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Hydride Reagents for Stereoselective Reductive Amination. An Improved Preparation of 3-Endo-Tropanamine

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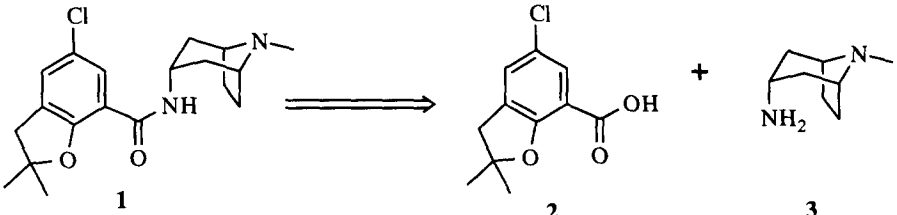
Abstract: The reductive amination of substituted cyclohexanones with sodium triacyloxyborohydrides derived from $NaBH_4$ and various carboxylic acids provides highly diastereoselective conversions to protected axial amines. This method was applied to the stereoselective preparation of 3-endo-tropanamine. Copyright © 1996 Elsevier Science Ltd

Zatosetron (**1**) is an antagonist of the $5HT_3$ (5-hydroxytryptamine) receptor which makes it potentially useful in the treatment of central nervous system disorders such as emesis induced by oncolytic drugs, migraine, dementia, anxiety, schizophrenia and substance abuse.[2] The biological activity of zatosetron resides essentially with the endo isomer of the azabicyclooctane moiety. Zatosetron is prepared by combining the acid chloride derived from 5-chloro-2,3-dihydro-2,2-dimethyl-7-benzofuran carboxylic acid[2,3] **2** ($SOCl_2$, toluene, reflux) and 3-endo-tropanamine[4] **3**. The published method of tropanamine preparation relies on the catalytic hydrogenation (Pt, EtOH, H_2) of the imine derived from tropinone **4** and benzylamine to introduce the endo amine functionality. In practice this method yields an 8:1 mixture[5] of endo:exo tropanamine which is difficult to separate. After acylation with the acid chloride of **2**, the exo isomer can be removed by recrystallization of the zatosetron maleate salt from ethanol/ethyl acetate.[2] Since the endo-amide isomer is required for activity, it was desirable to have an isomerically pure source of endo-tropanamine to increase the efficiency of the zatosetron synthesis. For this reason, an alternative method for stereoselective production of 3-endo-tropanamine was pursued.

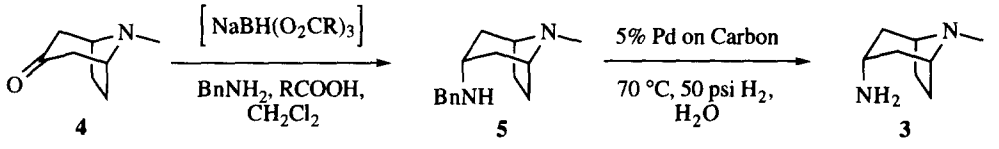


1 Zatosetron **2** **3**

Trialkylborohydride [$LiBH(s\text{-}C_4H_9)_3$] reduction of cyclohexylimines[6] provides a method that preferentially gives axial amine products with high stereoselectivity. However, this method requires formation of the imine or oxime prior to reduction, and the cryogenic conditions needed for the reaction are difficult to obtain in a manufacturing setting. Reductive amination using the Borch method ($NaBH_3CN$)[7] and more recently with borohydride exchange resin (BER)[8] are useful methods for introducing an amine functionality. Unfortunately, upon reductive amination of substituted cyclohexanones these methods afford diastereomeric mixtures where the equatorial amine predominates.[9] Alternatively, $NaBH(OAc)_3$ has been introduced as a mild

hydride source for reductive aminations.[10] Unlike $NaBH_4$ or $NaBH_3CN$, sodium triacetoxyborohydride preferentially gives equatorial hydride addition yielding predominately axial amine products from substituted cyclohexylimines.[9]

Reductive amination of tropinone **4** (1 eq.) and benzylamine (1.5 eq.) with $NaBH(OAc)_3$ (1.5 eq.) derived by adding acetic acid to $NaBH_4$ in CH_2Cl_2, produced a 12:1 mixture of predominately endo-N-benzyltropanamine **5** (Eq. 1). Substantial quantities of N-benzylacetamide (15-20%) were observed in the reaction mixture. Presumably, this byproduct was formed by the addition of benzylamine to the acetoxyborohydride.[11] Hydrogenolysis (H_2O, 5% Pd/C, 70 °C, 50 psi H_2) of the benzyl substituent afforded 3-endo-tropanamine **3** in high diasteroselectivity (Eq. 1). We were encouraged by the increased selectivity for endo tropanamine seen in the $NaBH(OAc)_3$ reduction, but upon acylation with the acid chloride of **2**, separation of the zatosetron exo-isomer was still necessary.



4 **5** **3** **(1)**

In an effort to further increase the selectivity for the endo isomer, we explored the use of different acyloxyborohydrides prepared from $NaBH_4$ and various carboxylic acids of increasing steric bulk. The preparation of triacyloxyborohydrides by the combination of 3 equivalents of a carboxylic acid to $NaBH_4$ has been previously demonstrated.[12] The hydride reagents were prepared *in situ* and used directly in the reductive amination of tropinone. Because the reagents are prepared *in situ*, the exact reducing species is not known and therefore may be a mixture of substituted acyloxyborohydride species.[13] The ratio of endo:exo amine products observed in the reductions with the different reagents is given in Table I.[14] As anticipated, the selectivity for the axial amine product is enhanced by increasing the steric bulk of the carboxylic acid moiety of the acyloxyborohydride reagent. The hydride reagent derived from (±)-2-ethylhexanoic acid (entry 10) gave the highest percentage of 3-endo-tropanamine.

TABLE I. Ratio of Endo/Exo Tropanamine from the Reductive Amination using Acyloxyborohydrides Dervived from Various Carboxylic Acids.

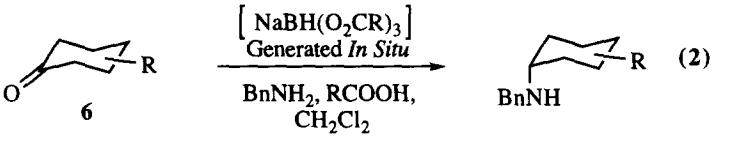
Entry	Carboxylic Acid (RCOOH)	Endo:Exo Ratio[A]	Yield[B] (%)
1	Acetic acid	12 : 1	88
2	Propionic acid	14 : 1	88
3	Isobutyric acid	16 : 1	83
4	Pivalic acid	15 : 1	89
5	Butyric acid	14 : 1	84
6	Valeric acid	13 : 1	81
7	Hexanoic acid	14 : 1	77
8	Cyclohexanecarboxylic acid	8 : 1	81
9	2-Ethylbutyric acid	30 : 1	83
10	(±)-2-Ethylhexanoic acid	>50 : 1	85
11	$NaBH_3CN$ or BER	2 : 1	Not Isolated

A. Ratios determined by GC analysis of the crude reaction mixtures. See reference 5.

B. Yield of endo-3-tropanamine, isolated as dihydrochloride salt.

This preparation of 3-endo-tropanamine can be performed in one pot since the isolation and purification of the intermediate secondary benzyl amine is unnecessary. After quenching the excess hydride reagent with aqueous NaOH (5 M), the N-benzyltropanamine **5** is separated from the organic medium by extracting with aqueous HCl. Subsequent hydrogenolysis (5% Pd/C, 70 °C, 50 PSI of H_2) of the benzyl protecting group conveniently affords an aqueous solution of endo-tropanamine which is suitable for use in a Schotten-Baumann acylation procedure. Alternatively, pure endo-tropanamine can be isolated from the reaction mixture as a dihydrochloride salt (mp = >250 °C, decomp.).

Further demonstration of the increased selectivity for equatorial hydride addition in the reductive amination of cyclohexanones **6** with tri-2-ethylhexanoyloxyborohydride is outlined in Table II (Eq. 2). Besides the enhanced stereoselectivity, the reagent derived from (±)-2-ethylhexanoic acid has several distinct advantages over $NaBH(OAc)_3$. It is completely soluble in CH_2Cl_2; thus the homogeneous reactions are readily stirred and easily sampled. Most of the other hydride reagents (see Table I), including $NaBH(OAc)_3$, form thick slurries or gelatinous reaction mixtures which are a clear disadvantage, particularly on large scale. Additionally, unlike reductions with $NaBH(OAc)_3$, tri-2-ethylhexanoylborohydride reactions show no N-benzyl amide impurity, thereby facilitating purification.



(2)

TABLE II. Ratio of Cis/Trans Cyclohexylamines from the Reductive Amination using $NaBH(OAc)_3$ and Sodium Tri-2-ethylhexanoyloxyborohydride.

Entry	Ketone 6	Amine Cis:Trans Ratio[A] [$NaBH(OAc)_3$]	Amine Cis:Trans Ratio[B] [$NaBH(O_2CR)_3$][D]	Yield[C]
1	R = 4-tBu	4 : 1	7 : 1	80 %
2	R = 4-Ph	4 : 1	7 : 1	85 %
3	R = 4-Me	2.5 : 1	4 : 1	50 %
4	R = 3-Me	1 : 4.5	1 : 8	85 %
5	R = 2-Me	8 : 1	11 : 1	82%

A. Ratios determined by GC analysis of the crude reaction mixtures. See reference 5.

B. Cis and Trans structural assignments were made by comparison of the ^1H NMR. See reference 6a and 9.

C. Yield of the product hydrochloride salt isolated from the (±)-2-ethylhexanoyloxyborohydride reactions.

D. Reagent derived by the addition of 3.5 equivalents of (±)-2-ethylhexanoic acid to $NaBH_4$.

In conclusion, we have demonstrated the use of sodium tri-2-ethylhexanoyloxyborohydride for highly stereoselective reductive amination of cyclohexanones. This methodology was applied to an improved stereoselective preparation of endo-3-tropanamine. This simple and inexpensive method is a viable alternative to the use of bulky hydride reagents.

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5. Ratios were obtained by capillary gas chromatography CAM Capillary column (15 m x 0.5 m I.D.). GC measurements were performed on a Hewlett-Packard 5200 GC instrument equipped with a flame ionization detector (FID) and a Hewlett-Packard electronic integrator. The carrier gas (helium) flow rate is 1 mL/min. with a 20:1 split ratio. The oven temperature is increased from 100 °C to 220 °C over 30 minutes.
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13. The reagent prepared from (±)-ethylhexanoic acid could also be a mixture of diastereomers.
14. GENERAL REDUCTIVE AMINATION PROCEDURE. The requisite carboxylic acid (350 mmol) was added to a slurry of $NaBH_4$ (100 mmol) in CH_2Cl_2 (150 mL) at ambient temperature over a period of 4-5 hours. The reaction mixture was stirred at ambient temperature under a nitrogen atmosphere until the hydrogen evolution was compete (15 h). The desired ketone (50 mmol) and benzylamine (75 mmol) in CH_2Cl_2 (50 mL) were added and the reaction mixture was stirred at ambient temperature until reaction was complete. The reaction was quenched by the slow addition of 5 M NaOH solution (200 mL). After stirring 15 minutes, the CH_2Cl_2 layer was separated, dried (Na_2SO_4) and concentrated. The crude amine product was either hydrogenolyzed (5% Pd/C) to remove the benzyl group or isolated as an HCl salt by the addition of anhydrous HCl.

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