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Asymmetric synthesis of ephedrine analogs

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Abstract

Addition of nitromethane to the chiral chromium tricarbonyl complex of *o*-tolualdehyde (**1**) gives, under conditions of kinetic control, the nitroalcohol **2** with ~ 95% of asymmetric induction. Compound **2** then gives, in 3 steps, the corresponding aminoalcohol in about 40% yield. Use of nitroethane gives the nitroalcohol with a small diastereoselectivity at C(2)-C(3) (d.e. = 30 and 55%), but analogs of ephedrine and pseudoephedrine can be obtained optically pure by chromatography.

Introduction

Ephedrine, which is present in the ancient Chinese drug Ma-huang, is extracted from various species of Ephedra. Because of their action on the sympathetic nervous system, natural D(−) ephedrine (2*R*, 3*S*), L(+) pseudoephedrine (2*S*, 3*S*), and analogs constitute an important class of bioactive compounds [1].

The main route to racemic 2-aminoalcohols of this type has been hydride reduction of free or protected cyanohydrins [2] and reduction of free or protected nitroalcohols [3]. Our main objective was to synthesize those aminoalcohols optically pure.

In the course of our study [4–6] on chiral and acyclic arenechromiumtricarbonyl complexes **1** it appeared that condensation of nitroalkanes with chiral and optically pure [7] chromiumtricarbonyl complexes of *ortho*-substituted benzaldehydes could provide a route to optically active 2-aminoalcohols of this type [8]. However, it was necessary to avoid thermodynamic control as far as possible, since work in our

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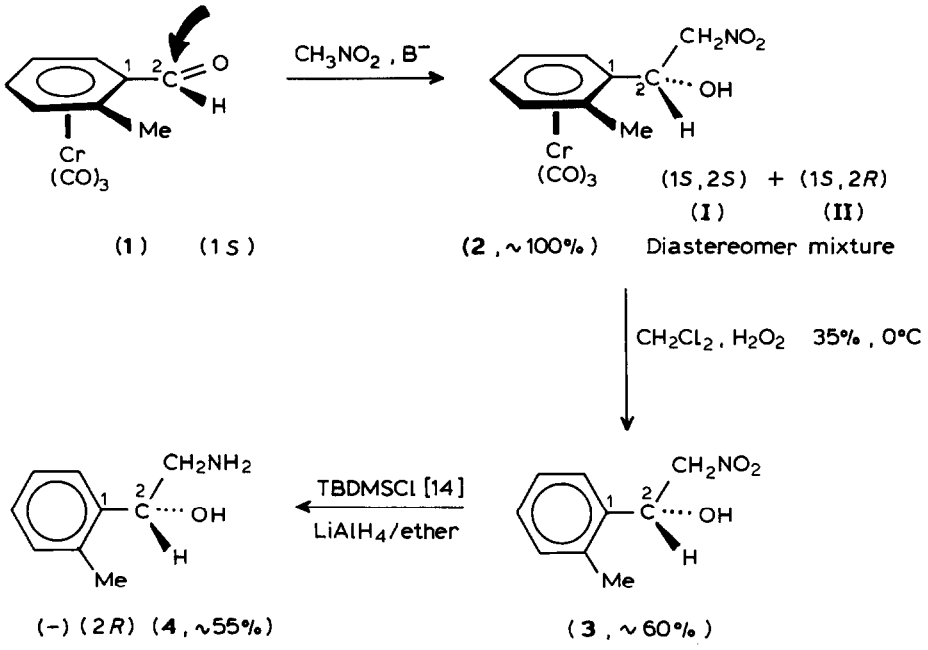


Scheme 1

group has shown that additions to a carbonyl α to a complexed substituted ring [9 *] occur with high degrees of asymmetric induction (90–95%) under kinetic control.

We present here the results of a study of the addition of nitromethane and nitroethane to complex **1** (racemic or optically pure), and hence a three-step route to 2-aminoalcohols which can be considered as an immolative-asymmetric-synthesis.

Results

Addition of nitromethane to complex **1** permits easy determination of the asymmetric induction during creation of the asymmetric carbon C(2). The results are shown in Table 1 and Scheme 1.

Three methods were used: (i) The Henry condensation [10] (Method A), in which the monoanion of nitromethane is generated in the presence of the complex **1** by addition of NaOH (10%) to a mixture of $MeNO_2$ and **1**. (ii) The Seebach condensation [11] (Method B), in which the lithium dianion of nitromethane is added to complex **1**. (iii) The Wollenberg nitroalkane synthesis [12] (Method C), in which KF in i-PrOH is used to promote condensation of $MeNO_2$ with **1**.

The percentage of asymmetric induction at C(2) is readily determined by ^1H NMR (200 MHz) spectroscopy on the crude products **2** or on the aminoalcohol **4** with $Eu(hfc)_3$ as shift reagent.

Determination of the yield and of the diastereomer ratio in **2** must be carried out on the crude products as rapidly as possible after isolation (1 to 2 h), as they

* Reference number with asterisk indicates a note in the list of references.

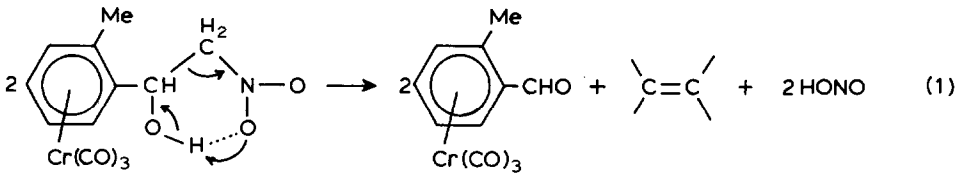
Table 1

Nitromethane addition to complex **1**

Starting complex **1**	Method [a]	T (°C)	**2** diastereomer ratio (1*SS*, 1*RR*)/(1*SR*, 1*RS*) (I/II)	(yield (%))	**4** Enantiomeric purity (%)
racemic	A	r.t.	64/36	(~100)	
	A	−20	92/8	(95)	
	A	−40	97/3	(90)	
(+)-1*S*	B	−40			90–92 $[\alpha]_D = -14°$ (*c* 0.62, $CHCl_3$)
racemic	C	20	40/60	(80)	
	C	0	88/12	(90)	

[a] Method A: CH_3NO_2/NaOH (10%) 1 equiv. [10]; Method B: CH_3NO_2/BuLi 2 equiv./THF/30% HMPT [11]; Method C: CH_3NO_2/KF traces, i-PrOH [12].

decompose on standing and regenerate the complexed aldehyde according to the eq. 1 probably because of the increased acidity of the hydroxylic proton due to complexation of the ring by the electron-withdrawing $CrCO_3$ group.



(1)

Because of the instability of **2**, decomplexation (which takes a few hours) gives low yields (~ 60%).

Because there is a temperature-dependent equilibrium (addition/retroaddition), the percentage of asymmetric induction depends on the temperature (28% at +20 °C and 94% at −40 °C), and the C(2) absolute configuration obtained at +20 °C is the opposite of that obtained at 0 °C (method C).

Consistent with these features is the observation in the case of method A that when the addition is performed at −40 °C and the reaction then quenched by pouring the mixture rapidly into a cold mixture of ether and aqueous NH_4Cl the asymmetric induction reaches 95% but is 80% or less if the reaction mixture is allowed to warm up to −10 or 0 °C before being added to ether/aqueous NH_4Cl mixture.

The (−) sign obtained for the $[\alpha]_D$ of aminoalcohol **4** implies that the absolute configuration is *R* according to Brewster's rules and to our model [13,5a].

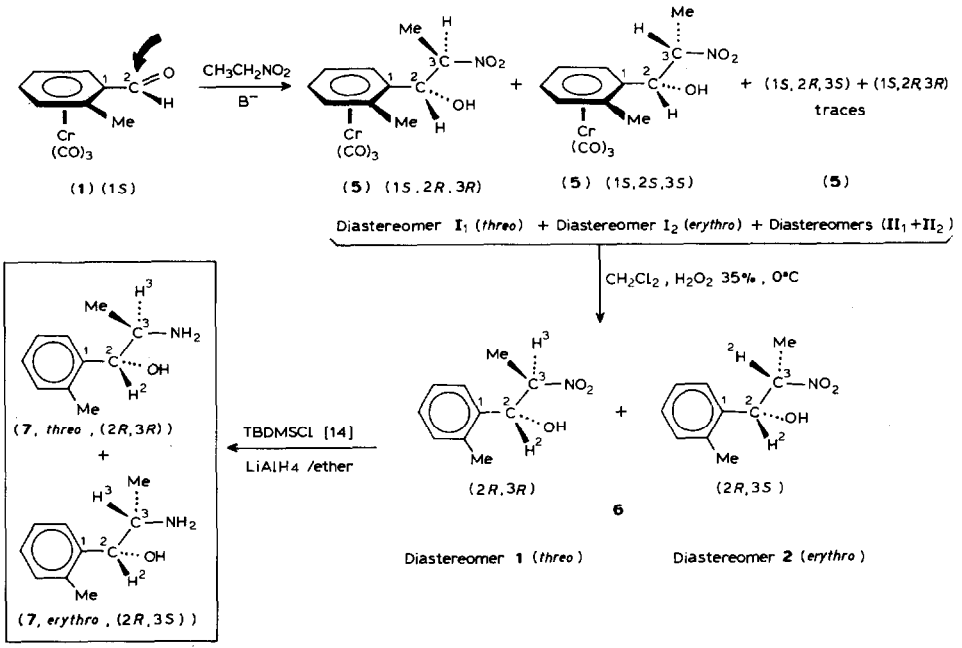
Addition of nitroethane was also examined and the results, shown in Table 2, correspond to the best reaction conditions for asymmetric induction as determined for nitromethane in method A (−40 °C) and method B (−40 °C).

Only two diastereomers $\mathbf{I}_1$ (C(2)–C(3) *threo*) and $\mathbf{I}_2$ (C(2)–C(3) *erythro*) were obtained; the two others, $\mathbf{II}_1$ and $\mathbf{II}_2$, were not detected by ^1H NMR spectroscopy. Assignment of diastereomer $\mathbf{I}_1$ to the C(2)–C(3) *threo* isomer and of $\mathbf{I}_2$ to the C(2)–C(3) *erythro* isomer in **5** and **6** was based on the 200 MHz ^1H NMR spectrum.

Table 2

Nitroethane addition to complex **1**

Starting **1**	Method (T −40 °C)	**5** diastereomer ratio ($\mathbf{I_1}/\mathbf{I_2}$) (yield (%))	**6** diastereomer ratio (**1**/**2**)
racemic	A	36/64 (90)	
racemic	B		77/23



Scheme 2

Natural ephedrine (*erythro*) shows a ^3J coupling of 4 Hz between H(2) and H(3). The aminoalcohol **4** shows an ABX system with two different coupling constants ^3J(AX) 4 and ^3J(BX) 8 Hz.

Because NO_2 group will form intramolecular H bonds as NH_2 group, the major conformation in the nitroalcohols and in the aminoalcohols can be expected to be of the same type, and so the ^{1}H NMR spectra of the nitroalcohols and aminoalcohols can be compared. For compound **5**, obtained from method A, the major diastereomer has a ^3J-coupling of 3 Hz and hence is assigned to the *erythro* isomer $\mathbf{I_2}$. The minor diastereomer shows a ^3J coupling of 7.5 Hz and is *threo*. For compound **6**, obtained by method B, the major diastereomer shows a ^3J coupling of 9.3 Hz and hence is assigned to the *threo* isomer **1**. The minor diastereomer shows a ^3J coupling of 3 Hz and is thus *erythro*.

It thus appears that method A leads to 64% of *erythro* and method B to 77% of *threo*, which is consistent with results obtained by Seebach [11]. Hence the com-

plexation of the ring does not drastically change the diastereoselectivities of these condensations.

Protection [14] and reduction [11] will lead to analogs of ephedrine (method A) or pseudoephedrine (method B) as the main compound.

It should be noted that if (+)-(1*S*) complex **1** leads (via method A) to the (2*R*, 3*S*) analog of ephedrine (corresponding to the natural isomer), the (2*S*, 3*S*) analog of pseudoephedrine will be obtained (via method B) from (−)-(1*R*) complex **1**. Optically pure *N*-methyl pseudoephedrine was obtained recently [15] from an arenechromium tricarbonyl complex, but in this case, the chirality comes from the ligand, which is optically pure (+) *N*,*N*-dimethylamphetamine.

In these three-step immolative asymmetric syntheses a very good asymmetric induction is obtained for the C(2) carbon, 95% e.e., but the asymmetric induction at C(3) is quite poor (28 to 54%) and leads to a mixture of *erythro* and *threo* isomers which must be separated. However, both diastereomers formed are optically pure. This method will thus be best suited for the synthesis of optically pure 2-aminoalcohols of type **4**, as isolation of optically pure analogs of ephedrine and/or pseudoephedrine involves a chromatographic separation.

Experimental

Method A

A mixture of complexed aldehyde **1** (1 mmol) and nitroalkane (2 mmol) in 20 ml EtOH is stirred for a time at −40 °C and aqueous NaOH 10% (2 mmol) is then added dropwise at −40 °C. The red solution rapidly becomes yellow, and is stirred for 30 min at −40 °C, then, still cold, is poured rapidly with stirring into a cold mixture of saturated aqueous NH_4Cl and ether (50/100). The ether layer becomes yellow and is separated from the aqueous layer, which is extracted twice with 20 ml ether. The ethereal layers are combined and dried over Na_2SO_4. After removal of the ether the residue (100% by weight) is checked by 200 MHz NMR and decomplexed without further purification.

Method B

To a stirred cold (−90 °C) solution of nitroalkane (2 mmol) (nitromethane or nitroethane) in 9 ml THF/HMPA (2/1) is slowly added a 1.37 *N* BuLi solution (4.1 mmol) in hexane. The solution is allowed to warm to −60 °C during 1 h then cooled to −78 °C, and the complexed aldehyde **1** (2 mmol in 3 ml THF) is added. After stirring for 1.5 h between −70 and −60 °C and 3 h between −45 and −40 °C, the mixture is cooled rapidly to −90 °C and acidified with 1.5 ml of a 3.5/3 acetic acid/THF mixture, the internal temperature being kept below −85 °C. The acidified mixture is then allowed to warm to room temperature and poured into a mixture of ether (60 ml) and water (20 ml). The organic phase is separated, washed with water (8 × 15 ml) dried ($MgSO_4$) and evaporated under vacuum to give 100% yield of crude residue, is decomplexed without further purification.

Method C

A mixture of complexed aldehyde **1** (1 mmol) in 6 ml of anhydrous i-PrOH and 5 mg of KF is stirred at 0 °C and pure nitromethane (2 mmol) then added dropwise at 0 °C. The red solution is stirred 8 h at 0 °C then kept overnight in the refrigerator

(+5°C), during which it slowly becomes yellow. The cold solution (+5°C) is then poured rapidly into a cold mixture of saturated aqueous NH_4Cl and ether (50/100). The yellow ether layer is separated, and the aqueous layer which is extracted twice with 20 ml lots of ether. The ethereal extracts are combined, dried over Na_2SO_4, and evaporated. The residue (100% by weight) is checked by 200 MHz NMR spectroscopy and decomplexed without further purification.

200 MHz ^1H NMR ($CDCl_3$/TMS) (δ, ppm)

Complex I. 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 (td, 1H arom., H(1), ^3J 6.5, ^4J 1 Hz), 6.06 (dd, 1H arom., H(3), ^3J 6.5, ^4J 1 Hz), 9.82 (s, 1H).

Complex 2. Diastereomer I: 2.27 (s, 3H, CH_3), 2.9 (b, 1H, OH), 4.5 (AB from ABX, 2H, CH_2), 5.17 (d, 1H arom., ^3J 6.5 Hz), 5.28 (t, 1H arom., ^3J 6.5 Hz), 5.40 (X from ABX, 1 H, CH), 5.46 (td, 1H arom., ^3J 6.5, ^4J 1 Hz), 5.82 (dd, 1H arom., ^3J 6.5, ^4J 1 Hz).

Diastereomer II: 2.35 (s, 3H, CH_3), 3.1 (b, 1H, OH), 4.65 (AB from ABX, 2H, CH_2), 5.11 (d, 1H arom., ^3J 6.5 Hz), 5.45 (X from ABX, 1H, CH and 1H arom.), 5.55 (t, 1H arom., ^3J 6.5 Hz), 5.73 (d, 1H arom, ^3J 6.5 Hz).

Aminoalcohol 4. 2 (s, b, 1H, OH), 2.31 (s, 3H, CH_3), 2.86 (AB from ABX, 2H, CH_2), 4.86 (dd, 1H, CH), 7.2 (m, 3H arom.), 7.5 (m, 1H arom.).

Complex 5. Diastereomer I_2 (erythro): 1.05 (d, 3H, CH_3), 2.26 (s, 3H, CH_3), 4.56 (qd, 1H, CH_3, $^3J_{23}$ 3, ^3J 6.5 Hz), 5.16 (d, 1H arom.), 5.27 (t, 1H arom.), 5.37 (d, 1H, CH(2), $^3J_{23}$ 3 Hz), 5.45 (t, 1H arom.), 5.80 (d, 1H arom.).

Diastereomer I_1 (threo): 1 (d, 3H, CH_3, ^3J 7 Hz), 2.27 (s, 3H, CH_3), 4.68 (quint., 1H, CH(3), ^3J 7, $^3J_{23}$ 7.5 Hz), 5.04 (d, 1H, CH(2), $^3J_{23}$ 7.5 Hz), 5.11 (d, 1H arom.), 5.25 (t, 1H arom.), 5.51 (t, 1H arom.), 5.71 (d, 1H arom.).

300 MHz ^1H NMR ($CDCl_3$/TMS) (δ, ppm)

Nitroalcohol 6. Diastereomer 2 (erythro): 1.4 (d, 3H, CH_3, ^3J 6.5 Hz), 2.55 (s, 3H, CH_3), 4.54 (qd, 1H, CH(3), ^3J 6.5, $^3J_{23}$ 3 Hz), 5.16 (d, 1H, CH(2), $^3J_{23}$ 3 Hz), 7.08 (m, 3H, arom.), 7.21 (m, 1H, arom.).

Diastereomer 1 (threo): 1.2 (d, 3H, CH_3, ^3J 7 Hz), 2.33 (s, 3H, CH_3), 4.76 (qd, 1H, CH(3)), ^3J 7, $^3J_{23}$ 9.3 Hz), 5.25 (d, 1H, CH(3), ^3J 9.3 Hz), 7.08 (m, 3H arom.), 7.21 (m, 1H arom.).

Acknowledgments

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References

1 Phenethylamine with asymmetry at both α and β carbons: Stereochemistry and biological activity of drugs, Blackwell Scientific Publications, Oct. 1982, p. 103.
2 (a) D.A. Evans, G.L. Carroll and L.K. Truesdale, J. Org. Chem., 39 (1974) 914; (b) D. Cantacuzene, K.L. Kirk, D.H. McCulloh and C.R. Creveling, Science, 204 (1979) 1217.
3 E.W. Colvin and D. Seebach, J. Chem. Soc., Chem. Commun., (1978) 689.
4 (a) A. Solladié-Cavallo and E. Tsamo, J. Organomet. Chem., 172 (1979) 165; (b) E. Tsamo, Thèse d'Etat, Strasbourg, 1979.

5 (a) A. Solladié-Cavallo, J. Suffert and J.L. Haesslein, Angew. Chem. Int. Ed. Engl., 19 (1980) 1005; (b) A. Solladié-Cavallo and J. Suffert, Synthesis, (1985) 659.
6 A. Solladié-Cavallo and D. Farkhani, Tetrahedron Lett., 27 (1986) 1331.
7 For resolution of those complexes see: A. Solladié-Cavallo, G. Solladié and E. Tsamo, Inorg. Synthesis, John Wiley and Sons, Vol. 23, p. 85.
8 A. Solladié-Cavallo, 189th ACS National Meeting in Miami, 1985, invited communication.
9 High stereoselectivity during addition of Grignard reagents on chiral and acyclic arenechromiumtricarbonyl complexes was noted as early as 1967 (J. Tirouflet and J. Besançon, Tetrahedron Lett., (1967) 4221), but we have shown that the ring must be *ortho*-substituted and that use of *meta*-substituted complexed benzaldehydes leads to quite poor asymmetric induction 30%. ([4a,b]).
10 R.A. Heacock and O. Hutzinger, Can. J. Chem., 41 (1963) 543.
11 D. Seebach, A.K. Beck, T. Mukhpadhyay and E. Thomas, Helv. Chim. Acta, 65 (1982) 1101; E.W. Colvin, A.K. Beck and D. Seebach, Helv. Chim. Acta, 64 (1981) 2264.
12 R.H. Wollenberg and S.J. Miller, Tetrahedron Lett., (1978) 3219.
13 A. Solladié-Cavello and J. Suffert, Tetrahedron Lett., 25 (1984) 1897.
14 E.J. Corey and A.Venkateswarlu, J. Am. Chem. Soc., 94 (1972) 6190.
15 J. Blagg and S. Davies, J. Chem. Soc., Chem. Commun., (1985) 653.