A Simple Synthesis of Dihydroxybipyridyls

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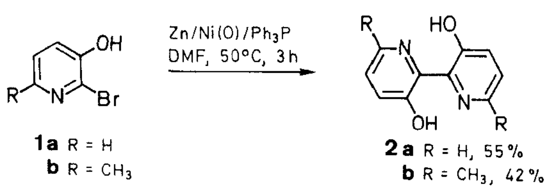
Dihydroxybipyridyls (dihydroxybipyridines), laser dyes with large Stokes shifts, are prepared by a simple one-step synthesis from the corresponding 2-bromo-3-hydroxypyridines, 3-bromo-4-hydroxyisoquinoline and 2-bromo-3-hydroxyquinoline, using zinc, and nickel(0) in yields up to 45%.

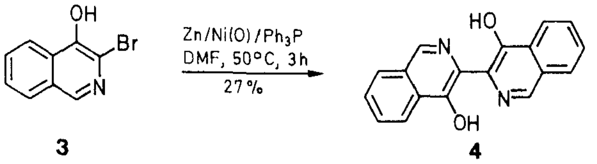
Dihydroxybipyridyls (dihydroxybipyridines exhibit unusually high Stokes shifts caused by a proton-transfer mechanism after electronic excitation,[1-3] and for this reason they are of interest for dye laser applications. The unsubstituted 3,3′-dihydroxy-2,2′-bipyridyl (**2a**) can be prepared from furfural by a simple reaction sequence.[1] Homologues, however, cannot be synthesised in this way,[1] hence a general preparative procedure is required.

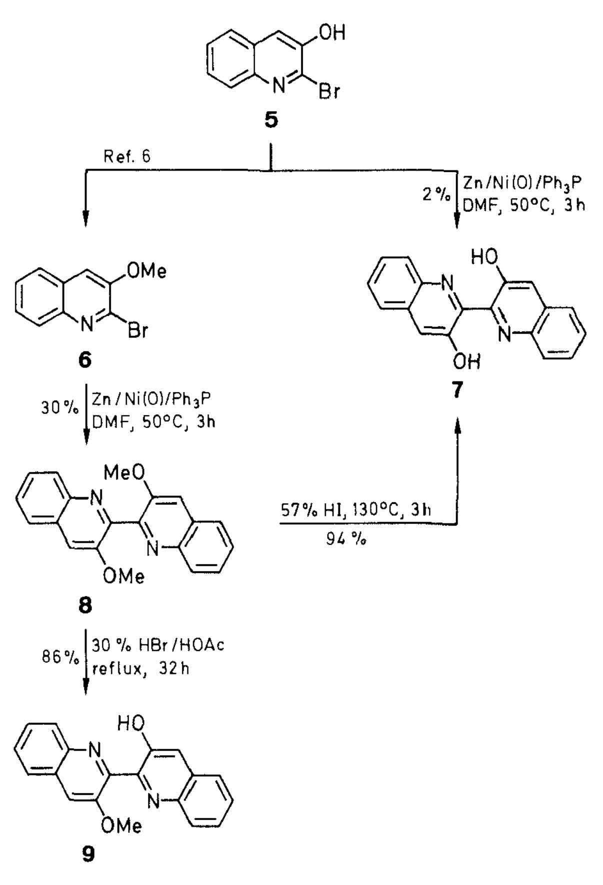
Aryl coupling by the phenol oxidation of 3-hydroxypyridines gives very poor yields.[1] Therefore, a reductive organometallic coupling of the easily prepared 2-bromo-3-hydroxypyridines is an attractive way of synthesising **2a** and its homologues. However, the acidity of the phenolic hydroxy group prohibits most organometallic reactions so that protective groups are needed.[4] We found that zinc in dimethylformamide as a solvent gives aryl coupling even in the presence of phenolic hydroxy groups. However, the isolated yields of the coupling products are low, probably due to a further reduction of the dihydroxybipyridiyl to an aminocarbonyl derivative during the course of the reaction. The yield of the reaction product is dramatically increased by metal complexation. The complexation protects the product from further reaction. This is easily achieved by nickel(0) in the presence of triphenylphosphine. Nickel(0) is conveniently prepared *in situ* by the reduction of nickel(II) with zinc (see ref. 5 for the use of nickel(0) and zinc). This simplifies the preparation procedure and a constant activation of the zinc surface for the aryl coupling is maintained. Furthermore, the nickel complexes of the reaction products can be precipitated, allowing a simple workup.

The general preparative procedure is similar to that of ref 5. The reaction can be carried out even in the presence of small amounts of water. This allows the use of nickel salts with water of crystallization and technical grade solvents. Exclusion of air is somewhat helpful, but not essential.

The starting materials for 3,3′-dihydroxy-2,2′-bipyridyl and its homologues are well known in the literature (see experimental part). They are prepared by bromination of the corresponding 3-hydroxypyridines. The one step preparation of 3,3′-dihydroxy-2,2′-biquinoline (**7**) is difficult due to the low solubility of the reaction product, which interfers considerably with the separation of the product from zinc hydroxide. Therefore, the better soluble methoxy derivative **8** was prepared first. Ether cleavage with hydrobromic acid gives the monomethoxy derivative **9** and with hydroiodic acid the bishydroxy compound **7**.







The prepared dihydroxybipyridyls are dyes with large Stokes shifts in solution. Some of them have a strong solid state fluorescence. The UV/VIS spectroscopic properties of the dyes will be reported in some other context.

3-Hydroxyquinoline, precursor to 2-bromo-3-hydroxyquinoline (**5**),[13] was prepared by the following procedure.

3-Hydroxyquinoline:

A mixture of 3-aminoquinoline (1.0 g, 6.9 mmol) and 5 N H_2SO_4 (10 mL) is cooled to 5°C and solid $NaNO_2$ (0.5 g, 7.2 mmol) is added with stirring and cooling so that the temperature does not exceed 5°C. The solution is stirred 10 min without further cooling and than added dropwise (5 min) with stirring to 2 N H_2SO_4 (30 mL) which is at 70°C. Afterwards, the mixture is kept 1 h at this temperature and then allowed to cool down until a precipitate forms. The precipitate is filtered off, dissolved in 2 N NaOH an brought to pH 8 by the addition of 2 N HCl. The reaction product is filtered off, washed with distilled water, and recrystallized from EtOH (50 mL). Further crude reaction product can be obtained from the H_2SO_4 solution by the addition of 2 N NaOH (pH 8); yield: 0.92 g (92%) (Lit.[12], 65%); mp 192–193 °C (lit.[12] mp 198 °C); R_F (silica gel/EtOH) = 0.75.

IR (KBr): ν = 3441, 3049 (m), 2957, 2675 (m, OH), 1612 (w), 1576 (s), 1345 (s), 1312 (m), 1291 (s), 1246 (s, C–O), 1185 (m, C–O), 1152 (s, C–O), 1091 (s, C–O), 974 (w), 906 (w), 789 (m), 725 (m), 623, 598 cm^{-1} (m).

^1H-NMR (DMSO-d_6/TMS): δ = 7.40–7.57 (m, 2 H, H-6, H-7), 7.70–8.87 (m, 2 H, H-5, H-8), 8.75 (d, 1 H, $J_{2,4}$ = 2.0 Hz, H-2), 10.32 (s, 1 H, OH).

3,3'-Dihydroxy-2,2'-bipyridiyl (2a):

$NiCl_2 \cdot 6H_2O$ (4.06 g, 17.2 mmol) is completely dissolved in technical grade (DMF (75 mL) and Ar gas is passed through the solution. Ph_3P (17.92 g, 68.96 mmol) is added (the color of the solution turns to dark blue) and the mixture is heated to 50 °C. Zinc powder (3.10 g, 47.7 mmol) is added and the mixture is kept for 1 h at this temperature with stirring (the color turns to turquoise and then to red-brown). Solid 2-bromo-3-hydroxypyridine[6] (3.00 g, 17.2 mmol) is added and the mixture is kept for another 2 h at 50 °C with stirring. The still warm mixture is poured into 2 N NaOH (300 mL) and vigorously stirred for 10 min. The precipitated Ph_3P is filtered, shaken once more with 2 N NaOH (300 mL), and then discarded. The reaction product is precipitated by the addition of conc HCl to the combined NaOH phases until a pH value of 4–7 is reached. The completeness of the precipitation is controlled by the use of a fluorescence lamp (365/366 nm); the blue fluorescence of the solution turns to the green solid state fluorescence of **2a**. The solid is immediately filtered, washed with distilled water until neutral, dried in a dessicator (*Caution!* volatile), and recrystallised from distilled toluene (25 mL, impurities of heavy metals cause losses by complexation). Further purification can be obtained by a column chromatography on silica gel using $CHCl_3$ as eluent; yield: 0.89 g (55%); mp 194–195 °C (Lit.[1] mp 195 °C); R_f (silica gel, petroleum ether (bp 60–80 °C)/Et_2O = 9 : 1] = 0.20.

IR (KBr): ν = 3435, 2541 (m, OH), 1601 (w), 1572 (m, C=C_{arom}), 1494 (s), 1442 (s), 1357 (w), 1344 (w), 1307 (s, C–O), 1253 (w), 1235 (w), 1116 (m), 1067 (w), 879 (m), 840 (w), 799 (s), 728 (m), 650 (m), 645 (m), 535 (w), 458 cm^{-1} (w).

3,3'-Dihydroxy-6,6'-dimethyl-2,2'-bipyridyl (2b):

2-Bromo-3-hydroxy-6-methylpyridine[7] (3.24 g, 17.2 mmol) is coupled and worked up as given above for **2a**; yield: 0.78 g (42%); mp 189–190 °C; R_f (silica gel, $CHCl_3$) = 0.82.

$C_{12}H_{12}N_2O_2$	calc.	C 66.65	H 5.59	N 12.95
(216.2)	found	66.59	5.61	12.65

IR (KBr): ν = 3440 (m), 3100–2200 (m, OH), 1496 (s, C=C_{arom}), 1457 (w), 1447 (w), 1392 (m), 1369 (m), 1322 (m, OH), 1293 (s), 1239 (s), 1225 (m), 1133 (m, C–O), 1069 (m, C–O), 888 (s), 832 (s), 824 (s), 757 (w), 661 (m), 487 cm^{-1} (w).

UV ($CHCl_3$): λ_{max} (ε) = 353 nm (16671).

^1H-NMR ($CDCl_3$/TMS): δ = 2.20 (s, 6 H, CH_3), 7.03, (d, 2 H, $J_{5,4} = J_{5',4'}$ = 9 Hz, H-5, H-5'), 7.27 (d, 2 H, $J_{4,5} = J_{4',5'}$ = 9 Hz, H-4, H-4').

MS (70 eV): m/z (%) = 217 (13, M^+ + 1), 216 (100, M^+), 215 (6), 200 (11), 199 (79, M^+ – OH), 188 (9), 187 (15), 159 (8), 135 (11), 118 (4), 108 (4), 92 (4), 91 (4), 79 (5), 80 (15), 53 (22), 40 (7).

4,4'-Dihydroxy-3,3'-biisoquinoline (4):

3-Bromo-4-hydroxyisoquinoline[11] (**3**; 3.84 g, 17.2 mmol) is coupled and worked up as given above for **2a**. However, the crude reaction product has no strong solid state fluorescence. Therefore, conc HCl is added to the alkaline solution until the precipitate coagulates (pH 6–7). The product is extracted with $CHCl_3$ and dried (Na_2SO_4). The residue obtained after removal of the solvent is purified by column chromatography on silica gel using petroleum ether (bp 60–80 °C)/Et_2O, (9 : 1) as eluent and recrystallized from distilled toluene (50 mL); yield: 0.68 g (27%); mp 270 °C; R_f (silica gel, $CHCl_3$) = 0.72.

$C_{18}H_{12}N_2O_2$	calc.	C 74.99	H 4.19	N 9.71
(288.3)	found	75.20	4.32	9.79

IR (KBr): ν = 3060 (w), 2960–2470 (m, OH), 1592 (m), 1570 (m), 1489 (s), 1456 (m), 1398 (s, OH), 1336 (s, OH), 1315 (s, OH), 1224 (m), 1170 (m, C–O), 1156 (m, C–O), 1123 (m, C–O), 889 (m), 856 (w), 822 (m), 749 (s), 744 (s), 586 (m), 563 (m), 508 cm^{-1} (m).

UV ($CHCl_3$): λ_{max} (ε) = 388 nm (27677), 372 (24217).

^1H-NMR (DMSO-d_6/TMS): δ = 7.78 (t, 2 H, $J_{7,8} = J_{7,6} = J_{7',8'} = J_{7',6'}$ = 7.5 Hz, H-7, H-7'), 7.88 (t, 2 H, $J_{6,5} = J_{6,7} = J_{6',5'} = J_{6',7'}$ = 7.5 Hz, H-6, H-6'), 8.22 (d, 2 H, $J_{8,7} = J_{8',7'}$ = 8.2 Hz, H-8, H-8'), 8.35 (d, 2 H, $J_{5,6} = J_{5',6'}$ = 8.7 Hz, H-5, H-5'), 9.02 (s, 2 H, H-1, H-1').

MS (70 eV): m/z (%) = 289 (57, M^+ + 1), 288 (100, M^+), 271 (71, M^+ – OH), 231 (22), 204 (21), 171 (16), 144 (19), 116 (15), 89 (71), 63 (31), 39 (21).

3,3'-Dihydroxy-2,2'-biquinoline (7):

2-Bromo-3-hydroxyquinoline[13] (**5**; 1.50 g, 6.74 mmol) is coupled and worked up as given above for **2a**. However, the reaction product has a very low solubility in organic solvents, hence the separation from the zinc hydroxide is difficult. Therefore, the crude solid reaction product is treated with warm DMSO (20 mL) and column chromatographed on silica gel using toluene/HOAc (4 : 1) as eluent; yield: 20 mg (2%); mp > 360 °C; for a better procedure see below.

3,3'-Dimethoxy-2,2'-biquinoline (8):

2-Bromo-3-methoxyquinoline[8] (**6**; 1.0 g, 4.2 mmol) is coupled using $NiCl_2 \cdot 6H_2O$ (0.99 g, 4.20 mmol), Ph_3P 4.41 g, 16.8 mmol) and zinc powder (2.00 g, 30.8 mmol) in DMF (100 mL) as given for **2a** (see ref. 5). After 8 h, the still warm mixture is poured into 2 N HCl (200 mL). The precipitate is filtered and the yellow solution is brought to pH 12 by the addition of 10% NaOH. The voluminous precipitate is filtered, washed with water, dried, and extracted with toluene. The solvent is evaporated and the residue treated with conc HCl (10 mL). The mixture is filtered and the solution is again brought to pH 12 by the addition of 10% NaOH. The product is filtered, washed with water to neutral pH value, dried, and recrystallized from toluene (30 mL); yield: 0.20 g (30%); mp 258 °C; R_f (silica gel, toluene/HOAc, 80 : 20) = 0.49.

$C_{20}H_{16}N_2O_2$	calc.	C 75.93	H 5.10	N 8.85
(316.3)	found	75.82	5.28	8.66

IR (KBr): ν = 3439 (m), 3060 (w), 3035 (w), 3012 (w), 2968 (w), 2945 (w), 2840 (w), 1574 (s), 1565 (m), 1508 (m), 1497 (s), 1474 (s), 1303 (s), 1279 (s), 1237 (m), 1234 (m), 1141 (m), 1070 (m), 1052 (m), 1017 (m), 971 (m), 786 (m), 771 (s), 595 cm^{-1} (w).

UV ($CHCl_3$): λ_{max} (ε) = 338 (10023), 326 (9647), 299 nm (7674).

^1H-NMR (DMSO-d_6/TMS): δ = 3.98 (s, 6 H, OCH_3), 6.99 (d, 2 H, $J_{5,6} = J_{5',6'}$ = 8.3 Hz, H-5, H-5'), 7.39 (t, 2 H, $J_{6,5} = J_{6,7} = J_{6',5'} = J_{6',7'}$ = 8.0 Hz, H-6, H-6'), 7.61 (t, 2 H, $J_{7,8} = J_{7,6} = J_{7',8'} = J_{7',6'}$ = 8.0 Hz, H-7, H-7'), 8.09 (d, 2 H, $J_{8,7} = J_{8',7'}$ = 8.4 Hz, H-8, H-8'), 9.13 (s, 2 H, H-4, H-4').

MS (70 eV): m/z (%) = 317 (22, M^+ + 1), 316 (100, M^+), 301 (9, M^+ – CH_3), 286 (6), 285 (6), 273 (13), 258 (13), 242 (12), 229 (13), 216 (15), 203 (15), 189 (5), 176 (8), 44 (6), 43 (6).

3-Hydroxy-3'-methoxy-2,2'-biquinoline (9):

3,3'-Dimethoxy-2,2'-biquinoline (**8**; 240 mg, 0.75 mmol) is added to 30% HBr (15 mL) in HOAc.[9] The solution is refluxed for 8 h. 30% HBr/HOAc (5 mL) is added and refluxing continued for another 24 h. The solution is poured into distilled water (100 mL). Solid NaOH is added till pH = 11, and the solution is extracted with $CHCl_3$ (50 mL). The aqueous phase is brought to a pH value of 6 by the addition of conc. HCl and then extracted with $CHCl_3$ (250 mL). The solvent is evaporated and the residue column chromatographed on silica gel using $CHCl_3$ as eluent. The product is further purified by recrystallization from distilled toluene (10 mL); yield: 0.19 g (86%); mp 255 °C (dec); R_f (silica gel, toluene/HOAc, 4 : 1) = 0.26.

$C_{19}H_{14}N_2O_2$	calc.	C 75.53	H 4.67	N 9.27
(302.1)	found	75.24	4.69	9.52

IR (KBr): ν = 3422 (m), 3066 (m), 2938 (m), 2842 (m), 3010–2280 (m, OH), 1576 (m), 1501 (m), 1465 (m), 1424 (w), 1375 (w), 1332 (m), 1309 (s, C−O−C), 1279 (s, C−O−C), 1241 (m, C−O−C), 1214 (w, C−O), 1200 (w), 1161 (w, C−O), 1143 (s), 1061 (w), 995 (w), 758 cm^{-1} (s).

UV ($CHCl_3$): λ_{max} (ε) = 335 (8326), 327 (8062), 298 nm (6134).

^{1}H-NMR (DMSO-d_6/TMS, 500 MHz, 323 K): $\delta = 3.90$ (s, 3 H, OCH_3), 6.94 (d, 1 H, $J_{5,6} = 8.0$ Hz, H-5), 7.05 (d, 1 H, $J_{5',6'} =$ 8.0 Hz, H-5'), 7.32 (t, 1 H, $J_{6,7} = J_{6,5} = 8.0$ Hz, H-6), 7.36 (t, 1 H, $J_{6',5'} = J_{6',7'} = 8.0$ Hz, H-6'), 7.51 (t, 1 H, $J_{7,8} = J = {}_{7,6} = 8.0$ Hz, H-7), 7.60 (t, 1 H, $J_{7',8'} = J_{7',6'} = 8.0$ Hz, H-7'), 8.02 (d, 1 H, $J_{8,7} = 8.0$ Hz, H-8), 8.08 (d, 1 H, $J_{8',7'} = 8.0$ Hz, H-8'), 8.72 (s, 1 H, 4-H), 9.09 (s, 1 H, 4'-H). Line broadening is observed at 295 K for the signals at $\delta = 6.94$, 7.32, 7.51, 8.02, and 8.72.

MS (70 eV): m/z (%) = 303 (18, $M^+ + 1$), 302 (100, M^+), 301 (9), 288 (8), 287 (46, $M^+ - CH_3$), 286 (6), 271 (4), 259 (11), 258 (5), 242 (5), 241 (5), 231 (13), 230 (5), 229 (4), 204 (7), 203 (10), 177 (4), 176 (10), 88 (5), 57 (5), 43 (5), 41 (6).

3,3'-Dihydroxy-2,2'-biquinoline (7):

3,3'-Dimethoxy-2,2-biquinoline (**8**; 200 mg, 0.63 mmol) is heated with 57% HI[9] (10 mL) at 130°C. After 3 h the mixture is poured into distilled water (60 mL). 2 N NaOH is added to neutralize the mixture. The yellow precipitate is filtered, washed with distilled water, dried, and recrystallized by extraction[10] from 2-propanol (40 mL) yield: 0.17 g (94%); mp > 360°C; R_f (silica gel, 2-propanol) = 0.82.

$C_{18}H_{12}N_2O_2$	calc.	C 74.99	H 4.19	N 9.72
(288.3)	found	74.73	4.34	9.79

IR (KBr): ν = 3420 (m), 3067−2550 (m, OH), 1574 (m), 1508 (m), 1503 (m), 1466 (m), 1425 (w), 1400 (w), 1376 (m), 1332 (s), 1281 (w), 1249 (w), 1217 (s, C−O), 1161 (w), 1141 (s), 755 cm^{-1} (s).

UV ($CHCl_3$): λ_{max} (ε) = 339 (9202), 328 nm (7975).

^{1}H-NMR (DMSO-d_6/TMS): $\delta = 7.59$ (d, 2 H, $J_{5,6} = J_{5',6} =$ 8.7 Hz, H-5, H-5'), 7.90 (t, 2 H, $J_{6,5} = J_{6,7} = J_{6',5'} = J_{6',7'} =$ 7.5 Hz, H-6, H-6'), 8.18 (t, 2 H, $J_{7,8} = J_{7,6} = J_{7',8'} = J_{7',6'} = 7.5$ Hz, H-7, H-7'), 8.58 (d, 2 H, $J_{8,7} = J_{8',7'} = 8.7$ Hz, H-8, H-8'), 9.36 (s, 2 H, H-4, H-4').

MS (70 eV): m/z (%) = 289 (18, $M^+ + 1$), 288 (100, M^+), 287 (16), 271 (7, $M^+ - OH$), 260 (7), 259 (17), 232 (5), 231 (9), 204 (7), 176 (5), 88 (4).

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