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Stereoselective reduction of enaminones to *syn* γ-aminoalcohols

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Abstract—One-pot reduction of enaminones to *syn* γ-aminoalcohols can be efficiently performed by lithium borohydride in the presence of cerium chloride as Lewis acid. Selectivities are very good with respect to classical reduction method of these products.

The structural unit of γ-aminoalcohol is present with a stereodefined geometry in many compounds having interesting pharmacological and biological properties.[1] In addition, aminols are often useful building blocks in the synthesis of many natural products.[2]

The reduction of β-enaminoketones is certainly a very useful tool in the hand of the organic chemists to build 1,3-aminoalcohols, because many available functionalisation opportunities exist.

Some years ago, we studied both the regioselective synthesis of enaminones[3] and their dianion reactivity.[4] On that occasion, reduction of the enaminone unit was set up by sodium in isopropanol,[5] since catalytic hydrogenation of these compounds takes place with difficulty,[6] and, in our hands, reduction with metal hydrides alone or together with Lewis acids afforded no appreciable results.[5a] However, high diastereoselectivity was not generally reached.

More recently, we well explored the reduction of carbonyl bidentate compounds with borane complexes or $LiBH_4$ in the presence of $TiCl_4$ and $CeCl_3$ and suggested the rules to predict the stereochemistry of reduction.[7]

We have re-investigated reduction of enaminones with hydrides under these new conditions and results are reported in this paper.

In the first phase of this work, we tested $TiCl_4$ mediated reduction. The reduction of 1,3-amidoketones is, in fact, reported to occur with high diastereoselectivity in the presence of $LiAlH_4$ and $TiCl_4$ as chelating agent.[8] A useful method to obtain 1,3-aminols from enaminones was not found. Reduction of 3-(*N*-methylamino)-1-phenylbut-2-en-3-one (**1b**) was carried out with various agents and the reaction was monitored by GC/MS. BH_3/Py gives good diastereomeric ratios, but products cannot be separated from pyridine. BH_3/THF and BH_3/Et_2NH give compounds whose mass spectra can be rationalised as boron complexes with 1,3-aminols which are very difficult to decompose; BH_3/Me_2S gives low diastereoisomeric ratios (ranging from 1/1 to 3/2) and often low yielding owing to the presence of many such as monoreduced and dehydrated by-products; $LiBH_4$ gives only by-products.

Therefore, we focused our attention to the alternative $CeCl_3$ mediated reduction, but it was also unsuccessful with many reducing agents: DIBAH and Red-Al are non-reactive; BH_3/THF, Superhydride and L-Selectride give only by-products; $NaBH_4$ had already been unsuccessfully tested.[5a] Only $LiBH_4$ was able to efficiently reduce enaminones in the presence of $CeCl_3$ as promoting Lewis acid at −20°C (Table 1).[9]

The reaction usually proceeds with high yields, the low recovered yields of 3-(*N*-isopropylamino)-2-pentanol (**2l**, entry 12) being very likely due to inefficient extraction from water, because no by-products were detected even in traces by GC/MS on the crude reaction before quenching.[10]

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Table 1. Reduction of enaminones **1a–m** in the presence of $CeCl_3/LiBH_4$ system at −20°C

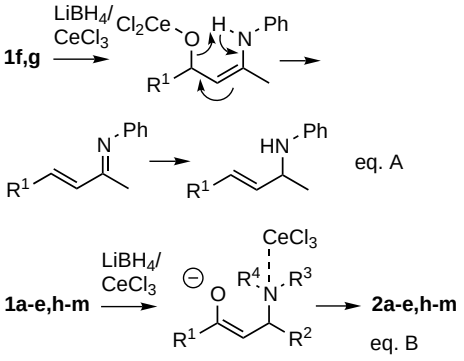
Entry	Cmpd	R^1	R^2	R^3	R^4	Time (h)	Yield (%)	*syn*/*anti*
1	**2a**	Ph	Me	H	H	16	76	67/33
2	**2b**	Ph	Me	H	Me	2.5	90	93/7
3	**2c**	Ph	Me	H	Et	5	66	88/12
4	**2d**	Ph	Me	H	*i*-Pr	8	76	85/15
5	**2e**	Ph	Me	H	*t*-Bu	144	96	78/22
6	**2f**	Ph	Me	H	Ph	8	0[a]	–
7	**2g**	Me	Me	H	Ph	5	19[b]	50/50
8	**2h**	Ph	Me		$(CH_2)_5$	16	96	84/16
9	**2i**	Ph	*i*-Bu	H	Me	72	96	91/9
10	**2j**	Ph	*i*-Pr	H	Me	144	89	85/15
11	**2k**	Ph	*i*-Bu	H	*i*-Pr	270	87	86/14
12	**2l**	Me	Me	H	*i*-Pr	58	32	84/16
13	**2m**	*i*-Bu	Me	H	*i*-Pr	295	80	93/7

[a] *N*,4-Diphenylbut-3-en-2-amine was only recovered.
[b] *N*-Phenylpent-3-en-2-amine was also recovered in about 30% yield.

Compared with reported enaminone reductive methods it appears much more useful. In fact, reduction with $NaBH_4$ alone did not exceed 3/2 diastereoselective ratios and its application is very restricted.[11] Palmieri's reduction with sodium and isopropanol has good selectivity only with cyclic compounds.[5] Grenhill's catalytic hydrogenation gives good 15/1 selectivity but takes place with difficulty.[6] Finally, Barluenga's reduction of 4-amino-1-azadienes is a three-step procedure, if high stereoselectivity must be obtained.[8]

The most remarkable finding is a strong dependence of the reaction from the nitrogen substituent. A phenyl group linked to the nitrogen atom favours a dehydration reaction leading to significative or exclusive formation of substituted allylamines (entries 6 and 7). We previously found that the site of organocerium addition depends from nitrogen substituents.[12] An aryl group lowers ability of nitrogen atom to co-ordinate cerium, enhancing therefore co-ordination to oxygen atom and consequently 1,2-addition to carbonyl function. On the other hand, an alkyl nitrogen substituent favours cerium co-ordination to nitrogen atom allowing 1,4-addition to unsaturated carbonyl moiety. In a fashion of such a mechanism also in the present reaction *N*-phenylallylamine arises from *N*-phenyl substituted enaminones via carbonyl reduction, elimination, and imine reduction steps (Scheme 1, Eq. (A)). On the other hand, 1,3-aminols come from *N*-alkyl substituted enaminones via 1,4-reduction, followed by carbonyl reduction (Scheme 1, Eq. (B)). Actually, β-(*N*-alkylamino)ketone can be detected in the first times of the reaction by monitoring the reaction progress by GC/MS.[13]

Rationalisation of the actual transition state which is travelled in the second reductive step is highly speculative.[14] Some features can be deduced, however, from results reported in Table 1. The transition state should have a geometry which accounts for a strong dependence of reaction times from steric hindrance. Increasing bulkiness both on the nitrogen atom (entries 1–5) and in the α′ (entries 4, 12, and 13) or in γ-positions



Scheme 1.

(entries 2, 9–11) reaction times prolong significantly, allowing for a growing difficulty of the incoming hydride to approach the reaction centre. Between the nitrogen substituents the alkyl one should occupy a position able to discriminate among different transition states, as demonstrated by the high increase in selectivity which occurs passing from no substituents to the methyl group (entries 1 and 2), while R^3 substituents seems to have no influence (entries 4 and 8). However, every increase in crowding the nitrogen atom or the γ position decreases selectivities, accounting for transition states strongly influenced by steric interactions between these substituents. On the other hand, bulkier α′ substituents increase selectivity (entries 4, 12, and 13).

Compound identification was made by comparison of vicinal coupling constants. It is well-established that both *syn* and *anti* isomers should be featured as chair-shaped molecules, owing to the strong intramolecular hydrogen bond between the amino and the hydroxy functions[15] In the most stable conformation, the *anti* isomer would have H_a and H_b in a diaxial relationship, giving rise to a larger coupling constant than the *syn* isomer, which will have H_a and H_b in a axial–equatorial relationship in both conformations. On these bases, all authors are always in agreement to attribute the larger coupling constant to the *anti* isomer.[5,8,15,16]

In conclusion, the present results offer an interesting synthetic procedure to obtain *syn* 1,3-aminoalcohols, particularly easy to perform, from easy available and functionalisable starting materials. Diastereoselectivities reported are generally high compared with reported in related reactions. From this paper the optimum conditions to obtain high diastereoselectivity in reduction of enaminones can be deduced, i.e. the presence of a little nitrogen substituent is necessary.

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9. **General procedure**: A solution of β-enaminoketone **1a–l** (5 mmol) in dry THF (10 mL) was added dropwise to a cold (−78°C) suspension of $CeCl_3$ (5 mmol) in dry THF (15 mL). The mixture was stirred for 1 h at this temperature and $LiBH_4$ (22.5 mmol, 2 M solution in THF) was then added. The mixture was allowed to stir for an appropriate time (Table 1), before adding dropwise 10% aqueous HCl and then NaOH pellets were added up to basic pH. The crude product was extracted with AcOEt, then dried over Na_2SO_4 and concentrated under reduced pressure. Flash column chromatography (eluent $CHCl_3$/MeOH, 95:5) gave diastereoisomeric mixture of *syn* and *anti* γ-aminoalcohols as pale yellow syrups.
10. Spectroscopic data of unknown compounds follow: **3-Amino-1-phenyl-1-butanol, 2a**: δ_H 1.14 (d, 2H, $J=6.37$, C$\underline{H}_3$CH), 1.15 (d, 1H, $J=6.37$, C$\underline{H}_3$CH), 1.48 (dt, 1H, $J=10.46$, 14.19 C$\underline{H}$HCHOH), 1.73 (dt, 1H, $J=3.02$, 14.19 C$\underline{H}$HCHOH), 2.81–3.20 (m, 4H, O$\underline{H}$, C$\underline{H}$N$\underline{H}_2$), 4.88 (dd, 0.67H, $J=2.01$, 10.46 C$\underline{H}$OH), 5.30 (dd, 0.33H, $J=4.02$, 7.04 C$\underline{H}$OH), 7.03–7.50 (m, 5H, Ar). *m/z* (%): 165 (M^+ 1), 148 (12.5), 104 (25), 77 (25), 44 (100). Anal. calcd for $C_{10}H_{15}NO$: C, 72.69; H, 9.15; N, 8.48. Found: C, 72.60; H, 9.15; N, 8.50%. **3-*N*-(Methylamino)-1-phenyl-1-butanol, 2b**: δ_H 1.07–1.12 (bs, 2H, O$\underline{H}$, N$\underline{H}$), 1.09 (d, 3H, $J=6.18$ C$\underline{H}_3$CHNH), 1.49 (dt, 1H, $J=10.82$, 14.29 C$\underline{H}$HCHOH), 1.67 (dt, 1H, $J=2.07$, 14.29 C$\underline{H}$HCHOH), 2.42 (s, 3H, C$\underline{H}_3$NH), 2.82–2.92 (m, 1H, C$\underline{H}$NH), 4.89 (dd, 0.93H, $J=1.93$, 10.82 C$\underline{H}$OH), 5.04 (dd, 0.07H, $J=3.09$, 7.34), 7.21–7.37 (m, 5H, Ar). *m/z* (%): 179 (M^+ 3), 148 (4), 107 (5), 79 (6), 77 (8), 58 (100). Anal. calcd for $C_{11}H_{17}NO$: C, 73.70; H, 9.56; N, 7.81. Found: C, 73.75; H, 9.55; N, 7.80%. **3-*N*-(Ethylamino)-1-phenyl-1-butanol, 2c**: δ_H 1.11 (d, 3H, $J=6.03$ C$\underline{H}_3$CHNH), 1.12 (t, 3H, $J=7.38$ C$\underline{H}_3$CH$_2$NH), 1.11–1.15 (bs, 2H, O$\underline{H}$, N$\underline{H}$), 1.49 (dt, 0.88H, $J=10.73$, 14.42 C$\underline{H}$HCHOH), 1.69 (dt, 0.88H, $J=2.17$, 14.42 C$\underline{H}$HCHOH), 1.72 (ddd, 0.12H, $J=3.69$, 6.71, 14.42 C$\underline{H}$HCHOH), 1.84 (ddd, 0.12H, $J=3.36$, 7.38, 14.42 C$\underline{H}$HCHOH), 2.56 (dq, 1H, $J=7.38$, 11.41 C$\underline{H}$HCH$_3$), 2.87 (dq, 1H, $J=7.38$, 11.41 C$\underline{H}$HCH$_3$), 2.94–3.05 (m, 1H, C$\underline{H}$NH), 4.91 (dd, 0.88 H, $J=2.01$, 10.73 C$\underline{H}$OH), 5.05 (dd, 0.12 H, $J=3.36$, 7.38), 7.11–7.43 (m, 5H Ar). *m/z* (%): 193 (M^+ 4), 107 (4), 79 (7), 77 (9), 72 (100). Anal. calcd for $C_{12}H_{19}NO$: C, 74.57; H, 9.91; N, 7.25. Found: C, 74.60; H, 9.95; N, 7.20%. **3-*N*-(Isopropylamino)-1-phenyl-1-butanol, 2d**: δ_H 1.10 (d, 3H, $J=5.92$ (C$\underline{H}_3$)$_2$CHNH), 1.12 (d, 3H, $J=5.41$ (C$\underline{H}_3$)$_2$CHNH), 1.27 (d, $J=3.98$, 3H CH$_3$), 1.48 (dt, $J=11.13$, 14.49, 1H C$\underline{H}$HCHOH), 1.64 (dt, $J=2.34$, 14.16, 1H C$\underline{H}$HCHOH), 3.01–3.18 (m, 4H, C$\underline{H}$(CH$_3$)$_2$, C$\underline{H}$N$\underline{H}$, O$\underline{H}$), 4.91 (dd, $J=1.68$, 10.44, 0.85H C$\underline{H}$OH), 5.07 (m, 0.15H C$\underline{H}$OH). *m/z* (%): 207 (M^+ 3), 120 (20), 105 (100), 77 (65). Anal. calcd for $C_{13}H_{21}NO$: C, 75.32; H, 10.21; N, 6.76. Found: C, 75.40; H, 10.20; N, 6.70%. **3-*N*-(*t*-Butylamino)-1-phenyl-1-butanol, 2e**: δ_H 1.13 (s, 3H

($C\underline{H}_3)_3C$), 1.15 (d, 0.66H, $J=7.04$ $C\underline{H}_3CH$), 1.10–1.22 (bs, 2H, O$\underline{H}$, N$\underline{H}$), 1.21 (s, 6H ($C\underline{H}_3)_3C$), 1.27 (d, 2.34H, $J=6.71$ $CH_3C\underline{H}$), 1.47 (dt, 1H, $J=11.06$, 14.09 C$\underline{H}$HCHOH), 1.69 (ddd, 1H, $J=1.68$, 3.02, 14.09 C$\underline{H}$HCHOH), 3.14–3.22 (m, 1H, C$\underline{H}$NH), 4.85 (dd, 0.78H, $J=1.34$, 11.06, C$\underline{H}$OH), 5.07 (dd, 0.22H, $J=2.35$, 9.73, C$\underline{H}$OH), 7.18–7.41 (m, 5H, Ar). *m/z* (%): 221 (M^+ 13), 206 (35), 188 (6), 100 (73), 84 (100), 79 (22), 77 (23), 58 (43). Anal. calcd for $C_{14}H_{23}NO$: C, 75.97; H, 10.47; N, 6.33. Found: C, 76.00; H, 10.45; N, 6.35%. **3-Piperidinyl-1-phenyl-1-butanol, 2h**: δ_H 0.96 (d, 3H, $J=6.81$ $C\underline{H}_3CH$), 1.22–1.85 (m, 14H $(CH_2)_5$, $C\underline{H}_2CHO\underline{H}$, N$\underline{H}$), 2.69–2.90 (m, 1H, C$\underline{H}$NH), 4.90 (dd, 0.84H, $J=2.28$, 11.04, C$\underline{H}$OH), 5.14 (m, 0.16H, C$\underline{H}$OH), 7.1–7.4 (m, 5H, Ar). *m/z* (%): 233 (M^+ 3), 112 (100). Anal. calcd for $C_{15}H_{23}NO$: C, 77.21; H, 9.93; N, 6.00. Found: C, 77.20; H, 9.90; N, 6.00%. **3-*N*-(Methylamino)-1-phenyl-5-methyl-1-hexanol, 2i**: δ_H 0.81–0.96 (bs, 2H, O$\underline{H}$, N$\underline{H}$), 0.91 (d, 5.4H, $J=5.94$ $(C\underline{H}_3)_2CH$), 1.02 (d, 0.6H, $J=6.33$ $(C\underline{H}_3)_2CH$), 1.47 (dt, 1H, $J=10.79$, 14.52 C$\underline{H}$HCHOH), 1.48–1.63 (m, 3H, $(CH_3)_2C\underline{H}C\underline{H}_2$), 1.72 (dt, 1H, $J=2.61$, 14.52 C$\underline{H}$HCHOH), 2.79–2.89 (m, 1H, C$\underline{H}$NH), 2.43 (s, 3H, $C\underline{H}_3NH$), 4.89 (dd, 0.91H, $J=2.23$, 10.79 C$\underline{H}$OH), 5.06 (dd, 0.09H, $J=2.61$, 8.56, C$\underline{H}$OH), 7.21–7.40 (m, 5H, Ar). *m/z* (%): 221 (M^+ 2), 176 (24), 164 (37), 146 (34), 100 (93), 79 (20), 77 (30), 58 (100). Anal. calcd for $C_{14}H_{23}NO$: C, 75.97; H, 10.47; N, 6.33. Found: C, 75.90; H, 10.45; N, 6.30%. **3-*N*-(Methylamino)-1-phenyl-4-methyl-1-pentanol, 2j**: δ_H 0.78 (d, 3H, $J=7.08$ $(C\underline{H}_3)_2CH$), 0.92 (d, 3H, $J=7.08$ $(C\underline{H}_3)_2CH$), 0.83–0.97 (m, 1H, $(CH_3)C\underline{H}$), 1.23–1.39 (m, 2H, $C\underline{H}_2CHOH$), 2.30–2.41 (m, 1H, C$\underline{H}$NH), 2.45 (s, 1H, $(C\underline{H}_3)NH$), 4.86 (dd, 0.85H, $J=2.23$, 10.79 C$\underline{H}$OH), 5.10 (m, 0.15H, C$\underline{H}$OH), 7.20–7.39 (m, 5H, Ar). *m/z* (%): 164 (M^+–43, 46), 146 (20), 107 (23), 86 (22), 79 (22), 77 (19), 58 (100). Anal. calcd for $C_{13}H_{21}NO$: C, 75.32; H, 10.21; N, 6.76. Found: C, 75.30; H, 10.20; N, 6.80%. **3-*N*-(Isopropylamino)-1-phenyl-5-methyl-1-hexanol, 2k**: δ_H 0.88 (d, 3H, $J=6.31$ $(C\underline{H}_3)_2CHCH_2$), 0.90 (d, 3H, $J=6.67$ $(C\underline{H}_3)_2CHCH_2$), 1.10 (d, 3H, $J=6.32$ $(C\underline{H}_3)_2CHNH$), 1.14 (d, 3H, $J=5.96$ $(C\underline{H}_3)_2CHNH$), 1.27–1.65 (m, 3H, $(CH_3)_2C\underline{H}$, $C\underline{H}_2CHOH$), 1.78–1.88 (m, 2H, $(CH_3)_2CHC\underline{H}_2$), 2.85–3.05 (m, 4H, $HNC\underline{H}(CH_3)_2$, C$\underline{H}$N$\underline{H}$, O$\underline{H}$), 4.89 (dd, 0.89H, $J=1.51$, 10.52, C$\underline{H}$OH), 5.07 (dd, 0.11H, $J=2.8$, 8.07 C$\underline{H}$OH), 7.21–7.44 (m, 5H, Ar). *m/z* (%): 249 (M^+ 6), 217 (40), 160 (100), 132 (35). Anal. calcd for $C_{16}H_{27}NO$: C, 77.06; H, 10.91; N, 5.62. Found: C, 77.00; H, 10.95; N, 5.65%. **2-*N*-(Isopropylamino)-6-methyl-4-heptanol, 2m**: δ_H 0.91 (d, 3H, $J=6.78$ $C\underline{H}_3CH$), 0.92 (d, 3H, $J=6.78$ $C\underline{H}_3CH$), 1.05 (d, 3H, $J=6.17$ $(C\underline{H}_3)_2CHNH$), 1.06 (d, 3H, $J=5.85$ $C\underline{H}_3CH$), 1.08 (d, 3H, $J=6.24$ $(C\underline{H}_3)_2CHNH$), 1.10–1.28 (m, 1H, $CH_2C\underline{H}CH_3$), 1.35–1.45 (m, 3H, CH$\underline{H}$CHOH, $(CH_3)_2CHC\underline{H}_2$), 1.51 (dt, 1H, $J=1.85$, 14.18 CH$\underline{H}$CHOH), 2.87–3.15 (m, 2H, C$\underline{H}$NHC$\underline{H}(CH_3)_2$), 3.88–3.94 (m, 0.93H, C$\underline{H}$OH), 3.98–4.12 (m, 0.07H C$\underline{H}$OH). *m/z* (%): 187 (M^+ 5), 172 (9), 130 (9), 86 (100), 72 (9), 44 (45). Anal. calcd for $C_{11}H_{25}NO$: C, 70.53; H, 13.45; N, 7.48. Found: C, 70.50; H, 13.50; N, 7.50%.

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13. All mass spectra associated to these peaks show aciluim ion ($R^1C{\equiv}O^+$) and retroaldol reaction ion [$R^1C(=O)CH_2^+$] typical of a carbonyl compound rather than of an allyl alcohol.
14. In our opinion, the formation of an enol ester borohydride intermediate in analogy with the reported reductions of enaminoesters and β-hydroxybenzyl oximes cannot be invoked. This intermediate should transfer hydride to the carbon–carbon double bond, but this double bond appears electrophilic rather than nucleophilic. Alternatively boron could link in the α-position giving rise to a β-enaminoketone, whose reduction can occur either intramolecularly or intermolecularly as in the β-hydroxyketone system. Finally the water molecule, which seems to be present also in 'dry' cerium chloride could be the proton source which allows keto–enol tautomerism, followed by reduction of the β-enaminoketone. Intramolecular shift of a hydrogen atom from nitrogen to oxygen atom is discarded because reduction occurs also with *N,N*-dialkylamino derivatives (entry 8).
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