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A highly stereoselective reductive amination of 3-ketosteroid with amines: an improved synthesis of 3α-aminosteroid

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Abstract—A highly stereoselective reductive amination method was developed based on in situ generated sodium acyloxyborohydride and was successfully applied to a steroidal skeleton with various amine sources. High yield (96%) and a de of up to 95% were achieved by modifying the reducing reagent. The effect of this reagent will be discussed.

The reduction of aldehyde or ketone with an amine source in the presence of a reducing agent is reductive amination (RA). This is among the most useful and important tools in the introduction of a nitrogen atom in intermediates, which find its vast application in the synthetic processes of natural products. Stereoselective reduction has always been a focus of attraction in synthetic chemistry for many decades. There are numerous examples in the literature that requires a high degree of stereoselectivity. One such example is Squalamine, which is well known for its antibiotic properties against Gram positive and Gram negative bacteria. Also, an antifungal, an anticancer, and inhibits angiogenesis (Fig. 1).[1] Attempts have been made to lead its analogues, appeared biologically more active.[2] In another example, neurosteroid Funtumin, a known alkaloid, which is 3α-amino-5α-pregnan-20-one, increased the binding of [^{3}H]flunitrazepam at the GABA$_A$ receptor in the primary culture of cortical neurons.[3]

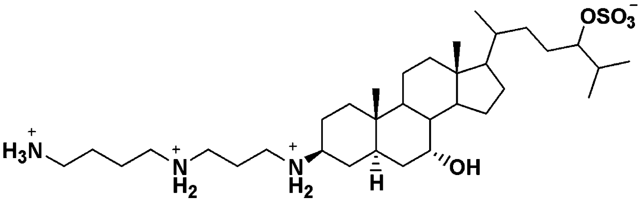

Figure 1. Squalamine.

There are two methods available for RA, out of which a direct reductive amination (DRA) method is involved with a heterogeneous protocol. Such methods have limitations including the production of side products and low yields, as compared to a stepwise or indirect reaction, which utilizes hydride reducing agents. A variety of reducing agents, such as $NaBH(OAc)_3$,[4] $NaBH_4$,[5a] $NaBH_3CN$,[5b] pyridine–borane (py–BH_3),[5c] $Ti(Oi\text{-}Pr)_4/NaBH_4$,[5d] borohydride exchange resin,[6] $Zn(BH_4)_2/SiO_2$,[7] Bu_3SnH/SiO_2,[8] $PhSiH_3/Bu_2SnCl_2$,[9] $BH_3S(Me)_2$,[10] $Zr(BH_4)_2Cl_2(dabco)_2$,[11] $ZnCl_2/NaBH_4$,[12] $NiCl_2/NaBH_4$,[13] Bu_2SnHCl and Bu_2SnHI,[14] and $Ti(Oi\text{-}Pr)_4/I_2$,[15] a microwave assisted $NaBH_4$/clay,[16] have been used.

We are interested in exploring the stereochemistry of 3-ketosteroid with various amine sources and reagents. Hence, we selected steroid moiety as a cyclic ketone and chose some commonly available amine sources along with spermidine and spermine as more specific examples. By carefully selecting ketosteroid and amine, it could be explored as an intermediate in the course of squalamine analogue preparation. Almost all of the synthetic methods that lead to squalamine involve the RA of polyamine and a steroidal skeleton. Of all the methods that have been put forth, only one enantiomer was emphasized. In all cases, however, a diastereomeric mixture was obtained. 3α Isomer is proved to be more potent in some instances.[1] It is difficult to generalize the ratio of diastereomers because it depends upon various parameters including reagents, reaction conditions, and stoichiometry. By employing a selective reducing reagent, the ratio of products can be varied effectively. The relative ratio of stereoisomer depends upon the size of

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Keywords: Reductive amination; Stereoselective; 3α-Aminosteroid.

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the reagents and how it attacks the carbonyl carbon, axial or equatorial. As a result, the selection of the reagent is very crucial.

$NaBH_4$, which is used for reductive amination by Kinney and co-workers[5a] requires harsh reaction conditions, $NaBH_3CN$ is toxic and produces residual cyanide. Care must be taken to control pH. For a successful RA, it should be ~6. Moreover, at pH 3–4 it reduces aldehyde and ketone to alcohol.[5b] $NaBH(OAc)_3$ is versatile, and is mildly used in many instances. In the past, $NaBH_4$ was modified by its reaction with various carboxylic acids, leading to the in situ generation of sodium triacyloxyborohydrides, which is a less reactive species than their mono or diacyloxyborohydride counterparts.[17] It was evident that the 2 M equiv of a hydride reacts more rapidly than a 3 M equiv at room temperature. The fourth molar does not react.[18] High stereoselectivity was achieved by modifying $NaBH_4$ with different carboxylic acids in the synthesis of zatosetron maleate.[19] We have investigated the effect of sodium triacyloxyborohydride [$NaBH(OCOR)_3$] in the RA of a steroid with various amine sources.

$$NaBH_4 + 3RCOOH \xrightarrow{CH_2Cl_2} NaBH(OCOR)_3 + 3H_2 \quad (1)$$

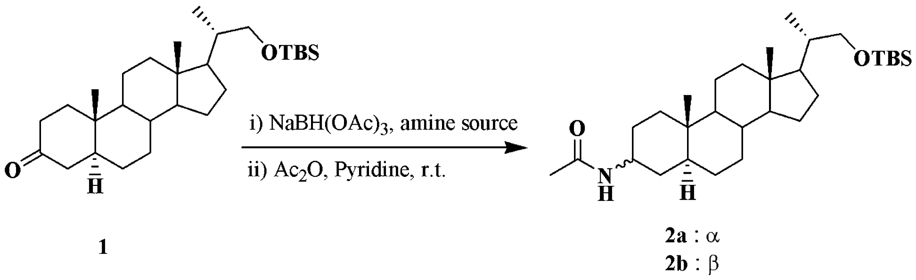
By using a general procedure for reductive amination, ketosteroid **1** was treated with various ammonia sources in the presence of $NaBH(OAc)_3$ and gave **2a/2b** as a mixture of 3α/3β (Table 1 and Scheme 1). The acetylation of a formed primary amine was performed for the ease of separation. Among the tested ammonia sources, $CH_3CO_2NH_4$, HCO_2NH_4, NH_4Cl, NH_4OT_f, and $CF_3CO_2NH_4$, an ammonium triflate (NH_4OT_f) provided improved yields as they pertains to their excellent solubility in a THF, which facilitate imine formation easily, as compare to others. This may account for poor solubility.

Table 1. The RA under various ammonia sources

Entry	Ammonia source (10 equiv)	Yield (%)
1	$CH_3CO_2NH_4$	44
2	HCO_2NH_4	No reaction
3	NH_4Cl	No reaction
4	NH_4OT_f	90
5	$NH_4CO_2CF_3$	No reaction

The reaction has been examined with several different solvents including DCM, DCE, THF, and MeOH. The solvents have been evaluated based on yield and reaction time. THF proved to be the best solvent in terms of the RA. The effect of stoichiometry for NH_4OT_f was scrutinized and it was observed that 5 equiv of NH_4OT_f was not sufficient to drive the reaction into forward direction. On the other hand, 10 equiv provided better results. By increasing the amount of $NaBH(OAc)_3$ from 1.5 to 2 equiv, this showed an improved yield although the reaction time was not greatly affected. These results suggested that 1 equiv of ketone and 10 equiv of NH_4OT_f with 2 equiv of $NaBH(OAc)_3$ could be the standard stoichiometry required for the reaction (Table 2). $NaBH(OAc)_3$ provides a mixture of 3α/3β in a ratio of 1:1 (Table 2, entry 6).

In order to increase the selectivity of the 3α isomer, various acyloxyborohydrides were prepared from $NaBH_4$ and carboxylic acid of increasing bulkiness. $NaBH_4$ (1 equiv), with a carboxylic acid (3.5 equiv), generated in situ sodium triacyloxyborohydride (Eq. 1). It was observed that the increase in the bulkiness of carboxylic acid, stereoselectivity was biased toward the 3α isomer in Scheme 1 (Table 3). Pivalic acid results showed a lower yield because it was unable to form a triacyloxyborohydride derivative completely, hence, ketone was reduced and phenylacetic acid showed no reactivity with $NaBH_4$. 2-Ethylhexanoic acid improved stereoselectivity



Scheme 1. Reductive amination of **1** with various amine sources.

Table 2. Effect of stoichiometry on the RA in Scheme 1

Entry	Ketone (equiv)	$NaBH(OAc)_3$ (equiv)	NH_4OT_f (equiv)	Solvent	Time (h)	Yield	Ratio (3α/3β)
1	1	1.5	5	THF	No reaction		
2	1	1.5	10	DCE	No reaction		
3	1	1.5	10	MeOH	No reaction		
4	1	1.5	10	DCM	20	70	1:1
5	1	1.5	10	THF	8	88	1:1
6	1	2.0	10	THF	8	96	1:1

Table 3. RA using in situ generated various sodium acyloxyborohydrides in Scheme 1

Entry	Carboxylic acid (RCOOH)	Abbreviation	Yield	Ratio (3α/3β)
1	Acetic acid	NaBH(OAc)$_3$	94	1:1
2	Butyric acid	NaBH(OAc)$_3$	85	2.7:1
3	Isobutyric acid	NaBH(O*i*Bu)$_3$	86	3.0:1
4	Isovaleric acid	NaBH(O*i*val)$_3$	95	4.3:1
5	Pivalic acid	NaBH(Opiv)$_3$	37	5.7:1
6	2-Ethylbutyric acid	NaBH(OEb)$_3$	92	7.3:1
7	2-Ethylhexanoic acid	NaBH(OEh)$_3$	96	9.0:1

dramatically and the rate of reaction also increased, it provided 3α/3β a ratio of 9:1 (Table 3).

Encouraged by these results, the RA was elaborated to spermidine and spermine. Ketosteroid **1** (1 equiv) and 2.5 equiv of spermidine with 2 equiv of reagent provided a diastereoselective ratio of 3α/3β of 19:1, with a tris[2-(ethylhexanoyl)oxy]borohydride reagent [NaBH(OEh)$_3$] (Table 4, entry 2).[20] NaBH(OEh)$_3$ was compared with other reagents and it gave a higher 3α product. In another attempt, we used the polymer-bound reagent MP-triacetoxyborohydride (Table 4, entry 5). It gave similar results as NaBH(OAc)$_3$, however, the polymer was unable to remove unreacted spermidine, hence, purification was necessary.[21] NaBH$_3$CN exhibits more selectivity toward the 3β isomer. The pH dependence and size of NaBH$_3$CN may be attributed to the stereoselectivity of product (Scheme 2).

Results with spermine showed further improvement in selectivity, 3α/3β as 24/1 (Table 4). The effect of size of the amine was also observed. As the size increases, the difference in the ratio of the 3α/3β products was also greater and more 3α products were obtained. The mechanism for selectivity has several explanations in the literature but none of them are satisfactory for all situations. Hutchins et al. explained how hydride reagents attack whether they are axial or equatorial in a cyclic ketone, and its preferred mode of attack on carbonyl carbon depends upon the bulkiness of the reagent. The steric environment around the carbonyl is also responsible for the difference in diastereoselectivities.[22]

Table 4. Reductive amination of **1** with Boc protected spermidine and spermine with various reducing reagent

Entry	Reducing reagent	Yield	Amine source	Ratio (3α/3β)
1	NaBH(OEh)$_3$	97	Spermine	24:1
2	NaBH(OEh)$_3$	96	Spermidine	19:1
3	NaBH(OAc)$_3$	95	Spermine	3:1
4	NaBH(OAc)$_3$	98	Spermidine	3:1
5	MP–BH(OAc)$_3$[a]	92	Spermidine	3:1
6	NaBH$_3$CN	90	Spermine	0.65:1
7	NaBH$_3$CN	91	Spermidine	0.6:1

[a] Polymer bound triacetoxyborohydride.

In this letter, we have described a method with high stereoselectivity, which will be useful in the synthesis of a squalamine analogue. It could be promising for synthetic applications and it will give a better insight into understanding the effect of reagents.

Acknowledgments

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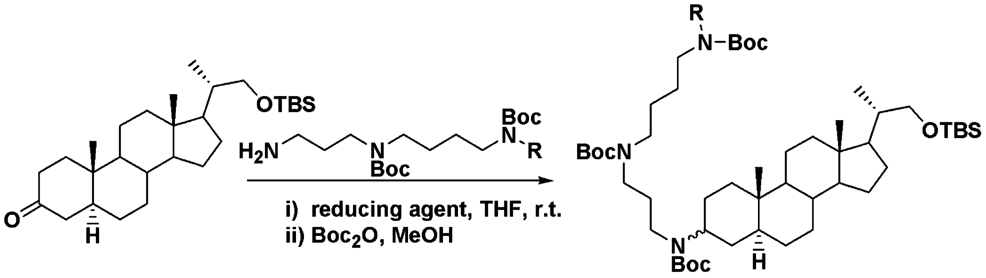

1

3a : α, R = H
3b : β, R = H
4a : α, R = (CH$_2$)$_3$NHBoc
4b : β, R = (CH$_2$)$_3$NHBoc

Scheme 2. Reductive amination of **1** with Boc protected spermidine and spermine.

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20. (i) $NaBH(OEh)_3$ was prepared by the slow addition of 2-ethylhexanoic acid (28 ml, 175.7 mmol) to $NaBH_4$ (1.9 g, 50.2 mmol) in CH_2Cl_2 in an ice bath, and stirred for 72 h. (ii) A mixture of **1** (200 mg, 0.45 mmol) and spermidine (380 mg, 1.1 mmol) in THF reacted with 2 equiv $NaBH(OEh)_3$ at room temperature under an inert atmosphere. After the reaction was completed, the solvent was removed and extracted with EtOAc, dried over Na_2SO_4, and concentrated to dryness. The reaction mixture further reacted with di-*tert*-butyl dicarbonate (1.2 equiv) in MeOH. The solvent was removed and extracted with EtOAc. Chromatography on a silica gel column gave **3a** (361 mg, 92%) and **3b** (19 mg, 8%) in 96% yield.
    Compound (**3a**) R_f 0.36 (EtOAc/hexane 1:4); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.63 (s, 3H, 18-CH_3), 0.77 (s, 3H, 19-CH_3), 0.86 (s, 9H, $(CH_3)_3$), 0.95 (d, $J = 6.5$ Hz, 3H, 21-CH_3), 1.42 (s, 27H, Boc-H), 3.21 (dd, $J = 7.5$, 9.5 Hz, 1H, 22-H_a), 3.54 (dd, $J = 3.0$, 9.5 Hz, 1H, 22-H_b), 4.04 (br s, 1H, 3β-H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 157.5, 157.2, 157.0, 80.8, 80.6, 69.4, 57.7, 54.3, 51.2, 44.2, 43.9, 41.4, 40.6, 37.1, 36.5, 33.4, 31.2, 30.3, 30.1, 29.9, 29.2, 28.9, 27.5, 27.2, 26.6, 25.8, 22.4, 19.9, 18.4, 14.8, 13.7, −3.7. Anal. Calcd For $C_{50}H_{93}N_3O_7$ Si: C, 68.52; H, 10.70; N, 4.79. Found: C, 68.48; H, 10.67; N, 4.77.
    Compound (**3b**) R_f 0.33 (EtOAc/hexane 1:4) ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.63 (s, 3H, 18-CH_3), 0.76 (s, 3H, 19-CH_3), 0.86 (s, 9H, $(CH_3)_3$), 0.95 (d, $J = 6.5$ Hz, 21-CH_3), 1.43 (s, 27H, H-Boc), 3.21 (dd, $J = 7.6$, 9.5 Hz, 1H, 22-H_a), 3.54 (dd, $J = 3.0$, 9.5 Hz, 1H, 22-H_b), 4.60 (br s, 1H, 3α-H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 57.5, 157.1, 157.0, 148.2, 86.7, 80.8, 80.6, 69.4, 57.7, 55.7, 54.3, 44.2, 41.4, 40.6, 37.0, 33.5, 31.2, 30.3, 30.1, 30.0, 29.9, 29.2, 28.9, 27.5, 27.2, 25.9, 22.6, 19.9, 18.4, 14.0, 13.7, −3.7. Anal. Calcd for $C_{50}H_{93}N_3O_7Si$: C, 68.52; H, 10.70; N, 4.79. Found: C, 68.44; H, 10.72; N, 4.78.
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