Synthesis of Unsymmetrical 5,5′-Disubstituted 2,2′-Bipyridines[1]

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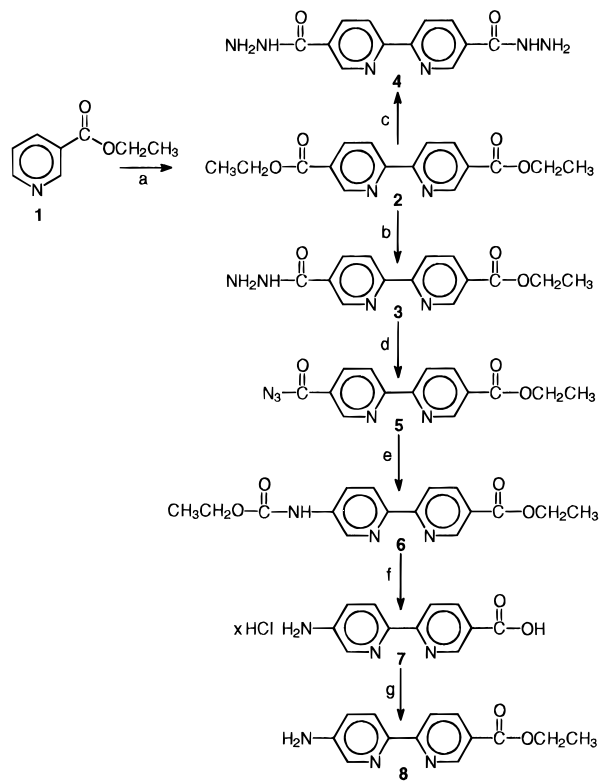
The preparation of unsymmetrical 6,6′-disubstituted 2,2′-bipyridines has generally occurred by the stepwise mono-*N*-oxidation,[2] followed by a Boekelheide-type rearrangement[3] or by a coupling of different pyridine precursors;[4] both procedures are plagued with difficulties. It was, however, demonstrated[5] that, in THF at −60 °C with 1 equiv of butyllithium, 6,6′-bis(hydroxymethyl)-2,2′-bipyridine[2] was transformed to the monoalkoxide, which was trapped as the monomesylate in an overall 96% yield. This procedure takes advantage of the different solubility characteristics of the intermediates vs the starting material; this monolithium alkoxide is insoluble under these specific reaction conditions. Application of this general procedure was used[6] to afford 6-(bromomethyl)-6′-(hydroxymethyl)-2,2′-bipyridine, which was subsequently converted to functionalized oligobipyridines. In that we needed unsymmetrical 5,5′-disubstituted 2,2′-bipyridines for the synthesis of specifically located binding loci within dendrons, we herein describe the use of similar solubility differences of the intermediate(s) to prepare 5′-amino-2,2′-bipyridine-5-carboxylic acid in excellent overall yield from the symmetrical diethyl 2,2′-bipyridine-5,5′-dicarboxylate.

The synthesis of 5,5′-diamino-2,2′-bipyridine from diethyl 2,2′-bipyridine-5,5′-dicarboxylate (**2**) had been previously reported by Whittle.[7] The desired diester **2** was prepared by refluxing neat ethyl nicotinate **1** with palladium on charcoal for 6 days under a partial vacuum; the catalyst and starting ester were removed and recycled (Scheme 1). Diester **2** was isolated in ca. 35% yield on the first cycle, and its simple NMR spectra supported the structure. By taking advantage of the low solubility of carbohydrazides, the exclusive formation of the monocarbohydrazide **3** was achieved by the use of approximately 1.5 equiv of hydrazine and by adjusting either the polarity of the solvent system (ethanol/toluene) or the reaction temperature (80 °C). The monocarbohydrazide **3** precipitated under these conditions and was obtained in 85% yield. Although **3** is nearly insoluble in many organic solvent, its ^{1}H NMR spectrum in DMSO clearly showed two doublets (J = 2 Hz) at δ 9.1 and 9.2 for the two different 6,6′-pyH, respectively, confirming the unsymmetrical substitution pattern. Treatment of **2** with excess hydrazine hydrate under more drastic conditions afforded (100%) the symmetrical dicarbohydrazide **4**, which is insoluble in most common organic solvents.

Scheme 1[a]



[a] Key: (a) 10% Pd/C; (b) 1.5 equiv of $NH_2NH_2 \cdot H_2O$, EtOH, toluene, 80 °C; (c) 2 equiv of $NH_2NH_2 \cdot H_2O$, EtOH, toluene, 115 °C; (d) HCl, 0 °C, aqueous $NaNO_2$; (e) EtOH, xylene, reflux; (f) EtOH, 2.5 N aqueous NaOH, 75 °C; (g) EtOH, concentrated H_2SO_4, reflux.

Reaction of monocarbohydrazide **3** with $NaNO_2$ in concentrated HCl gave (ca. 100%) the corresponding carbazide **5**, whose IR spectrum clearly demonstrates the presence of the characteristic carbazide stretch at 2181 and 2143 cm^{-1} as well as the shift (^{13}C NMR) from δ 163.8 to 171.0 for the carbonyl groups supporting the conversion. Subsequent Curtius rearrangement of carbazide **5** provided (82%) urethane **6**; the ^{13}C NMR for **6** shows the expected upfield shift from δ 171.0 to 153.3 for the urethane moiety. Saponification of **6** afforded (89%) the desired 5′-amino-2,2′-bipyridine-5-carboxylic acid hydrochloride **7** supported by the carbonyl absorption at δ 176.0 and the disappearance of the peak for the urethane carbonyl. The bright yellow salt is soluble in aqueous base but shows only very low solubility in organic solvent other than DMSO.

In order to enhance the solubility characteristics, the amino acid **7** was subjected to Fischer esterification conditions affording the ethyl ester **8**, as a pale yellow solid. The enhanced organic solubility and the appearance of the typical ethyl absorption in the NMR spectra support the assigned structure.

Application of the selective reactivity due to solubility differences has great potential in the preparation of unsymmetrical heterocycles[8] and is being pursued in other *N*-heterocyclic functionalizations.

Experimental Section

General Comments. All melting points were taken in capillary tubes and are uncorrected. The ^{1}H and ^{13}C NMR

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spectra were obtained in $CHCl_3$, unless otherwise stated. All reagents were purchased from Aldrich and were used without further purification.

Diethyl 2,2′-Bipyridine-5,5′-dicarboxylate (2). Neat ethyl nicotinate [**1**; 82 g, 540 mmol; bp 222−224 °C (lit.[9] bp 223−224 °C)] with 10% Pd/C was refluxed under reduced pressure (16 mmHg) for 6 days. The reaction mixture was diluted with hexane, and then the catalyst was filtered and extracted with toluene in a soxlet extractor. The combined organic solution was concentrated affording crude product, which was recrystallized from EtOH: 28.67 g (35.2%); mp 145−147 °C (lit.[10] mp 149 °C); ^{1}H NMR δ 1.41 [t, J = 7.1 Hz, 6H], 4.42 (q, J = 7.1 Hz, 4H), 8.41 (dd, ^3J = 8.3 Hz, ^4J = 2.15 Hz, 2H), 8.54 (dd, J = 8.3, 0.8 Hz, 2H), 9.27 (dd, J = 2.15, 0.8 Hz, 2H); ^{13}C NMR δ 14.3, 61.5, 121.2, 126.5, 138.1, 150.5, 158.3, 165.1; IR 1721 (C═O), 1269, 1112 (CO_2) cm^{-1}. Anal. Calcd for $C_{16}H_{16}N_2O_4$: C, 63.97; H, 5.37; N, 9.32. Found: C, 64.07; H, 5.64; N, 9.42.

Ethyl 5′-Carbohydrazido-2,2′-bipyridine-5-carboxylate (3). A mixture of diethyl 2,2′-bipyridine-5,5′-dicarboxylate (7 g, 23.3 mmol) and hydrazine hydrate (1.75 mL, 35 mmol) in a solution of EtOH (20 mL) and toluene (60 mL) was heated at 80 °C for 30 h. The precipitate was filtered, washed with CH_2Cl_2 to remove unreacted starting material, and dried in vacuo to give (85%) the pure monocarbohydrazide: mp 235−238 °C; ^{1}H NMR (DMSO-d_6) δ 1.35 (t, 3H), 4.37 (q, 2H), 4.63 (br, 2H), 8.35 (dd, ^3J = 8.4 Hz, ^4J = 2 Hz, 1H), 8.45 (dd, ^3J = 8.4 Hz, ^4J = 2 Hz, 1H), 8.52 (d, ^3J = 8.4 Hz, 1H), 8.57 (d, ^3J = 8.4 Hz, 1H), 9.1 (d, ^4J = 2 Hz, 1H), 9.2 (d, ^4J = 2 Hz, 1H), 10.1 (br, 1H); ^{13}C NMR (DMSO-d_6) δ 14.1, 61.3, 120.9, 120.9, 126.1, 129.6, 136.2, 138.2, 148.1, 150.0, 155.8, 157.8, 163.8, 164.5; IR 3325, 3187 (NH), 1721, 1715 (C═O) cm^{-1}. Anal. Calcd for $C_{14}H_{14}N_4O_3$: C, 58.72; H, 4.92; N, 19.57. Found: C, 58.59; H, 4.70; N, 19.82.

5,5′-Dicarbohydrazido-2,2′-bipyridine (4) was formed under similar conditions except that the temperature was maintained at 115 °C for 3 h. The creamy insoluble (acid, base, and most common organic solvents) solid was washed with boiling EtOH to give (98%) the pure dicarbohydrazide: mp >300 °C; IR 3300, 3262, 3199 (NH), 1677 (C═O) cm^{-1}.

Ethyl 5′-Carbazido-2,2′-bipyridine-5-carboxylate (5). A stirred solution of 5-(ethoxycarbonyl)-5′-carbohydrazido-2,2′-bipyridine (5.7 g, 20 mmol) in concentrated HCl (100 mL) was cooled to 0 °C, and then an aqueous solution of $NaNO_2$ (1.73 g, 25 mmol; 15 mL) was added dropwise, maintaining the temperature below 5 °C. After 60 min, the yellow solution was diluted with water (300 mL) to precipitate (95%) the monoester **5** as a colorless powder (5.1 g), which was filtered, washed with water, and recrystallized (acetone): mp 134−135 °C; ^{1}H NMR δ 1.44 (t, J = 7.13 Hz, 3H), 4.45 (q, J = 7.13 Hz, 2H), 8.41 (dd, ^3J = 5.6 Hz, ^4J = 1.8 Hz, 1H), 8.44 (dd, ^3J = 5.6 Hz, ^4J = 1.8 Hz, 1H), 8.57 (d, J = 5.6 Hz, 1H), 8.60 (d, J = 5.6 Hz, 1H), 9.26 (d, J = 1.8 Hz, 1H), 9.29 (d, J = 1.8 Hz, 1H); ^{13}C NMR δ 14.2, 61.5, 121.4, 126.7, 126.8, 137.8, 138.1, 150.3, 150.6, 157.8, 159.4, 165.0, 171.0; IR 2181, 2143 (N_3), 1721, 1715 (C═O), 1294, 1244 (CO_2) cm^{-1}. Anal. Calcd for $C_{14}H_{11}N_5O_3$: C, 56.64; H, 3.72; N, 23.56. Found: C, 56.50; H, 3.96; N, 23.84.

Ethyl 5′-[(Ethoxycarbonyl)amino]-2,2′-bipyridine-5-carboxylate (6). A solution of ethyl 5′-carbazido-2,2′-bipyridine-5-carboxylate (5.1 g, 19 mmol) in a mixture of EtOH (60 mL) and xylene (60 mL) was refluxed for 4 h. The solvent was evaporated in vacuo, and the residue was recrystallized from EtOH to yield (82%) **6** as a colorless solid: mp 208−211 °C; ^{1}H NMR δ 1.32 (t, J = 7.2 Hz, 3H), 1.41 (t, J = 7.2 Hz, 3H), 4.25 (q, J = 7.2 Hz, 2H), 4.41 (q, J = 7.2Hz, 2H), 6.81 (s, 1H), 8.08 (dd, ^3J = 8 Hz, ^4J = 2 Hz, 1H), 8.35 (dd, ^3J = 8.3 Hz, ^4J = 2 Hz, 1H), 8.40 (dd, ^3J = 8.3Hz, ^5J = 1 Hz, 1H), 8.43 (d, ^3J = 8 Hz, 1H), 8.58 (d, ^4J = 2 Hz, 1H), 9.22 (d, ^4J = 2 Hz, ^5J = 1 Hz, 1H); ^{13}C NMR δ 14.3, 14.5, 61.4, 61.9, 119.9, 122.2, 125.4, 126.0, 135.7, 137.9, 139.5, 150.01, 150.51, 153.30, 158.97, 165.43; IR 3320 (NH), 1724, 1704 (C═O) cm^{-1}; ESI-MS 317.1 ($M^+ + 1$).

5′-Amino-2,2′-bipyridine-5-carboxylic Acid Hydrochloride (7). A stirred solution of ethyl 5′-[(ethoxycarbonyl)amino]-2,2′-bipyridine-5-carboxylate (4.85 g, 15.3 mmol) in a mixture of EtOH (50 mL) and 2.5 N aqueous NaOH (50 mL) was heated at 75 °C for 14 h. The EtOH was concentrated in vacuo, and the aqueous solution was acidified with HCl to afford a bright yellow precipitate, which was filtered, washed with cold water, and dried in vacuo (89%). The resultant solid was recrystallized from concentrated HCl to give **7·HCl** as a bright yellow solid: mp 286−290 °C dec; ^{1}H NMR (D_2O/NaOD) δ 7.00 (dd, ^3J = 8.5 Hz, ^4J = 2.8 Hz, 1H), 7.55, 7.61 (d, ^3J = 8.5 Hz, 2H), 7.81 (d, ^4J = 2.8 Hz, 1H), 7.98 (dd, ^3J = 8.5 Hz, ^4J = 2.8 Hz, 1H), 8.65 (d, ^4J = 2.8 Hz, 1H); ^{13}C NMR (D_2O/NaOD) δ 123.15, 125.96, 126.49, 133.69, 139.82, 141.34, 147.39, 147.45, 152.33, 159.57, 176.04; IR 3356, 3287 (NH), 1721 (C═O), 1225 (CO_2) cm^{-1}. Anal. Calcd for $C_{11}H_{10}N_3O_2Cl$: C, 52.57; H, 4.01; N, 16.72; Cl, 13.92. Found: C, 51.77; H, 4.27; N, 16.28; Cl, 13.87.

Ethyl 5′-Amino-2,2′-bipyridine-5-carboxylate (8). To a stirred solution of **7** (200 mg, 900 μmol) in ethanol (25 mL), was added concentrated H_2SO_4 (2mL), and then the mixture was refluxed for 12 h. The solid went into the solution in 1 h. The reaction mixture was cooled, kept on ice bath, neutralized with ammonium hydroxide, and concentrated in vacuo. The residue was extracted with ether (3 × 10 mL); the extract was concentrated in vacuo to give the ester as a pale yellow solid: mp 130−132 °C; ^{1}H NMR δ 1.39 (t, J = 7, 13 Hz, 3H), 4.38 (q, J = 7, 13 Hz, 2H), 3.82 (s, 2H), 7.06 (dd, ^3J = 8.5 Hz, ^4J = 2.8 Hz, 1H), 8.14 (d, ^4J = 2.8 Hz, 1H), 8.25 (d, ^3J = 8.5 Hz, 1H), 8.3 (d, ^3J = 1, 5 Hz, 2H), 9.17 (t, ^4J = 1, 5 Hz, 1H); ^{13}C NMR δ 14.2, 61.1, 119.0, 121.5, 122.6, 124.5, 136.4, 137.6, 143.6, 145.3, 150.3, 159.5, 165.5; IR 3426 (NH), 3344 (NH), 1715 (C═O), 1294 (CO_2) cm^{-1}; ESI-MS 243.8 ($M^+ + 1$).

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