Tetrahedron Letters, Vol.22, No.36, pp 3447 - 3450, 1981
Printed in Great Britain

0040-4039/81/363447-04$02.00/0

A GENERAL, HIGHLY STEREOSELECTIVE SYNTHESIS OF AMINES

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Summary: The stereochemical course of cycloalkanone imine reductions by a variety of boron hydride reagents is described; very high stereoselectivity with substituted alkali metal borohydrides is reported.

To anyone familiar with the principal molecular mechanisms of drug action, the role of amines as pharmacophoric groups in biologically active substances is readily comprehended. Consequently any method for making substituted amines of known configuration from common precursors like carbonyl compounds is of interest to synthetic and pharmaceutical chemists. Ketone-to-amine transformations could be of special utility in the construction of aminosugars. Such saccharides are important constituents of the glycolipids and glycoproteins which mediate cell-cell recognition and adhesion,[2] influence cellular growth and development, and act as receptors for hormones, vitamins and toxins at the cell membrane.[3] Only a scattering of papers has been published on the conversion of $\backslash C{=}N-$ species to amines,[4] notable among which is the process of reductive amination using $NaBH_3CN$.[5,6] This reaction seems to form predominant amounts of equatorial amines,[7] although its stereochemistry has not been systematically investigated. Our own experiments confirm that the conventional Borch procedure does afford impractical mixtures of stereoisomeric amines. In this Letter, we report studies on the design of more effective reagents for the stereocontrolled reduction of imines.

We chose to focus on the addition of complex hydrides to preformed N-benzylimines of representative cyclic ketones. Debenzylation of the expected secondary amine products could then furnish primary amines stereoselectively, if desired. The requisite imines were best obtained in pure form by modifying the procedure of Stork and Dowd.[8] Thus, dropwise addition of 2-methylcyclohexanone

to a benzene solution of $PhCH_2NH_2$ (2.5 equiv.) at reflux with azeotropic removal of water (45 min) gave 1 in 80% distilled yield. Reduction of 1 with $NaBH_3CN$ in CH_3OH-HCl proved only marginally selective [Table, Entry 1], affording a preponderance of axial amine 2.[9] Authentic 2 and 3 were prepared by reductive alkylation of (2-methylcyclohexyl)amine (5:2 trans:cis, Aldrich) with benzaldehyde and $NaBH_3CN$. As an additional standard, pure trans-3 was synthesized from 2-methylcyclohexanone oxime.[4a] In all cases we examined, of the two possible epimeric N-benzylamines, the axial isomer consistently displayed the more upfield benzylic methylene ^{1}H-NMR absorption as well as the more downfield aminocyclohexyl methine signal.

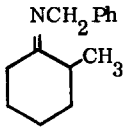
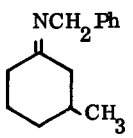
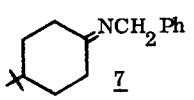
Since the substitution of alkyl groups at boron dramatically enhances borohydride selectivity in ketone reductions,[10] we reasoned that correspondingly modified cyanoborohydride salts might be highly stereodiscriminating reagents for $\backslash C{=}N-$ reductions at low pH. Like sodium 9-cyano-9-hydrido-9-borabicyclo[3.3.1]nonane (9BBN-NaCN),[11] a series of dialkylcyanoborohydrides could be prepared by stirring NaCN with the appropriate R_2BH in THF until homogeneous. Entries 2-9 in the Table indicate somewhat greater stereoselectivity associated with these reagents, and even with 9-BBN itself.

Unlike imine 1, the N,N-dibenzyl enamine of 2-methylcyclohexanone could avoid A-strain[12] by shifting its methyl substituent axial,[13] consequently it should be reduced exclusively to the cis-isomer. However all efforts to prepare this sterically congested enamine failed.

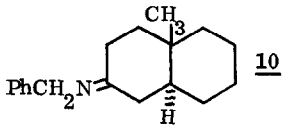
Exposure of 1 to lithium tri-sec-butylborohydride (L-Selectride™), either alone or in the presence of a Lewis acid,[14] caused no reduction. Maryanoff et al have also noted a similar finding with an alkylcyclohexanone anil.[4d] However 1 formed a 97:3 mixture of 2 and 3 when treated with excess Superhydride™ (Entry 12). As the Table indicates, trialkylborohydrides provide a convenient access to axial amines in the substituted cyclohexyl series 4 and 7 as well as in the bicyclic system 10. In each of these latter cases, uniformly higher selectivity was achieved using L-Selectride.

This method, which is simple and inexpensive, complements the synthesis of equatorial amines from ketones by the dissolving metal reduction of oximes.[4a] Applications to aminosugars are planned.[15]

TABLE

Entry	Imine	Reducing Agent (equiv)	Conditions ‡ (Yield)	Products Ratio
(1)	 1	$NaBH_3CN$ (1.14)	A, 74h (82%)	cis (2) : trans (3) 64 : 36
(2)	1	9-BBN-NaCN (1.2)	A, 10h (80%)	84 : 16
(3)	1	disiamylBH-NaCN (1.7)	A, 23h (73%)	81 : 19
(4)	1	diisopinocamphenylBH-NaCN (1.2)	A, 1h (69%)	82 : 18
(5)	1	dicyclohexylBH-NaCN (1.4)	A, 14h (79%)	80 : 20
(6)	1	9-BBN-Bu_4NCN (1.1)	A, 17h	82 : 18
(7)	1	9-BBN-CuCN (2)	A, 13h	—
(8)	1	9-BBN (1.4)	B, 49h (70%)	83 : 17
(9)	2-Me-cyclohexanone	NH_4OAc (8) 9-BBN-NaCN (1.1)	A, 42h, 31	2-Me-cyclohexylamine cis : trans 70 : 30
(10)	1	 $NH_2 \cdot BH_3$ (1.2)	B, 59h (78%)	90 : 10 (2 : 3)
(11)	1	L-Selectride (6)	B, 72h	—
(12)	1	Superhydride (6)	B, 72h (84%)	97 : 3 (2 : 3)
(13)	 4	$NaBH_3CN$ (1)	A, 23h (90%)	trans (5) : cis (6) 42 : 58
(14)	4	Superhydride (6)	B, 29h (90%)	84 : 16
(15)	4	L-Selectride (6)	B, 69h (81%)	96 : 4
(16)	 7	$NaBH_3CN$ (1)	A, 43h (97%)	cis (8) : trans (9) 35 : 65

(continued on next page)

Entry	Imine	Reducing Agent (equiv)	Conditions‡ (Yield)	Products Ratio
(17)	7	Superhydride (6)	B, 75h (89%)	67 : 33
(18)	7	L-Selectride (6)	B, 52h (95%)	98 : 2
(19)	7	$nBuBH_3Li$ (6)	B, 67h (92%)	20 : 80
(20)	 10	$NaBH_3CN$ (1.1)	A, 31h (89%)	3α-amine : 3β-amine (11) (12) 30 : 70
(21)	10	Superhydride (6)	B, 75h (89%)	67 : 33
(22)	10	L-Selectride (6)	B, 75h (76%)	97 : 3

‡Conditions: (A) Methanolic imine solutions (~5 mmol, .25M) containing the reducing agent (added pure or 1M in THF) were treated dropwise with 5N HCl-CH_3OH (2 mL) under N_2. After 10-20h, excess 10% H_2SO_4 was added, CH_3OH removed in vacuo, and the product isolated by acid, then ether, extraction. (B) Commercial hydride solutions (Aldrich) were added to the imine (2.5 mmol) in THF (10 mL, 0°, N_2). After the stated times, water was added, the bulk of THF removed in vacuo and the product isolated by extraction into 10% H_2SO_4.

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(15) Acknowledgment is made to the Donors of the Petroleum Research Fund, administered by the ACS, and to the National Institutes of Health for partial support of this research.

(Received in USA 22 May 1981)