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STEREOSELECTIVE REDUCTION OF α -HYDROXY OXIME ETHERS: A CONVENIENT ROUTE TO CIS-1,2-AMINO ALCOHOLS

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Summary

Reduction of cyclic α -hydroxyketoximes with borane provides an excellent, high yielding, regio- and stereoselective route to CIS-1, 2-aminoalcohols.

The stereocontrolled generation of CIS -1,2-aminoalcohols is currently receiving considerable attention because of their useful pharmacological properties¹, utility in natural product synthesis² and possible application as an amino acid surrogate for enzyme inhibitors. They represent important structural features of natural products such as aminocyclitol antibiotics³ and amino sugar derivatives eg. acosamine^{4a} and ristosamine^{4b}. Although, stereocontrolled functionalization of olefin systems has been established as a reliable method⁵, difficulties are often encountered in this process due to lack of regiochemistry, harshness of reaction conditions and availability of starting olefins. During the course of our investigation it became apparent that many of the CIS aminoalcohols we required could not be obtained in satisfactory yield using existing methodology⁵. We have consequently sought an effective route to CIS -1,2-aminoalcohols, and herein we report an efficient and stereoselective method for this transformation, which provides more general access to a variety of CIS- aminoalcohols.

Commercially available thiochroman-4-one **1** was converted to 3-hydroxy-4-thiochromanone dimethylketal **2** by use of Moriarty reaction⁶. Thus, the reaction of thiochromanone **1** with methanolic potassium hydroxide (3 equiv at 0°C for 15 min) and iodobenzene diacetate (15 equiv at 0°C to 23°C for 16h) afforded 3-hydroxy-4-thiochromanone dimethylketal **2** in 82% yield after silica gel chromatography. Hydrolysis of the ketal with 3N aqueous hydrochloric acid in ethanol at 23°C for 1h gave α -hydroxy ketone⁷ which was converted to the corresponding α -hydroxy benzyloxime **3** by treatment with 1.1 equiv of benzyloxyamine hydrochloride **III** in pyridine at 23°C for 16h to give mixture (3:2) of anti and syn oximes **3** in 78% isolated yield. The mixture of oximes was separated by silica gel chromatography (R_f =0.6 for anti isomer, R_f =0.71 for syn isomer) using ethyl acetate and hexane (3:1) as the solvent system.

The stereochemistry of oximes **3a** and **3b** was determined by NOE experiments. Reduction of anti-oxime **3a** with 3 equiv of borane-tetrahydrofuran complex in tetrahydrofuran at 0°C to 23°C for 16h resulted in CIS -1,2-aminoalcohol **4** stereoselectively (selectivity 95:5) in 89% isolated yield after workup according to the procedure of Feuer and co-workers⁸. When the reduction of the syn-oxime **3b** was carried out under identical conditions, a small amount

of starting oxime remained (<5%) but the aminoalcohol so produced contained CIS -isomer: as the major product (ratio 88:12). An equilibrium mixture (3:2) of anti and syn oximes were subjected to borane reduction conditions at 0°C to 23°C for 12h and 23°C to 45°C for 2h to afford 86% isolated yield of a (90:10) mixture of CIS and trans aminoalcohols⁹

The CIS stereochemistry of **4** was demonstrated by a 300 MHz ¹H-NMR spectrum where protons H_A and H_B of **4** showed a coupling constant of 36 Hz in keeping with CIS orientation. The stereochemistry of **4** and **5** was further established by their conversion to the corresponding oxazinones, **6** and **7**. Thus, reaction of the mixture of aminothiochromanols with sodium hydride and ethyl chloroacetate in tetrahydrofuran at 0°C for 5h resulted in oxazinones **6** and **7** in 91% yield. Oxazinones **6** and **7** exhibited coupling constants of J_{AB}=37 Hz and J_{AB}=88 Hz respectively in accordance with the postulated CIS and trans stereochemistry.

Various α-hydroxy oximes (table I, entries 1-4) were prepared, generally in excellent yield from the corresponding ketone by the sequence of reactions described above. In case of entry 5, α-hydroxy ketone **15** was prepared from commercially available triacetox-D-glucal by a sequence involving (a) hydrolysis of the acetates with triethylamine in aqueous methanol at room temperature for 10h (b) selective protection of the primary alcohol as *tert*-butyldimethylsilyl ether¹⁰ with *tert*-butyldimethylsilyl chloride and pyridine at 0°C (c) allylic oxidation with activated manganese dioxide in methylene chloride to give α-hydroxy ketone **15**. Catalytic hydrogenation of **15** over 5% Pd-C in ethyl acetate followed by formation of oxime with benzyloxyamine hydrochloride in pyridine afforded a mixture of α-hydroxy oximes **16** in 51% overall yield starting from glucal **14**.

The resulting O-benzyl oximes (CIS and trans mixture) were subjected to borane reduction in THF at 0°C to room temperature for 16h and the results are listed in table I. As shown, the method is quite general and CIS aminoalcohols were obtained stereoselectively in excellent yield. The assignment of stereochemistry in each case was made on the basis of ¹H NMR coupling constants between protons H_A and H_B of the corresponding oxazinones. The magnitude of J_{AB} (2–4 Hz) for these oxazinones is diagnostic of the CIS isomer.

The degree of selectivity associated with these reduction processes¹¹ could be explained based on the following hypothesis. The reaction of borane with α-hydroxy oxime first generates the alkoxy borinate and subsequently reduction of oxime occurs from the less hindered side i.e. away from the bulky borinate to give CIS aminoalcohol.

In summary, the method described in this report provides an efficient and convenient route to a variety of CIS aminoalcohols. The application of this methodology in the synthesis of various enzyme inhibitors and biologically active aminoalcohols is in progress.

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Scheme I.

Scheme II.

Table I

Reduction Of O-benzyl oxime with BH_3 THF^a

Entry	Substrate (Yield)	Ratio of aminoalcohol ^b Cis/Trans (Yield) ^c	Oxazinone	Coupling (J_{AB})
1	3	(81%) 90 10 (86%)	6	37 Hz
2	8	(79%) 92 8 (81%)	9	39 Hz
3	10	(73%) 88 12 (81%)	11	39 Hz
4	12	(72%) 84 16 (74%)	13	21 Hz
5	16	(68%) 96 4 (68%)	18	24 Hz

^a All reductions were carried out under N₂ atmosphere

^b Isomer ratios were based on ¹H NMR integration and HPLC analysis

^c Yield of pure products after silica gel chromatography (2–10 mmole scale)

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