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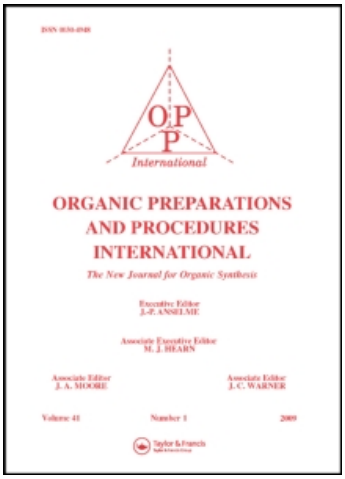

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STEREOSELECTIVE REDUCTION OF 2-QUINOLIZIDINONES WITH LITHIUM TRI-s-BUTYLBOROHYDRIDE

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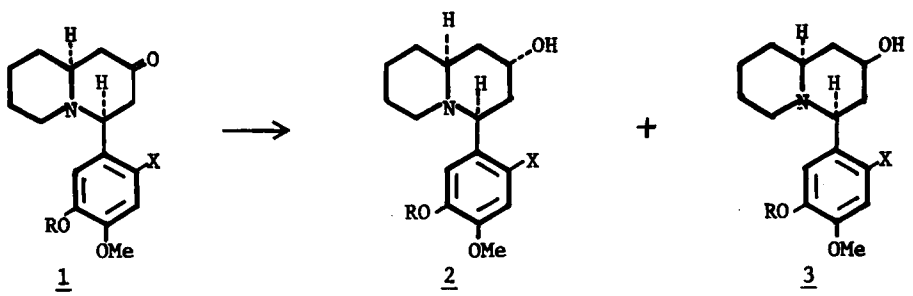
Although the stereoselective reduction of 2-quinolizidinones has been reported [e.g., 1a⟶2a and 3a (9:1)],[1] the need to improve stereoselectivity and avoid the use of the expensive iridium tetrachloride used in the Henbest procedure[2] prompted us to examine other procedures. The reported stereoselective platinum-catalyzed hydrogenation of 2-quinolizidinones in aqueous base[3] was ineffective for the reduction of 1a and 1b, even with ethanol as a co-solvent.



1 2 3

a. R = Me; X = Br b. R = Me; X = H c. R = C(O)CH$_3$; X = H
d. R = X = H e. R = $CH_2OCH_2CH_2OCH_3$; X = H f. R = $CH_2C_6H_5$; X = H

Although reduction of 1a with $NaBH_4$ resulted in a 1:3 mixture of 2a and 3a, the successful use of complex borohydrides for the stereoselective reductions of alkanones[4] encouraged us to attempt their use in the reduction of these quinolizidinones. In fact, when a solution of 1a in THF was treated with lithium tri-s-butylborohydride[5] (L-Selectride)[6] at -78° for 0.5 h followed by slow warming to room temperature, a 12:1 ratio of 2a to

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TABLE

Compound	mp	NMR ($CDCl_3$) δ	IR cm^{-1}	Analysis/Mass Spectra
1b	78-81°	3.25 (dd, J_1= 10 Hz, J_2= 4 Hz, 1H), 3.87 (s, 3H) 3.93 (s, 3H) 6.4-6.8 (m, 3H)	2935, 1720 (KBr)	Calcd for $C_{17}H_{23}NO_3$: 289.16779 Found: 289.16848
2b	oil	3.3 (m, 1H), 3.80 (s, 3H), 3.84 (s, 3H), 4.06 (brm, 1H), 6.6-7.2 (m, 3H)	3400, 2950, 1590 (film)	m/e 291
1c	102-3°	2.23 (s, 3H), 3.20 (dd, J_1= 10 Hz, J_2= 4 Hz, 1H), 3.74 (s, 3H), 6.8-7.1 (m, 3H)	2940, 1765, 1720 (KBr)	Calcd for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.39; N, 4.41 Found: C, 68.25; H, 7.39; N, 4.37
1e	oil	3.30 (s, 3H), 3.82 (s, 3H), 5.27 (s, 2H), 6.9-7.2 (m, 3H)	2950, 1723 (film)	Calcd for $C_{20}H_{29}NO_5$: C, 66.09; H, 8.04; N, 3.85; Found: C, 66.30; H, 8.11; N, 3.69
2e	oil	3.30 (s, 3H), 3.80 (s, 3H), 4.06 (brm, 1H), 5.23 (s, 2H), 6.9-7.1 (m, 3H)	3400, 2930 (film)	m/e 365
2e Acetate	oil	2.12 (s, 3H), 3.46 (s, 3H), 3.84 (s, 3H), 5.03 (brt, 1H), 5.31 (s, 2H), 6.8-7.1 (m, 3H)	2930, 1730 (film)	Calcd for $C_{22}H_{33}NO_6$: C, 64.84; H, 8.16; N, 3.44 Found: C, 64.91; H, 7.93; N, 3.39
3e	oil	3.30 (s, 3H), 3.77 (s, 3H), 5.23 (s, 2H), 6.9-7.1 (m, 3H)	3400, 2930 (film)	
3c Acetate	oil	1.63 (s, 3H), 3.46 (s, 3H), 3.80 (s, 3H), 4.7 (m, 1H), 5.24 (s, 2H) 6.6-7.1 (m, 3H)	2920, 1735 (film)	Calcd for $C_{22}H_{33}NO_6$: C, 64.84; H, 8.16; N, 3.44 Found: C, 64.81; H, 8.01; N, 3.70

3a was obtained (the methyl of the axial acetate appears at δ 2.1 while that of the equatorial acetate is at δ 2.0[1]). This was confirmed by iso-

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lation of the two acetates. The observed stereoselectivity decreased when the reduction was performed at room temperature or when the low temperatures were not maintained for a time following the addition of L-Selectride.

Similarly, reduction of 1b afforded a 10:1 mixture of the two alcohols. The behavior of several phenol blocking groups was studied under these conditions. Reduction of the acetate[7] 1c with L-Selectride afforded a predominance of the axial alcohol but the aryl acetate was also cleaved to afford 2d. Furthermore, treatment of the benzyl ether 1f[8] afforded a complex mixture which contained 2d and 2f[8] as well as unreduced 1f. However, the MEM ether 1e[9] was cleanly reduced to 2e and 3e. The ratio of 2e to 3e ranged from 10:1 to 15:1 with this reagent.

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Separation of the products from the organoborane by-product is readily achieved during chromatographic separation of the isomeric acetates. If separation of the alcohols is not desired, the organoborane may be removed by an extraction procedure. Thus, after initial isolation, as in the procedure below, the chloroform solution is extracted with dilute acid. This is followed by basification and re-extraction into an organic solvent. Normal methods were then utilized to prepare the solution for further reactions or isolation.

Lithium tri-s-butylborohydride is a very effective and convenient reagent for the stereoselective reduction of 2-quinolizidinones to the axial alcohols. The Table summarizes the analytical data for the new compounds.

EXPERIMENTAL

L-Selectride Reduction of Quinolizidinone 1a. Typical Procedure. - A solution of 1a (2.6 g, 7.1 mmol) in 150 ml of dry tetrahydrofuran (THF), under a nitrogen atmosphere, was cooled with a Dry Ice-isopropanol bath. To this stirred solution, 10.6 ml (10.6 mmol) of L-Selectride[8] was added

dropwise. After remaining at the bath temperature for 0.5 h, the reaction mixture was allowed to warm slowly to room temperature. The reaction mixture was diluted with 75 ml of water and THF was removed in vacuo and the mixture was extracted several times with chloroform. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. After acetylation of the alcohols, 2a and 3a (acetic anhydride in pyridine), the acetates were separated by silica gel chromatography using benzene-ethyl acetate mixtures for elution. The acetate of 3a (190 mg) eluted first, followed by the acetate of 2a (2.31 g) for an 86% yield of 2a and 3a acetates in a ratio of 12:1.

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