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OPTICALLY ACTIVE ALKYLVINYLPYRIDINES: SYNTHESIS OF (+)-(S)-6-(1-METHYLPROPYL)-2-VINYLPYRIDINE

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ABSTRACT: A generalizable procedure for the preparation of optically active 6-alkyl-2-vinylpyridines from chiral 2-alkylpyridines without loss of optical purity is reported.

Chiral polymers have been developed over the last years as very powerful packings for direct resolution of enantiomers in liquid chromatography[1] and as supported reagents.[2]

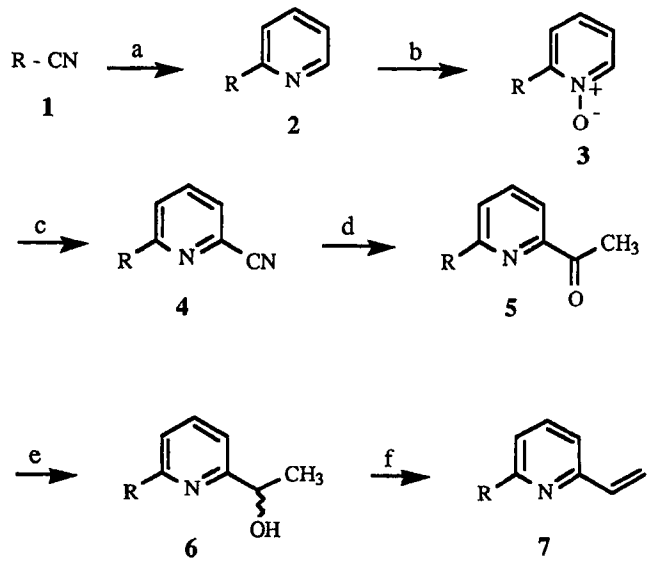
Although polymer-bound pyridines have received considerable attention[3], to our knowledge, only in a single instance a chiral pyridine has been incorporated into a polymer.[4] Moreover, there are only two literature reports of optically active vinylpyridines containing one chiral carbon atom adjacent to the heterocyclic ring, both concerning the synthesis of 5-alkyl-2-vinylpyridine.[5,6]

Since the best results in stereodifferentiating processes which use chiral pyridine ligands have been obtained when the chiral centre of the substituent is both bonded to the heterocyclic ring and in α-position with respect to the pyridine nitrogen,[7] we undertook a study

on general methods to obtain optically active 2-alkyl-4-vinyl- and 6-alkyl-2-vinylpyridines with high optical purity.

In this paper we report a generalizable procedure for the preparation of optically active 6-alkyl-2-vinylpyridines from chiral 2-alkylpyridines without loss of optical purity.

Scheme 1



R = C_2H_5 - CH(S) - CH_3

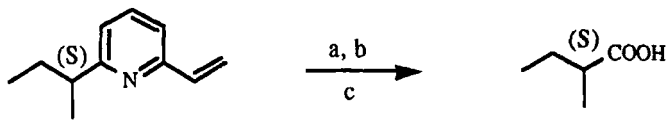
a: CpCo(COD), acetylene, 8 atm., 140 °C, 95%; b: MCPA, CH_2Cl_2, >95%; c: $(CH_3)_3SiCN$, $(CH_3)_2NCOCl$, CH_2Cl_2, r.t., 5 d, 95%; d: CH_3MgBr, Et_2O, 32%; e: $NaBH_4$, CH_3OH, 12 h, 95%; f: 85 % H_2SO_4, 110-120 °C, 2 h, 92%

As a prototype from which to develop the basic methodology we selected the (+)-(S)-2-(1-methylpropyl)pyridine (**2**) which is readily accessible in high chemical and optical yield by Co(I)-catalyzed co-cyclotrimerization of (+)-(S)-2-methylbutanenitrile[8] with acetylene[9,10] (**1**) (Scheme 1).

The reaction sequence leading to (+)-(S)-6-(1-methylpropyl)-2-vinylpyridine (**7**) is depicted in Scheme 1. Starting from **2** the corresponding N-oxide **3** was obtained in almost quantitative yield by oxidation with 3-chloroperbenzoic acid. The key intermediate nitrile **4** was obtained by treatment of **3** with trimethylsilylcyanide and dimethylcarbamoyl chloride at room temperature for 5 days (95% yield).[11] Compound **4** was converted into the pyridinecarbinol **6** by reaction with methyl magnesium iodide (32%) followed by reduction of the acylpyridine **5** with $NaBH_4$ (96%). Finally, vinylpyridine **7** was obtained in high yield (92%) by dehydration of **6** with 85% H_2SO_4 at 110-120 °C for 2h.

The minimum optical purity of the vinylpyridine **7** was determined by the method of standard cleavage of the heterocyclic nucleus to (+)-(S)-2-methylbutanoic acid (**8**) (Scheme 2).[12]

Scheme 2



7 **8**

$[\alpha]^{25}_D$	$[\alpha]^{25}_D$	Minimum optical purity, %
+29.83° cyclohexane	+14.48 ethyl ether	72

a: O_3, CCl_4, r.t.; b: CH_3OH, H_2O_2, 5 % NaOH; c: H_3O^+

The value of the optical purity for the recovered sample of this acid was assumed as the minimum for the optical purity of the relative pyridine, as the cleavage procedure employed by us should occur without remarkable racemization.

Thus, it can be established that the conversion of the (+)-(S)-2-(1-methylpropyl)pyridine (**2**) to (+)-(S)-6-(1-methylpropyl)-2-vinylpyridine (**7**) takes place without loss of optical purity, indicating that the asymmetric centre, even if directly bound with the heterocyclic ring, is not involved in the intermediary reaction complex.

EXPERIMENTAL

Boiling points are uncorrected. ^1H (300 MHz) NMR Fourier transform spectra were performed on a Varian VXR-300 spectrometer with TMS as internal standard. The optical rotations were measured by a Perkin-Elmer 142 automatic polarimeter in a 1 dm tube. Gas chromatographic analyses were performed by a Perkin-Elmer 8600 chromatograph using N_2 as a carrier gas on a 15 m DBWAX widebore capillary column (J&W).

Material: Methylmagnesium iodide (3M solution in Et_2O) was purchased from Aldrich. (+)-(S)-2-(1-Methylpropyl)pyridine (**2**) ($[\alpha]^{25}_D$ +23.69° (*c* 2.0, EtOH); 73.5% optical purity) was prepared by co-cyclotrimerization (+)-(S)-2-methylbutanenitrile[8,13] (**1**) with acetylene in the presence of (π-cyclopentadienyl)cobalt 1,5-cycloottadiene.[9,10] The N-oxide of (+)-(S)-2-(1-methyl propyl) pyridine (**3**)[14] was obtained in almost quantitative yield by adding of 3-chloroperbenzoic acid (20% excess) to a CH_2Cl_2 solution of **2**.

(+)-(S)-2-Cyano-6-(1-methylpropyl)pyridine (**4**).[14]

Dimethylcarbamyl chloride (5.35 g, 0.05 mol) was added dropwise to a solution of N-oxide of (+)-(S)-2-(1-methylpropyl)pyridine (**3**) (7.55 g, 0.05 mol) and

trimethylsilylcyanide (5.5 g, 0.055 mol) in CH_2Cl_2 (100 mL). The solution was stirred at room temperature for 5 days, then 10% K_2CO_3 was added and stirring continued for 15 minutes. The organic phase was separated, dried (Na_2SO_4), evaporated of the solvent and distilled to give **5** (7.6 g, 95%): bp 60 °C (0.01 mm); $[\alpha]^{25}_D$ +27.16° (*c* 2.6, cyclohexane). Analytical and spectral data were identical with an authentic sample.

(+)-(S)-2-Etanoyl-6-(1-methylpropyl)pyridine (**5**).

A 3M solution in Et_2O of methylmagnesium iodide (14 ml, 42 mmol) was added dropwise to a solution of **4** (6.4 g, 42 mmol) in anhydrous Et_2O (60 mL). The reaction mixture was stirred for one night. After hydrolysis with 5N HCl, the mixture was stirred for 12h and then alkalized with 10% NaOH. The organic layer was separated and the aqueous phase extracted with Et_2O. The ethereal solution was dried (Na_2SO_4), the solvent evaporated and the residue chromatographed on silica gel using benzene as the eluant to give pure **5** (2.4 g, 32%): bp 80 °C (0.01 mm); $[\alpha]^{25}_D$ +26.29° (*c* 2.0, cyclohexane); ^1H NMR ($CDCl_3$) δ, ppm: 7.83 (d, 1H), 7.66 (t, 1H), 7.24 (d, 1H), 2.82 (m, 1H), 2.65 (s, 3H), 1.69 (m, 1H), 1.62 (m, 1H), 1.26 (d, 3H), 0.82 (t, 3H). Elemental Analysis (Calcd. for $C_{11}H_{15}NO$): C, 74.73 (74.53); H, 8.51 (8.54); N, 7.82 (7.91).

(S)-2-(1-Hydroxyethyl)-6-(1-methylpropyl)pyridine (**6**).

A solution of **5** (4.42 g, 25 mmol) in MeOH (10 mL) was added dropwise to a mixture of $NaBH_4$ (1.1 g, 27.5 mmol) and NaOH (0.13 g) in MeOH (10 mL). The reaction mixture was stirred for 12 h and then treated with 10% NaOH (40 mL). Extraction with Et_2O (3 x 20 mL), drying (Na_2SO_4), evaporation of the solvent and distillation gave **6** (4.29 g, 96%): bp 90 °C (0.01 mm); ^1H NMR ($CDCl_3$) δ, ppm: 7.60 (t, 1H), 7.02 (d, 2H), 5.05 (s, broad, 1H), 4.83 (q, 1H), 2.80 (m, 1H), 2.65 (s, 3H), 1.68 (m, 1H), 1.45 (d, 1H), 1.26 (d, 3H), 0.82 (t, 3H). Elemental Analysis (Calcd. for $C_{11}H_{17}NO$): C, 73.73 (73.69); H, 9.51 (9.56); N, 7.92 (7.82).

(+)-(S)-2-(1-methylpropyl)-6-vinylpyridine (**7**)

A solution **6** (1.79 g, 0.01 mol) in 85% H_2SO_4 (15 mL) was heated at 110-120 °C for 2h. The solution was poured into ice and then alkalized with 10% NaOH. Extraction with Et_2O (3 x 20 mL), drying (Na_2SO_4), evaporation of the solvent and distillation gave **7** (1.48 g, 92%): bp 70 °C (0.4 mm); $[\alpha]^{25}_D$ +29.83° (*c* 2.4, cyclohexane); ^1H NMR ($CDCl_3$) δ, ppm: 7.52 (t, 1H), 7.11 (d, 1H), 6.69 (d, 1H), 6.82 (dd, 1H), 6.78 (d, 1H), 5.42 (d, 1H), 2.78 (m, 1H), 1.76 (m, 1H), 1.61 (m, 1H), 1.26 (d, 3H), 0.85 (t, 3H). Elemental Analysis (Calcd. for $C_{11}H_{15}N$): C, 82.10 (81.93); H, 9.58 (9.38); N, 8.82 (8.69).

Ozonization of (+)-(S)-2-(1-methylpropyl)-6-vinylpyridine (**7**) *to (+)-(S)-methylbutanoic acid* (**8**).

A solution of **7** (1.21 g, 7.5 mmol), $[\alpha]^{25}_D$ +29.83° (*c* 2.4, cyclohexane), in CH_2Cl_2 (35 mL) was treated with a stream of ozonized oxygen at room temperature for 24 h. After replacement of the solvent with the same volume of EtOH, 5% NaOH (10 mL) and then H_2O_2 (35%, 5 mL) were added slowly at 0 °C. The mixture was refluxed for 24 h, extracted with Et_2O and the aqueous solution alkalized with 10 % NaOH. Extraction *in continuum* with Et_2O, drying (Na_2SO_4), evaporation of the solvent and distillation gave (+)-(S)-methylbutanoic acid (**8**) (84 mg, 11%): 104 (20 mm), $[\alpha]^{25}_D$ +14.48° (*c* 1.0, Et_2O; 72% minimum optical purity).

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