Synthesis of Enantiopure C_2-Chiral Amidines

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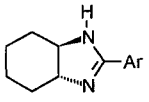
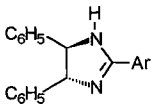
Starting from optically active 1,2-diamines the optically active C_2-chiral amidines **3a–e** and **4a,b** were prepared.

Optically active amidines with C_2-chirality are hitherto unknown. These strongly basic compounds can serve as auxiliary compounds for the NMR analysis of enantiomeric mixtures of weakly acidic compounds[1] or as ligands in catalysts for enantioselective synthesis. We describe here the synthesis of the optically active amidines **3a–e** and **4a,b** and their dynamic behaviour on the NMR time scale. The preparation of optically active guanidinium salts and reaction with chiral carboxylic acids have been reported.[2–4]

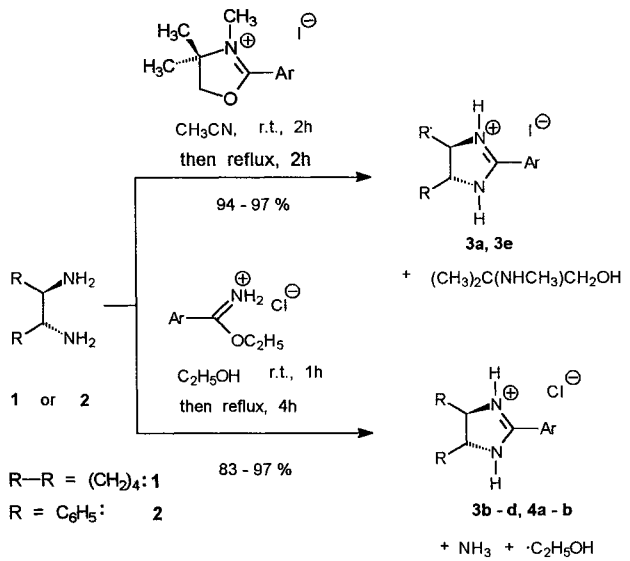




3	Ar
a	C_6H_5
b	$C_6H_4OCH_3$ (p)
c	$C_6H_4OC_2H_5$ (p)
d	C_6H_4O(2-propyl) (p)
e	1-naphthyl

4	Ar
a	C_6H_5
b	$C_6H_4OCH_3$ (p)

Hydrohalides of the hitherto unknown amidines **3a–e** and **4a,b** were prepared from 1,2-diamines **1** or **2** (optically active or racemic) and oxazolinium salts[5,6] or esters of imidic acid.[7] The amidines themselves were obtained by treating the reaction mixture with a base. To determine the optical purity, the amidines were reacted with (+)-1,1′-bi-2-naphthol in deuterochloroform, and the diastereomeric associates were analyzed by ^{1}H NMR spectroscopy. Separation of the signals was observed with racemic amidines, but not with optically active amidines, thus ee ≥ 98%.



The new amidines were characterized by elementary analyses and spectroscopy. The NMR spectra at room temperature in deuterochloroform (untreated) are in most cases in accord with the C_2-symmetry. However, in some cases line broadening occurs, especially for the ^{13}C NMR signals of the carbons connected to nitrogen via a single bond. Heavy line broadening and even splitting is observed when lowering temperature (down to −60 °C) or concentration, and using solvents (e.g. deuterochloroform) free from acid. Tautomerism A ⇄ B is in accord with this behaviour. Solvent assisted tautomerism in imidazole is reported in Ref. 8.

(−)-(1*R*,2*R*)-Diaminocyclohexane (**1**) and (+)-(1*R*,2*R*)-diphenylethylenediamine (**2**) were purchased from Fluka, Neu-Ulm, ee ≥ 98%. The reaction flasks were dried by heating at 140 °C over night. EtOH and MeCN were dried according to known procedures and stored under N_2 on 4 Å molecular sieves. All reactions were performed under dry N_2. Melting points are uncorrected. Microanalyses were carried out on a Carlo Erba Model 1106 microanalyzer. The ^{1}H NMR and ^{13}C NMR spectra were recorded on a GX 400 JEOL spectrometer, using TMS as internal standard. ^{1}H NMR signals were assigned by H,H-COSY, C,H-COSY and ^{1}H-NOE difference spectroscopy. IR spectra were recorded on a Perkin-Elmer System 2000 FTIR-spectrometer. Optical rotations were measured at 20 °C using a 10 cm tube in a Hartnack polarimeter. Mass spectra were obtained on a Finnigan MAT 90 mass spectrometer. For all new compounds satisfactory microanalyses obtained: C ± 0.5, H ± 0.4, N ± 0.5.

Amidines 3b–d, 4a,b from Imidic Ester Hydrochloride:
A solution of the enantiopure diamine **1** or **2** (4.7 mmol) and the corresponding ester of the imidic acid hydrochloride[9] (4.7 mmol) in anhydr. EtOH (15 mL) was stirred for 1 h at r.t. and for 4 h at reflux. After evaporation of the solvent at reduced pressure, the residue was dissolved in CH_2Cl_2 (150 mL) and the solution was extracted with 5% aq Na_2CO_3 (150 mL). The organic phase was dried (Na_2SO_4) and the solvent was evaporated at reduced pressure, leaving the amidine as an oil. The oil crystallized after addition of about 5 times the volume of Et_2O. Compounds **3b–d** could not be purified by additional crystallization due to high solubility in common organic solvents.

(+)-(3aR,7aR)-2-(4-Methoxyphenyl)-trans-3a,4,5,6,7,7a-hexahydrobenzimidazole (**3b**): From (−)-(1*R*,2*R*)-diaminocyclohexane (**1**; 0.56 g, 4.7 mmol) and the ethyl ester of *p*-methoxybenzoimidic acid hydrochloride (1.01 g, 4.7 mmol); yield: 0.90 g (83%); mp 130–132 °C; $[\alpha]_D$ + 187 (*c* = 4.6, pyridine).

IR (KBr): ν = 3421 (N–H), 2940 (C–H), 1614 (C=C) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 7.74, 6.90 (AA′XX′ spin system, J_{AX} = 9.0, $J_{AA'} = J_{XX'}$ = 4.3 Hz, 4 H_{arom}), 3.83 (s, 3 H, OCH_3), 3.10 (m, 2 H, 3a–H, 7a–H), 2.29 (m, 2 H, 4-H_e, 7-H_e), 1.84 (m, 2 H, 5-H_e, 6-H_e), 1.54 (m, 2 H, 4-H_a, 7-H_a), 1.36 (m, 2 H, 5-H_a, 6-H_a).

^{13}C NMR ($CDCl_3$): δ = 161.5 (s), 156.3 (s), 128.1 (d), 123.3 (s), 113.7 (d), 70.0 (br), 55.3 (q), 30.9 (t), 25.0 (t).

MS (70 eV): *m/z* (%) = 230 (M^+, 62), 187 (100).

(+)-(3aR,7aR)-2-(4-Ethoxyphenyl)-trans-3a,4,5,6,7,7a-hexahydrobenzimidazole **(3c)**: From (−)-(1*R*,2*R*)-diaminocyclohexane (**1**; 0.56 g, 4.7 mmol) and the ethyl ester of *p*-ethoxybenzoimidic acid hydrochloride (1.08 g, 4.7 mmol); yield: 1.00 g (87%); mp 160–160.5 °C; $[\alpha]_D$ + 157 (*c* = 7.5, pyridine).

IR (KBr): ν = 3435 (N–H), 2931 (C–H), 1614 (C=C) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 7.21, 6.88 (AA'XX' spin system, J_{AX} = 8.9, $J_{AA'} = J_{XX'}$ = 5.0 Hz, 4 H_{arom}), 4.05 (q, *J* = 7.0 Hz, 2 H, OCH_2), (cyclohexane moiety see **3b**), 1.42 (t, *J* = 7.0 Hz, 3 H, CH_3).

^{13}C NMR ($CDCl_3$): δ = 165.0 (s), 161.5 (s), 128.1 (d), 123.3 (s), 113.7 (d), 71.0 (br), 63.5 (t), 55.3 (q), 30.9 (t), 25.0 (t).

MS (70 eV): *m/z* (%) = 244 (M^+, 70), 201 (100).

(+)-(3aR,7aR)-2-(4-Isopropoxyphenyl)-trans-3a,4,5,6,7,7a-hexahydrobenzimidazole **(3d)**: From (−)-(1*R*,2*R*)-diaminocyclohexane (**1**; 0.56 g, 4.7 mmol) and the ethyl ester of *p*-isopropoxybenzoimidic acid hydrochloride (1.14 g, 4.7 mmol); yield: 1.12 g (92%); mp 157–158 °C; $[\alpha]_D$ + 150 (*c* = 7.0 pyridine).

IR (KBr): ν = 3434 (N–H), 2935 (C–H), 1613 (C=C) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 7.87, 7.70 (AA'XX' spin system, J_{AX} = 8.9 Hz, $J_{XX'}$ = 4.5, $J_{AA'}$ = 8.9 Hz, 4 H_{arom}), 4.59 [sept, *J* = 6.1 Hz, 1 H, $OC\underline{H}(CH_3)_2$], (cyclohexane moiety see **3b**), 1.33 [d, *J* = 6.1 Hz, 6 H, $CH(C\underline{H}_3)_2$].

^{13}C NMR ($CDCl_3$): δ = 165.0 (s), 159.8 (s), 128.1 (d), 123.0 (s), 115.3 (d), 69.8 (t), 67.8 (br), 30.9 (t), 25.4 (q), 25.0 (q), 21.9 (t).

MS (70 eV): *m/z* (%) = 258 (M^+, 43), 173 (100).

(+)-(4R,5R)-2,4,5-Triphenyl-trans-4,5-dihydroimidazole **(4a)**: From (+)-(1*R*,2*R*)-diphenylethylenediamine (**2**; 1.00 g, 4.7 mmol) and the ethyl ester of benzoimidic acid hydrochloride (0.87 g, 4.7 mmol); yield: 1.30 g (93%); mp 183–185 °C (toluene); $[\alpha]_D$ + 43 (*c* = 4.2 pyridine).

IR (KBr): ν = 3419 (N–H), 3029 (C–H), 1598 (C=C) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 7.97–7.26 (m, 15 H_{arom}), 4.93 (s, 2 H, CH), 1.7 (br s, 1 H, NH).

^{13}C NMR ($CDCl_3$): δ = 163.1 (s), 143.3 (s), 131.1 (d), 129.9 (d), 128.7 (d), 128.6 (d), 127.6 (d), 127.4 (d), 126.6 (d), 76.0 (br).

MS (70 eV): *m/z* (%) = 298 (M^+, 12), 106 (100).

(+)-(4R,5R)-2-(4-Methoxyphenyl)-trans-4,5-diphenyl-4,5-dihydroimidazole **(4b)**: From (1*R*,2*R*)-(+)-diphenylethylenediamine (**2**; 1.00 g, 4.7 mmol) and the ethyl ester of *p*-methoxybenzoimidic acid hydrochloride (1.01 g, 4.7 mmol); yield: 1.50 g (97%); mp 202–203 °C (toluene); $[\alpha]_D$ + 19 (*c* = 2.0, pyridine).

IR (KBr): ν = 3026 (C–H), 1601 (C=C) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 7.89, 6.96 (AA'XX' spin system, J_{AX} = 8.9, $J_{AA'} = J_{XX'}$ = 4.9 Hz, 4 H_{arom}), 7.37–2.27 (m, 5 H_{arom}), 5.32 (br, 1 H, NH), 4.88 (br, 2 H, CH), 3.87 (s, 3 H, OCH_3).

^{13}C NMR ($CDCl_3$): δ = 162.7 (s), 161.8 (s), 143.6 (s), 129.0 (d), 128.7 (d), 127.5 (d), 126.6 (d), 122.5 (s), 113.9 (d), 55.4 (q), C-4, C-5 not found because of line broadening.

MS (70 eV): *m/z* (%) = 328 (M^+, 10), 223 (100).

Amidines 3a,e From Δ^2-Oxazolinium Iodides:

A suspension of the enantiopure (−)-(1*R*,2*R*)-*trans*-diaminocyclohexane (**1**; 8.8 mmol) and the corresponding Δ^2-oxazolinium iodide[10] (8.8 mmol) in anhydr. MeCN (30 mL) was stirred for 2 h at r.t. and 2 h at reflux. After evaporation of the solvent at reduced pressure, the residue was dissolved in CH_2Cl_2 (150 mL) and extracted with 5% aq Na_2CO_3 (150 mL). The organic phase was dried (Na_2SO_4) and the solvent was evaporated at reduced pressure, leaving the amidine as an oil. The latter crystallized after addition of about 5 times the volume of Et_2O. Compounds **3a** and **3e** could not be purified by further crystallization due to the high solubility in common organic solvents.

(+)-(3aR,7aR)-2-Phenyl-trans-3a,4,5,6,7,7a-hexahydrobenzimidazole **(3a)**: From (−)-(1*R*,2*R*)-diaminocyclohexane (**1**; 1.05 g, 8.8 mmol) and 3,4,4-trimethyl-2-phenyl-Δ^2-oxazolinium iodide (2.70 g, 8.8 mmol); yield: 1.71 g (97%); mp 159–160 °C; $[\alpha]_D$ + 199 (*c* = 4.0, pyridine).

IR (KBr): ν = 2936 (C–H), 1600 (C=C) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 7.74–7.72, 7.37–7.28 (m, 5 H_{arom}), 5.30 (br, 1 H, NH), (cyclohexane moiety see **3b**).

^{13}C NMR ($CDCl_3$): δ = 165.8 (s), 131.0 (d), 129.8 (s), 128.4 (d), 126.8 (d), 69.0 (d), 30.5 (t), 24.7 (t).

EIMS (70 eV): *m/z* (%) = 200 (M^+, 41), 157 (100).

(+)-(3aR,7aR)-2-(1-Naphthyl)-trans-3a,4,5,6,7,7a-hexahydrobenzimidazole **(3e)**: From (−)-(1*R*,2*R*)-diaminocyclohexane (**1**; 1.05 g, 8.8 mmol) and 3,4,4-trimethyl-2-(1-naphthyl)-Δ^2-oxazolinium iodide (3.18 g, 8.8 mmol); yield: 2.20 g (94%); mp 217–218 °C; $[\alpha]_D$ + 98 (*c* = 5.2, pyridine).

IR (KBr): ν = 3435 (N–H), 2937 (C–H), 1584 (C=C) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 8.04–7.27 (m, 6 H_{arom}), 7.17 (br, 1 H, NH), (cyclohexane moiety see **3b**).

^{13}C NMR ($CDCl_3$): δ = 167.7 (s), 133.3 (s), 132.4 (d), 129.6 (s), 128.7 (d), 127.8 (d), 127.6 (d), 126.7 (d), 124.7 (d), 124.5 (d), 124.1 (s), 67.0 (d), 29.6 (t), 24.2 (t).

MS (70 eV): *m/z* (%) = 250 (M^+, 88), 249 (100).

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