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Stereoselective Syntheses of Ephedrine and Related 2-Aminoalcohols of High Optical Purity from Protected Cyanohydrins

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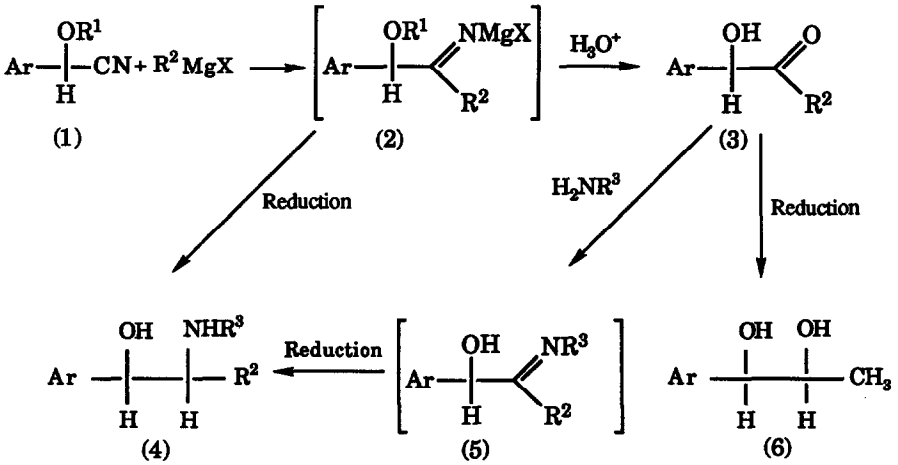
Abstract: Ephedrine and related optically active β-aminoalcohols can be prepared by zinc borohydride reduction of aryl O-protected magnesium imines and aryl α-hydroxyimines which in turn are readily available from optically active cyanohydrins.

There has been an upsurge of interest in synthetic procedures based on reactions of optically active cyanohydrins because of the ready availability of these compounds by a number of highly enantioselective reactions.[1,2,3] We now describe selective routes to ephedrine and a number of related *erythro*-aryl β-hydroxyamines from optically active cyanohydrins (1; R^1=H) prepared from arylaldehydes using the Inoue dipeptide catalyst system.[2]



Scheme

Initial reactions involved reduction of the magnesium imines (2) formed by reactions of the O-protected cyanohydrins with Grignard reagents.[4] A range of reagents were used under a variety of conditions and the results are summarised in Table 1.

Table 1 Reduction of some O-Protected Magnesium Imines[a] (2)

Entry	Ar	R^1	R^2	Red	Temperature	Ratio[c] Erythro/Threo
1	Ph	TMS	Me	$NaBH_4$	RT	68/32
2	Ph	TMS	Me	$NaBH_4$	-76°	69/31
3	Ph	TMS	Me	$Zn(BH_4)_2$	RT	79/21
4	Ph	TMS	Me	$Zn(BH_4)_2$	-76°	83/17
5	Ph	$CH(CH_3)OEt$	Me	$NaBH_4$	-76°	81/19
6	Ph	$CH(CH_3)OEt$	Me	$Zn(BH_4)_2$	-76°	88/12
7	4-MeOPh	TMS	Me	$NaBH_4$	RT	77/23
8	4-MeOPh	TMS	Me	$NaBH_4$	-76°	76/24
9	4-MeOPh	TMS	Me	$Zn(BH_4)_2$	RT	83/17
10	4-MeOPh	TMS	Me	$Zn(BH_4)_2$	-76°	85/15[b]
11	3,4-$(MeO)_2$Ph	TMS	Me	$NaBH_4$	-76°	79/21
12	3,4-$(MeO)_2$Ph	TMS	Me	$Zn(BH_4)_2$	-76°	86/14[b]
13	Ph	TMS	Ph	$NaBH_4$	-76°	88/12[b]
14	Ph	TMS	Ph	$Zn(BH_4)_2$	-76°	100/0
15	4-MeOPh	TMS	Ph	$NaBH_4$	-76°	89/11[b]
16	4-MeOPh	TMS	Ph	$Zn(BH_4)_2$	-76°	100/0

[a] All reactions were carried out in ether and gave yields better than 75%. The results are the average of two or more experiments. Isomer ratios varied by $\leq \pm 3\%$ in individual experiments. All new compounds gave satisfactory microanalyses.

[b] Recrystallization of a sample of this material from toluene/X4 afforded the pure *erythro*-isomer (^1H n.m.r.).

[c] Determined by ^1H n.m.r. (300 MHz)

All reductions led to a preference for the *erythro*-stereoisomer and very good stereoselectivity was obtained for reductions with zinc borohydride at -76°C in ether (see entries 4,6,10,12,14 and 16). The higher selectivity shown by zinc over sodium borohydride (compare e.g. entries 2 and 4, 8 and 10, 13 and 14) is in contrast to results reported previously for reductions of similar systems.[5] The high *erythro*-selectivity shown by zinc borohydride has been attributed to chelative effects and in our system is observed independant of the protecting group and the pattern of substitution on the arene ring.[6]

Reactions of protected benzoinimines gave even greater selectivity (entries 13 to 16) in keeping with the greater conformational preferences exerted by the second aryl group. Several *erythro*-β-aminoalcohols were obtained pure by crystallization (see Table 1). The aminoalcohol (4; Ar = Ph, R^2 = Ph, R^3 = H) was prepared from benzaldehyde cyanohydrin, $[\alpha]_D$ +34.4° (c = 5.3, benzene) (e.e. 83%). The product had an $[\alpha]_D$ -12.8° (c = 1.12, $CHCl_3$) corresponding to an e.e. value of ca. 90% based on a reported literature value of $[\alpha]_D$ -14.4° (c = 1.00, $CHCl_3$).[7] Thus no epimerisation had occurred either during the formation of the O-silyl compound or during the Grignard reaction. Optically pure (R)-4-methoxybenzaldehyde cyanohydrin, $[\alpha]_D$ +52.75° (c = 1.21, $CHCl_3$) was similarly converted into the (1R, 2S) - *erythro*-aminoalcohol

(4; Ar = 4-MeOPh, R^2 = Me, R^3 = H), $[\alpha]_D$ -7.13° (c = 0.56, $CHCl_3$) and (4; Ar = 4-MeOPh, R^2 = Ph, R^3 = H) $[\alpha]_D$ -8.83 (c = 1.44, $CHCl_3$).

Further evidence for retention of optical activity came from hydrolysis of the magnesium imines (2) to the corresponding benzoins (3). (R)-(-)-1-Hydroxy-1-(4'-methoxyphenyl)-2-propanone (3; Ar = 4-MeOPh; R^2 = Me) had $[\alpha]_D$ -344° (c = 0.21, $CHCl_3$) (lit.,[8] $[\alpha]_D$ -343° (c = 1, $CHCl_3$) for material of 96% e.e. and (R)-(-)-4-methoxybenzoin had m.p. 100-102°, $[\alpha]_D$ -69.8° (c = 0.21, acetone) (lit.,[9] m.p. 102.5-103.5° $[\alpha]_D$ -71.8° (c = 1, acetone). Similarly (R)-benzaldehyde cyanohydrin of e.e. 83% was converted into PAC and benzoin (3; Ar = Ph; R^2 = Me and Ph) without loss of optical purity.

Reductions of imines prepared from 1-hydroxy-1-phenyl-2-propanone, (PAC), (3; Ar = Ph, R^2 = Me) again showed high *erythro*-selectivities when zinc borohydride was used (entries 20,21,23, and 24), (See Table 2). In particular, ephedrine (4; Ar = Ph, R^2 =R^3= Me) could be obtained virtually free from the *threo*-isomer (pseudoephedrine) by reduction with zinc borohydride at -76°C. This represented a significant improvement over the stereoselectivity obtained when sodium borohydride was used either in this work (entries 17, 18 & 19) or in that reported previously.[10] When PAC of e.e. 80% R was used, ephedrine of 80% e.e. (1R, 2S) was obtained. It should be noted that the (R)-enantiomer of PAC is available in even higher optical purity when enzyme-derived cyanohydrin is used.[8]

Table 2: Reductions of imines derived from PAC[a] (5; Ar = Ph, R^2 = Me)

Entry	R^3	Reagent	Conditions	Ratio Erythro/Threo
17	Me	$NaBH_4$	MeOH, 10°	70/30
18	Me	$NaBH_4$	Ether, 10°	76/24
19	Me	$NaBH_4$	Ether, -76°	82/18
20	Me	$Zn(BH_4)_2$	Ether, 10°	91/9
21	Me	$Zn(BH_4)_2$	Ether, -76°	97/3
22	CH_2Ph	$NaBH_4$	Ether, -76°	80/20
23	CH_2Ph	$Zn(BH_4)_2$	Ether, 10°	83/17
24	CH_2Ph	$Zn(BH_4)_2$	Ether, -76°	86/14

a Yields were better than 75% for all the reactions.

High *erythro*-selectivity was also shown for reductions of the benzyl imine (5; Ar = Ph, R^2 = Me, R^3 = CH_2Ph) (entries 22-24). Thus this method represents a convenient, high-yielding laboratory preparation of optically active ephedrine and its derivatives which does not involve a complex hydrogenation procedure in contrast to many previous methods.[11]

Reduction of PAC, (3; Ar = Ph, R^2= Me) or its trimethylsilyl ether with zinc borohydride led predominantly to the *erythro*-diol (6) without loss of optical purity (entries 27-29, Table 3). These selectivities are better or equal to those obtained using aluminium hydrides bearing bulky substituents.[12]

Table 3: Reduction of PAC [a]

Entry	Reducing Agent	Conditions	Ratio [b] erythro/threo
25	$NaBH_4$	RT, EtOH	53/47
26	$NaBH_4$	RT, Ether	70/30
27	$Zn(BH_4)_2$	RT, Ether	81/19
28	$Zn(BH_4)_2$	-76°, Ether	87/13
29	$Zn(BH_4)_2$	RT, Ether	85/15[c]

a Yields of product >90%

b Determined from the ^1H n.m.r. spectra of the acetonide derivatives of (6)[13]

c Reaction of the $OSiMe_3$ derivative of PAC.

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