collect. Czech. Chem. Commun.* **1969**, 34, 849-856.
6. For review see: M. Cerny, *Levoglucosanone and Levoglucosanes, Chemistry and Applications*, Witczak, Z. J. (ed.). ATL PRESS **1994**, 121-146.
7. Representative conditions are: 0.77M LiOH/MeOH/H_2O: 3/1(v/v), 17h, r. t..
8. P. A. Seib, *J. Chem Soc. C*, **1969**, 2552-2559.
9. **3d**, (Table 1, entry 6): To a solution of 356mg (1mmol) **1b**, 861 (5mmol) of 1-α-naphtyl ethanol and 989µl of 15-crown-5 in 20ml dioxane was added 240mg of a NaH suspension in mineral oil (ca. 50%). The turbid reaction mixture was kept at 100°C for 2 hrs, then poured onto a slurry of dry ice and ethyl acetate. The organic layer was extracted with sat. aq. $NaHCO_3$, and brine successively. The product was purified from 1-(α-naphtyl) ethanol by chromatography on silica using toluene/ethyl acetate 4/1 (v/v). ^{1}H-NMR: 5.8-6.05 (m): -CH= of allyl; 5.15-5.42 (m): H1(sugar), $=CH_2$(allyl), α-CH(naphthyl ethyl); 1.68, 1.72: Me (2 diastereomers).
   3c (Table 1, entry 4): To a solution of 178mg (0.5mmol) **1b** and 207µl of benzyl alcohol in 10ml tert. amyl alcohol was added 561mg (5mmol) of KOtBu. The reaction mixture was kept at 100°C for 18 hrs and then poured onto sat. aq. NH_4Cl. The organic phase was subjected to an aq. workup.
   3c (Table 1, entry 9): To a solution of 178mg (0.5mmol) **1b** and 207µl of benzyl alcohol in 5ml dioxane was added 5ml of a 1M solution of P<t/4>-t-Bu in hexane (Fluka). The reaction mixture was refluxed for 45 min and then poured onto sat. aq. NH_4Cl and extracted with ethyl acetate. The organic phase was then extracted with 10% aq. citric acid, sat. aq. $NaHCO_3$, and brine successively. The product, present in the combined organic layers was chromatographed on silica using ether/hexane 7/3 (v/v) to remove excess BnOH. ^{1}HNMR: 5.45: H1(sugar); 1.6 (dd, $J_{H\text{-}H}$=7Hz, $J_{H\text{-}H}$<1Hz): CH_3(Z-propenyl); 4.62: CH_2(Bn).
10. a) R. Schwesinger, H. Schlemper, *Angew. Chem.* **1987**, 99, 1212-1214; *Angew. Chem. Int. Ed. Engl.* **1987**, 32, 1361-1363. b) B. Esswein, N. M. Steidel, M. Moeller, *Macromol. Rapid Commun.* **1996**, 17, 143-148.
11. R. Schwesinger, C. Hasenfratz, H. Schlemper, L. Walz, E. M. Peters, K. Peters, H. G. von Schnering, *Angew. Chem.* **1993**, 105, 1420-2; *Angew. Chem. Int. Ed. Engl.* **1993**, 32, 1361-1363.
12. a) F. Schmitt, P. Sinaÿ, *Carbohydrate Res.* **1973**, 29, 99-111; b) M. Cerny, O. Julakova, J. Pacak, *Collect. Czech. Chem. Commun.* **1974**, 39, 1391-1396.
13. C. E. Harris, G. B. Fisher, D. Beardsley, L. Lee, C, T. Goralski, L. W. Nicholson, B. Singaram, *J. Organ. Chem.* **1994**, 59, 7746-7751.
14. M. Chini, P. Crotti, F. Maccia, *Tetrahedron Lett.* **1990**, 32, 4661-4664.
15. **4d** (Table 2, entry 7): To 10 ml of a solution of 2,6-lutidine/morpholine 4/1 (v/v) were added 125mg (0.5mmol) of **2a** and 5.3mg (0.05mmol) of $LiClO_4$. The reaction mixture was kept at 100°C for 1.5 hrs. After evaporation to dryness, the reaction mixture was taken up in ethyl acetate and extracted with aq. sat. $NaHCO_3$ and brine successively. The combined organic layers were chromatographed on silica. MS: 338 $(M+H)^+$; ^{1}HNMR: 5.5ppm: H1(sugar); 2,43ppm: H2(sugar).
16. **7f** (Table 3, entry10): To a solution of 184 mg (1mmol) **2b** and 340µl (3mmol) of tert. butyl mercaptane in 15ml of dioxane were added 3ml of 1M $LiN(SiCH_3)_2$ in THF (Fluka). The reaction mixture was kept at 100°C for 1 hr. After evaporation to dryness, the reaction mixture was taken up in ethyl acetate and extracted with aq. sat. $NaHCO_3$ and and brine successively. The product, present in the combined organic layers was chromatographed on silica using ethyl acetate/hexane 1/1 (v/v). ^{1}HNMR: 5.42ppm: H1(sugar); 2.49(d): H2(sugar) 5.72-5.75ppm (m): -CH= (allyl); 1.19ppm (s): CH_3(tert. butyl.).