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New Optically Active Pyrrole-oxazolines
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14 new optically active pyrrole-oxazolines were synthesised from 2-pyrrole-carbonitrile or methyl 2-pyrrole-carboximidate and chiral amino alcohols. Their use in copper-catalysed enantioselective cyclopropagation reactions gave only low optical yields (3-14%ee).

Within the last years optically active oxazoline ligands have proven use in transition-metal catalysed asymmetric synthesis. In copper-catalysed cyclopropanation reactions oxazolines turned out to be the ligands of choice [2, 3]. Oxazolines substituted in 2-position with a heteroaromatic compound such as pyridine [4] gave good results in many systems of asymmetric catalysis, e. g., in enantioselective hydrosilylation [5 - 7]. However, in the copper-catalysed cyclopropanation only moderate stereoselectivities were obtained [8]. Therefore, we decided to replace the pyridine substituent by the pyrrole substituent [9]. Whereas pyridine-oxazolines are neutral bidentate ligands, pyrrole-oxazolines after deprotonation would act in a catalyst as anionic bidentate ligands. Only a few pyrrole-oxazolines are known [10], none of them in optically active form. This is surprising as various chiral thiophene-oxazolines have already been synthesised [11].

Results and Discussion

Established methodologies for the synthesis of oxazolines include the reaction of a nitrile (here 2-pyrrole-carbonitrile) with an amino alcohol in the presence of activated zinc(II) chloride [12] and the reaction of a carboximidate (here methyl 2-pyrrole-carboximidate) with an amino alcohol [13]. The synthesis of 2-pyrrrole-carbonitrile was carried out by dehydration of the oxime of 2-pyrrrole-carbaldehyde using acetic anhydride (60% yield) according to the literature [14]. However, further reactions with the nitrile prepared in this way failed, maybe because traces of acetic acid or acetic anhydride were left in the sample. Therefore, we turned to the reaction of hydroxylamine-O-sulfonate and 2-pyrrole-carbaldehyde [15], which gave the corresponding nitrile in even higher yields (76%). Attempts to prepare methyl 2-pyrrole-carboximidate from 2-pyrrole-carbonitrile in methanol in the presence of a catalytic amount of sodium methoxide [16] were not successful. However, the compound could be isolated, when the reaction of 2-pyrrole-carbonitrile with methanol was carried out with gaseous HCl. The carboximidate hydrochloride was then treated with NaHCO₃ to obtain the free imidate.

For the synthesis of the pyrrole-oxazolines 1-12 we used the commercially available amino alcohols (R)- and (S)-alaninol, (R)- and (S)-2-aminobutanol, (S)-valinol, (S)-leucinol, (2S,3S)-iso-leucinol, (S)-tart-leucinol, (S)-phenylalaninol, (R)-phenylglycine, (1R,2S)-norephedrine, and the aminodiol (+)-(1S,2S)-2-amino-1-phenyl-1,3-propanediol. The aminodiol required for the synthesis of 13 and 14 are derivatives of methyl L-serine and dimethyl L-aspartate, which were treated with two equivalents of PhMgBr [17].

The pyrrole-oxazolines 1-9 and 14 were prepared from 2-pyrrole-carbonitrile and the corresponding amino alcohols using activated ZnCl₂ (Scheme 1).

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Scheme 1: General Procedure A

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The compounds were suspended in chlorobenzene and refluxed for 24 h.

The pyrrole-oxazolines 10 - 13 were prepared from methyl 2-pyrrole-carboximidate and the respective amino alcohols by stirring in chlorobenzene at 80°C (Scheme 2). This method is also applicable to the synthesis of pyrrole-oxazolines 1 - 9 and 14. In both cases further purification was made by chromatography on silica gel and/or recrystallization.

Scheme 2: General Procedure B

All pyrrole-oxazolines are air-stable solids except 7 which is an oil. The protons of the pyrrole fragment exhibit in the NMR spectra chemical shifts between 6.90 and 6.15 ppm. Oxazoline ring protons are located between 4.60 and 3.20 ppm. If there is a phenyl substituent adjacent to the ring signals up to 5.70 ppm are observed due to anisotropy effects. The ring protons next to an asymmetric center do show diastereotopic character.

Former investigations had shown that the oxazoline-cyclization is regioselective [18]. Theoretically, there should be two possible isomers of the pyrrole-oxazolines 12 - 14 due to the two different OH functionalities in the amino alcohols. However, as shown by NMR only one of them is formed. The CH2 protons of compound 14 appear at 2.10 ppm, whereas the other possible isomer should have signals at much lower field according to their position at the oxazoline ring. Similarly, the low field shift of the protons of 13 prove that they are located at the ring.

The pyrrole-oxazolines were used as ligands in copper-catalysed asymmetric cyclopropanation reactions. Two typical systems were studied, (i) the reaction of ethyl diazoacetate with 1,1-diphenylethylene (Scheme 3) and (ii) the reaction of ethyl diazoacetate with styrene (Scheme 4). The catalysts were prepared "in situ" from CuI triflate and the respective ligand. The diazo compound was added dropwise over a period of two hours as described previously [9, 19].

In both cases only low optical yields resulted. In the 1,1-diphenylethylene system an enantiomeric excess between 3 and 14 % was found for ethyl 2,2-diphenylcyclopropanecarboxylate, with ligand 13 giving the best induction [9]. In the styrene system the optical yields for all ligands dropped to 4 - 7 %ee [9]. For the product ethyl 2-phenylcyclopropanecarboxylate the usual cis/trans ratio 38/62 was obtained [9].

Experimental

Solvents were dried and saturated with nitrogen according to standard procedures. Water was deaerated by bubbling N2 through it for at least 12 h. Liquid starting materials were distilled under N2 prior to use. Chromatographic materials (silica 60 (65-200 μm), Merck) were heated in vacuo for 24 h and then saturated with N2. EA = ethyl acetate, PE = petroleum ether (b.p. 40-60°C), Ox-Ch = oxazoline proton at C-4, Ox-Ch2 = cis-H and Ox-Ch3 = trans-H of the C-5 protons in the oxazoline ring with respect to the substituent at C-4.

Melting points (not corrected): SMP-20 (Büchi). - MS: MAT 112S (Finnigan), intensities are relative to the basic peak (I = 100%), possible interpretations within brackets. - Elemental analysis: Mikroanalytisches Labor of the Universität Regensburg. - 1H NMR: Bruker AC 250 (250 MHz), internal TMS. - Optical rotations: Perkin-Elmer polarimeter 241 (24°C).

General procedure A:

ZnCl2 (68 mg, 0.5 mmol) was melted in vacuo and then cooled under N2. Chlorobenzene (30 ml), the amino alcohol (10 mmol) and 2-pyrrole-carbonitrile (0.92 g, 10 mmol) were added. After refluxing for 24 h the solvent was evaporated and the resulting mixture was purified.

General procedure B:

The amino alcohol (10 mmol) and methyl 2-pyrrole-carboximidate (1.24 g, 10 mmol) were suspended in
chlorobenzene (50 ml) and heated to 80°C. After 20 -
26 h the solvent was evaporated, followed by purification as described for the individual compounds.

(+)-(4R)-4,5-Dihydro-4-methyl-2-(2-pyrrrolyl)oxazole (1)

According to general procedure A with (R)-alanimol. Recrystallization from ether/PE 1:1. Light red needles (0.43 g, 2.87 mmol, 29%), m.p. 145-147°C. [α]D = +81° (c = 2.22, CHCl3).

1H NMR (CDCl3, 250 MHz): δ = 1.33 (d, 3H, J =
6.4 Hz, CH3), 3.92 (dd, 1H, J = 7.8 Hz, Ox-CH=CH2), 4.30-4.39 (m, 1H, Ox-CH), 4.46 (dd, 1H, J = 9.0 Hz, Ox-CH=CH2), 6.23 (dd, 1H, J34 = 3.6 Hz, J34 = 2.4 Hz, Py-H4), 6.74 (dd, 1H, J34 = 1.4 Hz, Py-H3), 6.90 (dd, 1H, Py-H3), 10.63 (br s, 1H, NH). MS (EI): m/z (%) = 150 (89, M), 135 (100, M-CH3).

C9H8N2O (150.2)
Calcd C 63.98 H 6.71 N 18.65%
Found C 64.04 H 6.58 N 18.52%

(-)-(4S)-4,5-Dihydro-4-methyl-2-(2-pyrrrolyl)oxazole (2)

According to general procedure A with (S)-alanimol. Light red needles (0.60 g, 4.00 mmol, 40%), m.p. 145-
147°C. [α]D = -81° (c = 1.61, CHCl3). MS and 1H NMR identical to 1.

C9H8N2O (150.2)
Calcd C 63.98 H 6.71 N 18.65%
Found C 63.68 H 6.74 N 18.48%

(+)-(4R)-4-Ethyl-4,5-dihydro-2-(2-pyrrrolyl)oxazole (3)

According to general procedure A with (R)-2-
aminobutanol. Recrystallization from ether/PE 1:1. Light red needles (0.48 g, 2.92 mmol, 29%), m.p. 108-110°C. [α]D = +35° (c = 2.14, CHCl3). 1H NMR (CDCl3, 250 MHz): δ = 0.95 (t, 3H, J = 7.4 Hz, CH3), 1.52-1.65 (m, 1H, CH2H), 1.67-1.77 (m, 1H, CH2H), 4.03 (dd, 1H, J = 7.5 Hz, J = 9.0 Hz, Ox-CH=CH2), 4.15-4.27 (m, 1H, Ox-CH), 4.44 (dd, 1H, J = 9.0 Hz, Ox-CH=CH2), 6.23 (dd, 1H, J34 = 2.5 Hz, J34 = 3.6 Hz, Py-H4), 6.72 (dd, 1H, J35 = 1.4 Hz, Py-H3), 6.88 (dd, 1H, Py-H3), 10.79 (br s, 1H, NH). MS (EI): m/z = 164 (43, M), 135 (100, M-C2H5).

C10H10N2O (164.2)
Calcd C 65.83 H 7.37 N 17.06%
Found C 65.74 H 7.36 N 16.75%

(-)-(4S)-4-Ethyl-4,5-dihydro-2-(2-pyrrrolyl)oxazole (4)

According to general procedure A with (S)-2-
aminobutanol. Light red needles (0.44 g, 2.92 mmol, 29%), m.p. 108-110°C. [α]D = -35° (c = 2.92, CHCl3). MS and 1H NMR identical to 3.

C9H12N2O (164.2)
Calcd C 65.83 H 7.37 N 17.06%
Found C 65.88 H 7.35 N 17.05%

(+)-(4S)-4,5-Dihydro-4-isopropyl-2-(2-pyrrrolyl)oxazole (5)

According to general procedure A with (S)-valinol. Purification by chromatography (SiO2, ether/PE 1:1). Colourless powder (0.33 g, 1.85 mmol, 19%), m.p. 95-
96°C. [α]D = +9.4° (c = 2.13, CHCl3). 1H NMR (CDCl3, 250 MHz): δ = 0.89 (d, 3H, J = 6.7 Hz, CH3), 0.96 (d, 3H, J = 6.7 Hz, CH3), 1.72-1.85 (m, 1H, CH(CH3)2), 4.02-4.09 (m, 1H, Ox-CH=CH2), 4.11-4.16 (m, 1H, Ox-
CH), 4.35-4.41 (m, 1H, Ox-CH=CH2), 6.21 (dd, 1H, J34 = 2.4 Hz, J34 = 3.0 Hz, Py-H4), 6.71 (dd, 1H, J35 = 1.4 Hz, Py-H3), 6.87 (dd, 1H, Py-H3), 11.1 (br s, 1H, NH). MS (EI): m/z = 178 (24, M), 135 (100, M-C2H5).

C10H14N2O (178.2)
Calcd C 67.39 H 7.92 N 15.72%
Found C 67.65 H 7.85 N 15.75%

(+)-(4S,6S)-4-(2-Butyl)-4,5-dihydro-2-(2-pyrrrolyl)oxazole (6)

According to general procedure A with (2S,3S)-
-isoleucinol. Recrystallization from ether/PE 1:1. Colourless crystals (0.44 g, 2.29 mmol, 23%), m.p. 60-62°C. [α]D = -12° (c = 1.68, CHCl3). 1H NMR (CDCl3, 250 MHz): δ = 0.84 (d, 3H, J = 6.7 Hz, CH3CH2), 0.90 (t, 3H, J = 7.3 Hz, CH2CH2), 1.10-1.22 (m, 1H, CH2CH2), 1.51-1.69 (m, 2H, CH2CH2), 4.10-4.23 (m, 2H, Ox-CH=CH2 +
Ox-CH), 4.33-4.39 (m, 1H, Ox-CH=CH2), 6.22 (dd, 1H, J34 = 2.3 Hz, J34 = 3.6 Hz, Py-H4), 6.71 (dd, 1H, J35 = 1.5 Hz, Py-H3), 6.87 (dd, 1H, Py-H3), 10.85 (br s, 1H, NH). MS (EI): m/z = 192 (13, M), 135 (100, M-C3H9).

C11H16N2O (192.3)
Calcd C 68.72 H 8.39 N 14.57%
Found C 68.63 H 8.12 N 14.20%

(+)-(4S)-4,5-Dihydro-4-(1-isobutyl)-2-(2-pyrrrolyl)oxazole (7)

According to general procedure A with (S)-leucinol. Purification by chromatography (SiO2, ether/PE 1:1). Red oil (0.73 g, 3.81 mmol, 38%), which crystallized at -23°C. [α]D = -48° (c = 1.55, CHCl3). 1H NMR (CDCl3, 250 MHz): δ = 0.93 (d, 6H, J = 6.3 Hz, CH3(CH2)3), 1.18-1.23 (m, 1H, CH2CH2), 1.33-1.41 (m, 1H, CH2CH2), 1.60-1.79 (m, 1H, CH2CH2), 3.97 (dd, 1H, J = 7.5 Hz, J = 7.9 Hz, Ox-CH=CH2), 4.23-4.35 (m, 1H, Ox-CH), 4.46 (dd, 1H, J = 8.9 Hz, Ox-CH=CH2), 6.22 (dd, 1H, J34 = 2.5 Hz, J34 = 3.5 Hz, Py-H4), 6.72 (dd, 1H, J35 = 1.5 Hz, Py-H3),
(−)-(4S)-4-Tert-Butyl-4,5-dihydro-2-(2-pyrrolyl)oxazole (8)

According to general procedure A with (S)-tert-leucinol. On addition of 5 mL of CH₂Cl₂ unreacted leucinol precipitated and was filtered off. The resulting oil was treated with ether/PE to yield the product as a red precipitate. White powder (0.28 g, 1.32 mmol, 13%), m.p. 93-95°C. 

C₁₂H₁₈N₂O (223.3)
Caled C 68.82 H 8.27 N 14.40%
Found C 68.82 H 8.27 N 14.40%

(−)-(4R)-4,5-Dihydro-5-methyl-4-phenyl-2-(2-pyrrolyl)oxazole (9)

According to general procedure A with (R)-tert-leucinol. On addition of 5 mL of CH₂Cl₂ unreacted leucinol precipitated and was filtered off. The resulting oil was treated with ether/PE to yield the product as a red precipitate. White powder (1.29 g, 5.32 mmol, 29%), m.p. 190-191°C. [α]D = −13° (c = 1.29, CHCl₃).

C₁₂H₁₄N₂O (226.3)
Caled C 74.43 H 6.28 N 12.17%
Found C 74.40 H 6.28 N 11.66%

(−)-(4S,5S)-4,5-Dihydro-4-hydroxymethyl-5-phenyl-2-(2-pyrrolyl)oxazole (10)

According to general procedure B with (1S,2S)-2-amino-1,3-propanediol. By cooling the reaction mixture the product precipitated. White powder (1.31 g, 5.32 mmol, 53%), m.p. 190-191°C. [α]D = +9.6° (c = 0.52, DMSO).

C₁₂H₁₃NO (212.3)
Caled C 74.43 H 6.28 N 11.66%
Found C 74.30 H 6.28 N 11.66%

(−)-(4S)-4-Benzyl-4,5-dihydro-2-(2-pyrrolyl)oxazole (11)

According to general procedure B with (1R,2S)-norephedrine. Recrystallization from ether/PE 1:1. According to general procedure B with (1R,2S)-norephedrine. Recrystallization from ether/PE 1:1. White powder (0.65 g, 2.87 mmol, 29%), m.p. 106-109°C. [α]D = −322° (c = 1.94, CHCl₃).

C₁₃H₁₄NO (242.3)
Caled C 74.31 H 6.24 N 12.38%
Found C 74.43 H 6.28 N 12.17%

(−)-(4S,5S)-4,5-Dihydro-4-hydroxydiphenylmethyl-2-(2-pyrrolyl)oxazole (12)

According to general procedure B with (1S,2S)-2-amino-1,3-propanediol. Purification by chromatography (silica gel, EE/PE 1:1). Recrystallization from EE/PE 1:2. Colourless crystals (0.90 g, 2.83 mmol, 28%), m.p. 128-129°C. [α]D = +14° (c = 1.29, CH₂Cl₂).

C₁₄H₁₄NO (282.3)
Caled C 71.89 H 5.78 N 12.66%
Found C 71.89 H 5.78 N 12.66%

(−)-(4S)-4,5-Dihydro-4-hydroxydiphenylmethyl-2-(2-pyrrolyl)oxazole (13)

According to general procedure B with (2S)-2-amino-1,1-diphenyl-1,3-propanediol. Purification by chromatography (silica gel, EE/PE 1:1). Recrystallization from EE/PE 1:2. Colourless crystals (0.90 g, 2.83 mmol, 28%), m.p. 128-129°C. [α]D = +13° (c = 1.29, CH₂Cl₂).

C₁₆H₁₅NO (322.4)
Caled C 74.96 H 5.62 N 12.94%
Found C 74.96 H 5.62 N 12.94%
Py-H4), 6.70 (dd, 1H, J5 = 1.3 Hz, Py-H3), 6.74 (dd, 1H, J5 = 1.3 Hz, Py-H5), 6.71-7.53 (m, 10H, Ar-H), 10.21 (br s, 1H, NH).

MS (EI): m/z = 318 (5, M), 136 (100, M-Ph2 COH).

C20H18N2O2 (318.4)
Calcd C 75.54 H 5.70 N 8.81%, Found C 75.72 H 5.76 N 8.81%.

According to general procedure A with (2S)-2-amino-1,1,4,4-tetraphenyl-1,3-butanediol. Recrystallization from ether/PE 1:1. Orange powder (1.00 g, 2.06 mmol, 21%), m.p. 53-55°C. [a]D = -22° (c = 2.32, CHCl3).

'H NMR (CDCl3, 250 MHz): δ = 2.10 (dd, 1H, J = 14.0 Hz, V = 1.2 Hz, CH/H'), 2.20-4.20 (br, 1H, OH), 2.45 (dd, 1H, J = 11.0 Hz, CHF), 3.65 (dd, 1H, OX-CH), 6.21 (dd, 1H, J4 = 3.7 Hz, J5 = 2.7 Hz, Py-H4), 6.76 (dd, 1H, J5 = 1.2 Hz, Py-H5), 6.83 (dd, 1H, Py-H3), 7.10-7.82 (m, 20H, Ar-H), 9.41 (br s, 1H, NH). MS (El): m/z = 484 (2, M), 287 (70, M-CH2Ph2COH).

C33H28N2O2 (484.6)
Calcd C 81.79 H 5.82 N 5.78%, Found C 81.56 H 6.03 N 6.00%.

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