Synthesis of Unsymmetrical, Monosubstituted Bis-terpyridine Derivatives via Suzuki–Miyaura Cross-Coupling

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Abstract: As building blocks for metallo-supramolecular polymers, novel, unsymmetrical, monosubstituted bis-terpyridine derivatives with one electron-donating (OMe) or electron-withdrawing (CN or COOMe) group have been synthesized via the Suzuki–Miyaura cross-coupling reaction. This method is quick, efficient and suitable for the introduction of various substituents at the periphery of pyridine.

Key words: terpyridines, bis-terpyridines, oxidation, borylation, Suzuki–Miyaura cross-coupling

Metallo-supramolecular polymers have become of increasing interest over the last few decades for constructing macromolecular assembles and devices.[1] Many researchers have paid more attention to ditopic bis-terpyridines as organic ligands of the polymers for their structural advantages. This type of ligand is generally chemically and thermally stable, and has very high binding affinity towards a large variety of transition metal ions by forming octahedral coordination geometries.[2] The metallo-supramolecular polymers, which are prepared by complexation of the ligands with metal ions, have potential applications, such as in energy and information storage, chemical reactions and biorecognition.[3]

We have reported symmetrical bis-terpyridine derivatives with methoxy, methyl, cyano or bromo groups at the 6-position of the pyridine rings, or without substituents,[4,5] as well as unsymmetrical bis-terpyridines with two methoxy or cyano groups at one terpyridine moiety,[4a] which were prepared using the Kröhnke method and cross-coupling reactions.

Complexation of monosubstituted bis-terpyridines with two kinds of metal ions has the possibility to lead to the alternative introduction of the two metal ions in the metallo-supramolecular polymers, which are expected to show unique electronic properties. In particular, modification at the 6-position of pyridine is important, because it is close to the metal binding center. This will strongly influence the binding ability of the terpyridine moiety in the complexation.

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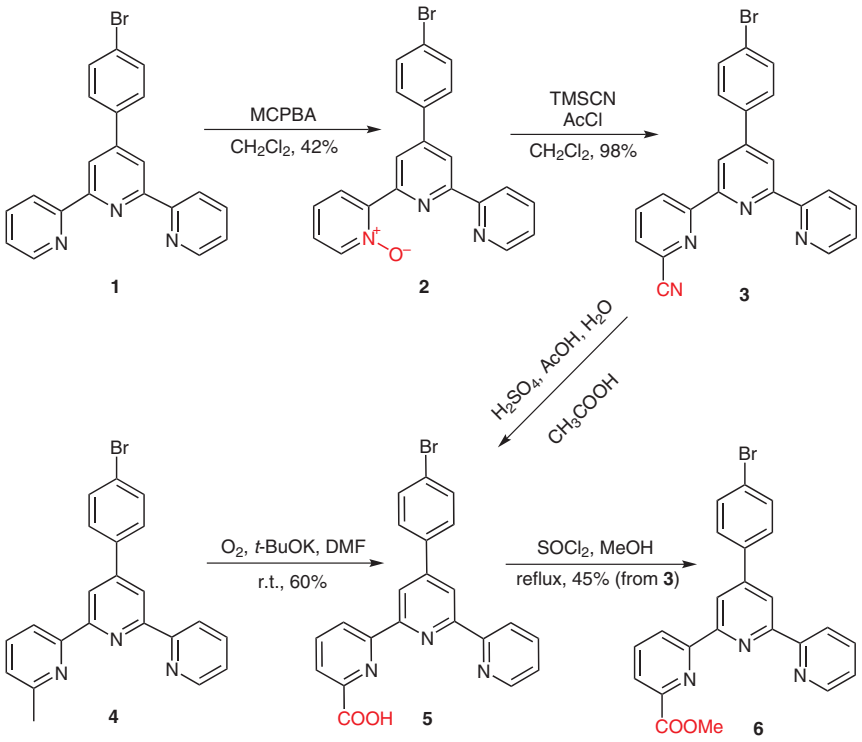
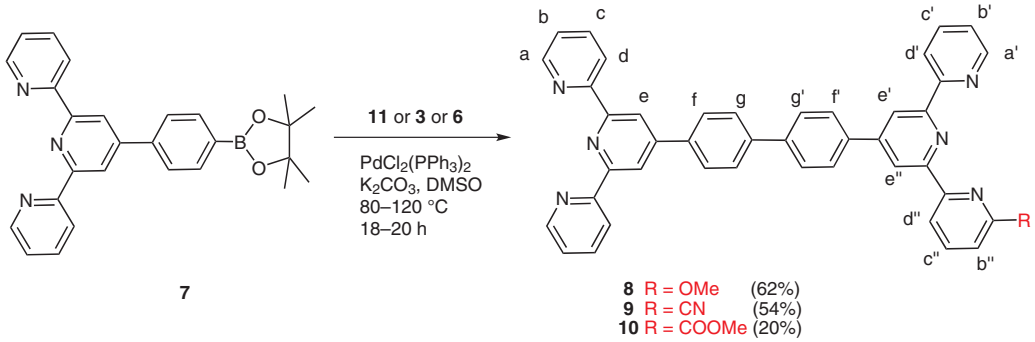
In this contribution, we present the design and synthesis of novel, unsymmetrical, monosubstituted bis-terpyridine derivatives with one electron-donating (OMe) or electron-withdrawing (CN or COOMe) group at the 6-position of the pyridine ring. The synthetic method is quick, efficient and suitable for the introduction of various substituents at the periphery of pyridine. In general, monosubstituted ligands are extremely difficult to synthesize and purify due to poor solubility, high polarity and instability. Our rationale for synthesizing this kind of unique ligand is to explore the synthesis and application of hetero-metallo-supramolecular polymers containing different metal ions.

The preparation of mono-terpyridine derivatives **1** and **4** followed the modified Kröhnke method.[4a,5] We have constructed two kinds of functionalized systems to modify the periphery of the terpyridine, by using electron-donating (OMe) group modification and electron-withdrawing (CN or COOMe) group modification. Thus, for further functionalization, terpyridine **1** was oxidized with *m*-chloroperoxybenzoic acid to provide the mono-*N*-oxide **2** in 42% yield (Scheme 1).[6a] The resulting oxide **2** was then subjected to a Reissert–Henze-type reaction to produce the 6-carbonitrile **3**.[6b] Oxidation of terpyridine **4** with molecular oxygen in the presence of potassium *tert*-butoxide afforded the 6-carboxylic acid **5** in 60% yield.[7] Hydrolysis of terpyridine **3** under strong acid conditions can also produce carboxylic acid **5**, which is then transformed to ester **6**.[6b] The corresponding methoxy-substituted terpyridine [4′-(4-bromophenyl)-6-methoxy-2,2′:6′,2″-terpyridine (**11**)] was prepared according to the literature method.[4a]

We then focused on a Suzuki–Miyaura cross-coupling strategy for the preparation of unsymmetrical, monosubstituted bis-terpyridines with a methoxy, cyano or methoxycarbonyl group. The Miyaura–Ishiyama borylation reaction between terpyridine **1** and bis(pinacolato)diboron with catalyst $[PdCl_2(PPh_3)_2]$ afforded boronic ester **7** without the homocoupled byproduct, the symmetrical bis-terpyridine (Scheme 2).[4a,8] In this process, potassium acetate is the most suitable base because stronger bases (such as K_3PO_4 and K_2CO_3) afford the symmetrical bis-terpyridine. Then, preparative HPLC was used to obtain pure ligand **7**. Using Suzuki–Miyaura cross-coupling, the desired unsymmetrical bis-terpyridines **8**–**10** with one electron-donating (OMe) or electron-withdrawing (CN or COOMe) group were formed (Scheme 2). It is very im-



Scheme 1 Synthesis of the 2,2′:6′,2″-terpyridine derivatives



Scheme 2 Synthesis of the unsymmetrical, monosubstituted bis-terpyridine derivatives

portant to avoid the formation of homocoupled byproduct, which has a similar high polarity as the desired ligand and is very difficult to remove.

New ligands **2**, **3**, **5**, **6** and **8** are readily soluble in common organic solvents (such as CH_2Cl_2, $CHCl_3$, THF and DMSO) which allowed us to conveniently obtain their ^1H, ^{13}C and 2D-COSY NMR spectra, and MALDI-TOFMS and HRMS data. In contrast, new ligands **9** and **10** show relatively low solubility in common organic solvents.

In summary, we have synthesized novel, rigid, conjugated, unsymmetrical, monosubstituted bis-terpyridine derivatives via Suzuki–Miyaura cross-coupling as the key reaction. This method is quick and efficient. It should be possible to synthesize versatile bis-terpyridines with different functional groups, such as esters and amides, by using the monosubstituted bis-terpyridine derivatives as starting materials. The design and synthesis of coordination polymers with unsymmetrical bis-terpyridines and different metal ions are in progress.

^1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ on a JEOL AL 300/BZ spectrometer operating at 300 and 75 MHz, respectively. Chemical shifts are reported in ppm downfield from $SiMe_4$ as an internal standard. High-resolution mass spectra (HRMS) were recorded on a Micromass LCT-LCMS-IT-TOF mass spectrometer. MALDI-MS data were recorded on a Shimadzu/Kratos TOF mass spectrometer using AXIMA-CRF.

4′-(4-Bromophenyl)-2,2′:6′,2″-terpyridine Mono-*N*-oxide (2)

To 4′-(4-bromophenyl)-2,2′:6′,2″-terpyridine (**1**; 1.02 g, 2.62 mmol) in CH_2Cl_2 (26 mL) was added a soln of 70% MCPBA (647 mg, 2.62 mmol) in CH_2Cl_2 (26 mL), and the mixture was allowed to stir at r.t. overnight. Then, the mixture was washed with 5% Na_2CO_3 soln (50 mL) and dried ($MgSO_4$). The solvent was evaporated and the residue was purified by column chromatography on activated basic alumina (CH_2Cl_2, then EtOAc) to give a white solid; yield: 448 mg (42%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.30 (d, *J* = 1.7 Hz, 1 H), 8.73 (m, 2 H), 8.54 (dd, *J* = 1.1, 0.9 Hz, 1 H), 8.44 (dd, *J* = 2.2, 2.2 Hz, 1 H), 8.36 (d, *J* = 6.6 Hz, 1 H), 7.86 (ddd, *J* = 1.8, 1.9, 1.8 Hz, 1 H), 7.75 (dd, *J* = 2.2, 2.2 Hz, 2 H), 7.63 (dd, *J* = 2.2, 1.7 Hz, 2 H), 7.38 (m, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.30, 155.70, 149.52, 149.22, 148.52, 147.36, 140.87, 137.13, 136.92, 132.16, 129.00, 128.13, 125.66, 125.28, 124.06, 123.65, 123.12, 121.27, 119.16.

MALDI-MS: *m*/*z* (%) = 403.94 (100) [M + H$^+$].

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{15}BrN_3O$: 404.0398; found: 404.0405.

4′-(4-Bromophenyl)-2,2′:6′,2″-terpyridine-6-carbonitrile (3)

To mono-*N*-oxide **2** (750 mg, 1.86 mmol) in CH_2Cl_2 (22 mL) was added TMSCN (256 mg, 2.58 mmol). After the solution had been stirred for 20 min, AcCl (79.5 mg, 0.992 mmol) was added dropwise and stirring was continued for 24 h. Then, the mixture was concentrated to half volume; 10% K_2CO_3 soln (45 mL) was added and the mixture was stirred for 1 h. The precipitate was collected by filtration and washed with H_2O; yield: 752 mg (98%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.91 (dd, *J* = 1.1, 1.1 Hz, 1 H), 8.75 (m, 3 H), 8.62 (dd, *J* = 0.9, 1.1 Hz, 1 H), 8.01 (dd, *J* = 7.7, 7.7 Hz, 1 H), 7.89 (ddd, *J* = 1.8, 1.9, 1.8 Hz, 1 H), 7.73 (m, 5 H), 7.38 (dddd, *J* = 1.1, 1.1, 1.1, 1.1 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.66, 156.40, 155.67, 154.01, 149.48, 149.28, 137.87, 137.00, 136.94, 133.29, 132.30, 128.87, 128.28, 124.47, 124.14, 123.84, 121.29, 119.60, 119.02, 117.40.

MALDI-MS: *m*/*z* (%) = 412.03 (100) [M$^+$].

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{14}BrN_4$: 413.0402; found: 413.0422.

4′-(4-Bromophenyl)-2,2′:6′,2″-terpyridine-6-carboxylic Acid (5)

A two-neck flask fitted with a stirrer bar and an oxygen gas inlet and outlet was charged with terpyridine **4** (76.7 mg, 0.19 mmol) and anhyd DMF (0.57 mL). A soln of *t*-BuOK (53.3 mg, 0.48 mmol) in DMF (1.9 mL) was added dropwise and the yellow mixture was stirred at r.t. for 1 h. Oxygen was then bubbled into the reaction mixture for 6 h and the resulting mixture was poured onto ice, diluted with H_2O (50 mL), neutralized with 0.1 mM HCl and extracted with $CHCl_3$ (5 × 30 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The solid was washed with EtOAc and cystallized in $CHCl_3$ to give white **5**; yield: 50.3 mg (60%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.88 (dd, *J* = 1.1, 1.3 Hz, 2 H), 8.71 (m, 3 H), 8.21 (m, 2 H), 8.03 (ddd, *J* = 1.5, 1.7, 1.8 Hz, 1 H), 7.92 (d, *J* = 8.4 Hz, 2 H), 7.80 (d, *J* = 8.4 Hz, 2 H), 7.53 (dd, *J* = 7.7, 7.7 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.70, 155.69, 154.79, 154.76, 154.61, 149.23, 148.37, 147.73, 138.82, 137.33, 136.53, 132.16, 129.03, 124.93, 124.50, 124.10, 123.01, 120.87, 118.32, 118.12, 79.08.

MALDI-MS: *m*/*z* (%) = 431.03 (100) [M$^+$].

HRMS: *m*/*z* [M – H]$^+$ calcd for $C_{22}H_{13}BrN_3O_2$: 430.0191; found: 430.0188.

Methyl 4′-(4-Bromophenyl)-2,2′:6′,2″-terpyridine-6-carboxylate (6)

A mixture of terpyridine **3** (174 mg, 0.42 mmol), concd H_2SO_4 (1.89 mL), AcOH (1.89 mL) and H_2O (0.42 mL) was stirred at 90–100 °C for 24 h, then the solution was added to ice water (16 mL). The precipitate was collected by filtration, washed with H_2O and MeCN, and dried in vacuo. To cooled (ice water bath) MeOH (12 mL) was added dropwise $SOCl_2$ (504 mg). The solution was stirred at r.t. for 15 min, then the above precipitate was added and the mixture was refluxed for 24 h. After concentration, $CHCl_3$ (21 mL) was added, and the solution was washed with 5% $NaHCO_3$ soln (50 mL) and dried (Na_2SO_4). The solvent was evaporated, and the residue was purified by silica gel column chromatography (CH_2Cl_2–MeOH, 99:1), then recrystallized (toluene); yield: 84.1 mg (45%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.86 (dd, *J* = 1.1, 1.1 Hz, 1 H), 8.75 (m, 3 H), 8.65 (dd, *J* = 0.9, 0.9 Hz, 1 H), 8.19 (dd, *J* = 1.1, 1.1 Hz, 1 H), 8.03 (dd, *J* = 7.9, 7.7 Hz, 1 H), 7.89 (ddd, *J* = 1.8, 1.8, 1.8 Hz, 1 H), 7.77 (dd, *J* = 2.0, 2.4 Hz, 2 H), 7.66 (dd, *J* = 2.0, 2.0 Hz, 2 H), 7.37 (dddd, *J* = 1.1, 1.3, 1.1, 1.1 Hz, 1 H), 4.06 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.83, 156.45, 156.19, 155.94, 155.25, 149.32, 149.18, 147.68, 137.75, 137.42, 136.82, 132.13, 128.95, 125.09, 124.54, 123.93, 123.54, 121.31, 119.13, 52.74.

MALDI-MS: *m*/*z* (%) = 445.04 (100) [M$^+$].

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{17}BrN_3O_2$: 446.0504; found: 446.0508.

Monosubstituted Bis-terpyridines 8–10; General Procedure

A reaction vessel was charged with boronic ester **7** (0.301 mmol), K_2CO_3 (125 mg, 0.903 mmol), terpyridine **3** or **6** or the corresponding methoxy derivative **11** (0.301 mmol), and $PdCl_2(PPh_3)_2$ (5 mol%), then DMSO (9 mL) was added. The mixture was then heated at 80–120 °C for 18–20 h. The catalyst was removed by filtration and washed with $CHCl_3$ and H_2O. The separated organic layer was concentrated and purified by silica gel column chromatography (EtOAc–MeOH, 1:1) and recycling preparative HPLC to give **8**–**10**.

6-Methoxy-4′-[4′-(2,2′:6′,2″-terpyridin-4′-yl)-1,1′-biphenyl-4-yl]-2,2′:6′,2″-terpyridine (8)

Yield: 120 mg (62%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.82 (s, 2 H, H^e), 8.76 (m, 5 H, H$^{e',e'',a,a'}$), 8.70 (d, *J* = 7.9 Hz, 3 H, H$^{d,d'}$), 8.30 (d, *J* = 7.3 Hz, 1 H, H$^{d''}$), 8.05 (dd, *J* = 8.3, 8.4 Hz, 4 H, H$^{g,g'}$), 7.84 (m, 8 H, H$^{c,c',f,f',c''}$), 7.37 (m, 3 H, H$^{b,b'}$), 6.84 (d, *J* = 8.3 Hz, 1 H, H$^{b''}$), 4.12 (s, 3 H, OMe).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.59, 156.34, 156.27, 156.03, 155.98, 155.95, 153.62, 149.68, 149.57, 149.17, 149.13, 141.02, 141.00, 139.36, 138.04, 137.70, 136.88, 127.86, 127.83, 127.78, 127.67, 127.58, 123.85, 123.82, 121.43, 121.40, 118.72, 118.61, 114.07, 111.18, 53.35.

MALDI-MS: *m*/*z* (%) = 646.97 (100) [M + H]$^+$.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{43}H_{31}N_6O$: 647.2559; found: 647.2568.

4′-[4′-(2,2′:6′,2″-Terpyridin-4′-yl)-1,1′-biphenyl-4-yl]-2,2′:6′,2″-terpyridine-6-carbonitrile (9)

Yield: 104 mg (54%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.91 (d, *J* = 8.1 Hz, 1 H, H$^{d''}$), 8.87 (d, *J* = 1.5 Hz, 1 H, H$^{e''}$), 8.83 (m, 3 H, H$^{e,e'}$), 8.75 (m, 3 H, H$^{a,a'}$), 8.69 (d, *J* = 7.9 Hz, 2 H, H^d), 8.63 (d, *J* = 8.1 Hz, 1 H, H$^{d'}$), 8.02 (m, 5 H, H$^{g,g',c''}$), 7.87 (m, 7 H, H$^{f,f',c,c'}$), 7.74 (d, *J* = 7.7 Hz, 1 H, H$^{b''}$), 7.36 (m, 3 H, H$^{b,b'}$).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.06, 156.50, 156.20, 156.07, 154.05, 150.22, 149.35, 149.23, 141.51, 141.04, 138.00, 137.77, 137.39, 136.78, 133.49, 128.15, 128.14, 127.91, 127.85, 127.81, 127.67, 124.48, 123.98, 123.77, 121.41, 121.31, 120.24, 119.86, 119.26, 118.85.

MALDI-MS: *m*/*z* (%) = 641.23 (100) [M$^+$].

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{43}H_{28}N_7$: 642.2406; found: 642.2397.

Methyl 4′-[4′-(2,2′:6′,2″-Terpyridin-4′-yl)-1,1′-biphenyl-4-yl]-2,2′:6′,2″-terpyridine-6-carboxylate (10)
Yield: 40.6 mg (20%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.88 (m, 2 H, $H^{d'',e''}$), 8.83 (m, 3 H, $H^{e,e'}$), 8.76 (d, *J* = 3.1 Hz, 3 H, $H^{a,a'}$), 8.69 (dd, *J* = 7.9, 5.9 Hz, 3 H, $H^{d,d'}$), 8.20 (dd, *J* = 0.9, 0.9 Hz, 1 H, $H^{b''}$), 8.04 (m, 5 H, $H^{g,g',c''}$), 7.87 (m, 7 H, $H^{f,f',c,c'}$), 7.37 (m, 3 H, $H^{b,b'}$), 4.08 (s, 3 H, COOMe).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.96, 156.75, 156.48, 156.29, 156.17, 155.30, 150.06, 149.75, 149.25, 149.21, 147.85, 141.20, 141.11, 137.88, 137.78, 137.70, 136.78, 127.93, 127.86, 127.63, 125.01, 124.56, 123.84, 123.75, 121.70, 121.40, 121.36, 119.38, 119.35, 118.82, 52.70.

MALDI-MS: *m*/*z* (%) = 674.24 (100) [M^+].

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{44}H_{30}N_6NaO_2$: 697.2321; found: 697.2328.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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