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

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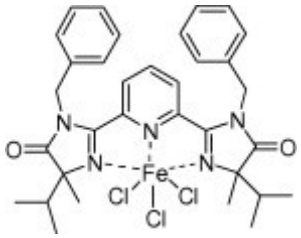
Abstract

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-1*H*-imidazol-5-on-2-yl) pyridines. Both the ligands and their complexes were characterised by ^{1}H and ^{13}C 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] Reviews[2] 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 1*H*-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)pyridine[7] and 2,6-bis(imidazol-2-yl)pyridine[8] (Fig. 1). However, no ligands based on imidazole derivatives containing stereogenic centres have been described as yet.

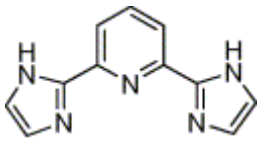
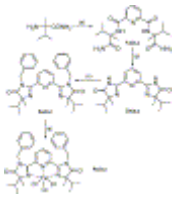


Figure 1. 2,6-Bis(imidazol-2-yl)pyridine.

Functionalised 1*H*-imidazol-5-ones are well-known and commercially available herbicides[9] and [10] derived from pyridine-2,3-dicarboxylic acid. Copper(II) complexes of the herbicide *Imazapyr* (2-(4-methyl-4-isopropyl-4,5-dihydro-1*H*-imidazol-5-on-2-yl)pyridine-3-carboxylic acid) have been described.[11] In our previous paper we dealt with the synthesis and NMR spectra of functionalised 4,4-dialkyl-4,5-dihydro-2-phenyl-1*H*-imidazol-5-ones.[12] 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-1*H*-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[13]). 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 (*R*)-2-amino-2,3-dimethylbutanamide and (*S*)-2-amino-2,3-dimethylbutanamide.[10] and [14] First we prepared the respective acylated butanamides[15] **1a**,**b** (*R*,*R*) and **1c** (*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 ^{1}H 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[16] 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-1*H*-imidazol-5-on-2-yl)pyridines **2b** (*R*,*R*) and **2c** (*S*,*S*) were prepared in the same way from amides **1b** (*R*,*R*) and **1c** (*S*,*S*). In an analogous manner,[17] benzylation[18] 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-1*H*-imidazol-5-on-2-yl)pyridines (Scheme 1): **3a** (*R*,*S*), **3b** (*R*,*R*) and **3c** (*S*,*S*). Using ^{15}N NMR, we confirmed the presence of three types of nitrogen atoms: *δ* 78 (*Py*), *δ* 109 (*C*=*N*), *δ* 222 (*Bz*–*N*).



Scheme 1. Reagents and conditions: (a) 2,6-py$(COCl)_2$/TEA, CH_2Cl_2, rt overnight; (b) CH_3ONa/CH_3OH rt 48 h; (c) $PhCH_2Br/K_2CO_3$, DMF reflux 48 h; (d) $FeCl_3$, 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).

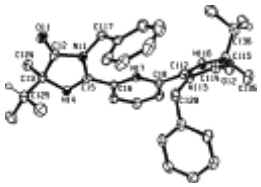


Figure 2. ORTEP representation of the structure of compound **3c**.

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[19] **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 $Cl2^{i}$ 87.5(1), Cl1 Fe1 N6 104.1(1), N6 Fe1 $N6^{i}$ 147.3(1), Cl1 Fe1 N1 171.7(1), Cl2 Fe1 $Cl2^{i}$ 168.77(5),Cl1 Fe1 $N6^{i}$ 108.3(1), N1 Fe1 N6 73.64(9). Symmetry code (i): 1/4-*y*, 1/4-*x*, 1/4-*y*.

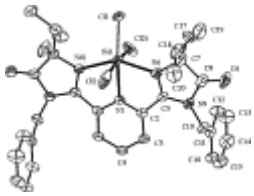


Figure 3. ORTEP representation of the structure of complex **4c**.

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 $N6^{i}$ 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 N_3Cl_3 donor sets (tridentate ligands).[20]

Acknowledgements

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[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 ^{1}H NMR (DMSO-d_6 500 MHz, ppm): δ 8.75 (s, 2H, *NH*), 8.25 (m, 3H, Py*H*), 7.41 (br s, 2H, NH_2), 7.24 (br s, 2H, NH_2), 2.31 (sp, 2H, *i*Pr*CH*), 1.63 (s, 6H, CH_3), 1.05 (d, ^{3}J = 6.8 Hz, 6H, *i*PrCH_3), 0.97, (d, ^{3}J = 6.8, 6H, *i*PrCH_3). ^{13}C NMR (DMSO-d_6 125 MHz, ppm): δ 174.7 ($CONH_2$), 161.9 (*CONH*), 149.1 (PyC_2, C_6), 139.9 (PyC_4), 124.1 (PyC_3, C_5), 62.5 ($C_{q.}$), 34.9 (*i*Pr*CH*), 17.6 (CH_3), 17.5 (*i*PrCH_3), 17.4 (*i* PrCH_3). For $C_{19}H_{29}N_5O_4$ (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-dimethylpropyl)-amide] (**1b**): 52% yield, mp = 227–230 °C, $[\alpha]_D^{25} = -63.5$ (*c* = 1, CH_3OH). ^{1}H NMR (DMSO-d_6 500 MHz, ppm): δ 8.67 (br s, 2H, *NH*), 8.25 (m, 3H, Py*H*), 7.41 (br s, 2H, NH_2), 7.18 (br s, 2H, NH_2), 2.27 (sep, ^{3}J = 6.8, 2H, *i*Pr*CH*), 1.62 (s, 6H, CH_3), 1.05 (d, ^{3}J = 6.8 Hz, 6H, *i*PrCH_3), 1.01 (d, ^{3}J = 6.8 Hz, 6H, *i*PrCH_3). ^{13}C NMR (DMSO-d_6 125 MHz, ppm): δ 174.5 ($CONH_2$), 161.9 (*PyCONH*), 149.2 (PyC_2, C_6), 139.9 (PyC_4), 124.1 (PyC_3, C_5), 62.5 (C_q), δ 35.1 (*i*Pr*CH*), 17.9 (CH_3), 17.4 (*i*PrCH_3), 17.35 (*i*PrCH_3). The elemental analysis is comparable with that of **1a**. (*S*,*S*)-Pyridine-2,6-dicarboxylic acid bis-[(1-carbamoyl-1,2-dimethylpropyl)-amide] (**1c**): 45% yield, mp 230–233 °C, $[\alpha]_D^{25} = 63.0$ (*c* = 0.9, CH_3OH). Elemental analysis is comparable with that of **1a** (**1b**), ^{1}H and ^{13}C NMR spectra are identical with those of the (*R*,*R*)-isomer

[16] (*R*,*S*)-2,6-Bis(4-isopropyl-4-methyl-4,5-dihydro-1*H*-imidazol-5-on-2-yl)pyridine (**2a**): A mixture of **1a** (780 mg, 2 mmol) and 20 mL 1 M CH_3ONa (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. ^{1}H NMR (DMSO-d_6 500 MHz, ppm): δ 11.59 (s, 2H, *NH*), 8.39 (d, ^{3}J = 7.9, 2H, PyH_3,H_5), 8.23 (t, ^{3}J = 7.9, 1H, PyH_4), 2.02 (sep, ^{3}J = 6.8, 2H, *i*Pr*CH*), 1.34 (s, 6H, CH_3), 1.04 (d, ^{3}J = 6.8, 6H, *i*PrCH_3), 0.84 (d, ^{3}J = 6.8, 6H, *i*PrCH_3). ^{13}C NMR (DMSO-d_6 125 MHz, ppm): δ 186.9 ($C{=}O$), 158.4 ($C{=}N$), 146.2 (PyC_2,C_6), 139.4 (PyC_4), 123.5 (PyC_3,C_5), 75.5 ($C_{q.}$), 34.3 (*i*Pr*CH*), 21.2 (CH_3), 17.0 (*i*PrCH_3), 16.80 (*i*PrCH_3). For $C_{19}H_{25}N_5O_2$ (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-1*H*-imidazol-5-on-2-yl)pyridine (**2b**): 71% yield, mp 284–28 6°C, $[\alpha]_D^{25} = 32.0$ (*c* = 1, CH_3OH). The elemental analysis is comparable with that of **2a**. (*S*,*S*)-2,6-Bis-(4-isopropyl-4-methyl-4,5-dihydro-1*H*-imidazol-5-on-2- yl)pyridine (**2c**): 69% yield, mp 281–283 °C, $[\alpha]_D^{25} = -32.3$ (*c* = 1, CH_3OH). Elemental analysis is comparable with that of **2a** (**2b**), ^{1}H and ^{13}C NMR spectra are identical with those of the (*R*,*R*)-isomer

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[18] (*R*,*S*)-2,6-Bis(1-benzyl-4-isopropyl-4-methyl-4,5-dihydro-1*H*-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. ^{1}H NMR (DMSO-d_6 500 MHz, ppm): δ 8.01 (m, 3H, *Py*), 7.18 (m, 6H, PhH_3,H_4), 6.90 (m, 4H, PhH_2), 4.60 and 4.68 (2 × d, ^{2}J = 15.8, 4H, BzCH_2), 2.11 (sep, ^{3}J = 6.8, 2H, *i*Pr*CH*), 1.40 (s, 6H, CH_3), 1.06 (d, ^{3}J = 6.8, 6H, *i*PrCH_3), 0.88 (d, ^{3}J = 6.8, 6H, *i*PrCH_3). ^{13}C NMR (DMSO-d_6 125 MHz, ppm): δ 185.7 ($C{=}O$), 158.3 ($C{=}N$), 147.9 (PyC_2,C_6), 139.1 (PyC_4), 137.5 (PyC_3,C_5), 128.5 (PhC_2,C_6), 127.2 (PhC_1), 126.4 (PhC_3,C_5), 125.8 (PhC_4), 73.4 (C_q), 44.0 (BzCH_2), 34.3 (*i*Pr*CH*), 21.4 (CH_3), 17.0 (*i*PrCH_3), 16.8 (*i*PrCH_3). ^{15}N NMR (NMR (DMSO-d_6 50 MHz, ppm): δ −78 (*Py*), δ −109 ($C{=}N$), −222 (*Bz–N*). For $C_{33}H_{37}N_5O_2$ (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-Bis(1-benzyl-4-isopropyl-4-methyl-4,5-dihydro-1*H*-imidazol-5-on-2-yl)pyridine (**3b**): 46% yield, mp 102–104 °C, $[\alpha]_D^{25} = 26.0$(*c* = 0.5, CH_3OH). The elemental analysis is comparable with that of **3a**, ^1H and ^{13}C NMR spectra are identical with those of **3a**. (*S*,*S*)-2,6-Bis(1-benzyl-4-isopropyl-4-methyl-4,5-dihydro-1*H*-imidazol-5-on-2-yl)pyridine (**3c**): 53% yield, mp = 103–105 °C, $[\alpha]_D^{25} = 25.9$(*c* = 0.5, CH_3OH). The elemental analysis is comparable with that of **3a** (**3b**), ^1H and ^{13}C NMR spectra are identical with those of the (*R*,*R*)-isomer. *Crystal data* for **3c**: $C_{33}H_{37}N_5O_2$ *M* = 535.70, monoclinic,*a* = 37.5360(6), *b* = 15.3370(2), *c* = 10.5450(2) Å, *β* = 104.9240(7)°, *V* = 5865.87(16) $Å^3$, *T* = 150(2), space group *C2*, *Z* = 8, *μ* (MoK_α) = 0.077 mm^1, 40,843 reflections measured, 13,341 unique (R_{int} = 0.039), which were used in all calculations, the final R_1 = 0.040. CCDC 236299

[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 $C_{33}H_{37}Cl_3FeN_5O_2$ (697.88) calculated C, 56.79; H, 5.34; N, 10.04%; found: C, 56.75 H: 5.36; N, 10.04%. *Crystal data* for **4a**: $C_{33}H_{37}Cl_3FeN_5O_2$ *M* = 697.88, tetragonal, *a* = 17.2950(2), *c* = 45.4100(4) Å, *V* = 13582.9(3) $Å^3$, *T* = 150(2), space group $I4_1/acd$, *Z* = 16, *μ*(MoK_α)=0.717 mm^1, 97309 reflections measured, 3748 unique (R_{int} = 0.039), which were used in all calculations, the final R_1 = 0.074. CCDC 236300. *Complex* **4b**: 75% yield, $[\alpha]_D^{25} = 49.7$(*c* = 0.2, DMF). For $C_{33}H_{37}Cl_3FeN_5O_2$ (697.88) calculated: C, 56.79; H, 5.34; N, 10.04%; found: C, 57.06 H, 5.56 N, 10.11%. *Complex* **4c**: 73% yield, $[\alpha]_D^{25} = 50.0$(*c* = 0.2, DMF). For $C_{33}H_{37}Cl_3FeN_5O_2$ (697.88) calculated: C, 56.79; H: 5.34; N, 10.04%; found: C, 56.95; H, 5,57; N. 10.03%

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