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Synthesis of bisfunctionalized-oligopyridines bearing an ester group

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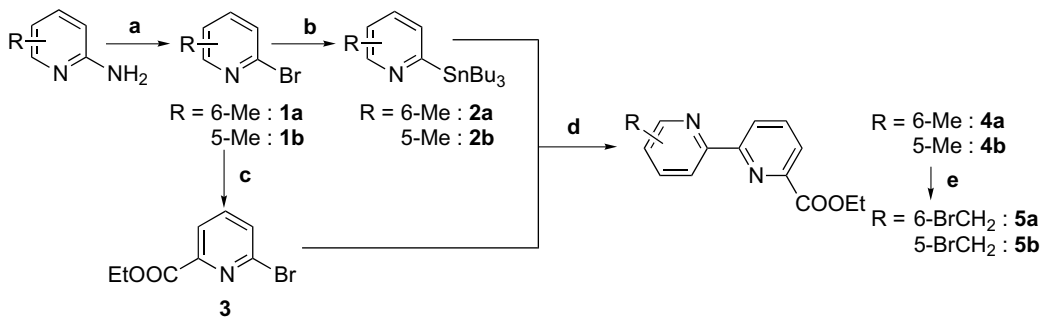
Abstract—The synthesis of 2,2′-bipyridine, 1,10-phenantroline and 2,2′:6′,2″-terpyridine substituted by an ethylester function is described. The 5- and 6-methyl-2,2′-bipyridines bearing an ethylester group on the 6′ position as well as the ethyl 6,6″-dimethyl-2,2′:6′,2″-terpyridine-4′-carboxylate moiety were synthesized via a Stille cross-coupling reaction, starting from bromo-picoline building blocks. A radical bromination of the methyl-oligopyridine gave selectively the corresponding benzylic bromide derivatives in fair yield.

The quest for highly long-lived luminescence lanthanide complexes has generated a great deal of interest among chemists since the middle of the 1980s.[1] The 2,2′-bipyridine chelate has been rapidly found to be one of the most suitable chromophores for the relayed excitation of the metallic center. Unfortunately, the bipyridine unit is a poor complexant for lanthanide(III) ions and does not lead to stable and soluble complexes in aqueous solution. Association of a bipyridine core with an anionic functionality forms a tridentate ligand, which should give an efficient coordination of lanthanide salts. It has been recently demonstrated by Ziessel and co-workers,[2–4] that a very efficient coordination ability, as well as high luminescence quantum yield of the corresponding Eu(III) complexes, could be obtained with bipyridine sub-units bearing a carboxylic group on the 6 position of the 2,2′-bipyridine. In addition, the association of three of these new tritopic sub-units on a molecular platform, led to a highly favorable nine-coordination site cavity for lanthanide(III) cations.[4] These authors were able to obtain this coordination motif by a very elegant palladium-catalyzed carbonylation of the corresponding bromo-bipyridine sub-unit, built via a classical Kröhnke synthesis.[3,5]

We now wish to present an alternative way to obtain, in good yields, oligopyridine ligands substituted both by an ester group and a benzylic bromide function allow-



Scheme 1. (a) HBr, $NaNO_2$, Br_2, –20°C. (b) i. 1 equiv. **1**, 1 equiv. *n*-BuLi, THF, –78°C; ii. Bu_3SnCl. (c) i. **1a**, CrO_3, H_2SO_4; ii. EtOH, H_2SO_4 cat. (d) 1 equiv. **2**, 1 equiv. **3**, $Pd(PPh_3)_4$, toluene, reflux, 2 days (70% for **4a** and 83% for **4b**). (e) NBS, AIBN, benzene, *hv*, reflux, 3 h (55% for **5a** and 56% for **5b**) or Br_2, benzene/H_2O, *hv*, reflux, 30 min (73% for **5b**).

Keywords: Stille cross-coupling; organotin pyridines; bipyridine; terpyridine; radical bromination.

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ing these molecules to readily react with a large variety of nucleophilic compounds.

The main difficulty for the synthesis of these ligands is related to their unsymmetrical features. To solve this problem, we decided to use a Stille cross-coupling reaction[6] between bromo-pyridine ester and organotin picoline units, followed by a radical bromination.

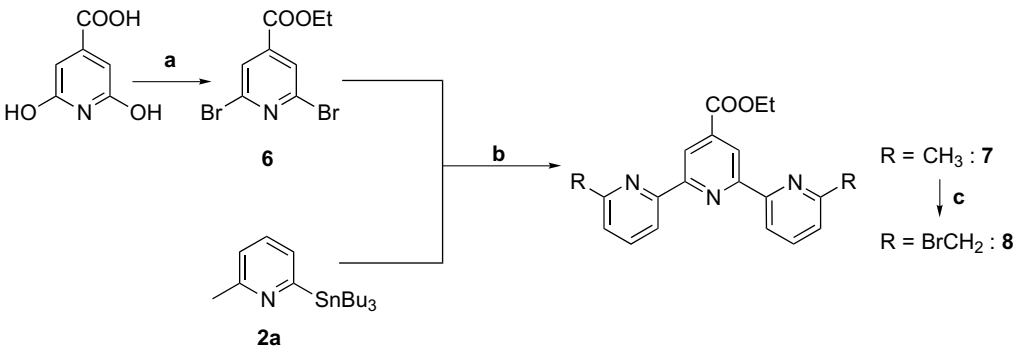
The methodology used for the preparation of organotin derivatives and their subsequent coupling reaction via palladium(0)-catalyzed cross-coupling was inspired from previous studies on the synthesis of 5,5″-bis-functionalized-2,2′:6′,2″-terpyridines[7] and pyridine-based oligotridentate ligands.[8]

We started these multi-step syntheses (Scheme 1) by reacting 2-bromo-6-methyl-pyridine (**1a**)[9] or 2-bromo-5-methyl-pyridine (**1b**)[10] with *n*-BuLi. The resulting organolithium compounds gave the corresponding organotin derivatives (**2a** and **2b**) by reaction with tri-*n*-butyl-tin chloride[8] with a good yield (96 and 82%, respectively).

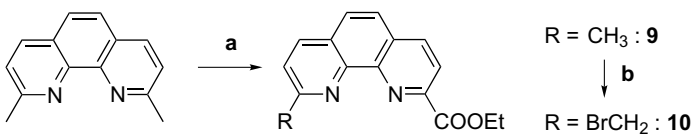
The halogen pyridine–ester building block **3** was obtained by oxidation of **1a** with chromium trioxide in concentrated sulfuric acid, and the corresponding carboxylic acid was further esterified with ethanol under catalytic acid conditions to give **3** (Scheme 1).[11] The bipyridine core, via Stille cross-coupling, was obtained by reacting one equivalent of organotin–picoline (**2a** or **2b**) with one equivalent of ethyl 2-bromo-pyridine-6-carboxylate **3** using a catalytic amount of $[Pd(PPh_3)_4]$ (10% molar) in refluxing toluene during two days (Scheme 1). The two ethyl bipyridine-6-carboxylate **4a** and **4b**† were obtained in respective yields of 70 and 83%.

Using the same catalytic conditions, we were able to prepare a polyfunctional terpyridine. By reacting one equivalent of ethyl 2,6-dibromo-pyridine-4-carboxylate **6**[12] (Scheme 2) and two equivalents of **2a**, we synthesized the symmetrical 6,6″-dimethyl-terpyridine **7**,‡ which possesses an ester function at the central 4′ carbon atom.

A controlled oxidation of neocuproine with selenium dioxide (1.5 equiv.) in pyridine, followed by an acid catalyzed esterification,[13] led to the rigid analog of the bipyridine-6-carboxylate derivatives (Scheme 3).



Scheme 2. (a) i. $POBr_3$, 3 h, 180°C; ii. EtOH, H_2SO_4 cat. (b) 2 equiv. **2a**, 1 equiv. **6**, $Pd(PPh_3)_4$, toluene, reflux, 2 days (44%). (c) NBS, AlBN, benzene, *hv*, reflux, 3 h, 27%.



Scheme 3. (a) i. SeO_2, 1.5 equiv. pyridine, 55°C; ii. EtOH, H_2SO_4, reflux. (b) NBS, AlBN, *hv*, reflux, benzene, 3 h (17%).

† [Ethyl 5′-methyl-2,2′-bipyridine-6-carboxylate (**4b**): mp: 84–85°C; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta=1.46$ (t, 3H, $^3J=7.1$ Hz), 2.39 (s, 3H), 3H), 4.49 (q, 2H, $^3J=7.1$ Hz), 7.64 (ddd, 1H, $^3J=8.1$ Hz $^4J=2.1$ Hz $^5J=0.7$ Hz), 7.92 (t, 1H, $^3J=7.8$ Hz), 8.09 (dd, 1H, $^3J=7.7$ Hz $^4J=1.2$ Hz), 8.46 (m, 2H), 8.56 (dd, 1H, ^3J 7.9 Hz $^4J=1.2$ Hz). ^{13}C NMR (50 MHz, $CDCl_3$): $\delta=14.2$ (CH_3), 18.3 (CH_3), 61.7 (CH_2O), 121.0 (CH), 123.7 (CH), 124.5 (CH), 133.8 (Cq), 137.4 (CH), 137.6 (CH), 147.6 (Cq), 149.5 (CH), 152.6 (Cq), 156.4 (Cq), 165.2 (C=O). IR (KBr pellets): $\nu=1738$ ($\nu_{C=O}$), 1588, 1556 cm^{-1}. MS (ES$^+$): $m/z=243.17$ (M+H$^+$), 265.15 (M+Na$^+$)].

‡ [Ethyl-6,6″-dimethyl-(2,2′:6′,2′-terpyridine)-4′-carboxylate: mp: 134–135°C; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta=1.47$ (t, 3H, $^3J=7.1$ Hz), 2.67 (s, 6H), 4.50 (q, 2H, $^3J=7.1$ Hz), 7.21 (d, 2H, $^3J=7.6$ Hz), 7.75 (t, 2H, $^3J=7.7$ Hz), 8.40 (d, 2H, $^3J=7.8$ Hz), 8.97 (s, 2H).^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta=14.4$ (CH_3), 24.6 (CH_3), 61.7 (CH_2O), 116.3 (CH), 120.1 (CH), 123.6 (CH), 137.0 (CH), 139.7 (Cq), 154.9 (Cq), 156.8 (Cq), 158.1 (Cq), 165.7 (C=O). IR (KBr): $\nu=1717$ ($\nu_{C=O}$), 1560 cm^{-1}. MS (FAB$^+$, *m*NBA): $m/z=334$ (M+H$^+$). Anal. calcd for $C_{20}H_{19}N_3O_2$: C, 72.05; H, 5.74; N, 12.60; found C, 71.86; H, 5.65; N, 12.39].

Functionalization of the methyl groups of our oligopyridine-esters (**4a**, **4b**, **7** and **9**) was achieved by a radical bromination. This method appears to be appropriate in the present case due to the presence of an ester group on the molecules. To increase the yield and the selectivity of the radical bromination[14] we used NBS, benzene as solvent and a catalytic amount of AIBN, at reflux and under irradiation (halogen-lamp 150 W). Benzene appeared to a better solvent for the mono-bromination of the benzylic methyl group than the classical CCl_4 solvent. Purification of the resulting benzylic bromides is thereby facilitated. In the case of **5b**,[§] a high yield for the radical bromination reaction was obtained by the use of bromine and a biphasic mixture of water and benzene, under irradiation. This method appeared to be very selective; a small amount of α-dibromomethyl derivative is formed (less than 5%). Improvement of the synthesis of bromomethyl oligopyridine derivatives is currently under investigation.[15]

In conclusion, a convenient synthesis of NNCOO–tridentate ligand precursors was developed. These compounds bearing benzylic bromide function on the opposite side of the molecule could be easily attached to various molecular platforms, such as macrocyclic polyamines, calixarenes or sugars, to create specific coordination cavities for target metallic ions.

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