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Stereoselective hydrogen bromide-promoted hydrogenation of an α-hydroxyoxime

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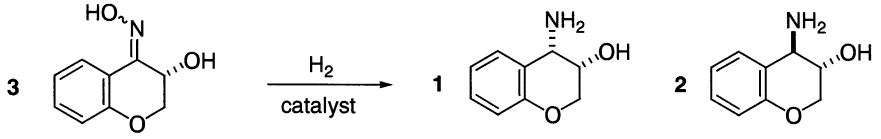
Abstract

Hydrogen bromide has been demonstrated to provide optimal *cis*-selectivity in the reduction of 4-chromanone α-hydroxyoxime (25:1 *cis*/*trans*) in 94% yield. This reaction is pivotal in the synthesis of *cis*-aminochromanol. © 2000 Elsevier Science Ltd. All rights reserved.

In the synthesis of the HIV protease inhibitor Crixivan®,[1] an expedient way of producing *cis*-aminoindanol and related aminoalcohols was established using a Jacobsen epoxidation/Ritter-type reaction sequence.[2] These aminoalcohols have been used successfully in a 'conformational toolbox' of oxazoline ligands.[3] Recently, we have begun to explore the use of aminoalcohols that are inaccessible via the Jacobsen/Ritter sequence, e.g. *cis*-aminochromanol **1**.[4] The racemic *cis*-aminochromanol has previously been prepared by reaction of chromene with INCO[5] and hydrolysis of the oxazolidinone or borane reduction of the *O*-benzyloxime.[6]



One of the most 'atom-economical' means of preparing an amine is hydrogenation of an oxime where the only by-product is water.[7] The hydrogenation of indane-derived keto- or hydroxy-oximes has been known for almost four decades.[8] The *cis*-aminoindanols are formed in acidic media[9] whereas the *trans* isomers are formed predominantly in neutral or alkaline solution. *Cis*-aminochromanol **1** might also be accessible via reduction of the hydroxyoxime **3** under acid conditions, although the outcome in this case would be less clear-cut than in the indane series due to the *plasticity* of the chromane ring system. In this paper we describe the

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discovery of a stereoselective hydrogen bromide promoted hydrogenation and our studies directed at understanding the origin of the stereoselectivity. For our initial studies in the racemic series, hydroxyoxime **3** was prepared as a crystalline solid in 85% overall yield from chromanone by Moriarty oxidation[10] and in situ oxime formation. Palladium black has often been used for oxime reductions but we have found the outcomes to be dependent on the catalyst vendor. High catalyst loadings were required and this coupled with the lack of availability at large scale drove our change to Pd/C as catalyst.[11] Hydrogenations using a variety of acids (1.0 equiv.) were run at 40 psig, 12 hours, 10°C, 0.3 M in methanol and with 3 mol% catalyst (Table 1).

Table 1

Entry	Acid	**1**/**2** *cis*/*trans*[a]	Assay yield[a] (%)
1		1.3:1	96
2	HF	2.2:1	79
3	HCl	7:1	95
4	HBr	23:1	94
5	HI		0
6	H_2SO_4	1.9:1	80
7	HNO_3	2.1:1	92
8	HPF_6	2.0:1	89
9	CF_3SO_3H	3.2:1	90
10	CH_3SO_3H	4.7:1	86
11	$B(OH)_3$	1.4:1	90
12	CF_3CO_2H	1.7:1	92
13	CH_3CO_2H	1.5:1	87
14	$(CF_3)_3COH$	6.3:1	52

[a] Based on HPLC assay.[13]

From this panel of experiments, it is clear that HBr provides optimal selectivity. Due to the levelling effect, there is no acid stronger than $MeOH_2^+$ ($pK_a = -2$ relative to water) in methanol. Hence, bromide ion (entry 4) and not acid strength is implicated as having a role in the hydrogenation selectivity.[12] HI (entry 5) led to precipitation of a palladium mirror which was not a competent catalyst. In order to determine if HBr was also causing desorption of the palladium, the reaction solution was analyzed but <1 ppm Pd was detected by ICP-MS.

Table 2

Entry	Halide (1.0 equiv.)	**1**/**2** *cis*/*trans*[a]	Assay yield[a] (%)
1	48% HBr	23:1	94
2	HBr (acetic acid)	23:1	93
3	Lutidine·HBr	3.8:1	74
4	Bu_4NBr	1.9:1	88
5	Bu_4NBr/HBr (1:1)	8.1:1	89
6	Bu_4NCl/HBr (1:1)	7.9:1	90
7	$Bu_4NBr/(CF_3)_3COH$ (1:1)	2.6:1	87

[a] Based on HPLC assay.

The role of bromide ion was examined in our next panel of experiments (Table 2). It seems clear that an acid and a bromide ion are required for high selectivity. Entries 5 and 6, both using 0.5 equiv. HBr gave the same selectivity irrespective of which supplemental halide was added to the reaction medium.

Solvent effects were also briefly examined (Table 3).[14] The use of higher levels of water significantly reduced the selectivity, presumably due to increased solvation of the bromide ion and attenuation of the system acidity ($pK_a = -1.7$). Having clearly defined the need for both bromide ion and proton we investigated the effect of stoichiometry (Table 4). Optimal selectivity was achieved using 1.0 equiv. of HBr (entry 5). From a practical sense, the use of higher levels of HBr leads to increased solvolysis to give **4** if hydrogenation is not begun promptly after the addition of the acid.

Table 3

Entry	Solvent	**1**/**2** *cis*/*trans*[a]	Assay yield[a] (%)
1	MeOH	23:1	94
2	1:1 MeOH/H_2O	12:1	92
3	1:2 MeOH/H_2O	11:1	89

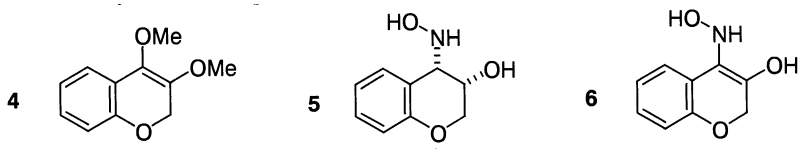
[a] Based on HPLC assay.

Table 4

Entry	Equiv. 48% HBr	**1/2** *cis*/*trans*[a]	Assay yield[a] (%)
1		1.3:1	96
2	0.25	5.4:1	94
3	0.50	12:1	92
4	0.75	17:1	96
5	1.00	23:1	94
6	1.25	23:1	93
7	1.50	23:1	91

[a] Based on HPLC assay.

The hydroxylamine **5**[15] was isolated at incomplete conversion. In the hydrogenation of oxime with 94% ee, the aminoalcohol is isolated with 94% ee,[16] i.e. the first reduction involves the C=N bond rather than the enamine tautomer **6**. NMR experiments indicated protonation of oxygen rather than at nitrogen. Whilst we have no clear explanation for the role of HBr, it might be speculated that it serves to reorganise the catalyst surface to provide an optimal site for selective hydrogenation.



With the optimal conditions selected, the hydrogenation of the racemic oxime was run at multi-kilo scale at 0–5°C (*cis*/*trans* 25:1, 94% assay yield). After filtration of the catalyst, ion exchange followed by concentration and addition of (*S*)-mandelic acid gave the (*S*,*S*,*S*) salt (>99% ee) free of the *trans* isomer in 40% overall yield from the racemic oxime.[17]

In summary, we have developed a highly selective synthesis of *S*,*S*-aminochromanol in 32% overall yield from chromanone. The synthesis involves a pivotal *cis*-selective hydrogenation of the hydroxyoxime either as a racemate or single enantiomer form. We are currently exploring the generality of the Pd/C–HBr catalyst system.

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10. Mp 122–123°C. *Anal.* C, 59.94; H, 5.17; N, 7.60. $C_9H_9NO_3$ requires C, 60.33; H, 5.06; N, 7.82; ^{1}H NMR (400 MHz DMSO-d_6) Major isomer: δ 9.70–9.93 (br, 1H), 8.35 (dd, 1H, J=7.8, 1.6), 7.86 (dt, 1H, J=7.8,1.7), 7.54 (dt, 1H, J=11.7, 1.1), 7.49 (dd, 1H, J=8.2, 1.1), 5.68 (t, 1H, J=2.2), 4.91 (dd, 1H, J=12.4, 2.3), 4.59 (dd, 1H, J=12.4, 2.1), 4.13–4.38 (br, 1H). Selected minor isomer peaks: δ 9.13 (dd, 1H, J=8.1, 1.7), 7.91 (dt, 1H, J=7.9, 1.7), 4.94 (dd, 1H, J=9.8, 2.6), 4.76 (dd, 1H, J=12.8, 2.8). Moriarty, R. M.; Hu, H.; Gupta, S. C. *Tetrahedron Lett.* **1981**, 2*32*, 1283. Moriarty, R. M.; Prakash, O.; Thachet, C. T. *Synth. Commun.* **1984**, *14*, 1373.
11. Rh/C gave 1.5:1 *cis* selectivity and no reaction in the presence of 1.0 equiv. HBr (18 h, 40 psig).
12. Bromide is believed to inhibit the non-selective hydrogenation sites in the Raney–Ni tartaric acid asymmetric reduction of methylacetoacetate. Harada, T.; Yamamoto, M.; Onaka, S.; Imaida, M.; Ozaki, H.; Tai, A.; Izumi, Y. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 2323.
13. YMC ODS AQ (4.6×250 mm, S-5 micron 120 Å). Eluent CH_3CN, 5 mM K_2HPO_4 at pH 8, 35°C.
14. Other polar solvents, e.g. DMF, DMPU gave 2:1 selectivity.
15. Mp 92–95°C; LC/MS m/z 181; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.25 (1H, dd, J=8, 1), 7.10 (1H, dt, J=8, 1), 6.83 (1H, dt, J=8, 1), 6.69 (1H, dd, J=8, 1), 5.15 (1H, br.s), 4.95 (1H, br.s), 4.55 (1H, d, 3.5), 3.96–3.99 (2H, m), 3.80–3.92 (2H, m).
16. Hydroxychromanone starting material had 94% ee by SFC assay—Chiralpak AD, 300 Bar; 4–40% MeOH at 2%/min; 1.5 mL/min; 35°C; 215 nm.

17. To a solution of oxime **3** (2.50 kg, 14 mol) in methanol (49 L) at 0°C was charged 48% aqueous HBr (1.9 L). 10% Pd/C (1.9 kg, 62% water wet) was charged and the mixture was hydrogenated in a stirred autoclave at 0–5°C, 40 psig for 12 h (*cis*/*trans* 25:1, 90% assay yield of *cis* isomer). The mixture was filtered through solka floc. The batch was eluted through Dowex 1x2 on the base-cycle using methanol. The solution of racemic amine was solvent switched to ethanol and *S*-mandelic acid (2.1 kg, 14 mol) was added in ethanol. The mixture was cooled and the mandelate salt was isolated by filtration. The batch was dried to give 1.8 kg of (*S*,*S*,*S*)-mandelate salt (>99% ee, 40% overall yield). To a slurry of the salt (1.7 kg) in isopropylacetate (IPAC) was added aq. ethanolamine (6 L). The layers were separated and the aqueous layer was extracted with IPAC (3×). The IPAC extracts were concentrated to ~8 L and crystallised by the addition of *n*-heptane (8 L). (*S*,*S*)-aminochromanol **1** was isolated by filtration and dried to give a colorless solid (0.80 kg, 93%). The rotation for (*S*,*S*)-aminochromanol (1% in MeOH, 405 nm) was −177.9, DSC onset 110°C, peak 111°C. (*R*,*R*)-aminochromanol was prepared similarly, rotation (1% in MeOH, 405 nm) −179.8, DSC onset 110°C, peak 112°C. Ee was determined by HPLC using a crownpak CR(+) column using $HClO_4$.