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Convenient synthesis of tridentate 2,6-di(pyrazol-1-yl)-4-carboxypyridine and tetradentate 6,6′-di(pyrazol-1-yl)-4,4′-dicarboxy-2,2′-bipyridine ligands

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ABSTRACT

Citrazinic acid is used as a convenient starting material for both tridentate 2,6-di(pyrazol-1-yl)-pyridine and tetradentate 6,6′-di(pyrazol-1-yl)-2,2′-bipyridine ligands containing carboxylic groups useful for further anchoring of sensitizer on TiO_2 for dye-sensitized solar cells (DSCs). Using 2,6-dichloro-4-carboxypyridine, the synthesis of the terdentate ligands was improved compared to previously used 2,6-dibromo-4-carboxypyridine or 2,6-dichloro-4-ethylcarboxylate pyridine. Controlling the reaction conditions, it is possible to efficiently obtain the monosubstituted 2-chloro-6-pyrazol-1-yl-4-carboxy-pyridine, a key intermediate for the preparation of tetradentate 6,6′-di(pyrazol-1-yl)-4,4′-dicarboxy-2,2′-bipyridine ligand.

1. Introduction

Multidentate N-heterocyclic ligands have been ubiquitously used as ligands for transition metal complexes. Terdentate ligands have been particularly appealing for building supramolecular systems with defined and finely controlled architecture, as they do not lead to optical and geometrical isomers. While 2,2′;6′,2″-terpyridines are certainly the most widely used N^N^N ligands,[1–3] other 2,6-di(*N*-heterocycle)-pyridine derivatives have been attracting attention. They allow variation in the N^N^N bite angle and access to different pK_a ultimately modifying the binding properties of the ligand. 2,6-Di(pyrazol-1-yl)-pyridine[4] has found particular interest, for example, in platinum,[5] ruthenium[6–8] and iron complexes.[9,10]

We have been interested in multidentate polypyridine ligands for many years for developing ruthenium sensitizers for dye-sensitized solar cells (DSC). Ruthenium complexes based on bipyridine ligands have been very successful for photovoltaic applications;[11] however, further improvement of power conversion efficiencies are limited by the lack of significant red and near infrared absorption. The near-IR absorption properties of ruthenium complexes have been improved by using terpyridine[12] and quaterpyridine.[13,14] However, this improvement is achieved at the expense of optimum redox properties. Consequently, while more photons are absorbed which increases the current, open circuit voltage drops due to less efficient electron transfer reactions. Ultimately, the power conversion efficiency of the device is not improved. To further tune the photophysical and electrochemical properties of the sensitizer, it appears promising to vary the skeleton of the ligand. Due to the high lying π^* orbitals, while having similar π orbitals than pyridine, pyrazoles are promising *N*-heterocycles to incorporate in multidentate ligands. Indeed their use should lead to more localization of the lowest unoccupied molecular orbital (LUMO) of ruthenium complexes on the central pyridine or bipyridine moiety, improving directionality and electronic coupling with the TiO_2, and the highest occupied molecular orbital (HOMO) of the complex could be independently tuned by varying substituents on the pyrazole cycle. The syntheses described herein were developed in order to obtain such divergent bifunctional ligands. The bifunctional character of either tris or tetradentate ligands developed in this paper is crucial for their potential applications in ruthenium-based dye-sensitized solar cell devices. Typically, one side of the ligand should act as a good chelate for the ruthenium photoactive centre whereas the second functionality should allow an effective attachment of the resulting complex on the nanocrystalline TiO_2 surface. To fulfil these requirements commercially available and inexpensive citrazinic acid **1** was used as the starting material.

Compound **1** can be easily converted into the known 2,6-dichloroisonicotinic acid **2**[15] when reacted with $POCl_3$ in the presence of benzyltriethylammonium chloride. Quenching the reaction with water at 0 °C afforded acid **2** in 81% yield (Scheme 1). Compound **2** can, therefore, be used as a key intermediate for the synthesis of both tris and tetradentate ligands **4a–b** and **8a–b**. Pure tridentate ligand **4a** and **4b** can be easily obtained in 80% and 71% yield, respectively, by reaction of substrate **2** with excess of **3a** or **3b** at a fairly elevated temperature and a fairly lengthy reaction time, typ-

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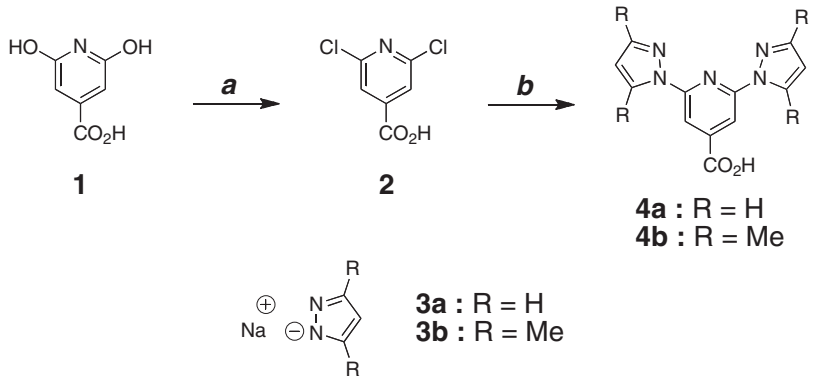


Scheme 1. Synthesis of tridentate bis(pyrazolyl)pyridine-based ligands. Reagents and conditions: (a) (i) $POCl_3$, $Bz(Et)_3N^+Cl^-$, Δ (ii) H_2O, 0 °C; (b) 5–6 equiv of **3a** or **3b**, DMF, 130 °C, three days.

ically 130 °C for three days (Scheme 1).[16,17] Compound **3a** and **3b** were generated in situ from reaction of commercially available 1*H*-pyrazole and 1*H*-3,5-dimethylpyrazole with NaH (55% in mineral oil).

Compound **4a** has been previously prepared following a similar strategy starting with the 2,6-dibromo-4-carboxypyridine derivative and diglyme as the solvent in 67% yield.[18] The ethyl ester version has been prepared by reaction of the ethyl ester of 2,6-dibromo-4-carboxypyridine in 40% yield.[19] In this case the authors inform that using the ethyl ester of 2,6-dichloro-4-carboxypyridine is unsuccessful. However, it has been reported for similar terdentate ligands that using 2,6-dibromopyridine or 2,6-dichloropyridine as starting materials does not significantly alter the yield of reaction.[17] Therefore, we assumed that the large difference in yield for **4a** or its ester as reported in the literature is due to the use of the carboxylic acid in one case and the ester in the other case. We anticipated then that using the 2,6-dichloro-4-carboxypyridine in place of its ester would lead to better results. By performing the reaction in DMF we could obtain 80% yield of **4a** terdentate ligands.

Monosubstituted compounds **7a** and **7b** were also required as intermediate building blocks for the synthesis of tetradentate analogues **8a–b**. As displacement of one halide decreases the reactivity of the second towards displacement, compounds **7a–b** resulting from the displacement of only one chloride by pyrazolyl derivatives can be easily obtained using milder reaction conditions than those employed for the synthesis of **4a** and **4b**. Then, reaction of compound **2** with **3a** or **3b** (2.1 equiv) in anhydrous DMF at lower temperature and for a shorter time, typically 60 °C for 24 h, respectively, afforded mixtures of mono and disubstituted compounds **4a**–**5a** and **4b**–**5b** (Scheme 2).

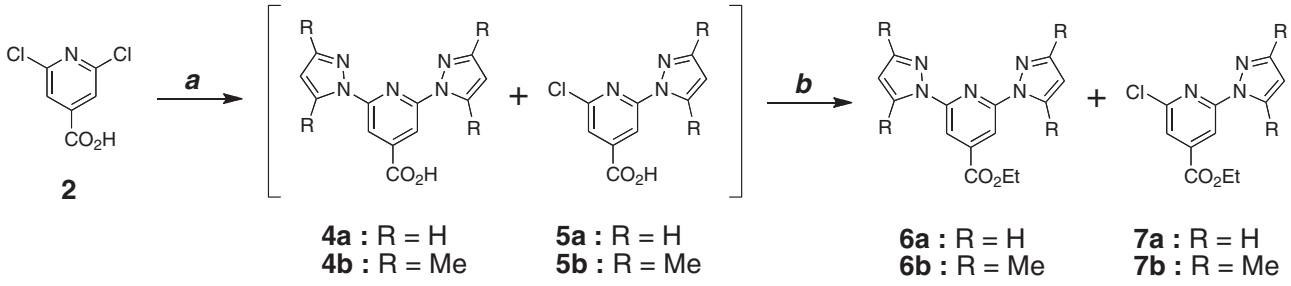
For easier purifications, mixtures **4a–5a** and **4b–5b** were directly converted into their ethyl ester derivatives **6a–7a** and **6b–7b** in a refluxing mixture of ethanol and catalytic amount of H_2SO_4. ^1H NMR analysis of both mixtures **6a–7a** and **6b–7b** revealed a mono/disubstituted pyrazolyl–pyridine ratio of approximately 6:1. Interestingly, while the monosubstituted dimethylpyrazolyl derivative **7b** was easily separated from its disubstituted analogue **7a** by chromatography purification, pyrazolyl derivative **7a** remained as a mixture with its disubstituted parent **6a**. In this case, the final homocoupling reaction was performed on the mixture of mono and disubstituted compounds **6a–7a**. Thus, mixture **6a–7a** or compound **7b** were subjected to a classical nickel-catalysed homocoupling reaction in anhydrous DMF at 60 °C to afford after purification the desired tetradentate ligands **8a** and **8b** in 30% and 52% yield, respectively (Scheme 3).

It is noteworthy that starting byproduct **6a** was now easily separable from the newly synthesized tetradentate compound **8a** by classical chromatography purification.

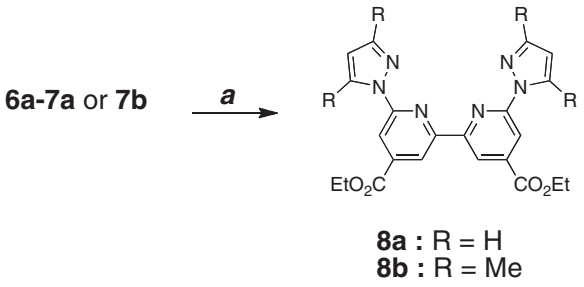
In conclusion we have presented an improved synthesis of terdentate 2,6-di(pyrazol-1-yl)-4-carboxypyridine and of previously unreported tetradentate 6,6′-di(pyrazol-1-yl)-4,4′-dicarboxy-2,2′-bipyridine. Those ligands have potential for ruthenium sensitizer for dye-sensitized solar cells. In addition it is expected that monosubstituted intermediates **5a** and **5b** could be used for disymmetrization of tridentate and tetradentate N-heterocyclic ligands for further fine tuning of the ruthenium complex properties.

2. Experimental section

All commercially available reagents were purchased from Fluka under puriss grade and used without further purification. Solvents for synthesis were dried and degassed by standard methods. All chemicals were purchased from Fluka and used without further purifications. Deuterated solvents were obtained from Dr. Glaser A.G. Synthesized compounds were purified by column chromatography on Kieselgel 60 (Fluka, 70–230 mesch). ^1H and ^{13}C NMR spectra were recorded on a Bruker 200 MHz spectrometer.



Scheme 2. Synthesis of monosubstituted pyrazolyl–pyridine. Reagents and conditions: (a) **3a** or **3b** (2.1 equiv), DMF, 60 °C, 24 h; (b) MeOH, cat. H_2SO_4, Δ.



Scheme 3. Synthesis of compounds **8a** and **8b** by nickel-catalysed homocoupling reaction. Reagents and conditions: (a) (i) $NiCl_2{\cdot}6H_2O$, PPh_3, Zn, DMF, 60 °C (ii) **6a–7a** or **7b**.

Compound **2**: Citrazinic acid **1** (20.0 g, 129 mmol) and benzyltriethylammonium chloride (32.3 g, 142 mmol) in 40 ml of $POCl_3$ were heated to 140 °C for 24 h under a $CaCl_2$ drying tube. After being cooled to room temperature, the brown mixture was poured on ice (400 g) and stirred for 2 h. The resulting brown solid was filtered off, washed with water and dissolved in EtOAc (400 ml). The organic phase was then washed with saturated NH_4Cl, dried over Na_2SO_4 and evaporated to dryness to afford 20 g (81%) of the desired compound as a brown solid. ^1H and ^{13}C NMR were in accordance with those already reported.[18]

2.1. General procedure for the synthesis of 4a and 4b

To a suspension of NaH (55–65% in mineral oil, 1.31 g, ≈30 mmol) in anhydrous DMF (30 ml) was dropwise added a solution of **3a** or **3b** (30 mmol) in anhydrous DMF (10 ml) at room temperature and under argon. The resulting slurry was heated to 100 °C for 45 min and compound **2** (1 g, 5.21 mmol) was added in one portion. The brown mixture was then heated to 130 °C under argon for three days. DMF was evaporated and water (100 ml) was added. The mixture was acidified with concd HCl and the formed precipitate was filtered and washed with water. The solid was dissolved in the minimum volume of hot acetone and let to stand overnight in the freezer. Compounds **4a** and **4b** were, respectively, obtained after filtration and washing with cold portions of acetone (3 × 5 ml).

Compound **4a**: 1.06 g, yield = 80%, white solid. ^1H and ^{13}C NMR were in accordance with those already reported.[18]

Compound **4b**: 1.16 g, yield = 71%, white solid. ^1H NMR (200 MHz, 25 °C, DMSO-*d*6) δ 2.22 (s, 6H), 2.57 (s, 6H), 6.16 (s, 2H), 8.05 (s, 2H). ^{13}C NMR (50 MHz, 25 °C, DMSO-*d*6) δ 13.7, 14.2, 109.9, 112.5, 141.2, 143.4, 150.3, 152.2, 165.5.

2.2. General procedure for the synthesis of 6a–7a and 7b

To a suspension of NaH (55–65% in mineral oil, 1.1 g, ≈25 mmol) in anhydrous DMF (40 ml) was dropwise added a solution of **3a** or **3b** (21 mmol) in anhydrous DMF (10 ml) at room temperature and under argon. The resulting slurry was heated to 60 °C for 45 min and compound **2** (2 g, 10 mmol) was added in one portion. The brown mixture was then heated to 60 °C under argon for 24 h. DMF was evaporated and water (100 ml) was added. The mixture was acidified with concd HCl and the formed precipitate was filtered and washed with water. The solid was dissolved in EtOAc, dried over $MgSO_4$ and evaporated to afford crude mixtures of compounds **4a–5a** (1.4 g) or **4b–5b** (1.65 g) as slightly brown solids. Crude mixture of **4a–5a** or **4b–5b** was refluxed overnight in 75 ml of EtOH and 2 ml of concd H_2SO_4. After being cooled to room temperature, EtOH was evaporated and the resulting residue was dissolved in CH_2Cl_2 (150 ml), successively washed with saturated $NaHCO_3$ solution (2 × 100 ml), water (100 ml), dried over $MgSO_4$ and finally evaporated to dryness. Purifications were performed as follows:

Compound **6a–7a**: the resulting brown solid was dissolved in the minimum volume of CH_2Cl_2 and hexane (100 ml) was added. The insoluble brown impurities were filtered off and the clear filtrate was evaporated to afford 1.4 g of a mixture composed of disubstituted **6a** and monosubstituted **7a** compound in a 1:6 ratio according to the ^1H NMR.

Compound **6b–7b**: the resulting brown solid was dissolved in the minimum volume of CH_2Cl_2 and purified by column chromatography (SiO_2, CH_2Cl_2) to afford 1.5 g (54%) of pure **7b** as a white solid (first band). ^1H NMR (200 MHz, 25 °C, $CDCl_3$) δ 1.43 (t, *J* = 7 Hz, 3H), 2.31 (s, 3H), 2.67 (s, 3H), 4.44 (q, *J* = 7 Hz, 2H), 6.02 (s, 1H), 7.68 (s, 1H), 8.35 (s, 1H).

2.3. General procedure for the synthesis of 8a and 8b

Zn powder (1.5 equiv) was added to a stirred solution of $NiCl_2{\cdot}6H_2O$ (1 equiv) and PPh_3 (4 equiv) in anhydrous DMF (50 ml) at 60 °C. The resulting solution was stirred at 60 °C under argon for 2 h during which time the colour changed from blue to dark red. A solution of **6a–7a** (1.4 g) or **7b** (1.43 g, 5.11 mmol) in anhydrous DMF (10 ml) was added via syringe and the resulting mixture allowed to be stirred at 60 °C for 20 h. DMF was evaporated and $CHCl_3$ (150 ml) was added followed by a 10% NH_4OH solution (100 ml). The organic phase was separated, washed with a 10% NH_4OH solution (100 ml), dried over $MgSO_4$ and evaporated. Et_2O was added and the slurry sonicated for 2 min. The resulting precipitate was filtered off and purified by column chromatography (SiO_2, CH_2Cl_2/MeOH; 95:5) to afford the desired compounds **8a** or **8b**.

Compound **8a**: 400 mg, ≈30%, white solid. ^1H NMR (200 MHz, 25 °C, $CDCl_3$) δ 1.49 (t, *J* = 7 Hz, 6H), 4.51 (q, *J* = 7 Hz, 4H), 6.57 (dd, *J* = 1.5 and 2.5 Hz, 2H), 7.83 (s, 2H), 8.59 (s, 2H), 8.78 (d, *J* = 2.5 Hz, 2H), 8.84 (s, 2H). ^{13}C NMR (50 MHz, 25 °C, $CDCl_3$) δ 14.3, 62.2, 108.3, 112.7, 118.0, 127.4, 141.9, 142.7, 151.9, 154.1, 164.5. Anal. Calcd for $C_{22}H_{20}N_6O_4{\cdot}H_2O$: C, 58.66; H, 4.92; N, 18.66. Found: C, 58.72; H, 4.97; N, 18.64. HRMS-ESI (*m*/*z*): 433.1629 (calcd 433.1624 for MH^+); melting point 210–212 °C.

Compound **8b**: 650 mg, 52%, white solid. ^1H NMR (200 MHz, 25 °C, $CDCl_3$) δ 1.47 (t, *J* = 7 Hz, 6H), 2.36 (s, 6H), 2.89 (s, 6H), 4.47 (q, *J* = 7 Hz, 4H), 6.10 (s, 2H), 8.54 (s, 2H), 8.75 (s, 2H). ^{13}C NMR (50 MHz, 25 °C, $CDCl_3$) δ 13.7, 14.2, 15.4, 61.9, 109.9, 115.4, 117.0, 141.4, 141.8, 150.5, 153.9, 154.0, 164.7. Anal. Calcd for $C_{26}H_{28}N_6O_4$: C, 63.92; H, 5.78; N, 17.20. Found: C, 63.96; H, 5.58; N, 16.86. HRMS-ESI (*m*/*z*): 489.2238 (calcd 489.2250 for MH^+); melting point 248–250 °C.

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