Pergamon

*Tetrahedron Letters*, Vol. 35, No. 39, pp. 7197-7200, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01573-2

# Chemoselective Reduction of 2,3-Epoxy Tosylates with DIBAL-H as a General Route to Enantiomerically-Enriched 1-Tosyloxy-2-alkanols

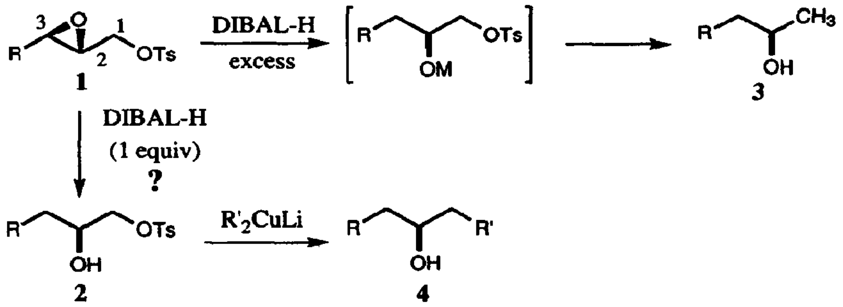
J. Michael Chong* and James Johannsen

Guelph-Waterloo Centre for Graduate Work in Chemistry
Department of Chemistry, University of Waterloo, Waterloo, Ontario, Canada N2L 3G1

***Abstract:*** *2,3-Epoxy tosylates may be reduced with DIBAL-H in $CH_2Cl_2$ or ether at -40 °C to 1-tosyloxy-2-alkanols in high (94-98%) yields.*

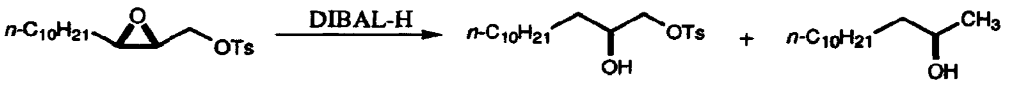
Two years ago, we reported that 2,3-epoxy tosylates (**1**, Scheme 1) may be reduced with excess DIBAL-H to provide 2-alkanols.[1] When coupled with Sharpless asymmetric epoxidation technology,[2] this chemistry provided ready access to methyl carbinols of high enantiomeric purity. We felt that a general synthesis of enantiopure secondary alcohols **4** could be developed if the reduction could be controlled to stop at hydroxy tosylate **2**, and have been actively studying this possibility. Recently, a 2-step conversion of **1**→**2** involving initial epoxide opening with a halide ion followed by reduction with $Bu_3SnH$ was reported.[3] It was suggested that direct reduction of 2,3-epoxy tosylates to 2-hydroxy tosylates is not possible. We now report that the direct transformation of **1** to **2** with DIBAL-H is possible and, in fact, is a very viable reaction which proceeds in high yields.

**Scheme 1**



A summary of initial studies with epoxy tosylate **1a** (R = *n*-$C_{10}H_{21}$) appears in Table 1. As expected,[1] reaction of **1a** with an 3 equivalents of DIBAL-H ($CH_2Cl_2$, -20 °C→rt) lead to the fully-reduced methyl carbinol **3a** in high yield. With only one equivalent of DIBAL-H, no reaction was observed. However, the use of two equivalents of DIBAL-H at low temperatures (-40 °C) gave the desired hydroxy tosylate **2a** in moderate yield (along with recovered **1a**) with no evidence of the over-reduced 2-alkanol (entry 3). Further increasing the amount of DIBAL-H to 3 equivalents allowed for a much faster reaction, and complete conversion of **1a** to **2a** was observed within 3 h at at -40 °C (entry 4) or 90 min at -20 °C (entry 5); **2a** was isolated in excellent yield and, very importantly, no over-reduction was observed. Essentially the same result was obtained with $Et_2O$ as solvent.[4] It is interesting to note that even a large excess of DIBAL-H did not lead to any over-reduction as long as the reaction was kept cold (entry 7).

Table 1. Reactions of Epoxy Tosylate **1a** with DIBAL-H.



**1a** **2a** **3a**

| Entry | equiv$^a$ | solvent | temp (°C) | time (h) | Ratio **2a**:**3a**$^b$ | %Yield **2a**$^c$ |
|---|---|---|---|---|---|---|
| 1 | 3 | $CH_2Cl_2$ | -20→rt | 3 | <2 : >98 | 0$^d$ |
| 2 | 1 | $CH_2Cl_2$ | 0 | 8 | --:-- | 0$^e$ |
| 3 | 2 | $CH_2Cl_2$ | -40 | 7 | >98 : <2 | 58$^f$ |
| 4 | 3 | $CH_2Cl_2$ | -40 | 3 | >98 : <2 | 96 |
| 5 | 3 | $CH_2Cl_2$ | -20 | 1.5 | >98 : <2 | 97 |
| 6 | 3 | $Et_2O$ | -40 | 3 | >98 : <2 | 94 |
| 7 | 8 | $Et_2O$ | -40 | 3 | >98 : <2 | 95 |
| 8 | 3 | THF | -40 | 6 | -- : -- | 0$^e$ |
| 9 | 3 | hexanes | -40 | 2.5 | <2 : >98 | 0$^d$ |
| 10 | 2 | hexanes | -40 | 2.5 | 85 : 15 | 64 |

[a] Molar equivalents of DIBAL-H used relative to **1a**.

[b] Ratios were determined by $^1H$ NMR analysis of crude reaction mixtures; >98:<2 indicates that no signals for the minor component were observed.

[c] Isolated yields of purified (flash chromatography) **2a**.

[d] Alcohol **3a** was isolated in 98% yield.

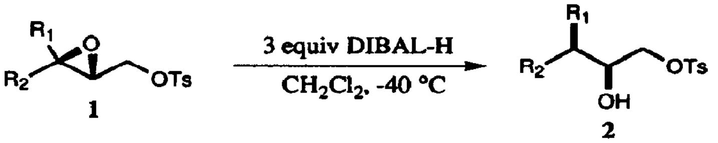
[e] Starting material was recovered in high (>95%) yield.

[f] Starting material (35%) was also isolated.

In other solvents under the same conditions (3 eq DIBAL-H, -40 °C), varying results were obtained. No reaction was observed in THF while complete reduction to alcohol **3a** occurred when hexanes was used. These results are consistent with the expected decrease in reactivity of DIBAL-H in more coordinating solvents.[5]

We examined the reduction of other epoxy tosylates[6] using conditions established with **1a**; results are shown in Table 2. These results are largely self-explanatory but it is worth noting that consistently high yields were observed with both cis- and trans-epoxides and even with the cyclohexyl-substituted epoxide **1f**.

Table 2. Preparation of Hydroxy Tosylates **2** from Epoxy Tosylates.[a]



**1** **2**

| entry | substrate | $R_1$ | $R_2$ | product (% yield)[b] |
|---|---|---|---|---|
| 1 | **1a** | $n$-$C_{10}H_{21}$ | H | **2a** (96) |
| 2 | **1b** | H | $n$-$C_{10}H_{21}$ | **2a** (96) |
| 3 | **1c** | $n$-$C_6H_{13}$ | H | **2b** (94) |
| 4 | **1d** | H | $n$-$C_6H_{13}$ | **2b** (96) |
| 5 | **1e** | H | Ph | **2c** (98) |
| 6 | **1f** | H | $c$-$C_6H_{11}$ | **2d** (96) |
| 7 | **1g** | $CH_3$ | $CH_3$ | **2g** (83)[c] |
| 8 | **1h** | $CH_3$ | $C_6H_{11}$[d] | **2h** (91)[e] |
| 9 | **1i** | $C_6H_{11}$[d] | $CH_3$ | **2i** (76)[f] |

[a] For entries 1-6, reactions were run for 1.5 h; for entries 7-9, 4.5 h.

[b] Isolated yields of purified (flash chromatography) products.

[c] The crude reaction mixture also contained some of the product arising from reduction at C-2 (ratio of C-3:C-2 opening = 15:1)

[d] $C_6H_{11}$ = 4-methyl-3-pentenyl

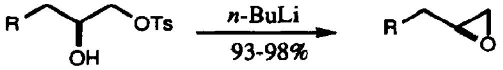
[e] Contaminated with **2i** (**2h**:**2i** = 2:1)

[f] Contaminated with **2h** (**2h**:**2i** = 1:7.5). The crude reaction mixture also contained some of the product arising from reduction at C-2 (ratio of C-3:C-2 opening = 5.5:1)

With trisubstituted epoxides such as **1g**, **1h**, and **1i** (which bear two alkyl groups at C-3), reaction still occurred selectively at C-3 but with some loss in stereochemical purity. Epoxy tosylate **1h**, derived from geraniol,[7] reacted with high regioselectivity (none of the 3-hydroxy tosylate was detected[8]) but the 2-hydroxy tosylate was isolated as a 2:1 (**2h**:**2i**) mixture of diastereomers. The stereoisomeric epoxy tosylate **1i**, derived from nerol, gave the same products but in a ratio of 1:7.5 (**2h**:**2i**) along with small amounts of the 3-hydroxy tosylate. These results are consistent with $S_N1$-like reactivity and might be expected given the Lewis acid properties of DIBAL-H.

The hydroxy tosylates prepared by this methodology should be useful as chiral building blocks for the preparation of simple or functionalized 2° alcohols. For example, treatment of **2a**, **2b**, **2c**, and **2d** with $n$-BuLi (THF, 0 °C) gave the expected epoxides in yields of 93%, 96%, 98%, and 96%, respectively (Scheme 2). It is well-documented[10] that these terminal epoxides may be transformed into 2° alcohols by reaction with a host of nucleophiles including amines,[11] alkynylmetallics,[12] azide,[13] cyanide,[14] malonate,[3] organocopper reagents,[15] and thiols.[16] It has also been shown that treatment of 1-tosyloxy-2-alkanols directly with organocopper reagents gives 2° alcohols.[3]

**Scheme 2**



R = $n$-$C_{10}H_{21}$, $n$-$C_6H_{13}$, Ph, $c$-$C_6H_{11}$

In conclusion, we have established conditions for the direct conversion of 2,3-epoxy tosylates to 2-hydroxy tosylates with DIBAL-H.[17] Given the ready availability of enantiomerically enriched 2,3-epoxy tosylates and the multitude of synthetic applications for the products, these results should be of some use.

Acknowledgements

We thank the Natural Sciences and Engineering Research Council of Canada for financial support.

## REFERENCES AND NOTES

1. Chong, J. M. *Tetrahedron Lett.* **1992**, *33*, 33-36.
2. Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765-5780.
3. Federici, C.; Righi, G.; Rossi, L.; Bonini, C.; Chiummiento, L.; Funicello, M. *Tetrahedron Lett.* **1994**, *35*, 797-800.
4. It has previously been reported that organoaluminum reagents do not react with 2,3-epoxy alcohols in ether or THF: Suzuki, T.; Saimoto, H.; Tomioka, H.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1982**, *23*, 3597-3600.
5. (a) Winterfeldt, E. *Synthesis* **1975**, 617-630.
   (b) Eisch, J. J.; Liu, Z.-R.; Singh, M. *J. Org. Chem.* **1992**, *57*, 1618-1621.
6. Epoxy tosylates were prepared via asymmetric epoxidation and in situ derivatization[2] or tosylation (TsCl, pyr, cat. DMAP) of isolated epoxy alcohols.
7. It has been reported that geraniol 2,3-epoxide reacts with DIBAL-H to give a mixture of products arising from reaction at C-3 and C-2 (to give a mixture of 1,2- and 1,3-diols) in a ratio of 1.2:1, respectively: Dai, L.-X.; Lou, B.-L.; Zhang, Y.-Z.; Guo, G.-Z. *Tetrahedron Lett.* **1986**, *27*, 4343-4346.
8. An authentic example of C-2 opened product was prepared by reduction of geraniol 2,3-epoxide with REDAL[9] followed by monotosylation (1 eq TsCl, $Et_3N$, cat. DMAP).
9. Viti, S. M. *Tetrahedron Lett.* **1982**, *23*, 4541-4544.
10. For a review of glycidol chemistry, see: Hanson, R. M. *Chem. Rev.* **1991**, *91*, 437-475.
11. (a) Jäger, V.; Hümmer, W. *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 1171-1173.
    (b) Yamada, J.-I.; Yumoto, M.; Yamomoto, Y. *Tetrahedron Lett.* **1989**, *30*, 4255-4258.
12. (a) Burgos, C. E.; Nidy, E. G.; Johnson, R. A. *Tetrahedron Lett.* **1989**, *30*, 5081-5084.
    (b) Yamaguchi, M.; Hirao, I. *Tetrahedron Lett.* **1983**, *24*, 391-394.
13. Sinou, D.; Emziane, M. *Tetrahedron Lett.* **1986**, *27*, 4423-4426.
14. Saïah, M.; Bessodes, M.; Antonakis, K. *Tetrahedron: Asymmetry* **1991**, *2*, 111-112.
15. Lipshutz, B. H.; Sengupta, S. *Org. React.* **1992**, *41*, 135-631.
16. Vougioukas, A. E.; Kagan, H. B. *Tetrahedron Lett.* **1987**, *28*, 6065-6068.
17. A representative procedure for the preparation of hydroxy tosylates follows. To a cold (-78 °C), stirred solution of epoxy tosylate **1a** (250 mg, 0.68 mmol) in $CH_2Cl_2$ (5 mL) was added DIBAL-H (1.36 mL of a 1.5 M solution in toluene, 2.0 mmol). The colourless solution was stirred at -78 °C for 5 min then warmed to -30 °C and stirred at that temperature for 90 min. The reaction was then quenched with a saturated solution of Rochelle's salt (5 mL) and allowed to warm to rt. The mixture was extracted with 2 x 20 mL of $CH_2Cl_2$. Drying ($MgSO_4$) and concentration of the organic layers followed by flash chromatography on silica gel (hex:ether, 1:1) afforded hydroxy tosylate **2a** (243 mg, 96%).

(*Received in USA* 4 *July* 1994; *accepted* 2 *August* 1994)