New chiral ligands and iron(III) complexes based on 2,6-bis(1-benzyl-4-isopropyl-4-methyl-4,5-dihydro-1H-imidazol-5-on-2-yl)pyridines

Miloš Sedláčk,a Pavel Drabin,a Ivana Císařová,b Aleš Růžičk,a Jiří Hanusek,a and Vladimír Macháček,a

aDepartment of Organic Chemistry, Faculty of Chemical Technology, University of Pardubice, Nám. Čs. Legií 565, 532 10 Pardubice, Czech Republic
bDepartment of Inorganic Chemistry, Faculty of Science, Charles University, Hlavova 2030, 128 43 Prague 2, Czech Republic

Abstract
New ligands and their complexes with iron(III) chloride have been suggested and prepared: (R,S)-, (R,R)- and (S,S)-2,6-bis(1-benzyl-4-isopropyl-4-methyl-4,5-dihydro-1H-imidazol-5-on-2-yl) pyridines. Both the ligands and their complexes were characterised by 1H and 13C NMR spectroscopy, optical rotation and X-ray diffraction.

Graphical abstract

Metal complexes of heterocyclic compounds containing a stereogenic centre have been used especially as homogeneous catalysts in a number of syntheses.1 Reviews2 and monographs[1], [3], [4] and [5] deal with chiral ligands possessing a chelate-forming grouping –N–C–C–N–C–C–N– that can produce stable complexes with transition metals. Connecting 1H-imidazol-5-ones to the 2- and 6-positions of pyridine affords new ligands structurally similar to the well-known ligands of oxazoline ('Pybox')5, terpyridine ('Terp')6 or 2,6-bis(1-methylbenz-imidazol-2-yl)pyridine7 and 2,6-bis(imidazol-2-yl)pyridine8 (Fig. 1). However, no ligands based on imidazole derivatives containing stereogenic centres have been described as yet.

Figure 1. 2,6-Bis(imidazol-2-yl)pyridine.
Functionalised 1H-imidazol-5-ones are well-known and commercially available herbicides derived from pyridine-2,3-dicarboxylic acid. Copper(II) complexes of the herbicide Imazapyr (2-(4-methyl-4-isopropyl-4,5-dihydro-1H-imidazol-5-on-2-yl)pyridine-3-carboxylic acid) have been described. In our previous paper we dealt with the synthesis and NMR spectra of functionalised 4,4-dialkyl-4,5-dihydro-2-phenyl-1H-imidazol-5-ones. The subject of the present paper is the synthesis and characterisation of new 2,6-bis(1-benzyl-4-isopropyl-4-methyl-4,5-dihydro-1H-imidazol-5-on-2-yl)pyridines and their complexes with iron(III) chloride. The complex compounds of iron or nickel represent relatively cheap catalysts and possible substitutes for platinum metals. Our ligands have the advantage of containing a quaternary asymmetric carbon atom, which prevents racemisation via cleavage of the α-hydrogen atom (for example, this takes place in the oxazolines based on natural amino acids).

The systems suggested by us can be relatively easily synthesised and/or further modified. The stereogenic centre of the imidazolone ring is derived from easily available, optically pure ((S),S)-2,3-dimethylbutanamide and (S)-2-amino-2,3-dimethylbutanamide. First we prepared the respective acylated butanamides (R,R) and (S,S) by reaction of pyridine-2,6-dicarboxylic acid dichloride with racemic 2-amino-2,3-dimethylbutanamide, (R)-2-amino-2,3-dimethylbutanamide, and (S)-2-amino-2,3-dimethylbutanamide. From the 1H NMR spectra we calculated that 1a contained about 20% of a mixture of 1b (R,R) and 1c (S,S) and 80% of the meso-form (R,S). Ring closure of 1a gave an analogous mixture of cyclic compounds, whose crystallisation provided only the meso-form 2a (R,S) as the least soluble component. The optically pure 2,6-bis(4-isopropyl-4-methyl-4,5-dihydro-1H-imidazol-5-on-2-yl)pyridines 2b (R,R) and 2c (S,S) were prepared in the same way from amidases of the meso-form 2a (R,S), 2b (R,R) and 2c (S,S) gave the respective 2,6-bis(1-benzyl-4-isopropyl-4-methyl-4,5-dihydro-1H-imidazol-5-on-2-yl)pyridines (Scheme 1):

\[ \text{Reagents and conditions: (a) 2,6-py(COCl)_{2}/TEA, CH}_2Cl_2, \text{ rt overnight}; (b) CH}_2ONa/CH}_2OH \text{ rt 48 h; (c) PhCH}_2Br/K_2CO}_3, \text{ DMF reflux 48 h; (d) FeCl}_3, \text{ MeOH rt overnight.} \]

The molecular structure of compound 3c (S,S) was obtained by X-ray techniques (Fig. 2, ORTEP—40% probability level). Only one molecule of two from the crystalline unit cell is shown; the hydrogen atoms are omitted for clarity. Selected interatomic distances [Å] and angles [°]: N11 C12 1.384(2), N11 C15 1.404(2), C12 O11 1.216(2), C13 N14 1.473(2), N14 C15 1.276(2), C16 N17 1.342(2), N17 C18 1.347(2), C18 C112 1.483(2), C112 N116 1.284(2), C112 N113 1.401(2), N113 C114 1.379(2), N113 C128 1.464(2), C114 O12 1.215(2), C115 N116 1.480(2), C12–N11–C15 107.08(13), C13–N14–C15 107.2(1), N14–C15–C16 121.0(1), C16–N17–C18 117.4(2), C18–C112–N116 123.3(1), N17–C18–C12 116.3(3), C112–N116–C115 106.3(1).
The bond distances and angles of the two crystallographically independent molecules were unexceptional, confirming the proposed structure and aromaticity of the corresponding rings. In both molecules, the imidazole rings deviate from the pyridine plane (Fig. 1, the torsion angles indicating this shape are: C19 C18 C112 N113 −136.0(2)°, C111 C16 C15 N11 −157.4(1)° and 136.1(2), 150.2(2) for the second molecule, respectively) in mutually opposite fashion. Three nitrogen atoms bearing benzyl groups (N11 and N113) are turned towards the pyridine nitrogen (N17) and the benzyl groups are situated in face of this atom.

The reactions of ligands \(3a, b\), and \(3c\) with anhydrous ferric chloride in methanol gave the complexes \(4a\) \((R, S)\): \(C_{33}H_{37}Cl_3FeN_5O_2\) (697.88) and \(4b\) \((R,R)\). In the case of complex \(4c\) \((S,S)\) the molecular structure was confirmed by X-ray techniques (Fig. 3, ORTEP—40% probability level; the molecule of \(4a\) is placed in a special position on a two-fold axis going through atoms Fe1, N1 and C4 in the crystal structure, however, the position of some atoms does not fulfil this symmetry exactly and these are disordered, most significantly Cl1. Only one position of the disordered atoms is shown and the hydrogens are omitted for clarity). Selected interatomic distances [Å] and angles [°]: Fe1 Cl1 2.268(4), Fe1 Cl2 2.337(1), Fe1 N1 2.167(3), Fe1 N6 2.127(3), N1 C2 1.337(4) 1.414, C2 C5 1.485(5), C5 N6 1.290(4), N6 C7 1.492(5) Cl1 Fe1 Cl2 103.7(1), Cl1 Fe1 Cl2 117.7(1), Cl1 Fe1 N1 104.1(1), N6 Fe1 N6 147.3(1), Cl1 Fe1 N1 171.7(1), Cl2 Fe1 Cl2’ 168.77(5), Cl1 Fe1 N6’ 108.3(1), N1 Fe1 N6 73.64(9).

Symmetry code (i): 1/4-y, 1/4-x, 1/4-y.

The iron coordination geometry in \(4a\) (Fig. 3) is a distorted octahedral with three nitrogen atoms relatively strongly bonded to the iron centre. The largest deviation from the ideal geometry is the N6 Fe1 N6’ angle. In comparison with the free ligand, both the pyridine and imidazole rings are coplanar and the aminobenzyl groups are turned away from the ligand coordination core. The benzyl moieties are situated above and below the ligand coordination plane (Fig. 3). The bond lengths and angles are very similar to previously published data for some examples of meridionally co-ordinated iron(III) complexes by N3Cl3 donor sets (tridentate ligands).\(^{20}\)
Acknowledgements

The authors wish to acknowledge Professor Jitka Moravcová (Institute of Chemical Technology Prague) for determinations of optical rotatory power and the financial support by the grant Agency of the Czech Republic (Grant No. 203/04/0646).

References and notes


[15] (Racemic)-pyridine-2,6-dicarboxylic acid bis-[(1-carbamoyl-1,2-dimethylpropyl)-amide] (1a): A solution of 2-amino-2,3-dimethylbutanamide (1.3 g, 10 mmol) and triethylamine (2.1 mL, 15 mmol) in dry dichloromethane (25 mL) was cooled to 0 °C and treated with a solution of pyridine-2,6-dicarboxylic acid dichloride (1.02 g, 5 mmol) in dichloromethane (15 mL) added over 15 min. The mixture was stirred overnight, whereupon the
solution was evaporated until dry. The residue was recrystallised from water to give 1.5 g of the product (77%), mp 250–260 °C (a 4:1 mixture of the meso-form and racemate). Data for the meso-form ¹H NMR (DMSO-d₆ 500 MHz, ppm): δ 8.75 (s, 2H, NH), 8.25 (m, 3H, PyH), 7.41 (br s, 2H, NH₂), 7.24 (br s, 2H, NH₂), 2.31 (sp, 2H, iPrCH), 1.63 (s, 6H, CH₃), 1.05 (d, ³J = 6.8 Hz, 6H, iPrCH₃), 0.97 (d, ³J = 6.8, 6H, iPrCH₃). ¹³C NMR (DMSO-d₆ 125 MHz, ppm): δ 174.7 (CONH₂), 161.9 (CONH), 149.1 (PyC₂, C₆), 139.9 (PyC₄), 124.1 (PyC₃, C₅), 62.5 (C₁₈), 34.9 (iPrCH), 17.6 (CH₃), 17.5 (iPrCH₃), 17.4 (iPrCH₂). For C₂₃H₂₆N₂O₄ (391.47) calculated: C, 58.30; H, 7.47; N, 17.89%; found: C, 58.75; H, 7.18; N, 17.56%. (R,R)-Pyridine-2,6-dicarboxylic acid bis[[1-carbamoyl-1,2-dimethyl(propyl)-amide] (1b): 52% yield, mp = 227–230 °C, [α]D²⁵ = −63.5°C (c = 1, CH₂OH). ¹H NMR (DMSO-d₆ 500 MHz, ppm): δ 8.67 (br s, 2H, NH), 8.25 (m, 3H, PyH), 7.41 (br s, 2H, NH₂), 7.18 (br s, 2H, NH₂), 2.27 (sep, ³J = 6.8, 2H, iPrCH), 1.62 (s, 6H, CH₃), 1.05 (d, ³J = 6.8 Hz, 6H, iPrCH₃), 1.01 (d, ³J = 6.8 Hz, 6H, iPrCH₃). ¹³C NMR (DMSO-d₆ 125 MHz, ppm): δ 174.5 (CONH₂), 161.9 (PyCONH), 149.2 (PyC₂, C₆), 139.9 (PyC₄), 124.1 (PyC₃, C₅), 62.5 (C₁₈), 35.1 (iPrCH), 17.9 (CH₃), 17.4 (iPrCH₃), 17.35 (iPrCH₂). The elemental analysis is comparable with that of 1a. (S,S)-Pyridine-2,6-dicarboxylic acid bis[[1-carbamoyl-1,2-dimethyl(propyl)-amide] (1c): 45% yield, mp 230–233 °C, [α]D²⁵ = 63.0°C (c = 0.9, CH₂OH). Elemental analysis is comparable with that of 1a (1b). ¹H and ¹³C NMR spectra are identical with those of the (R,R)-isomer

[16] (R,S)-2,6-Bis(4-isopropyl-4-methyl-4,5-dihydro-1H-imidazol-5-on-2-yl)pyridine (2a): A mixture of 1a (780 mg, 2 mmol) and 20 mL 1 M CH₃ONa (20 mmol) was stirred at room temperature. After 24 h, the mixture was neutralised with concd HCl to pH ~7 and evaporated to dryness. The residue was treated with water (10 mL), and the suspension formed was filtered and washed with hexane to give 0.57 g of the product (80%), mp 302–303 °C. ¹H NMR (DMSO-d₆ 500 MHz, ppm): δ 11.59 (s, 2H, NH), 8.39 (d, ³J = 7.9, 2H, PyH₂, H₄), 8.23 (t, ³J = 7.9, 1H, PyH₂), 2.02 (sep, ³J = 6.8, 2H, iPrCH), 1.34 (s, 6H, CH₃), 1.04 (d, ³J = 6.8, 6H, iPrCH₃), 0.84 (d, ³J = 6.8, 6H, iPrCH₃). ¹³C NMR (DMSO-d₆ 125 MHz, ppm): δ 186.9 (C=O), 158.4 (C=C=N), 146.2 (PyC₂, C₆), 139.4 (PyC₄), 123.5 (PyC₃, C₅), 75.5 (C₁₈), 34.3 (iPrCH), 21.2 (CH₃), 17.0 (iPrCH₃), 16.80 (iPrCH₂). For C₂₃H₂₆N₂O₂ (355.44) calculated: C, 64.20; H, 7.09; N, 19.70%; found: C, 64.18; H, 7.10; N, 19.65%. (R,R)-2,6-Bis(4-isopropyl-4-methyl-4,5-dihydro-1H-imidazol-5-on-2-yl)pyridine (2b): 71% yield, mp 284–286 °C, [α]D²⁵ = 32.0°C (c = 1, CH₂OH). The elemental analysis is comparable with that of 2a. (S,S)-2,6-Bis(4-isopropyl-4-methyl-4,5-dihydro-1H-imidazol-5-on-2-yl)pyridine (2c): 69% yield, mp 281–283 °C, [α]D²⁵ = −32.3°C (c = 1, CH₂OH). The elemental analysis is comparable with that of 2a (2b). ¹H and ¹³C NMR spectra are identical with those of the (R,R)-isomer


[18] (R,S)-2,6-Bis(1-benzyl-4-isopropyl-4-methyl-4,5-dihydro-1H-imidazol-5-on-2-yl)pyridine (3a): A mixture of 2a (1.78 g, 5 mmol), potassium carbonate (1.8 g, 13 mmol), benzyl bromide (2.05 g, 12 mmol), potassium iodide (50 mg) and dimethylformamide (15 mL) was refluxed for 48 h. Then, the mixture was filtered and the insoluble portion was washed with 20 mL DMF. The combined filtrates were evaporated in vacuo until dry. The residue was dissolved in 150 mL ethyl acetate and the solution was filtered through silica gel. The filtrate was evaporated to dryness and the residue was recrystallised from petroleum ether to give 1.4 g of the product (52%), mp 101–105 °C. ¹H NMR (DMSO-d₆ 500 MHz, ppm): δ 8.01 (m, 3H, PyH), 7.18 (m, 6H, PhH₂, H₄), 6.90 (m, 4H, PhH₂), 4.60 and 4.68 (2 × d, ³J = 15.8, 4H, BzCH₂), 2.11 (sep, ³J = 6.8, 2H, iPrCH), 1.40 (s, 6H, CH₃), 1.06 (d, ³J = 6.8, 6H, iPrCH₃). ¹³C NMR (DMSO-d₆ 125 MHz, ppm): δ 185.7 (C=O), 158.3 (C=C=N), 147.9 (PyC₂, C₆), 139.1 (PyC₄), 137.5 (PyC₃, C₅), 128.5 (PhC₂, C₆), 127.2 (PhC₆), 126.4 (PhC₆), 125.8 (PhC₆), 73.4 (C₁₈), 44.0 (BzCH₂), 34.3 (iPrCH), 21.4 (CH₃), 17.0 (iPrCH₃), 16.8 (iPrCH₂). ¹⁵N NMR (DMSO-d₆ 50 MHz, ppm): δ 78 (Py), δ 109 (C=C=N), −222 (Bz-N). For C₃₂H₃₂N₂O₅ (535.70) calculated: C, 73.99; H, 6.96;
N, 13.07%; found: C, 73.93; H, 7.18; N, 12.97%. \((R,R)-2,6\text{-Bis(1-benzyl-4-isopropyl-4-methyl-4,5-dihydro-1H-imidazol-5-on-2-yl)pyridine (3b):} 46\% \text{ yield, mp 102–104 °C, } [\alpha]_{D}^{25} = 26.0 (c = 0.5, \text{CH}_3\text{OH}). \text{The elemental analysis is comparable with that of 3a, } {^1}\text{H and } {^{13}}\text{C NMR spectra are identical with those of 3a.} (S,S)-2,6-Bis(1-benzyl-4-isopropyl-4-methyl-4,5-dihydro-1H-imidazol-5-on-2-yl)pyridine (3c): 53\% \text{ yield, mp = 103–105 °C, } [\alpha]_{D}^{25} = 25.9 (c = 0.5, \text{CH}_3\text{OH}). \text{The elemental analysis is comparable with that of 3a (3b), } {^1}\text{H and } {^{13}}\text{C NMR spectra are identical with those of the } (R,R)\text{-isomer.} \text{Crystal data for 3c: C}_{33}\text{H}_{37}\text{N}_{5}\text{O}_{2} \text{M} = 535.70, \text{monoclinic, } a = 37.5360(6), b = 15.3370(2), c = 10.5450(2) \text{Å, } \beta = 104.9240(7)^\circ, V = 5865.87(16) \text{ Å}^{3}, \text{T = 150(2), space group C2, } Z = 8, \mu (\text{MoK}) = 0.077 \text{ mm}^{-1}, 40,843 \text{ reflections measured, 13,341 unique } (R_{int} = 0.039), \text{ which were used in all calculations, the final } R_{1} = 0.040. \text{CCDC 236299.} \text{Complex 4a: } \text{A solution of 3a (107 mg, 0.2 mmol) and anhydrous ferric chloride (32.5 mg, 0.2 mmol) in absolute methanol (25 mL) was stirred overnight. The suspension obtained was evaporated to a volume of ca 5 mL, and the separated crystals were collected by filtration, washed with ether and dried to give 100 mg of the product (71\%). For C}_{33}\text{H}_{37}\text{Cl}_{3}\text{FeN}_{5}\text{O}_{2} (697.88) \text{ calculated: C, 56.79; H, 5.34; N, 10.04%; found: C, 56.75 H: 5.36; N, 10.04%. Crystal data for 4a: C}_{33}\text{H}_{37}\text{Cl}_{3}\text{FeN}_{5}\text{O}_{2} \text{M} = 697.88, \text{tetragonal, } a = 17.2950(2), c = 45.4100(4) \text{ Å, } V = 13582.9(3) \text{ Å}^{3}, \text{T = 150(2), space group I41/acd, } Z = 16, \mu (\text{MoK}) = 0.717 \text{ mm}^{-1}, 97309 \text{ reflections measured, 3748 unique } (R_{int} = 0.039), \text{ which were used in all calculations, the final } R_{1} = 0.074. \text{CCDC 236300. Complex 4b: 75\% \text{ yield, } [\alpha]_{D}^{25} = 49.7 (c = 0.2, \text{DMF). For C}_{33}\text{H}_{37}\text{Cl}_{3}\text{FeN}_{5}\text{O}_{2} (697.88) \text{ calculated: C, 56.79; H, 5.34; N, 10.04%; found: C, 57.06 H, 5.56 N, 10.11%. Complex 4c: 73\% \text{ yield, } [\alpha]_{D}^{25} = 50.0 (c = 0.2, \text{DMF). For C}_{33}\text{H}_{37}\text{Cl}_{3}\text{FeN}_{5}\text{O}_{2} (697.88) calculated: C, 56.79; H: 5.34; N, 10.04%; found: C, 56.95 H, 5.57; N. 10.03%.} \text{[19] Complex 4a: A solution of 3a (107 mg, 0.2 mmol) and anhydrous ferric chloride (32.5 mg, 0.2 mmol) in absolute methanol (25 mL) was stirred overnight. The suspension obtained was evaporated to a volume of ca 5 mL, and the separated crystals were collected by filtration, washed with ether and dried to give 100 mg of the product (71%). For C}_{33}\text{H}_{37}\text{Cl}_{3}\text{FeN}_{5}\text{O}_{2} (697.88) \text{ calculated: C, 56.79; H, 5.34; N, 10.04%; found: C, 56.75 H: 5.36; N, 10.04%. Crystal data for 4a: C}_{33}\text{H}_{37}\text{Cl}_{3}\text{FeN}_{5}\text{O}_{2} \text{M} = 697.88, \text{tetragonal, } a = 17.2950(2), c = 45.4100(4) \text{ Å, } V = 13582.9(3) \text{ Å}^{3}, \text{T = 150(2), space group I41/acd, } Z = 16, \mu (\text{MoK}) = 0.717 \text{ mm}^{-1}, 97309 \text{ reflections measured, 3748 unique } (R_{int} = 0.039), \text{ which were used in all calculations, the final } R_{1} = 0.074. \text{CCDC 236300. Complex 4b: 75\% \text{ yield, } [\alpha]_{D}^{25} = 49.7 (c = 0.2, \text{DMF). For C}_{33}\text{H}_{37}\text{Cl}_{3}\text{FeN}_{5}\text{O}_{2} (697.88) \text{ calculated: C, 56.79; H, 5.34; N, 10.04%; found: C, 57.06 H, 5.56 N, 10.11%. Complex 4c: 73\% \text{ yield, } [\alpha]_{D}^{25} = 50.0 (c = 0.2, \text{DMF). For C}_{33}\text{H}_{37}\text{Cl}_{3}\text{FeN}_{5}\text{O}_{2} (697.88) calculated: C, 56.79; H: 5.34; N, 10.04%; found: C, 56.95 H, 5.57; N. 10.03%.} \text{[20] (a)S.A. Cotton, V. Frankevicius and J. Fawcett, Polyhedron 21 (2002), p. 2055.} \text{(b)H. Adams, N.A. Bailey, J.D. Crane, D.E. Fenton, J.-M. Latour and J.M. Williams, J. Chem. Soc., Dalton Trans. (1990), p. 1727.}