Tetrahedron Letters,Vol.25,No.7,pp 695-698,1984
Printed in Great Britain

0040-4039/84 $3.00 + .00

HIGHLY STEREOSELECTIVE SYNTHESIS OF CYCLIC PRIMARY AMINES VIA HYDRIDE REDUCTIONS.

Robert O. Hutchins* and Wei-Yang Su

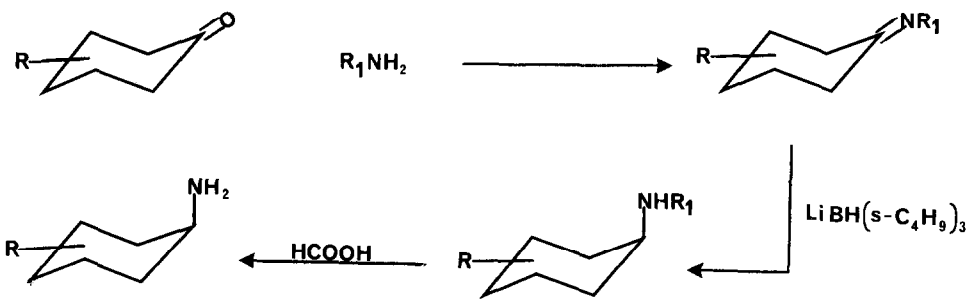
Department of Chemistry, Drexel University, Philadelphia, Pennsylvania 19104

Summary: The Reduction of p,p'-dimethoxybenzhydryl imines of substituted cyclohexanones with lithium tri-sec-butyl or tri-ethylborohydride and subsequent cleavage of the resulting secondary amines with formic acid affords the corresponding axial cyclohexyl primary amines with high stereoselectivity.

The reductions of readily available cyclohexylimines and iminium ions with the highly hindered reagents lithium and potassium tri-sec-butylborohydrides have recently been demonstrated to provide highly stereoselective (>90%) routes to axial secondary[1,2a,b] and tertiary[2a,b] amines, respectively, in analogy to similar stereoselective conversions of ketones to axial alcohols[3]. Corresponding axial primary cyclohexylamines are not as accessible, however, since imines of NH_3 are too unstable to serve as suitable intermediates for trialkylborohydride reductions. Furthermore, oximes, the simplest stable imine derivatives, are inert toward trialkylborohydrides[5] although reduction of these intermediates with $LiAlH_4$ or Na/C_2H_5OH provides fairly (>80%) stereoselective protocols for the corresponding equatorial primary amines.[2b,c] Axial primary amines are procurable via trialkylborohydride reduction of cyclohexyl benzylimines[1,2b] followed by benzyl cleavage using catalytic hydrogenation or hydrogenation of oximes via Pd or Ni catalysts.[2c]

Alternatively, a mild non-catalytic hydrogenolysis process involves reduction of imines derived from p,p-dimethoxybenzhydrylamine[6] with trialkylborohydrides to amines which are subsequently cleaved with warm formic acid to the primary derivatives (Scheme I). The method is essentially "one-pot" since isolation and purification of the crude intermediate imines and secondary amines is unnecessary. Table I presents results with variously substituted

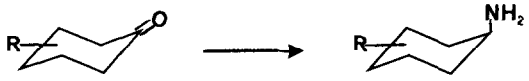
SCHEME I



$R_1 = -CH(C_6H_4OCH_3)_2$

TABLE I

STEREOSELECTIVE SYNTHESIS OF ALKYL-SUBSTITUTED CYCLOHEXYLAMINES



R	Hydride Reagent	Ratio[a] Cis/Trans	%Yield
4-t-C_4H_9	Li $BH(s\text{-}C_4H_9)_3$	99/1	59
4-CH_3	Li $BH(s\text{-}C_4H_9)_3$	89/11	65
3-CH_3	Li $BH(s\text{-}C_4H_9)_3$	5/95	70
2-CH_3	Li $BH(s\text{-}C_4H_9)_3$	-	<10
2-CH_3	Li $BH(C_2H_5)_3$	82/18[b]	58
2-CH_3	$BH(O_2CCH_3)_2$[c]	74/26[b]	71
norcamphor	Li $BH(C_2H_5)_3$	94/6[d]	72[e]

a. ratios obtained by GC using a 15% THEED on 100/120 Supelcoport column unless specified otherwise. b. determined using a 15% Sp 2250 on 100/120 Supelcoport column. c. prepared from t-butylamine borane and acetic acid. d. endo/exo ratio; determined by cyclization to the pyrrolidine derivatives (ref. 2b) and GC analysis via a 15% Sp 2250 column. e. isolated as the HCl salt.

cyclohexanones and illustrates that unhindered 3- and 4-substituted examples are adequately reduced by $LiBH(s\text{-}C_4H_9)_3$ to the axial amines with good to excellent stereoselectivity (89-99%). This is in spite of the fact that the relatively slow reduction of these imines with trialkylborohydrides necessitates the reactions to be conducted at reflux (66°C) for adequate conversions in reasonable times and this probably tempers the stereoselectivity which would be available at lower temperatures.[8] The more hindered ketones, 2-methylcyclohexanone and norcamphor, which bear alkyl groups flanking the carbonyl afforded disappointingly meager yields (10%) of primary amines. This reluctance of tri-sec-butylborohydride to reduce 2-alkylcyclohexyl imines has been noted previously[1,9] and presumably reflects the combined steric encumbrance introduced by the reagent and proximate alkyl appendages. Fortunately, the less bulky lithium triethylborohydride was successful in providing good yields of primary amines, albeit with lower stereoselectivity (82-94%). The less hindered reagent diacetoxyborane[10] afforded only a 74/26 cis/trans ratio of 2-methylcyclohexylamine isomers.

A representative procedure is presented for trans-3-methylcylohexylamine. 3-Methylcyclohexanone (2.82 g, 25 mmol) and p,p -dimethoxybenzhydrylamine[6] (6.08 g, 25 mmol) in 80 mL of benzene was refluxed 48 h while water was collected (Dean-Stark apparatus). Solvent was removed at reduced pressure, $LiBH(s\text{-}C_4H_9)_3$ in THF added (40 mL, 1M, 40 mmol) and the solution refluxed 24 h. Excess hydride was cautiously destroyed with 2 mL of water and the mixture oxidized with alkaline peroxide (2.32 g KOH in 16 mL H_2O, then 16 mL 30% H_2O_2, 5°C), stirred (ambient, 1h, 60°C, 1h), poured into ice-water, extracted thoroughly with ether, and evaporated. The residue was warmed (60-80°C) in formic acid (30 mL, 88%) for 24 h, evaporated to dryness in vacuo, diluted with water (50 mL), basified with 50% NaOH and thoroughly extracted with ether. Evaporation and flash distillation at reduced pressure gave 3-methylcyclohexylamine isomers (70%). GC analysis (15% THEED, 100/120 Supelcoport) indicated a trans/cis atio of 95/5. The trans isomer was characterized as the HCl salt, mp 212.5-214°C, lit.[11] 206-208°C. Alternatively, the primary amines may be isolated by passing dry HCl gas through the final ether solution and collection of the precipitated hydrochloride salts. This latter process allows the removal of any offending equatorial amine isomer by selective recrystallization.

Overall, the above method offers a convenient, direct, stereoselective route to axial cyclohexylamines which should be applicable to widely variant structural types. We are currently exploring the utility of the procedure for asymmetric synthesis of chiral primary amines using chiral, hindered reducing agents.

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(Received in USA 14 November 1983)