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Note

Preparation of *N*-nosyl-3,4-epimines derived from levoglucosan by sodium borohydride reduction

Jiří Kroutil[a,*] and Jindřich Karban[b]

[a]*Department of Organic and Nuclear Chemistry, Faculty of Science, Charles University, CZE-128 43 Prague 2, Czech Republic*
[b]*Institute of Chemical Processes Fundamentals, Academy of Sciences of the Czech Republic, CZE-160 00 Prague 6, Czech Republic*

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Abstract—Starting from 1,6-anhydro-β-D-glucopyranose **1** (levoglucosan), *N*-*o*-nitrobenzenesulfonyl (nosyl) 3,4-epimino derivatives with D-*allo*, D-*galacto*, and D-*talo* configurations have been prepared via $NaBH_4$ reduction of suitably substituted azido tosylates. The benefits and limitations of this method over the classical $LiAlH_4$ reduction method are discussed.

Keywords: Azide reduction; Stereospecific synthesis; NMR spectral data; Aziridines; *o*-Nitrobenzenesulfonyl derivatives

We have recently published[1] the preparation of a complete series of eight epimino derivatives of 1,6-anhydro-β-D-hexopyranoses via a reductive cleavage of vicinal azido tosylates by $LiAlH_4$ as starting materials for our studies on the reactivity of the aziridine ring in cleavage reactions with nucleophiles.[2] Due to the low reactivity of unsubstituted epimines, we have later prepared[3,4] their *N*-tosyl derivatives and elaborated experimental conditions for *trans*-diaxial aziridine ring cleavage with halides[3] and benzyl-substituted[4] nucleophiles (BnOH, BnSH, $BnNH_2$) resulting in regioselective formation of a single isomer of the corresponding sulfonamide in high yield. However, the use of the tosyl group for activation of the aziridine ring proved to be inconvenient in carbohydrate synthesis; in the case of some nucleophiles, for example, fluorides, its activating effect was too small to induce complete cleavage of the aziridine ring. In addition, the harsh conditions required for *N*-detosylation[5,6] substantially diminish the overall yields. We therefore designed *N*-*o*-nitrobenzenesulfonylepimines as an alternative, exploiting its higher activating effect and the smooth deprotection[7–11] of the *o*-nitrobenzenesulfonyl group. We have prepared[12] *N*-nosyl-2,3-epimines of the D-*manno* and D-*allo* configuration and tested[12] their reactivity in aziridine ring cleavage by halides. The regioselectivity observed for reactions of *N*-tosylepimines (trans-diaxial ring cleavage according to the Fürst–Plattner rule[13]) was retained and easy *N*-deprotection of the resulting nosylamides with benzenethiol under alkaline conditions together with high reaction yields were achieved.[12]

In this paper, we present the preparation of *N*-nosyl-3,4-epimines with the D-*allo*, D-*galacto*, and D-*talo* configurations based on the reduction of vicinal azido tosylates of 1,6-anhydro-β-D-hexopyranoses by sodium borohydride.

The key step in the synthesis of the epimines was the preparation of 2-*O*-benzyl-3,4-epoxides of 1,6-anhydro-β-D-hexopyranoses **2,4,5** (Scheme 1), which subsequently underwent azidolysis of the oxirane ring to afford (after *O*-tosylation) suitably substituted (with OTs, OBn, and N_3 groups) 1,6-anhydrohexoses with D-*gluco* and D-*manno* configurations (Scheme 2, azido tosylates **6**–**8**). The dianhydrides **2**–**5** were obtained from levoglucosan **1** via a set of reactions already published (for a review about preparation of dianhydrides of hexopyranoses—see Refs. 14 and 15). However, various procedures for the preparation of the derivatives shown in Scheme 1 have been published providing different reaction yields.

* Corresponding author. E-mail: kroutil@natur.cuni.cz

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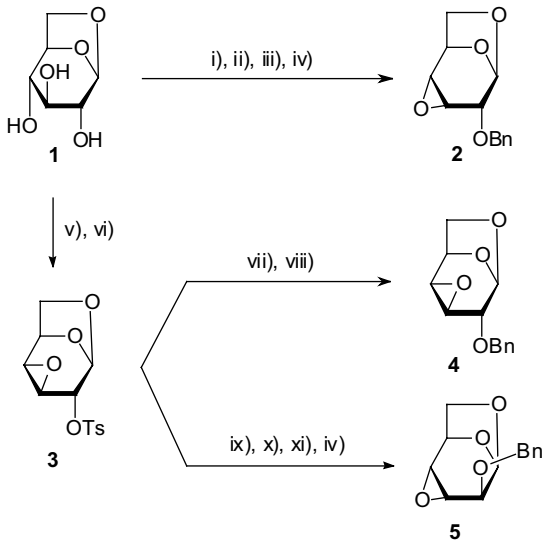
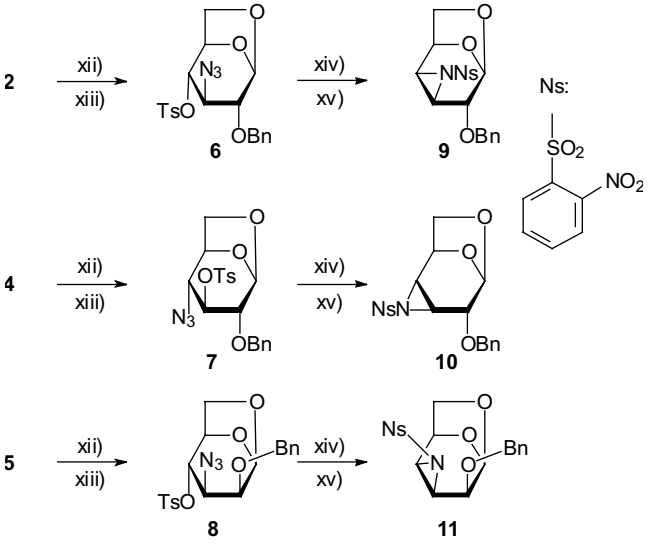


Scheme 1. Reagents and conditions: (i) $PhCH_2OCOCl/C_5H_5N$, −15 °C, 69%, Ref. 16; (ii) $MsCl/C_5H_5N$, −20 °C, 99%, Ref. 17; (iii) MeONa, MeOH, 84%, Ref. 17; (iv) BnBr/NaH/DMF + THF, −20 °C, (**2**—78%, Ref. 2; **5**—67%, Ref. 1); (v) $TsCl/C_5H_5N + Me_2CO$; (vi) $MeONa/MeOH + CHCl_3$, 45%, Refs. 16, 18, and 19; (vii) $NaHg_x$/MeOH, 98%, Refs. 20 and 21; (viii) $BnBr + Ag_2O$/DMF, Ref. 22, 85%; (ix) Ac_2O + AcOH + $BF_3{\cdot}Et_2O$/toluene, 94%, Ref. 23; (x) Amberlyst IRA 410 (OH^- cycle)/MeOH, 92%, Ref. 23; (xi) $NaOH/H_2O$, 88%, Ref. 23.



Scheme 2. Reagents and conditions: (xii) $NaN_3 + NH_4Cl/CH_3O(CH_2)_2OH + H_2O$, Ref. 1; (xiii) $TsCl/C_5H_5N$, Ref. 1; (xiv) 1. $NaBH_4$/THF, rt, 2. MeOH, reflux; (xv) $o\text{-}NO_2\text{–}C_6H_4\text{–}SO_2Cl/Et_3N$ + THF, −40 °C.

Keeping that in mind, we have selected the most convenient procedures in order to obtain epoxy derivatives **2**–**5** in high yields on multigram scale (5–10 g). All reactions used for the preparation of dianhydrides **2**–**5** with references to the original papers and with the yields obtained by us are depicted in Scheme 1.

Vicinal azido tosylates **6**–**8**, prepared according to Scheme 2, have been subjected to sodium borohydride reduction resulting in free epimines. Subsequent sulfonylation using *o*-nitrobenzenesulfonyl chloride in a triethylamine–tetrahydrofuran mixture at −40 °C afforded the desired *N*-nosylepimino derivatives **9**–**11**. The low temperature in sulfonylation was necessary to obtain high yields of *N*-*o*-nitrobenzenesulfonylated epimines. In comparison to nosylation of 2,3-epimines,[12] lowering of the reaction temperature from −30 to −40 °C improved the yields of *N*-nosyl-3,4-epimines, but further decrease of the temperature to −50 °C caused only retardation of the reaction.

In comparison to the $LiAlH_4$ reduction of vicinal azido tosylates described previously[1,3,4] for the preparation of sugar aziridines, $NaBH_4$ reduction afforded cleaner products (non-contaminated with sulfide impurities, which were obviously formed as by-products in subsequent reaction of $LiAlH_4$ with the tosylate anion) and provided better (nearly quantitative yields for D-*allo* and D-*galacto* epimines in contrast to 64% and 56%, respectively) or comparable (64% vs 81% for D-*talo* epimine) yields of free epimines. The reasons are likely the use of a milder reductive agent, which does not cause the overreduction of the resulting epimine (this is particularly true for the D-*galacto* epimine) and avoiding tedious separation of the epimines from huge amounts of hydrated alumina, which diminishes yields of isolated epimines. In the 1,6-anhydro-β-D-hexopyranose series, $NaBH_4$ reduction now represents a much more effective alternative to $LiAlH_4$ reduction for the preparation of aziridines. However, the use of $NaBH_4$ reduction is limited to the vicinal azido tosylates, which form the 2,3-*exo*-, 3,4-*exo*-, and 3,4-*endo*-oriented aziridine rings (all 3,4-epimines studied and also 2,3-D-*allo*-epimine[12]) otherwise the slow and incomplete formation of epimines together with free amines as by-products may appear. The limitation is due to steric and polar interactions between in situ formed nucleophile and 1,6-anhydro bridge, which lower S_N2-type reactivity at C-2 and cause rather slow formation of 2,3-*endo*-oriented ring (for comparison of the reactivity of 2-, 3-, and 4-*O*-tosyl derivatives of 1,6-anhydro-β-D-glucopyranose toward alkaline formation of oxirane rings—see Refs. 3 and 24). This behavior was experimentally observed in the preparation of 2,3-D-*manno*-epimine[12] and 2,3-D-*talo*-epimine[25] by $NaBH_4$ reduction of the corresponding vicinal azido tosylates.

The structure of epimino derivatives **9**–**11** was determined by ^1H and ^{13}C NMR spectroscopy (for NMR data—see Tables 1 and 2). Structural assignment of protons and carbon atoms resulted from correlated homonuclear 2D-COSY and heteronuclear ^1H, ^{13}C-2D-HMQC spectra. The presence of the aziridine ring in **9**–**11** is supported by the characteristic upfield shifted signals for >CH–NNs protons (δ 3.33–3.95 ppm) and

Table 1. Proton NMR data for compounds **9**–**11** ($CDCl_3$)

Compd	Chemical shifts (ppm)/signal multiplicity										
	H-1	H-2	H-3	H-4	H-5	H-6en	H-6ex	OCH_2(Bn)		Bn	Ns
9	5.30 dd	3.58 bs	3.33 dd	3.85 dd	4.96 dd	3.85 d	3.47 dd	4.85 d	4.71 d	7.29–7.40 (5H)	8.21–8.19 (1H) 7.77–7.82 (3H)
10	5.29 m	3.54 dd	3.40 m	3.52 dd	4.94 dd	3.98 d	3.76 dd	4.88 d	4.68 d	7.30–7.38 (5H)	8.33–8.32 (1H) 7.82–7.69 (3H)
11	5.32 dd	3.70 dd	3.43 dd	3.95 dd	4.93 dd	3.96 d	3.56 dd	4.80 d	4.67 d	7.30–7.36 (5H)	8.36–8.33 (1H) 7.78–7.68 (3H)
	Coupling constants (Hz)										
	J(1,2)	*J*(2,3)	*J*(3,4)	*J*(4,5)	*J*(5,6en)	*J*(5,6ex)	*J*(6en,6ex)	*J*(*gem*)(OBn)	*J*(1,3)	*J*(2,4)	*J*(3,5)
9	1.0	≈0	7.3	6.1	≈0	4.6	6.7	11.9	1.5	≈0	≈0
10	0.9	4.9	5.5	1.5	≈0	4.4	7.5	12.0	1.8	≈0	<1
11	3.5	4.7	7.5	6.1	≈0	4.6	6.9	12.2	1.1	≈0	≈0

Table 2. ^{13}C NMR data of compounds **9**–**11** ($CDCl_3$)

Compd	C-1	C-2	C-3	C-4	C-5	C-6	Other carbons
9	99.52	71.21	38.67	42.99	69.87	65.63	OBn: 72.52 (OCH_2), 128.54 (2), 128.02 (2), 132.18, 128.09 Ns: 148.37, 134.70, 132.67, 131.38, 124.71, 137.06
10	100.88	69.41	36.12	41.85	69.14	66.03	OBn: 70.53 (OCH_2), 132.43, 128.43 (2), 128.00 (2), 127.92 Ns: 148.21, 137.14, 134.54, 132.83, 131.91, 124.59
11	97.17	70.46	37.46	47.23	70.29	65.92	OBn: 70.71 (OCH_2), 131.91, 128.51 (2), 128.03 (3) Ns: 148.24, 137.11, 134.54, 132.66, 131.87, 124.48

upfield shift of their carbon atoms in position 3 and 4 (δ 36–47 ppm). Vicinal coupling constants of aziridine-ring protons *J*(3,4) are in the range 5.5–7.5 Hz, significantly higher than the corresponding constants in epoxides (cf. Ref. 1). The configuration at C-2 was evidenced by the value of the coupling constant *J*(1,2), which is small (0.9–1.0 Hz) for *trans*-diequatorially oriented protons (D-*allo* and D-*galacto*) and large (3.5 Hz) for *cis*-oriented protons (D-*talo*).[1]

1. Experimental

1.1. General methods

Melting points were determined on a Boëtius melting-point microapparatus and are uncorrected. The optical rotations were measured on an Autopol III (Rudolph Research, Flanders, NJ) polarimeter at range 23–25 °C. ^1H and ^{13}C NMR spectra were measured on a Varian INOVA-400 (^1H at 400 MHz and ^{13}C at 100 MHz) instrument in $CDCl_3$ (ref.: TMS for ^1H and the $CHCl_3$ signal at δ 77.0 ppm for ^{13}C) at 25 °C. The ^1H–^1H COSY and ^1H–^{13}C HMQC techniques were used for structural assignments. TLC was carried out on E. Merck DC Alufolien with Kiesegel F_{254} with 3:2 hexane–EtOAc. TLC plates were visualized by UV detection at 254 nm and by an anisaldehyde soln in H_2SO_4. Column chromatography was performed on E. Merck Silica Gel 60 (70–230 mesh ASTM) with an hexane–EtOAc gradient. The solvents were evaporated on a rotary evaporator at 40 °C. Light petroleum (PE) refers to the 40–60 °C bp fraction. *o*-Nitrobenzenesulfonyl chloride (purity 99%) was purchased from Fluka. Reactions were carried out under an argon atmosphere. The ^1H NMR spectral parameters are given in Table 1 and those for ^{13}C NMR in Table 2.

1.2. 1,6-Anhydro-2-*O*-benzyl-3,4-dideoxy-3,4-(*N*-*o*-nitrobenzenesulfonylepimino)-β-D-galactopyranose (9)

1,6-Anhydro-3-azido-2-*O*-benzyl-3-deoxy-4-*O*-tosyl-β-D-glucopyranose (**6**)[1] (4.31 g, 10 mmol), $NaBH_4$ (760 mg, 20 mmol) and THF (50 mL) were mixed and stirred at rt. After consumption of the starting azido tosylate (TLC, 2 d reaction time), MeOH (20 mL) was carefully added dropwise while cooling with an ice-water bath. The mixture was refluxed for 10 h, cooled to rt and evaporated under diminished pressure to give a solid residue. The residue was extracted with CH_2Cl_2 (3×30 mL), combined extracts were stirred with anhyd Na_2SO_4 and charcoal, filtered and evaporated. The resulting oil was dried in a vacuum desiccator over P_2O_5 to give the free epimine (2.33 g). In the next step, a soln of *o*-nitrobenzenesulfonyl chloride (3.31 g, 15 mmol) in THF (25 mL) was gradually added into the soln of free epimine (2.33 g, 10 mmol) and triethylamine (2.1 mL, 15 mmol) in THF (30 mL) under cooling to −40 °C in a solid CO_2–EtOH bath. The stirring was continued for an additional 1 h at −40 °C and overnight at rt. The reaction mixture was poured onto crushed ice (200 g) and extracted with CH_2Cl_2 (3×100 mL).

Organic layers were washed with 5% HCl, 10% $NaHCO_3$, and water. After drying over anhyd Na_2SO_4 and evaporation of the solvent, the residue was chromatographed on silica gel (150 g) with 3:1–3:2–1:1 hexane–EtOAc to give a colorless oil. The oil crystallized in the refrigerator (−30 °C) after a while. Analytical samples were recrystallized (EtOAc–Et_2O–PE) to afford pure nosylepimine **9**. Yield 2.44 g (58%); mp 122–124 °C; $[\alpha]_D$ +1.5 (*c* 0.33 $CHCl_3$). Anal. Calcd for $C_{19}H_{18}N_2O_7S$: C, 54.54; H, 4.34; N, 6.70; S, 7.66. Found: C, 54.38; H, 4.41; N, 6.59; S, 7.71.

1.3. 1,6-Anhydro-2-*O*-benzyl-3,4-dideoxy-3,4-(*N*-*o*-nitrobenzenesulfonylepimino)-β-D-allopyranose (10)

1,6-Anhydro-4-azido-2-*O*-benzyl-4-deoxy-3-*O*-tosyl-β-D-glucopyranose (**7**)[1] (4.34 g, 10.05 mmol), $NaBH_4$ (800 mg, 21 mmol), THF (60 mL), and MeOH (10 mL) were treated as for **9** resulting in 2.34 g (100%) of free epimine, which was subsequently nosylated using *o*-nitrobenzenesulfonyl chloride (3.31 g, 15 mmol) and Et_3N (2.1 mL, 15 mmol). The crude dichloromethane extracts were evaporated under diminished pressure and the residue was crystallized (EtOAc–Et_2O–PE) to afford pure nosylepimine **10**. Yield 3.51 g (84%); mp 134–135 °C; $[\alpha]_D$ +3 (*c* 0.65 $CHCl_3$). Anal. Calcd for $C_{19}H_{18}N_2O_7S$: C, 54.54; H, 4.34; N, 6.70; S, 7.66. Found: C, 54.53; H, 4.30; N, 6.58; S, 7.56.

1.4. 1,6-Anhydro-2-*O*-benzyl-3,4-dideoxy-3,4-(*N*-*o*-nitrobenzenesulfonylepimino)-β-D-talopyranose (11)

To a soln of 1,6-anhydro-3-azido-4-*O*-benzyl-3-deoxy-4-*O*-tosyl-β-D-mannopyranose (**8**)[1] (1.703 g, 3.95 mmol) in THF (25 mL), finely ground $NaBH_4$ (430 mg, 11.3 mmol) was added with stirring and cooling in an ice-water bath. The resulting suspension was stirred for an additional 2 d at rt until the starting azido tosylate disappeared. MeOH (2.5 mL) was added and the soln was refluxed for 13 h in order to complete the formation of the free epimine. After dilution of the reaction mixture with EtOAc (10 mL), the mixture was filtered and the filtrate was evaporated under diminished pressure. The residue was dissolved in a small volume of CH_2Cl_2, the soln was dried over anhyd Na_2SO_4, filtered, and evaporated. Crystallization (Et_2O) of the residue afforded the 3,4-D-*talo*-epimine (585 mg, 64%) identical with a sample prepared elsewhere.[1] The epimine (580 mg, 2.5 mmol) was nosylated following the same procedure as described for **9** (NsCl 830 mg, 3.7 mmol; Et_3N 0.52 mL, 3.7 mmol) except for chromatography. Direct crystallization (EtOAc–Et_2O–PE) of the oily residue afforded pure **11**. Yield 842 mg (81%); mp 125–127 °C; $[\alpha]_D$ −30 (*c* 0.39 $CHCl_3$). Anal. Calcd for $C_{19}H_{18}N_2O_7S$: C, 54.54; H, 4.34; N, 6.70; S, 7.66. Found: C, 54.40; H, 4.52; N, 6.65; S, 7.54.

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References

1. Karban, J.; Buděšínský, M.; Černý, M.; Trnka, T. *Collect. Czech. Chem. Commun.* **2001**, *66*, 799–819.
2. Kroutil, J. PhD Thesis, Charles University, Prague, 2000.
3. Kroutil, J.; Trnka, T.; Buděšínský, M.; Černý, M. *Eur. J. Org. Chem.* **2002**, 2449–2459.
4. Kroutil, J.; Karban, J.; Trnka, T.; Budešínský, M.; Černý, M. *Collect. Czech. Chem. Commun.* **2002**, *67*, 1805–1819.
5. Kocienski, P. J. *Protecting Groups*, 3rd ed.; Thieme: Stuttgart, 2004.
6. Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley: New York, 1999.
7. Mao, H.; Joly, G. J.; Peeters, K.; Hoornaert, G. J.; Compernolle, F. *Tetrahedron* **2001**, *57*, 6955–6967.
8. Maligres, P. E.; See, M. M.; Askin, D.; Reider, P. J. *Tetrahedron Lett.* **1997**, *38*, 5253–5256.
9. Farrás, J.; Ginesta, X.; Sutton, P. W.; Taltavull, J.; Egeler, F.; Romea, P.; Urpí, F.; Vilarrasa, J. *Tetrahedron* **2001**, *57*, 7665–7674.
10. Fujiwara, A.; Kan, T.; Fukuyama, T. *Synlett* **2000**, 1667–1669.
11. Favre-Réguillon, A.; Segat-Dioury, F.; Nait-Bouda, L.; Cosma, C.; Siaugue, J.-M.; Foos, J.; Guy, A. *Synlett* **2000**, 868–870.
12. Kroutil, J.; Karban, J.; Buděšínský, M. *Carbohydr. Res.* **2003**, *338*, 2825–2833.
13. Fürst, A.; Plattner, P. A. In *12th Internat. Congr. Pure & Appl. Chem*. Abstract of Papers; New York, 1951; p 409.
14. Černý, M. *Adv. Carbohydr. Chem. Biochem.* **2003**, *58*, 121–198.
15. Černý, M. In *Frontiers in Biomedicine and Biotechnology. Levoglucosenone and Levoglucosans, Chemistry and Applications*; Witzcak, Z. J., Ed.; ATL: New York, 1994; pp 121–146.
16. Černý, M.; Gut, V.; Pacák, J. *Collect. Czech. Chem. Commun.* **1961**, *26*, 2542.
17. Černý, M.; Staněk, J.; Pacák, J. *Collect. Czech. Chem. Commun.* **1969**, *34*, 3377.
18. Carlson, L. J. *J. Org. Chem.* **1965**, *30*, 3953–3955.
19. Grindley, T. B.; Reimer, G. J.; Kralovec, J.; Brown, R. G.; Anderson, M. *Can. J. Chem.* **1987**, *65*, 1065–1071.
20. Höök, J. E.; Lindberg, B. *Acta Chem. Scand.* **1966**, *20*, 2363–2369.
21. MacLeod, J. M.; Schroeder, L. R.; Seib, P. A. *Carbohydr. Res.* **1973**, *30*, 337–347.
22. Prystaš, M.; Šorm, F. *Collect. Czech. Chem. Commun.* **1971**, *36*, 1448–1471.
23. Doležalová, J.; Trnka, T.; Černý, M. *Collect. Czech. Chem. Commun.* **1982**, *47*, 2415–2422.
24. Černý, M.; Staněk, J.; Pacák, J. *Collect. Czech. Chem. Commun.* **1969**, *34*, 849–856.
25. Karban, J., personal communication.