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Highly stereoselective hydrocyanation of optically pure α-sulfinylaldehydes

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Abstract

Diastereoselective hydrocyanation of enantiomerically pure 2-*p*-tolyl-sulfinylacetaldehyde and 2-*p*-tolylsulfinylpropanal with Et_2AlCN catalyzed by $ZnBr_2$ is described. The sulfur configuration controls the stereochemical course of the reaction. Hydrolysis of the resulting cyanohydrins and further desulfurization yielded the corresponding α-hydroxyamides in high ees (90%).

1. Introduction

Enantiomerically pure cyanohydrins derived from aldehydes are interesting building blocks in asymmetric synthesis.[1] Most of their preparation procedures reported in the literature make use of a homochiral catalyst to induce the formation of just one enantiomer of the cyanohydrin.[2] The behavior of different catalysts has been investigated, including enzymes, polymeric reagents, organometallic species, and peptides. Under these catalytic conditions, the most frequently used hydrocyanating reagents are HCN, trimethylsilylcyanide or acetone cyanohydrin, and in many cases only one configuration of the cyanohydrin is accessible due to the nature of the catalyst. In recent years we have developed a synthetic method which produces enantiomerically and diastereomerically pure β-sulfinylcyanohydrins in high yields by reaction of enantiomerically pure α-sulfinylketones with Et_2AlCN.[3] The configuration of the hydroxylic carbon is dependent on that of the sulfoxide. In order to expand the scope of this reaction we have investigated the hydrocyanation reaction of sulfinyl aldehydes using enantiomerically pure **1** and **2** (**a**+**b** mixture of epimers at C-α; Scheme 1). The obtained cyanohydrins **3** and **4** were hydrolyzed and further desulfurized into their corresponding hydroxyamides **7** and **8**.

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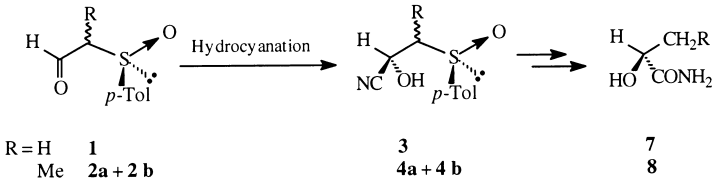
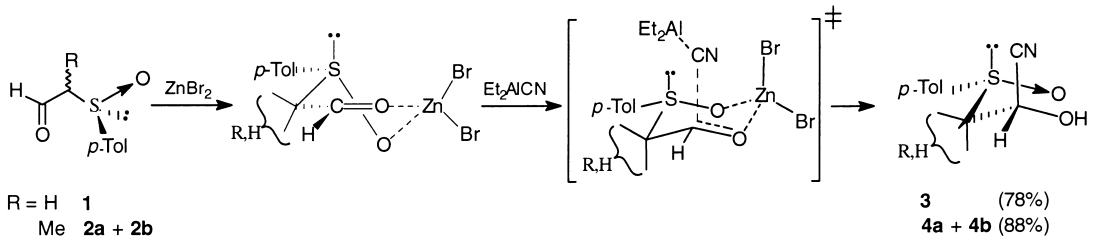


Scheme 1.

2. Results and discussion

The synthesis of the starting materials (α-sulfinylacetaldehyde **1** and α-sulfinylpropanal **2**) was accomplished by reaction of (*R*)-(+)-alkyl (methyl or ethyl) *p*-tolyl sulfoxide with *N*-formylpiperidine in the presence of LDA following the previously described procedure,[4] slightly modified.[5] Nevertheless, we have not been able to isolate either **1** or **2** due to their instability.[6] Starting from ethyl *p*-tolyl sulfoxide, a 60:40 mixture of α-methyl derivatives **2a** and **2b** was obtained. The major epimer **2a** shows a lower δ value for methyl at the stereogenic carbon than that corresponding to the minor epimer **2b**. Both epimers could not be separated by chromatography. The spectroscopic data of the crude mixtures did not allow us to assign the configuration of these epimers.

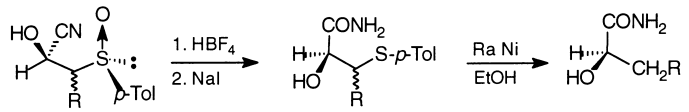
Reaction of **1** and **2** (as an epimeric mixture of **2a** and **2b**) with Et_2AlCN in toluene–THF (at 0°C for **1** and −20°C for **2**) in the presence of $ZnBr_2$ afforded cyanohydrins **3** and **4** (as a mixture of epimers **4a**+**4b**; Scheme 2). The reaction conditions were similar to those previously described for the hydrocyanation of α-sulfinylketones,[3] the order of the addition of the reagents being critical to obtain cyanohydrins in good yields. Despite the higher reactivity of the aldehydic carbonyl group as compared with the ketonic one, all the attempts to achieve hydrocyanation of sulfinylaldehydes in the absence of $ZnBr_2$ were unsuccessful.



Scheme 2.

The stereochemical results of the reaction (only the *R*-configuration at the hydroxylic carbon was obtained) could be explained by assuming an intermolecular transfer of the cyanide from the reagent (Et_2AlCN) on the most favored face (from steric and stereoelectronic points of view) of a chelated species of both carbonylic and sulfinylic oxygens with the metal, such as had been previously proposed in the case of α-sulfinylketones.[3] The intermolecular attack of the cyanide will give rise to the corresponding diastereomerically pure β-sulfinylcyanohydrin. As in the case of the reaction of α-sulfinylketones, the configuration at C-α has no influence on the stereochemical course of the reaction, which is exclusively controlled by the sulfur configuration.

β-Sulfinylcyanohydrins **3** and **4a**+**4b** were treated under the previously described conditions[3e,7] to give β-sulfenylamides **5** and **6a**+**6b** respectively in high yields (Scheme 3). The reaction consisted of the treatment of sulfinyl cyanohydrins with HBF_4 in CH_2Cl_2, followed by NaI. The reaction means the transformation of the cyanide group into carboxamide with concomitant reduction of the sulfoxide into sulfide, such has been proposed to explain the results of the hydrolysis of α-sulfinylcyanohydrins derived from α-sulfinylketones under the same reaction conditions.



R = H **3** **5** (87%) **7** (72%)
Me **4a + 4b** **6a + 6b** (70%) **8** (70%)

Scheme 3.

Reductive cleavage of **5** and a **6a**+**6b** mixture using Raney nickel in ethanol[3] gave hydroxyamides **7** and **8**, respectively (Scheme 3). The sign of the specific rotation of the obtained **7** is the same as that of the (*R*)-(+)-lactamide commercially available from Aldrich Chemical Co and their enantiomeric excess (90% ee) was established by ^{1}H-NMR from their corresponding Mosher (*R*)-MTPA and (*S*)-MTPA esters.[8] As the transfer of cyanide has given rise to only one diastereoisomeric cyanohydrin **3** or a mixture of epimers at the C-α carbon (**4a**+**4b**), the observed slight loss of enantiomeric purity must have taken place either during the hydrolysis stage of sulfinyl cyanohydrin into sulfenyl carboxamide (partial enolization of the carbonyl group of the carboxamide moiety under the reaction conditions), or during the desulfinylation stage (secondary alcohols have been reported to suffer epimerization with Raney nickel).[9]

3. Experimental

3.1. General methods

All reactions were carried out in flame dried glassware under an argon atmosphere. Flash chromatography was performed with silica gel 60 (230–400 mesh ASTM). Melting points were determined in a Gallenkamp apparatus in open capillary tubes and are uncorrected. The optical rotations were measured at room temperature (20–23°C) using a Perkin–Elmer 241 MC polarimeter (concentration in g/100 mL). The ^{1}H and ^{13}C NMR spectra were recorded at 200 (or 300) and 50 (or 75) MHz respectively in a Bruker AC-200 (or AC-300) spectrometer using $CDCl_3$ solutions; δ chemical shifts refer to TMS (^{1}H) or deuterated chloroform (^{13}C) signals. Elemental analyses were performed with a Perkin–Elmer 2400 CHN analyser.

3.2. Synthesis of α-sulfinylaldehydes

Compounds **1** and **2** were obtained from methyl or ethyl *p*-tolyl sulfoxide (1.0 eq), respectively, HMDSL (1.1 eq) and *N*-formylpiperidine (0.5 eq) following the method described in the literature.[4,5] These compounds were used directly after workup without further purification.[5,6]

*3.3. 2-(*p*-Tolylsulfinyl)propanal **2***

Compound **2** was obtained as a 60:40 mixture of **2a**+**2b**, epimers at C-2: δ_H ($CDCl_3$) of a **2a**+**2b** mixture: 9.70 (d, 1H, J 2.1 Hz, CHO (**2a**)), 9.51 (d, 1H, J 2.2 Hz, CHO (**2b**)), 7.42 and 7.38 (AA′BB′ system, 8H, C_6H_4 (**2a**) and C_6H_4 (**2b**)), 3.65 (dq, 4H, J 7.0 and 9.0 Hz, CHSO (**2a**) and CHSO (**2b**)), 2.38 (s, 6H, CH_3Ar (**2a**) and CH_3Ar (**2b**)), 1.35 (d, 3H, J 7.0 Hz, CH_3 (**2b**)), 1.20 (d, 3H, J 7.0 Hz, CH_3 (**2a**)).

3.4. Hydrocyanation of α-sulfinylaldehydes

To a solution of 337 mg (1.5 mmol) of $ZnBr_2$ in 12 mL of anhydrous THF, a solution of 1 mmol of α-sulfinylaldehyde in 6 mL of anhydrous THF was added. The reaction mixture was stirred at room temperature for 30 min and then added to a cold (0°C for **1** and −20°C for **2a**+**2b**) 1 M solution of 4 mL (4 mmol) of Et_2AlCN in toluene, diluted in 12 mL of anhydrous THF. The mixture was stirred for 5 min at the corresponding temperature and then transferred by cannula under argon into a cold (−78°C) solution of 5 mL of concentrated HCl in 5 mL of methanol. The mixture was stirred for 1 h, poured into 5 mL of concentrated HCl in 5 mL of ice water, and then extracted with CH_2Cl_2 (3×6 mL). The extracts were washed with water (2×4 mL) and the solvent was evaporated under reduced pressure.

3.5. (2R,(S)S)-2-Hydroxy-3-(p-tolylsulfinyl)propanenitrile **3**

Compound **3** (de >96%) was obtained from **1** in 78% yield after chromatography (eluent ethyl acetate:hexane=1:1) and further crystallization (ethyl acetate), mp 162–164°C (white solid); $[\alpha]_D$ +309.6 (c 0.5, chloroform); δ_H ($CDCl_3$) 7.54 and 7.39 (AA′BB′ system, 4H, C_6H_4), 5.60 (bs, 1H, OH), 5.03 (m, 1H, CH), 3.32 (dd, 1H, J 9.6 and 13.3 Hz, CH_2), 3.04 (dd, 1H, J 2.4 and 13.3 Hz, CH_2), 2.45 (s, 3H, CH_3); δ_C ($CDCl_3$) 142.9 (C-4 Tol), 138.5 (C-1 Tol), 130.5 (C-3 and C-3′ Tol), 124.0 (C-2 and C-2′ Tol), 118.3 (CN), 59.8 (CH), 56.4 (CH_2), 21.5 (CH_3); anal. calcd for $C_{10}H_{11}NO_2S$: C 57.30, H 5.30, N 6.69, S 15.32. Found: C 57.30, H 5.41, N 6.30, S 15.15.

3.6. (2R,3R,(S)S) and (2R,3R,(S)S)-2-Hydroxy-3-(p-tolylsulfinyl)butanenitrile **4a**+**4b**

A 2:1 mixture of **4a**+**4b** was obtained from **2a**+**2b** (88% yield after treatment identical to **3**) as a white solid. $[\alpha]_D$ +172.8 (c 0.5, chloroform); δ_H ($CDCl_3$) (**4a**) 7.43 and 7.40 (AA′BB′ system, 4H, C_6H_4), 6.78 (bs, 1H, OH), 4.75 (dd, 1H, J 5.0 and 9.1 Hz, CHCN), 3.10 (dc, 1H, J 7.1 and 9.1 Hz, CHSO), 2.44 (s, CH_3Ar), 1.06 (d, 3H, J 7.1 Hz, CH_3); δ_H ($CHCl_3$) (**4b**) 7.59 and 7.47 (AA′BB′ system, 4H, C_6H_4), 5.78 (bs, 1H, OH), 5.13 (m, 1H, CH), 2.99 (dc, 1H, J 7.1 and 9.1 Hz, CHCN), 2.44 (CH_3Ar), 1.32 (d, 3H, J 7.0 Hz, CH_3); δ_C ($CDCl_3$) (**4a**) 142.3 (C-4 Tol), 134.7 (C-1 Tol), 130.4 (C-3 and C-3′ Tol), 125.0 (C-2 and C-2′ Tol), 118.1 (CN), 62.2 (C-OH), 61.2 (CHSO), 21.4 (CH_3Ar), 6.5 (CH_3); anal. calcd for $C_{11}H_{13}NO_2S$: C 59.17, H 5.87, N 6.27, S 14.33. Found for a **4a**+**4b** mixture: C 59.17, H 5.43, N 6.67, S 14.04.

3.7. Hydrolysis of sulfinylcyanohydrins into sulfenylhydroxyamides

To a cold (0°C) solution of 1 mmol of β-sulfinylcyanohydrin in 30 mL of anhydrous CH_2Cl_2, 1 mL of freshly distilled HBF_4 was added. The mixture was stirred at 0°C for 3 h, and then 1.6 g (11 mmol) of NaI was added. The resulting mixture was vigorously stirred at room temperature for 15 h. Water (15 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3×5 mL). The extracts were washed with aqueous $Na_2S_2O_5$ (2×5 mL) and concentrated under reduced pressure.

3.8. (R)-2-Hydroxy-3-(p-tolylsulfenyl)propanamide **5**

Compound **5** was obtained from **3** in 81% yield, after chromatography (eluent acetone:hexane=1:2) and crystallization (ethyl acetate), mp 115–116°C (white solid); $[\alpha]_D$ +45.5 (c 1.0, acetone); δ_H ($CDCl_3$) 7.33 and 7.12 (AA′BB′ system, 4H, C_6H_4), 6.68 (bs, 1H, NH), 5.42 (bs, 1H, NH), 4.04 (dd, 1H, J 4.0

and 8.9 Hz, CH), 3.48 (dd, 1H, J 4.0 and 14.4 Hz, CHS), 3.29 (bs, 1H, OH), 3.01 (dd, 1H, J 8.9 and 14.4 Hz, CHS), 2.33 (s, 3H, CH_3); δ_C (methanol-d_4) 178.4 ($CONH_2$), 138.2 (C-4 Tol), 132.3 (C-1 Tol), 131.6 (C-3 and C-3′ Tol), 130.7 (C-2 and C-2′ Tol), 71.8 (COH), 40.7 (CH_2S), 21.1 (CH_3); anal. calcd for $C_{10}H_{13}NO_2S$: C 56.85, H 6.20, N 6.63, S 15.17. Found: C 57.08, H 5.74, N 5.83, S 14.54.

*3.9. (2*R*,3*R*) and (2*R*,3*S*)-2-Hydroxy-3-(*p*-tolylsulfenyl)butanamide **6a**+**6b***

A 2:1 mixture of **6a**+**6b** was obtained from a 2:1 mixture of **4a**+**4b**. After chromatography (eluent acetone:hexane=1:2) of the crude reaction only the major diastereoisomer (**6a**) was isolated. It was crystallized from ethyl acetate (yield 87%), mp 121–122°C (white solid); $[\alpha]_D$ −7.5 (c 0.3, acetone); δ_H (methanol-d_4) 7.35 and 7.10 (AA′BB′ system, 4H, C_6H_4), 4.16 (dd, 1H, J 3.0 Hz, C*H*OH), 3.60 (dc, 1H, J 3.0 and 7.0 Hz, CHS), 3.01 (dd, 1H, J 8.9 and 14.4 Hz, CHS), 2.29 (s, 3H, CH_3Ar), 1.41 (d, 3H, J 7.0 Hz, CH_3); δ_C (methanol-d_4) 178.0 ($CONH_2$), 138.2 (C-4 Tol), 133.7 (C-3 and C-3′ Tol), 132.7 (C-1 Tol), 130.6 (C-2 and C-2′ Tol), 76.1 (CHOH), 49.6 (CHS), 21.1 (CH_3Ar), 19.8 (CH_3); anal. calcd for $C_{11}H_{15}NO_2S$: C 58.64, H 6.72, N 6.22, S 14.20. Found: C 58.15, H 6.39, N 6.02, S 14.11.

3.10. Desulfurization of sulfenylhydroxyamides

This was carried out with Raney nickel following the previously described procedure.[3] (*R*)-(+)-Lactamide **7** was prepared from **5** in 72% yield; $[\alpha]_D$ +10.7 (c 0.25, methanol:ethanol=1:1). Spectroscopic data were identical to those obtained from a sample from Aldrich: δ_H (methanol-d_4) 4.10 (c, 1H, J 6.2 Hz, CH), 1.37 (d, 3H, J 6.2 Hz, CH_3); δ_C (methanol-d_4) 181.1 ($CONH_2$), 68.9 (CHOH), 18.4 (CH_3).

*3.11. (*R*)-(+)-2-Hydroxybutanamide **8***

Compound **8** was prepared in 70% yield from the mixture of **6a**+**6b**; $[\alpha]_D$ +5.14 (c 1.3, acetone); δ_H (methanol-d_4) 4.00 (dd, 1H, J 4.0 and 7.1 Hz, CH), 1.95–1.55 (m, 2H, CH_2), 1.00 (t, 3H, J 7.1 Hz, CH_3); δ_C (methanol-d_4) 180.1 ($CONH_2$), 73.7 (CHOH), 28.6 (CH_2), 9.6 (CH_3).

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5. The previously described procedure (Ref. 4) for the synthesis of **1** uses a 1.0:1.1:1.1 sulfoxide:base:*N*-formylpiperidine ratio. We have used a 1.0:1.1:0.5 ratio in order to avoid the presence of *N*-formylpiperidine which contaminates the reaction product, since it was not possible to eliminate it either in this step or in a further one. Under these conditions a mixture of the corresponding aldehyde **1** or **2** and the unchanged alkyl (methyl or ethyl) *p*-tolyl sulfoxide was obtained. All attempts to isolate pure aldehyde by chromatography (either with silica gel or alumina) were unsuccessful. Hence, these mixtures were used as the starting material in further reactions. The resulting excess of unchanged sulfoxide can be easily removed in the following step. Difficulties in the purification of α-sulfinylaldehydes may be responsible for the fact that despite the synthesis of compound **1** described in 1988 (Ref. 4), to our knowledge this work is the first application of this compound in asymmetric synthesis so far reported in the literature.
6. Previously it had been reported that α-sulfinylacetaldehyde **1** could not be prepared due to its instability (Banfi, L.; Colombo, L.; Gennari, C. *Synthesis* **1982**, 829).
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