Synthesis and Reactivity of Disubstituted 4,4'-Bipyrimidines: Preparation of a New Pentadentate Ligand

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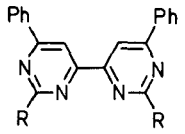
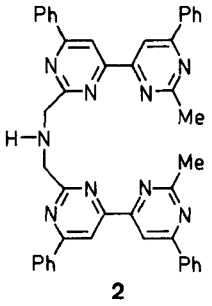
Synthesis of 2,2'-disubstitued 6,6'-diphenyl-4,4-bipyrimidines (bpm) and their reactivity towards oxidation and bromination is investigated. Preparation of a pentadentate ligand by a template reaction from 2-bromomethyl-4,4'-bipyrimidine unit is reported.

The coordination chemistry of 2,2'-bipyridine (bpy) ligands has received considerable interest in the past two decades.[1-2] Rigid macrobicyclic structures containing bpy subunits yield photoactive metal-cage complexes in particular with lanthanides[3] and ruthenium.[4] Less rigid (e. g. acyclic or branched) polydentate complexing agents allow binding properties and structural flexibility to be combined. Such assemblies containing bipyridine units[5] as well as other heterocycles[6] have been described in the literature.

We report here the synthesis of the hitherto unknown 2,2'-disubstituted 6,6'-diphenyl-4,4'-bipyrimidines (bpm) **1a–c**. The presence of both inner nitrogen metal coordination centers and external pH dependent electroactive centers in the system such as **2** will be of interest for the development of new electroactive assemblies[7] and also future new potential photoactive polydentates. Experiments to coordinate **2** with transition metals will be reported elsewhere.



1a R = Me
b R = Et
c R = *i*-Pr



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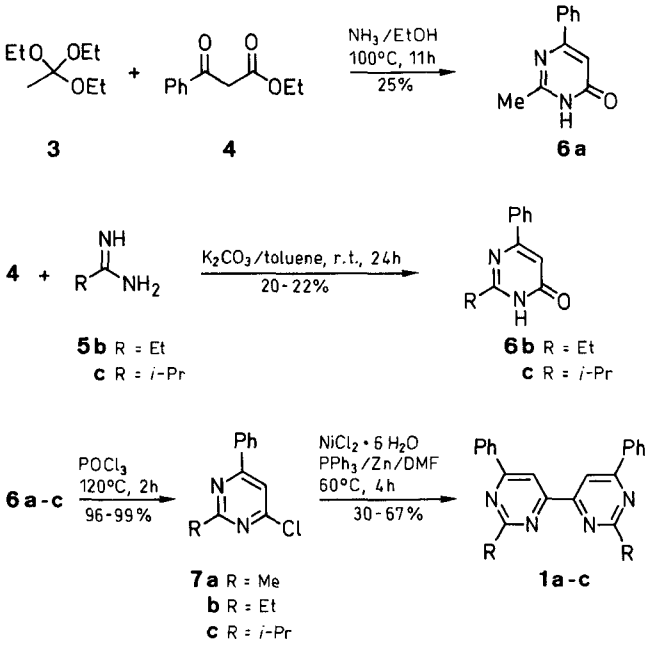
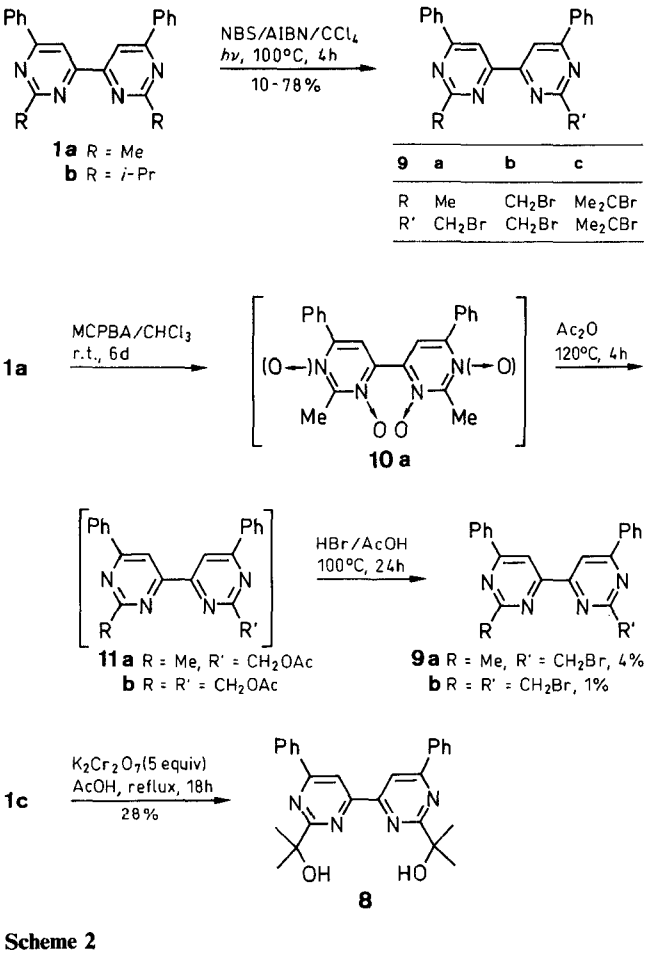
The starting materials for the synthesis of disubstituted 4,4'-bipyrimidines are well known in the literature (see experimental part). They are prepared by two methods: i. the condensation of triethyl orthoacetate **(3)** and ethyl benzoyl acetate **(4)** in presence of an excess of ammonia; ii. a modified condensation[8] between amidines **5b,c** and **4** in the presence of potassium carbonate. The resulting pyrimidones **6a–c** are classically halogenated by phosphorous oxychloride[8] in good yields (96–99 %). Finally, the coupling reaction of 4-chloropyrimidines **7a–c** is achieved by nickel(0) complex to give **1a–c** in moderate to good yields. The general preparative procedure is very similar to that given in Ref. 9 (Scheme 1).

For the functionalization of 4,4-bipyrimidines prepared, we have studied their reactivity towards bromination and oxidation reactions (Scheme 2). Direct oxidation of the side chain in position two of bpm **1a,b** fails, both with weak or strong oxidants respectively: selenium dioxide in



Scheme 1



Scheme 2

Table. Compounds **1**, **6**, **7** and **9** Prepared

Product	Yield (%)	mp (°C)	Molecular Formula[a]	^{1}H NMR (220 MHz, $CDCl_3$/TMS) δ, J (Hz)	MS (70 eV) m/z (%)
1a	52	250	$C_{22}H_{18}N_4$ (338.4)	2.89 (s, 6H, 2 × CH_3), 7.53 (m, 6H, C_6H_5), 8.23 (m, 4H, C_6H_5), 8.66 (s, 2H, H-5,5′)	338 (M^+, 100), 297 (11), 194 (22), 153 (15), 128 (23), 102 (28), 77 (17), 44 (15)
1b	30	178	$C_{24}H_{22}N_4$ (366.5)	1.50 (t, 6H, J = 7.1), 2 × CH_2CH_3), 3.20 (q, 4H, J = 7.1), 2 × CH_2CH_3), 7.55 (m, 6H, C_6H_5), 8.25 (m, 4H, C_6H_5), 8.70 (s, 2H, H-5,5′)	366 (M^+, 31), 262 (93), 183 (100), 108 (37), 77 (12), 51 (15)
1c	67	202	$C_{26}H_{26}N_4$ (394.5)	1.60 [d, 12H, J = 7.1, 2 × $CH(CH_3)_2$], 3.50 [sept. 2H, 2 × $CH(CH_3)_2$], 7.55 (m, 6H, C_6H_5), 8.30 (m, 4H, C_6H_5), 8.70 (s, 2H, H-5,5′)	394 (M^+, 100), 379 (91), 366 (10), 128 (13)
6b	20	255	$C_{12}H_{12}N_2O$ (200.3)	1.40 (t, 3H, J = 7.1, CH_2CH_3), 2.80 (q, 2H, J = 7.1, CH_2CH_3), 6.75 (s, 1H, H-5), 7.50 (m, 3H, C_6H_5), 8.00 (m, 2H, C_6H_5)	200 (M^+, 100), 199 (97), 171 (16), 104 (16), 77 (19), 56 (17)
6c	22	238	$C_{13}H_{14}N_2O$ (214.3)	1.35 [t, 6H, J = 7.1, $CH(CH_3)_2$], 3.00 [quint, 1H, $CH(CH_3)_2$], 6.50 (s, 1H, H-5), 7.30 (m, 3H, C_6H_5), 7.90 (m, 2H, C_6H_5)	214 (M^+, 57), 192 (100), 186 (13), 146 (20), 104 (16), 103 (17)
7a	96	59	$C_{11}H_9ClN_2$ (204.7)	2.73 (s, 3H, CH_3), 7.47 (m, 4H, C_6H_5 + H-5), 8.02 (m, 2H, C_6H_5)	204 (M^+, 40), 169 (10), 128 (100), 77 (21), 61 (11), 51 (18), 43 (17)
7b	99	255	$C_{12}H_{11}ClN_2$ (218.7)	1.40 (t, 3H, J = 7.1, CH_2CH_3), 3.10 (q, 2H, J = 7.1, CH_2CH_3), 7.60 (m, 4H, C_6H_5 + H-5), 8.10 (m, 2H, C_6H_5)	217 (M^+, 100), 128 (23), 101 (11), 77 (30), 51 (11)
7c	96	oil	$C_{13}H_{13}ClN_2$ (232.7)	1.60 [t, 3H, J = 7.1, $CH(CH_3)_2$], 3.50 [quint, 1H, J = 7.1, $CH(CH_3)_2$], 7.55 (m, 3H, C_6H_5), 8.30 (m, 2H, C_6H_5), 8.70 (s, 1H, H-5)	233 (M^+, 100), 217 (90), 204 (31), 197 (17), 128 (57), 102 (18)
9a	25	> 260	$C_{22}H_{17}BrN_4$ (337.4)	2.85 (s, 3H, CH_3), 4.90 (s, 2H, CH_2Br), 7.60 (m, 6H, C_6H_5), 8.30 (m, 4H, C_6H_5), 8.67, 8.77 (2s, 1H each, H-5, H-5′)	416 (M^+, 17), 337 (24), 102 (14), 79 (85), 52 (100)
9b	10	200	$C_{22}H_{16}Br_2N_4$ (496.4)	4.90 (s, 4H, 2 × CH_2Br), 7.67 (m, 6H, C_6H_5), 8.30 (m, 4H, C_6H_5), 8.78 (s, 2H, H-5,5′)	496 (M^+, 100), 415 (72), 335 (31), 232 (26), 193 (19), 148 (21), 128 (46), 102 (62), 91 (35), 77 (83), 51 (30)
9c	78	224	$C_{26}H_{24}Br_2N_4$ (552.5)	2.35 [m, 12H, 2 × $C(CH_3)_2$], 7.65 (m, 6H, C_6H_5), 8.30 (m, 4H, C_6H_5), 9.75 (s, 2H, H-5,5′)	551 (M^+, 3), 471 (60), 391 (100), 196 (29), 128 (44), 103 (58), 77 (23)

[a] Satisfactory microanalyses obtained: C ± 0.4, H ± 0.1, Cl ± 0.21, N ± 0.38, exception **7a**: Cl + 0.55.

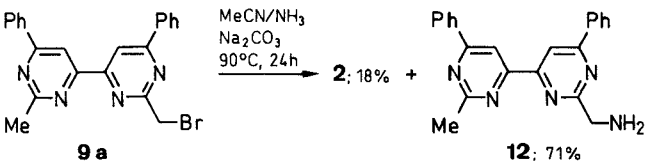
neutral conditions and potassium bichromate or chromic trioxide in acidic medium. The same results were observed also with potassium permanganate. The starting material is recovered unchanged. Similar results on monoalkyl pyrimidines[10] and polymethyl pyrimidines have been observed by other groups.[11]

Nevertheless, in the above cited conditions (potassium bichromate/acetic acid) a successful result has been obtained with the isopropyl derivative **1c**, giving the corresponding diol **8** in a moderate yield (30%). All further attempts to oxidize the diol to the acid derivative failed.

Brominated compounds from **1a** and **1c** have been synthesized by two ways: i. by reacting **1a** with *N*-bromosuccinimide (NBS) in the presence of azobisisobutyronitrile (AIBN) as initiator and tungsten lamp (100 Watt, $\lambda > 320$ nm) under argon and reflux, gave a mixture of **9a,b** as mono and dibromo derivatives, which were separated by chromatography in 25% and 10% yield, respectively. Under the same conditions, **1c** gave the dibromo derivative **9c** in a good yield (78%) as it might be predicted by the higher stability of the radical intermediate; ii. the *N*-oxidation of **1a** afforded **10a** as a mixture of mono and polysubstituted *N*-oxides even with a large excess of *m*-chloroperbenzoic acid (MCPBA). Unfortunately experiments to control the conditions of *N*-oxidation, in order to obtain only one isomer; could not be reached and separation of each isomer was confirmed to be impossible by chromatography because of the decomposition of the *N*-oxides on a stationary phase. Nevertheless, this difficulty was resolved by using the crude mixture of **10** for the following Boekelheide rearrangement with acetic anhydride to obtain a mixture of mono and diacetate **11a,b**. Treatment of the latter by hydrobromic acid (33%) in acetic acid at 100°C for one day, gave a mixture of mono and dibromo compounds **9a,b**. Separation by chromatography afforded each compound in disappointingly poor overall yields, 4% and 1%, respectively (based on **1a**), compared to the case of the 2,2′-bipyridine system under the same conditions.[12]

Condensation of two molecules of **9a** (Scheme 3) was conducted in an alkali metal assisted reaction with anhydrous sodium carbonate in presence of ammonia in anhydrous acetonitrile and led to a mixture of aminomethyl derivative **12** (71%) and the pentadentate ligand **2** (18%). Separation was realized by chromatography.

Traces of the probable podentate with three bipyrimidine building blocks have been also observed by NMR on an impure fraction of chromatography, (1.4%), the sepa-



Scheme 3

rated quantity was too low to allow a purification and analyses. Further attempts to improve yields of the podentate exclusively are in progress.

^{1}H NMR spectra were obtained on a Bruker AC 200 NMR spectrometer. All NMR measurements were performed at 25 °C ± 4 °C in DMSO-d_6 or $CDCl_3$. Mass spectra (EI) were recorded on a NERMAG R10-10C, by direct introduction, at 70 eV. Elemental analyses were performed at the microanalytical center of the C.N.R.S. at Vernaison. Melting points were obtained on a Kofler block and are uncorrected.

2-Methyl-6-phenyl-4(3*H*)-pyrimidone **(6a)** was synthesized by the published procedure.[13]

Pyrimidones 6b–c; General Procedure:
To a solution of the appropriate amidine **5b,c** (0.16 mol) and K_2CO_3 (193.2 g, 1.4 mol) in toluene, was added dropwise ethyl benzoylacetate (**4**; 26.9 g, 0.14 mol). The mixture was stirred at r.t. After 24 h, the solution was poured into H_2O neutralized with conc. HCl and extracted with CH_2Cl_2 (3 × 300 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated. The resulting solid was washed with Et_2O, filtered and recrystallized from acetone (Table).

4-Chloropyrimidines 7; General Procedure:
A mixture of **6** (1 mmol) and $POCl_3$ (6.1 g, 40 mmol) was heated at 120 °C for 2 h. The mixture was evaporated to dryness, the residue treated with H_2O and extracted with CH_2Cl_2 (3 × 100 mL). The organic layer was dried (Na_2SO_4) and the solvent evaporated. The product was collected by filtration and washed with petroleum ether (bp 60–80 °C) (Table).

Bipyrimidines 1; General Procedure:
To a stirred solution of Ph_3P (1.23 g, 4.7 mmol) and $NiCl_2 \cdot 6H_2O$ (285 mg, 1.2 mmol) in DMF (30 mL) at 50 °C was added Zn powder (79 mg, 1.2 mmol). After 15 min the color of the mixture had changed to red brown. To the mixture was added **7** (1 mmol) and stirred at 50 °C for 4 h. The mixture was cooled and poured into a mixture of NH_4OH (14 mL) and H_2O (36 mL), stirred for 12 h and extracted with CH_2Cl_2 (3 × 100 mL) in the presence of ethylenediamine tetraacetic acid to break the emulsion. The organic layer was washed with H_2O, dried (Na_2SO_4) and evaporated. The residue was triturated with Et_2O, filtered and the product was recrystallized from Et_2O/CH_2Cl_2 (Table).

2,2′-Bis(2-hydroxy-2-methylethyl)-6,6′-diphenyl-4,4′-bipyrimidine (8):
To a solution of **1c** (700 mg, 177 mmol) in AcOH (50 mL) was added portionwise $K_2Cr_2O_7$ (2.61 g, 8.88 mmol). The mixture was refluxed for 18 h, cooled and poured into H_2O. The solution was neutralized with sat. aq $NaHCO_3$ solution and extracted with CH_2Cl_2 (3 × 150 mL). The organic phase was dried (Na_2SO_4), filtered and evaporated; yield: 210 mg (28 %); mp > 300 °C (EtOH).

$C_{26}H_{26}N_4O_2$	calc.	C 73.22	H 6.15	N 13.14
(426.5)	found	73.27	6.15	13.39

^{1}H NMR (200 MHz, $CDCl_3$/TMS): δ = 1.75 (t, 12 H, 4 × CH_3), 5.00 (q, 2 H, OH), 7.60 (m, 6 H, C_6H_5), 8.30 (m, 4 H, C_6H_5), 8.80 (s, 2 H, H-5,5′).

MS: *m/z* (%) = 426 (M^+, 18), 411 (100), 393 (94), 198 (17), 128 (15), 103 (19), 77 (23).

Bromomethylbipyrimidines 9; General Procedures:
Method A: A solution of **1** (0.5 mmol), NBS (0.196, 1.1 mmol) and AIBN (28 mg, 0.17 mmol) in CCl_4 (52 mL) was heated at 100 °C with irradiation from a 100 Watt tungsten lamp. After 4 h, the mixture was cooled, washed with H_2O (3 × 100 mL), dried (Na_2SO_4) and the solvent evaporated (Table).

Method B: *i. N-Oxidation of* **1a**: A solution of dry MCPBA (21.1 g, 85 mmol) in $CHCl_3$ (125 mL) was added slowly to a solution of **1a** (4.13 g, 12 mmol) in $CHCl_3$ (100 mL) at r.t. under Ar atmosphere. After 6 d, the mixture was filtered and the filtrate was washed with sat. aq $NaHCO_3$ solution (250 mL). The organic layer was dried ($MgSO_4$) and evaporated. The solid residue was chromatographed on alumina using petroleum ether (bp 60–80 °C)/CH_2Cl_2 (1:1) as eluent to afford a mixture of *N*-oxides **10a** (2.4 g), which was used as such in the next reaction.

ii. Conversion of N-Oxides **10a** *to the Acetates* **11a,b:** A mixture of **10a** (2.4 g) was dissolved in Ac_2O (200 mL) at r.t. and kept at 120 °C for 4 h. Excess of Ac_2O and the resulting AcOH was evaporated, the oily residue precipitated with acetone and filtered. A white solid (1.21 g) was obtained as a mixture of acetates **11a,b**. The crude mixture was used for the next reaction.

iii. Bromination of Acetates **11a,b** *to Bromomethylpyrimidines* **9a,b**: The mixture of **11a,b** was dissolved in a solution of 33 % HBr in AcOH (95 mL) at r.t. and kept at 60 °C. After 24 h, the solution was cooled, diluted with H_2O (100 mL) and neutralized with sat. aq $NaHCO_3$ solution. The organic phase was dried ($MgSO_4$) and the solvent was evaporated. The residue was chromatographed on silica gel using petroleum ether (bp 60–80 °C) as eluent to afford **9a** (yield: 200 mg, 4 %) and **9b** (yield: 59 mg, 1 %).

[Bis(6,6′-diphenyl-2′-methyl-4,4′-bipyrimidin-2-yl)methyl]amine (2) and 2-Aminomethyl-6,6′-diphenyl-2′-methyl-4,4′-bipyrimidine (12):
Compound **9a** (137 mg, 0.33 mmol) was dissolved in a solution of anhydr. MeCN (10 mL) saturated with ammonia. A suspension of Na_2CO_3 (350 mg, 3.3 mmol) in MeCN (2.5 mL) was added and the mixture was heated at 90 °C under Ar for 24 h. Water was added (50 mL) and the product was extracted with CH_2Cl_2 (3 × 50 mL). The organic phase was dried (Na_2SO_4), evaporated and the residue was purified by column chromatography on silica gel using CH_2Cl_2/MeOH (99:1) as eluent.

2; yield: 20.4 mg (18 %).

$C_{44}H_{35}N_9$	calc.	C 76.53	H 5.07	N 18.28
(689.9)	found	76.85	4.97	17.90

^{1}H NMR (200 MHz, $CDCl_3$/TMS): δ = 2.20 (s, 1 H, NH), 2.85 (s, 6 H, 2 × CH_3), 4.50 (s, 4 H, CH_2NHCH_2), 7.48 (m, 12 H, C_6H_5), 8.10 (m, 8 H, C_6H_5), 8.61 (s, 4 H, 2 × H-5,5′).

MS: *m/z* (%) = 689 (M^+, 21), 367 (14), 352 (28), 338 (100), 324 (13), 128 (21), 102 (26), 77 (26).

12; yield: 83 mg (71 %).

$C_{22}H_{19}N_5$	calc.	C 74.70	H 5.38	N 19.81
(353.4)	found	74.82	5.37	19.90

^{1}H NMR ($CHCl_3$/$CDCl_3$): δ = 1.77 (s, 2 H, NH_2), 2.83 (s, 3 H, CH_3), 5.10 (s, 2 H, CH_2), 7.35 (m, 6 H, C_6H_5), 8.02 (m, 2 H, C_6H_5), 8.18 (m, 2 H, C_6H_5), 8.55 (s, 2 H, H-5,5′).

MS: *m/z* (%) = 353 (M^+, 7), 338 (100), 324 (12), 297 (12), 194 (23), 154 (12), 128 (32), 102 (59), 77 (22).

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