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Highly Diastereoselective Synthesis of Aminoalcohols of Ephedrine Type

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Analogs of ephedrine are obtained in 80% yield in 3 steps from chiral arenechromium tricarbonyl complexes. Hence optically pure complexes afford optically pure analogs of ephedrine.

Aminoalcohols of ephedrine type constitute an important class of bioactive compounds and of efficient inducers of chirality.1)

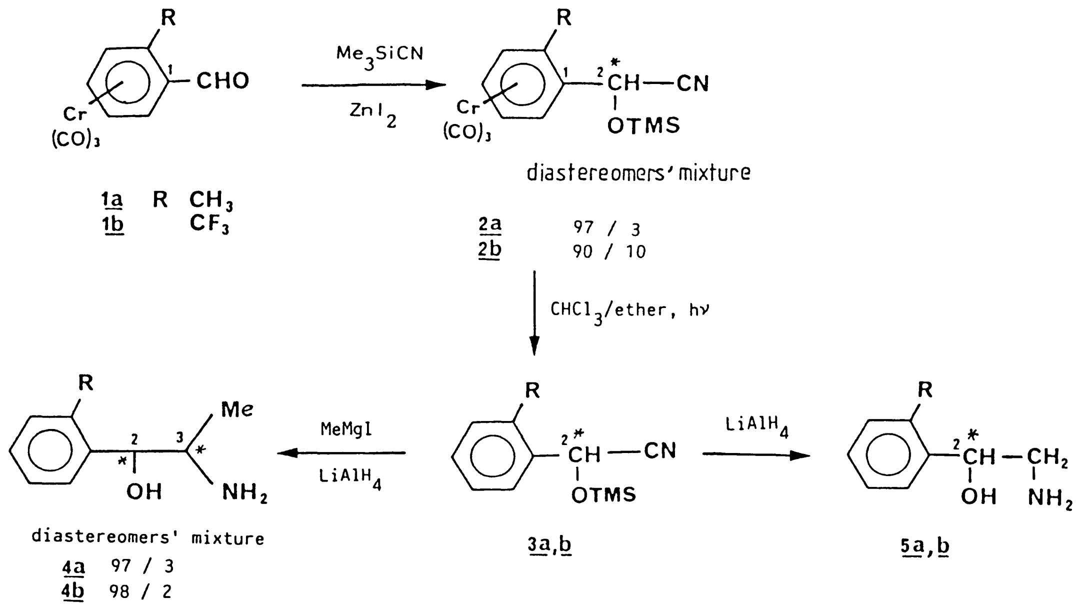
In the course of our study on asymmetric synthesis using optically pure chiral arenechromium tricarbonyl complexes,2) we have investigated, as a way to synthesize optically active aminoalcohols of ephedrine type, addition of trimethylsilyl cyanide3) on complexes 1a4) and 1b4) followed by addition of methyl Grignard5) and LiAlH$_4$ reduction (Scheme 1). We report here our first results obtained from racemic complexes.

Crude products are checked after each step by 200 MHz ^{1}H NMR, thus avoiding false conclusions through modification of diastereomer ratios during isolation. Then the compounds (2a,b, 3a,b, 4a,b, and 5a,b) are isolated, purified and checked again by 200 MHz ^{1}H NMR. ^{19}F NMR (376.3 MHz) of trifluoromethyl compounds is also used to check the diastereoselectivity obtained in complex 2b and the purity of 3b.

The addition of Me$_3$SiCN proceeded under mild conditions and afforded quantitatively 2a and 2b with a high percentage of asymmetric induction in the case of 2a6) (≈ 94%) and a lower one in the case of 2b,7) (≈ 80%) as shown in Table 1 and Fig. 1.

Complexes 2a and 2b do not react either with LiAlH$_4$ or with Grignard reagents,8) and decomplexation9) must be performed at that stage, that is after creation of the first asymmetric center C-2. A chromatographic purification of the diastereomeric mixture 2a and 2b will provide pure diastereomer. Hence, optically pure complexes 1a and 1b will lead (after addition, purification and decomplexation) to optically pure 3a and 3b.

Addition of methyl Grignard to 3a10) and/or 3b10) followed by reduction with LiAlH$_4$ afforded the aminoalcohols 4a11) and/or 4b11) in good yield (80-85%) as a 97-98/3-2 mixture of erythro (major) and threo (minor) diastereomers. (Table 1 and Fig. 1), according to Rasmussen model.5) In this model LiAlH$_4$ attacks from the



Scheme 1.

less hindered side of the cyclic iminium salt (Scheme 2).

Assignment of the major diastereomers, 4a I and 4b I, is confirmed from their 200 MHz ^{1}H NMR patterns by comparison with natural ephedrine and with aminoalcohols 5a,b.12) Natural ephedrine is erythro and shows a ^{3}J of 3.9 Hz between H_2 and H_3. The aminoalcohols 5a,b show ABX systems with two different coupling constants : $^{3}J_{AX}$=4 Hz and $^{3}J_{BX}$=8 Hz in the case of 5a ; $^{3}J_{AX}$=3.5 Hz and $^{3}J_{BX}$=8.5 Hz in the case of 5b.

In compound 4a, the major diastereomer I (≥ 97%) shows a ^{3}J of 4.5 Hz between H_2 and H_3 and is hence, assigned to the erythro form.

In compound 4b the major diastereomer I (≥ 98%) shows a ^{3}J of 4.5 Hz between H_2 and H_3 and is also assigned to the erythro form.

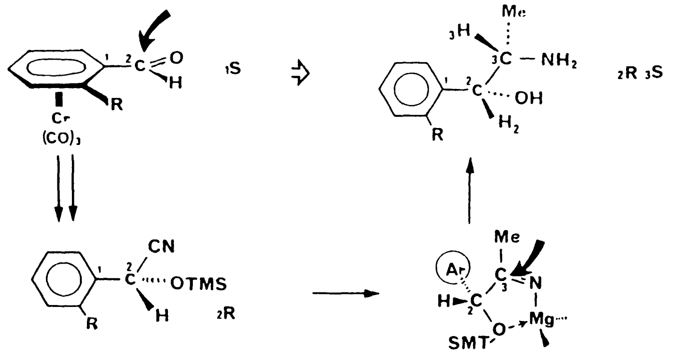
Table 1.

Starting complex	2		4	
	Yield/%	I / II	Yield/%	I / II
1a	2a : 100 a)	97/3	4a : 85	97/3
1b	2b : 100 b)	90/10	4b : 80	98/2

a) 3-5% decomplexation. b) 6-8% decomplexation.

According to our model of approach concerning kinetically controlled additions on complexed ortho substituted aldehydes one can predict that the 1S complexes 1a and 1b will lead to (2R,3S)-4a and 4b, analogs of ephedrine, (Scheme 2).

Hence, an optically pure analog of ephedrine 4a will be available in 3 steps and 80% global yield from the optically pure complex 1a.13) The optically pure complex 1b14) leads also to the corresponding trifluoromethylated analog 4b but in a lower yield of 70% because of the necessary purifications of 2b.



Scheme 2.

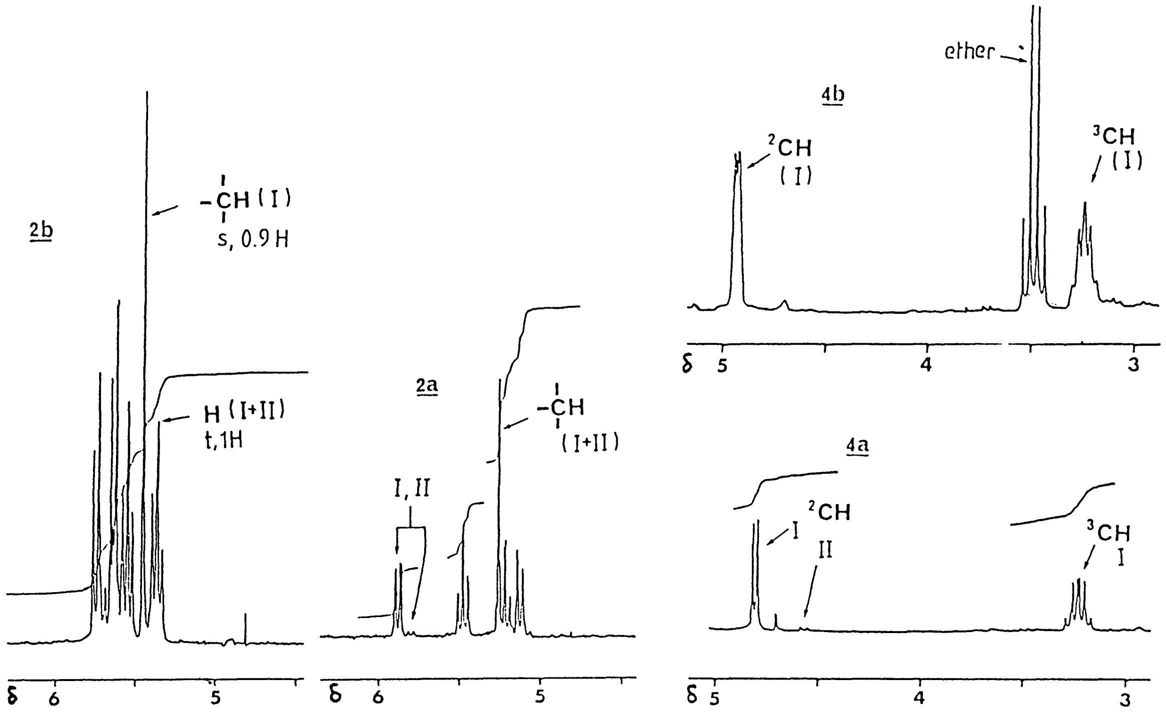


Fig. 1. ^{1}H NMR (200 MHz) of 2a, 2b, 4a, and 4b ($CDCl_3$-TMS).

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4) ^{1}H NMR (200 MHz, Bruker WP 200 SY) δ ppm

1a : 2.54 (s, 3H, CH_3), 5.04 (d, 1H arom., ^3J=6.5 Hz), 5.24 (t, 1H arom., ^3J=6.5 Hz), 5.74 (t.d, 1H arom., ^3J=6.5 Hz, ^4J=1 Hz), 6.06 (d.d., 1H arom., ^3J=6.5 Hz, ^4J=1 Hz), 9.82 (s, 1H).

1b : 5.48 (t, 1H arom., ^3J=6.5 Hz), 5.60 (d, 1H arom., ^3J=6.5 Hz), 5.69 (t, 1H arom., ^3J=6.5 Hz), 6.11 (d, 1H arom., ^3J=6.5 Hz), 9.93 (s, 1H).

Some signals show long distance coupling constant, probably with CF_3.

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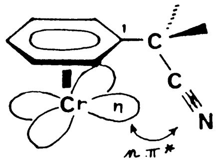
6) The other diastereomer detected on the NMR spectrum might be an impurity.

7) A ratio of 85/15 is obtained from ^{1}H NMR and a ratio of 90/10 is obtained from ^{19}F NMR ($CDCl_3/CFCl_3$ internal) : $\delta\, CF_3$ = -56.2 (major) and -56.6 (minor).

8) An n-π*-π interaction between the lone-pairs of the chromium and the π*, π orbitals of the C≡N triple bond might be responsible for the absence of reactivity of the complexed ligand in 2a and 2b. Molecular-models show clearly that the geometry is optimal for such an interaction in the conformation drawn below.



9) Decomplexation can also be performed under CO pressure in this method $Cr(CO)_6$ is recovered, see K.H. Dotz, Pure Appl. Chem., 55, 1689 (1983).

10) ^{1}H NMR (200 MHz, Bruker WP 200 SY) δ ppm

3a : 0.25 (s, 9H, 3Me), 2.47 (s, 3H, CH_3), 5.58 (s, 1H, CH), 7.25 (m, 3H arom.), 7.55 (m, 1H arom.).

3b : 0.25 (s, 9H, 3Me), 5.82 (s, 1H, CH), 7.52 (t, 1H arom.), 7.68 (m, 2H arom.), 7.98 (d, 1H arom.).

^{19}F (376.3 MHz, Bruker AM 400) δ ppm

3b : - 58.9 (s, 3F, CF_3) with broad-band ^{1}H decoupling. Without decoupling a multiplet is obtained : J = 0.5 - 0.7 Hz.

11) ^{1}H NMR (200 MHz, Bruker WP 200 SY) δ ppm

4a : 1 (d, 3H, CH_3, ^3J=6.5 Hz), 2,3 (s, 3H, CH_3), 3.22 (q.d., 1H, CH-N, ^3J=6.5 Hz, ^3J=4.5 Hz), 4.81 (d, 1H, CH-O, ^3J=4.5 Hz), 7.2 (m, 3H arom.), 7.5 (m, 1H arom.).

4b : 1 (d, 3H, ^3J=6 Hz), 3.25 (q.d., 1H, CH-N, ^3J 6 Hz, ^3J 4.5 Hz), 4.90 (d, 1H, CH-O, ^3J 4.5 Hz), 7.30 (t, 1H arom.), 7.50 (t, 1H arom.), 7.55 (d, 1H arom.), 7.70 (d, 1H arom.).

12) ^{1}H NMR (200 MHz, Bruker WP 200 SY) δ ppm

5a : 2.32 (s, 3H, CH_3), 2.85 (AB from ABX, 2H, $\Delta\nu_{AB}$=48 Hz, ^2J=-12.5 Hz, $^3J_{AX}$=4 Hz, $^3J_{BX}$=8 Hz), 4.90 (X from ABX, 1H), 7.15 (m, 3H arom.), 7.5 (m, 1H arom.).

5b : 2.87 (AB from ABX, 2H, $\Delta\nu$ =66 Hz, $^2J_{AB}$=-13 Hz, $^3J_{AX}$=3.5 Hz, $^3J_{BX}$=8.5 Hz), 4.90 (X from ABX, 1H), 7.3 (t, 1H arom.), 7.5 (t, 1H arom.), 7.6 (d, 1H arom.), 7.7 (d, 1H arom.).

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