On the Way to Unsymmetrical Terpyridines Carrying Carboxylic Acids

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For the first time an unsymmetrical 2,2'-6'2"-terpyridine carry two carboxylic acids has been prepared using Hantzsch's method for pyridine ring formation and furan as a latent carboxylic group.

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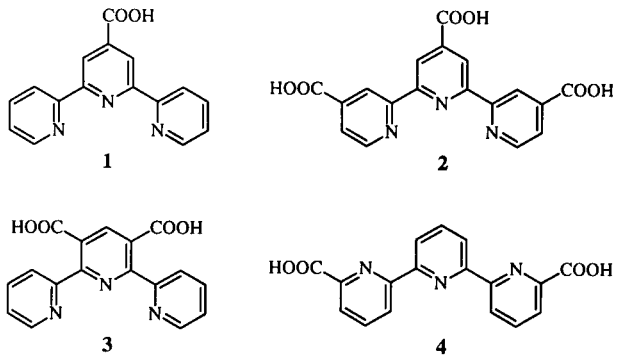
To the best of our knowledge, only four terpyridines carrying carboxylic acids as the only functional group have been prepared, each one being symmetrical (Scheme 1) [1]. This was due to better synthetic accessibility of the symmetrical terpyridines by the well known one-pot method of Hantzsch. This has been used for the preparation of compounds **1-4**. Kröhnke [2] has prepared several unsymmetrical terpyridines but only one carrying two carboxylic acids, starting from pyridinium salts.

Scheme 1



In our investigations to obtain functionalized ligands for both transition metal complexation and anchorage on metal oxide, we had to prepare a particular 2,2'-6',2"-terpyridine carrying *ortho*-dicarboxylic acids which mimics phthalic acid.

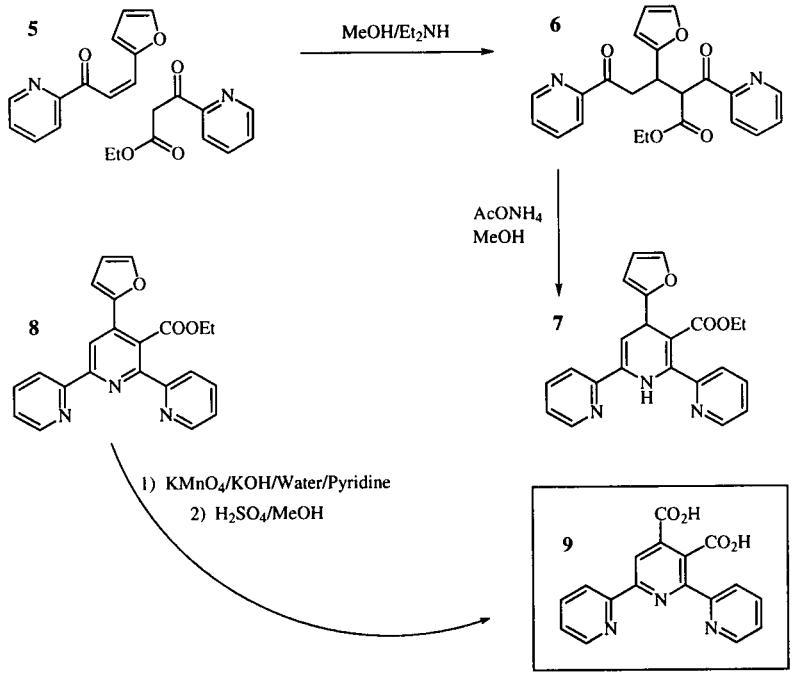
We present here the synthesis of this new ligand from the terpyridine series carrying two carboxylic acids on the same ring. Direct introduction of a carboxylic group at a determined position of a terpyridine was a difficult task. We chose to introduce a furan as a potential carboxylic group, allowing at the same time the formation of the chalcone **5** (Scheme 2) by aldol condensation between furfural and 2-acetylpyridine [3]. This method gave us a quantitative yield of **5** with a *Z*-conformation; other methods [4] gave lower yields and oily products.

1,4-Michael addition of 3-oxo-3-pyridylpropanoic acid ethyl ester to **5** at room temperature in the presence of diethylamine afforded the 1,5-diketone **6** as a yellow oil. ^{1}H nmr shows a complex spectrum due to the presence of two diastereoisomers together with the enol form of the β-oxo-ester. Compound **6** was cyclized with ammonium acetate at room temperature to give a mixture of the expected 1,4-dihydropyridine **7** and a small part of the oxidized compound **8**. Compound **7** could be separated by column chromatography but direct oxidation of the obtained mixture gave only terpyridine **8**. We have chosen to use benzoquinone as a mild oxidizing agent instead of stronger ones like nitrous acid [5] or manganese dioxide [6] which were commonly used for dihydropyridine oxidation, because of side reactions in the case of nitrous acid or adsorption of the compounds in the case of manganese dioxide. Neither air nor oxygen oxidation gave significant results. Oxidation of the furan ring on **8** needed 12 equivalents potassium permanganate in a solution of pyridine-water. Acidification with sulfuric acid precipitated **9** as light yellow crystals in 68% yield. In order to minimize the side reactions in decreasing the amounts of potassium permanganate, we tried first to saponify the ethyl ester on **8** using potassium hydroxide-water-ethanol but even after several days at 100 °C, only traces of saponified product were present. Steric hindrance could be the reason for the failure.

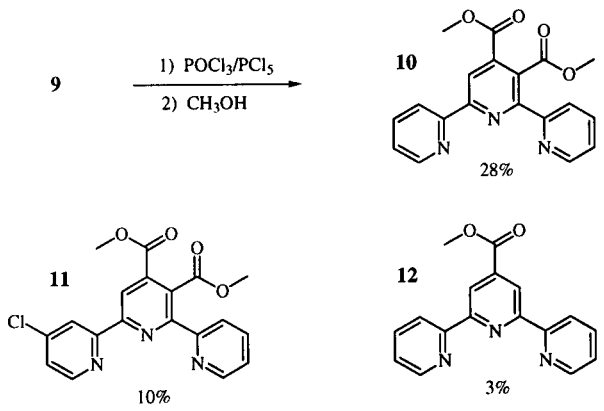
COSY nmr study of **9** shows the presence of an intramolecular hydrogen bond. The 5' hydrogen signal exhibits two singlets in dimethylsulfoxide-d_6, one for the hydrogen-bonded form and one for the non-bonded form. These two singlets collapse into one signal when sodium deuteroxide was added to the sample.

Because of the complexation ability of the two vicinal carboxylic acids, and in particular because we have first to coordinate the terpyridine to the transition metal before linking to metal oxide, we protected them as methyl esters. The acid chloride from **9** was generated using phosphorous oxychloride-phosphorous pentachloride ($POCl_3$-PCl_5) mixture (Scheme 3). The acid chloride treated with methanol gave **10** as major product in low yield. A ring-chlorinated terpyridine **11** and a small part of monodecarboxylated terpyridine **12** were also isolated.

Scheme 2



Scheme 3



EXPERIMENTAL

All melting points were determined on a Reichert hot plate apparatus and were uncorrected. The ^1H and ^{13}C nmr spectra were recorded either on a Bruker AC-250, Bruker AC-200 or Bruker AC-400 instrument in deuteriochloroform or in hexadeuteriodimethylsulfoxide, as specified below. Mass spectra were obtained using electrospray technique on a VG BIOQ with a triple quadripole. Microanalyses were performed on a Carlo Erba 1106 elemental microanalyser.

1-(2-Pyridyl)-3-(2-furyl)-prop-2-ene-1-one (**5**).

In a round bottom flask at 0 °C under nitrogen, 12.1 g (0.1 mole) of 2-acetylpyridine, 20 mL of methanol and 9.69 g (0.1 mole) of freshly distilled furfural were stirred together, then 10 drops of a 15% sodium hydroxide solution were added. After 2 hours, 10 mL of water was added dropwise, and stirring was continued for 2 hours until crystallization occurs. Then 10 mL of water was added over 1 hour. The precipitate was filtered, washed with water and dried under vacuum over diphosphorous pentoxide, yielding 19.9 g (≅100%) of yellow crystals, mp = 54 °C (lit = 52-54 °C). Further recrystallization in ethyl alcohol didn't improve purity. The ^1H nmr (250 MHz, deuteriochloroform): δ 6.50-6.52 (1H, dd, J = 1.7, 3.4), 6.76-6.78 (1H, d, J = 3.4), 7.45-7.50 (1H, ddd, J = 1.1, 4.9, 7.4), 7.54 (1H, d, J = 1.7), 7.66-7.73 (1H, d, J = 15.8), 7.83-7.90 (1H, ddd, J = 1.6, 3.7, 7.7), 8.10-8.18 (1H, d, J = 15.8), 8.15-8.18 (1H, d, J = 7.7), 8.73-8.75 (1H, dd, J = 1.4, 3.7).

Anal. Calcd. for $C_{12}H_9NO_2$: C, 72.35; H, 4.55; N, 7.03. Found: C, 72.05; H, 4.70; N, 6.92.

Ethyl 2-(2-Pyridoyl)-3-(2-furyl)-5-oxo-5-(2-pyridyl)pentanoate (**6**).

A mixture of 15.5 g (0.08 mole) of ethyl 3-oxo-3-(2-pyridyl)propionate, 16.0 g (0.08 mole) of **5**, 5 mL of methanol and 2 mL of diethylamine were mixed and allowed to stand at room temperature for 2 days. Solvents and light products were removed under reduced pressure, yielding 31.5 g of crude **6** as an orange oil. For an analytical sample, 0.5 g of this oil was filtered over silica gel, eluent: dichloromethane-Light petroleum-methanol = 2:7:1 to yield 0.3 g (60%) of pure **6**. The ^1H nmr (250 MHz, deuteriochloroform): δ 8.66-8.62 (2H, m), 8.04-7.95 (2H, m), 7.88-7.75 (2H, m), 7.26 (1H, d), 7.16 (1H, d), 6.20-6.00

(2H, m), 5.37-5.27 (1H, 2d, J = 8.1, 7.5), 4.55 (1H, m), 4.24-3.92 (4H, m), 3.81-3.55 (1H, ddd, J = 4.6, 18.2, 44.3), 1.24-1.00 (3H, td, J = 7.1, 19.8).

*Anal.*Calcd. for $C_{22}H_{20}N_2O_5$: C, 68.33; H, 5.14; N, 7.14. Found: C, 68.15; H, 5.25; N, 7.22.

1',4'-Dihydro-3'-ethoxycarbonyl-4'-(2-furyl)-2,2'-6',2"-terpyridine (**7**).

A solution of 31.0 g (0.08 mole) of crude **6**, in 240 mL ethanol and 8.6 g (1.12 moles) ammonium acetate were stirred in a round bottom flask under nitrogen until completion of the reaction (approximately 5 hours). The resulting mixture was filtered, the residue was washed with dichloromethane and the combined organic phases were evaporated. The residue was extracted with dichloromethane, washed with water, brine, and dried over anhydrous sodium sulfate. The solvent was removed, yielding 31.0 g (96%) of a brown oil containing 95% of **7** and 5% of **8** by ^{1}H nmr. The crude product was used rapidly for the next step due to the instability of **7**. Filtration over silica gel of 0.5 g of the previous oil with ammonium hydroxide-methanol-chloroform = 0.5-5-48 gave 0.1 g (25%) of a pure analytical sample. The ^{1}H nmr (250 MHz, deuteriochloroform): δ 8.72-8.70 (1H, d, J = 4.8), 8.50-8.48 (1H, d, J = 4.7), 8.36 (1H, s), 7.72-7.69 (1H, d, J = 7.8), 7.68-7.66 (2H, d, J = 3.5), 7.57-7.54 (1H, d, J = 7.8), 7.33 (2H, m), 7.21 (1H, dd, J = 4.8, 8.6), 6.30 (1H, s), 6.17-6.16 (1H, d, J = 3.0), 5.80-5.78 (1H, d, J = 6.0), 5.04-5.02 (1H, d, J = 6.0), 3.98-3.89 (2H, q, J = 7.1), 0.96-0.91 (3H, t, J = 7.1).

Anal. Calcd. for $C_{22}H_{19}N_3O_3$: C, 70.76; H, 5.13; N, 11.25. Found: C, 70.98; H, 5.25; N, 11.15.

3'-Ethoxycarbonyl-4'-(2-furyl)-2,2'-6',2"-terpyridine (**8**).

A solution of 28.2 g of crude **7** in 250 mL dichloromethane, was added 8.65 g (0.08 mole) of benzoquinone.The suspension was allowed to stand for a few minutes and then filtered. The filtrate was evaporated under reduced pressure to yield 25 g (87%) of **8**. Recrystallization from methanol affords 22 g (77%) of colorless crystals, mp = 142-144 °C. The ^{1}H nmr (250 MHz, deuteriochloroform): δ 8.80 (1H, s), 8.74-8.72 (1H, d, J = 4.4), 8.60-8.57 (2H, d, J = 7.8), 8.49-8.46 (1H, d, J = 7.9), 7.89-7.83 (1H, t, J = 7.8), 7.88-7.82 (1H, t, J = 7.9), 7.58 (1H, d, J = 1.5), 7.38-7.29 (2H, m), 7.01-6.99 (1H, d, J = 3.5), 6.55-6.53 (1H, dd, J = 2.2, 3.8), 4.49-4.40 (2H, q, J = 7.1), 1.35-1.29 (3H, t, J = 7.1).

Anal. Calcd. for $C_{22}H_{17}N_3O_3$: C, 71.15; H, 4.61; N, 11.32. Found: C, 71.35; H, 4.70; N, 11.55.

2,2'-6',2"-Terpyridine-3',4'-dicarboxylic Acid (**9**).

To 0.04 mole of **8** dissolved in 300 mL of pyridine and 300 mL of water, 80 g (0.51 mole) of potassium permanganate was carefully added by portions of 10 g. The brown-violet solution was stirred 24 hours at room temperature, then 100 g of filteraid was added. The suspension was filtered and washed several times with boiling water. Water was evaporated and the resulting crystalline mass was dissolved in the minimum of ethanol. Sulfuric acid (10%) was added until *p*H = 3-4. The solution was extracted with chloroform, washed with brine and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the product was recrystallized from methanol to give 8.7 g (68%) of **9** as yellow crystals, mp = 213-217 °C (dec). The ^{1}H nmr (400 MHz, deuteriochloroform): δ 8.81-8.79 (1H, d, J = 9.8), 8.72-8.70 (1H, d, J = 8.1), 8.67-8.65 (1H, d, J = 4.9), 8.63-8.59 (1H, dd, J = 5.5, 8.1), 8.36-8.33 (1H, dd, J = 3.5, 8.1), 8.17-8.12 (1H, td, J = 1.6, 8.1), 8.10, 8.05 (1H, td, J = 1.6, 8.1), 7.66-7.61 (1H, dd, J = 6.5, 13.0), 7.58-7.54 (1H, dd, J = 4.9, 8.1). ms: 348 ($M+OH^-$, 60%), 320 ($M-H^-$, 45%), 304 ($M-OH^-$, 11%), 276 ($M-CO_2-H^-$, 100%), 232 ($M-2CO_2-H^-$, 90%).

Anal. Calcd. for $C_{17}H_{11}N_3O_4$: C, 63.55; H, 3.45; N, 13.08. Found: C, 63.65; H, 3.28; N, 13.10.

2,2'-6',2"-Terpyridine-3',4'-dicarboxylic Acid Disodium Salt.

The ^{1}H nmr (400 MHz, deuteriochloroform): δ 8.66-8.64 (1H, d, J = 4.5), 8.57-8.55 (1H, d, J = 4.5), 8.45 (1H, s), 8.38-8.35 (1H, d, J = 8.0), 8.00-7.97 (1H, d, J = 8.0), 7.93-7.87 (1H, dd, J = 1.6, 8.0), 7.85-7.81 (1H, dd, J = 1.6, 8.1), 7.44-7.37 (1H, dd, J = 5.1, 7.1), 7.33-7.27 (1H, dd, J = 5.1, 6.4).

2,2'-6',2"-Terpyridine-3',4'-dicarboxylic Acid Dimethyl Ester (**10**).

To a solution of 0.01 mole of **9** in 25 mL of phosphorous oxychloride ($POCL_3$) was added 4.16 g (0.02 mole) of phosphorous pentachloride (PCl_5). The solution was refluxed for 1.5 hours and cooled. Excess of reagents was removed under reduced presure. The flask was cooled to 0 °C and 100 mL methanol was added. The solution was brought to reflux for 0.5 hour and the methanol was distilled under reduced presure. The residue was extracted with 150 mL of ethyl acetate, washed with 100 mL of water then with a solution of sodium carbonate. The organic phase was dried with anhydrous sodium sulfate. The solvent was removed and the crude solid was filtered over silica gel using first dichloromethane as eluent then dichloromethane-diethyl ether. The first compound released was **11**; 375 mg, (1 mmole), 10%, then **10**; 980 mg, (2.8 mmoles), 28% and **12**; 88 mg, (0.3 mmole), 3%. The ^{1}H nmr (200 MHz, deuteriochloroform): δ 8.94 (3'-H, s), 8.78-8.72 (6"-H, ddd, J = 4.9, 1.7, 1.0), 8.66-8.61 (6'-H, ddd, J = 4.9, 1.7, 1.0), 8.61-8.56 (3"-H, td, J = 7.9, 1.0), 8.48-8.43 (3-H, td, J = 7.9, 1.0), 7.92-7.83 (4"-H, td, J = 7.9, 1.7), 7.91-7.82 (4-H, td, J = 7.9, 1.7), 7.42-7.35 (5"-H, ddd, J = 7.9, 4.9, 1.2), 7.38-7.31 (5-H, ddd, J = 7.9, 4.9, 1.2), 3.99 (4'-CH_3, s), 3.97 (5'-CH_3, s); ms: 349 ($M^{+\bullet}$, 15%), 334 ($M-CH_3^+$, 30%), 318 ($M-OCH_3^+$, 100%), 304 ($M-C_2H6O^+$, 4%, (anhydride)), 290 ($M-CO_2CH_3^+$, 5%), 259 ($M-C_2H_6O_3^+$, 6%), 233 ($M-C_4H_6O_4^+$, 33%, (2,2'-6',2"-terpyridine)), 78 (pyridine-H^+, 35%).

Anal. Calcd. for $C_{19}H_{15}N_3O_4$: C, 65.32; H, 4.33; N, 12.03. Found: C, 65.60; H, 4.20; N, 11.90.

4-Chloro-2,2'-6',2"-Terpyridine-4',5'-dicarboxylic Acid Dimethyl Ester (**11**).

The ^{1}H nmr (200 MHz, deuteriochloroform): δ 8.98 (3'-H, s), 8.77-8.73 (6"-H, ddd, J = 5.7, 1.7, 1.0), 8.61-8.56 (3"-H, td, J = 7.9, 1.0), 8.55-8.52 (6-H, dd, J = 5.2, 0.5), 8.47-8.46 (3-H, J = 2.1, 0.5), 7.95-7.85 (4"-H, td, J = 7.9, 1.7), 7.49-7.37 (5"-H, ddd, J = 7.8, 4.8, 1.1), 7.38-7.34 (5-H, dd, J = 5.2, 2.1), 3.99 (4'-CH_3, s), 3.96 (5'-CH_3, s); ms: 383 ($M^{+\bullet}$, 10%), 368 ($M-CH_3^+$, 14%), 352 ($M-OCH_3^+$, 100%), 338 ($M-C_2H_6O^+$, 2%, (anhydride)), 324 ($M-CO_2CH_3^+$, 2%), 293 ($M-C_2H_6O_3^+$, 4%), 267 ($M-C_4H_6O_4^+$, 26%, (4-chloro-2,2'-6',2"-terpyridine)), 112 (4-chloro-pyridine-H^+, 11%), 78 (pyridine-H^+, 26%).

Anal. Calcd. for $C_{19}H_{14}ClN_3O_4$: C, 59.45; H, 3.67; N, 10.95. Found: C, 59.35; H, 3.70; N, 11.05.

2,2'-6',2"-Terpyridine-4'-carboxylic Acid Methyl Ester (**12**).

The ^{1}H nmr (250 MHz, deuteriochloroform): δ 8.98 (3'-H + 5'-H, s), 8.76-8.74 (6-H + 6"-H, d, J = 4.1), 8.64-8.61 (3-H + 3"-H, d,

J = 7.8), 7.91-7.85 (4-H + 4"-H, td, J = 7.8, 1.1), 7.39-7.34 (5-H + 5"-H, dd, J = 7.8, 4.1, 1.1), 4.01 (4'-CH_3, s); ms: 291 ($M^{+\bullet}$, 10%), 276 (M-CH_3^+, 14%), 260 (M-OCH_3^+, 100%), 232 (M-$CO_2CH_3^+$, 26%, (2,2'-6',2"-terpyridine)), 78 (pyridine-H^+, 26%).

Anal. Calcd. for $C_{17}H_{13}N_3O_2$: C, 70.09; H, 4.50; N, 14.43. Found: C, 69.95; H, 4.65; N, 14.68.

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