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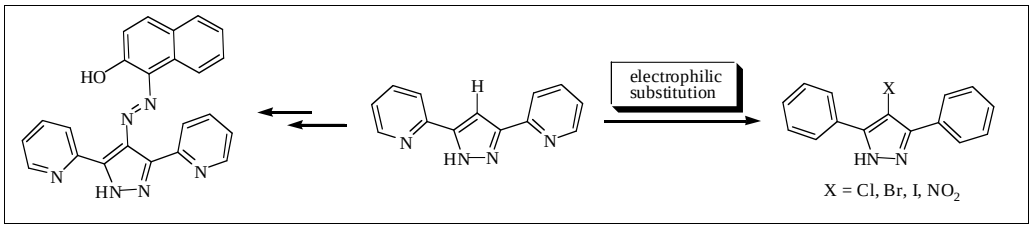

Several 4-substituted-3, 5-bis(2-pyridyl)-1*H*-pyrazoles, where the substituent is chloro, bromo, iodo, nitro, diazo, were synthesized under mild reaction conditions in high yields. The structures of the products were characterized by ^{1}H NMR, ^{13}C NMR, ESI-MS, IR and elemental analyses.

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Introduction.

Pyrazoles are important heterocyclic compounds, which have received considerable investigative attention with regard to their syntheses and their potential applications, including in medicine, agriculture, and other fields [1-3]. Research on the coordination chemistry of pyrazole-derived ligands has increased very rapidly in the last few years. Some of them are used to synthesize Ru or Mn complex to mimic the structure or function of the oxygen-evolving complex (OEC) in Photosystem II (PSII), which catalyzes the oxidation of water to molecular oxygen [4-7]. Recently, Llobet *et al*. presented the first example of a well characterized (from structural and electrochemical viewpoints) dinulear Ru complex capable of oxidizing water to O_2 in the homogeneous phase and in the absence of light. In this complex, the two metal Ru have been deliberately placed in close proximity and in an adequate orientation using the planar dinuclear 3,5-bis(2-pyridyl)pyrazole (Hbpp) (Figure 1) and the meridional 2, 2′; 6′,2′′-terpyridine (trpy) ligands. In connection with our research work on mimicking the OEC active center, we decided to step further based on Llobet's work by starting to synthesize 4-substituted Hbpp, which might be a starting candidate for the connection of a photosensitizer to the 4-position of Hbpp. But to the best of our knowledge, few of the 4-substituted derivatives for Hbpp has been reported. In this paper, we report the preparation of 4-chloro, bromo, iodo, nitro and diazo derivatives of Hbpp.

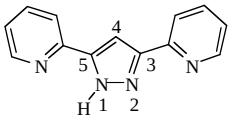


Figure 1

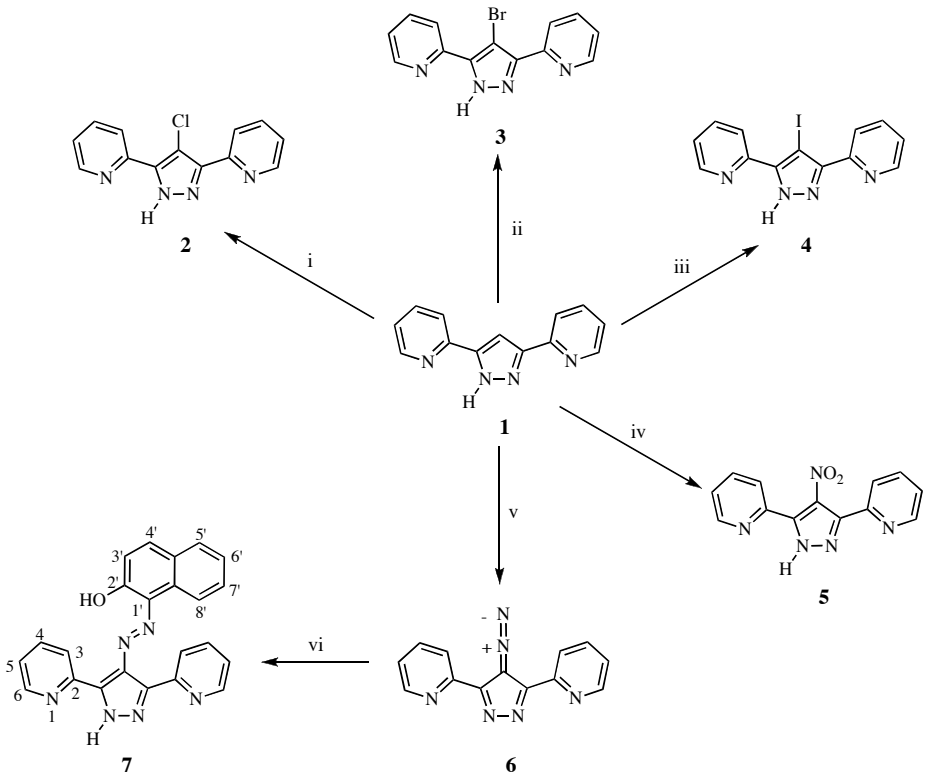
Results and Discussion.

Theoretically, the 4-position of Hbpp is expected to be difficult to attack by electrophilic reagents for its 3- and 5-position were substituted by two pyridine rings which bring strong passivation and steric hindrance. Of the several electrophilic substitutions, bromination was studied first. There are two usual reagents, bromine and *N*-bromo-acetamide, for the bromination of the 5-membered N-containing heterocycles. According to literature [8], we chose bromine as the electrophile. Thus, treatment of Hbpp with excessive bromine at 0-5 °C in the presence of aqueous sodium carbonate produced rapidly the anticipated 4-bromo product **3** in 85% yield. The ^{1}H NMR, ^{13}C NMR, ESI-MS and elemental analysis confirm the structure of this product. Compared to its parent molecule Hbpp, we observed that all of the peaks shift to lower field in its ^{1}H NMR spectrum after the introduction of 4-bromo, and the protons on 3-position of the two pyridine rings were much more affected. The iodination was performed in a similar way by using I_2 / KI in basic conditions, giving compound **4** in almost quantitative yield.

The chlorination reaction was performed by using Cl_2 dissolved in an aqueous solution of Na_2CO_3. We found the yield of 4-chloro derivative **2** was seriously affected by the ratio of chlorine and sodium carbonate, which was difficult to control. We optimised this reaction in acidic conditions [9]. Thus, the solution of Hbpp in HCl (6%) reacted with saturated chlorine in water at room temperature and the product **2** precipitated upon neutralization. The yield was improved to as high as 89%.

Nitration of Hbpp proceeded under different conditions. This reaction did not work at room temperature when using nitric acid alone or mixtures of nitric acid and sulfuric acid. According to the literature [9], this reaction can occur only in much more harsh conditions by using the

Scheme 1



i. saturated Cl_2 / H_2O, 6% HCl, 25 °C, 89%
ii. Br_2 / 1N Na_2CO_3 , 0-5 °C, 85%
iii. I_2 / KI / 1N Na_2CO_3, 25 °C, 98%
iv. 65% HNO_3 / 80%H_2SO_4, 100 °C, 80%
v. $NaNO_2$ / Ac_2O / HOAc, 25 °C, 79%
vi. β-naphthol / 1N NaOH / benzene, reflux, 84%

mixture of 65% nitric acid and 80% sulfuric acid at 100 °C for 6 h, and 4-nitro-Hbpp **5** was isolated in 80% yield under those conditions.

The preparation of heterocyclic amine is often tedious and the products are frequently unstable. Success in preparing 4-diazopyrazoles by direct introduction of the diazonium group led us to extend this work to Hbpp [10]. Treating Hbpp with sodium nitrite and acetic anhydride in an excess of acetic acid as solvent, we obtained a yellow solution of the diazonium salt. By neutralization, yellow 4-diazo-bpp **6** precipitated in 79% yield, which gave strong absorptions in the infrared at 2177 cm^{-1}. In order to identify the activity of this compound, coupling reaction was carried out with β-naphthol in boiling benzene to give a new red azo-dye **7**.

An attempt to formylate Hbpp under Vilsmeir-Haack conditions failed, although diverse experimental conditions were tried. It seems that the molecule Hbpp behaves like 1-*p*-nitrophenylpyrazoles [11] and 2-(pyrazol-1'-yl)pyridine [12], which are resistant to attack in this reaction.

From the results of these electrophilic substitution reactions, we may deduce that the 4-position of pyrazole ring in Hbpp easily undergoes this kind of reaction. These different 4-substitutent groups of Hbpp can be modified to afford further derivatives and at the same time make our work possible to be developed.

EXPERIMENTAL

The NMR spectra were recorded on a Varian INOVA spectrometer at 400 MHz. Chemical shifts were given in δ units relative to the tetramethylsilane (TMS) signal as an internal reference. IR were recorded on a NEXUS spectrometer. ESI-MS spectra were obtained on HP1100LCMS spectrometer. TOF MS EI+ spectra were obtained on GCT CA156. Melting points were measured on X-4 apparatus and not corrected. Elemental analyses were carried out on a CARLO ERBA MOD-1106 elemental analyzer. The starting material Hbpp was prepared according to the literature method [13,14].

4-Chloro-3, 5-bis(2-pyridyl)-1*H*-pyrazole (**2**).

Compound **1** (111 mg, 0.5 mmol) was dissolved in HCl (6%, 5 mL) and stirred at room temperature while a saturated solution of chlorine in water (25 mL) was added dropwise over a period of 20 minutes. After another 2 hours, the solution was neutralized with NaOH (1 *N*). The resulting pale pink precipitate was collected by filtration as crude product. The aqueous phase was

extracted with dichloromethane (2×20 mL). The organic phases were combined, dried with anhydrous Na_2SO_4, and the solvent was evaporated *in vacuo* to afford more product. Further purification was conducted by column chromatography on silica gel with eluent of CH_2Cl_2/MeOH (40:1, v/v) to give a pale pink solid, 114 mg (89%), mp 228-229 °C; ms: *m/z* 257.1 ($[M+H]^+$); ir (KBr): ν (NH) 3150 cm^{-1}; ^1H nmr ($CDCl_3$): δ 8.75 (brs, 2H, pyridyl H_6), 8.20 (d, $^3J_{3,4}$ = 7.6 Hz, 2H, pyridyl H_3), 7.87 (t, $^3J_{4,3}$ = $^3J_{4,5}$ = 7.6 Hz, 2H, pyridyl H_4), 7.36 (t, *J* = 6.0 Hz, 2H, pyridyl H_5); ^{13}C nmr ($CDCl_3$): δ 149.6, 148.9, 137.1, 123.4, 121.9, 107.2.

Anal. Calcd. for $C_{13}H_9ClN_4$: C, 60.83; H, 3.53; N, 21.83. Found: C, 60.72; H, 3.54; N, 21.68.

4-Bromo-3, 5-bis(2-pyridyl)-1*H*-pyrazole (**3**).

Compound **1** (111 mg, 0.5 mmol) was dissolved in 10 mL of CH_2Cl_2 at 0-5 °C. A solution of bromine (0.1 mL) in Na_2CO_3 (1N, 10 mL) was added. Stirring was continued for 30 minutes at 0-5 °C. Then, NaOH (1 *N*) was added until decolorization and organic phase was separated. The aqueous phase was extracted with dichloromethane (3×10 mL), the organic phases were combined and dried with anhydrous Na_2SO_4. The solvent was evaporated *in vacuo* to afford the crude product. Further purification was conducted by column chromatography on silica gel with eluent of CH_2Cl_2/MeOH (20:1, v/v) to give a pale yellow solid, 128 mg (85%), mp 202-204 °C; ms: *m/z* 301.0 ($[M+H]^+$); ir (KBr): ν (NH) 3141cm^{-1}; ^1H nmr ($CDCl_3$): δ 8.76 (d, $^3J_{6,5}$ = 4.0 Hz, 2H, pyridyl H_6), 8.27 (d, $^3J_{3,4}$ = 8.0 Hz, 2H, pyridyl H_3), 7.88 (t, $^3J_{4,3}$ = $^3J_{4,5}$ = 8.0 Hz, 2H, pyridyl H_4), 7.38 (t, *J* = 6.2 Hz, 2H, pyridyl H_5); ^{13}C nmr ($CDCl_3$): δ 149.5, 149.1, 144.9, 137.2, 123.5, 122.2, 91.6.

Anal. Calcd. for $C_{13}H_9BrN_4$: C, 51.85; H, 3.01; N, 18.60. Found: C, 51.60; H, 3.04; N, 18.37.

4-Iodo-3, 5-bis(2-pyridyl)-1*H*-pyrazole (**4**).

Compound **1** (111 mg, 0.5 mmol) was dissolved in CH_2Cl_2 (10 mL). A solution of Na_2CO_3 (1 *N*, 10 mL) containing iodine (190 mg, 0.75 mmol) and KI (250 mg, 1.5 mmol) was added. Stirring was continued for 4 hours at room temperature. Then, NaOH (1 *N*) was added until decolorization and organic phase was separated. The aqueous phase was extracted with dichloromethane (3×10 mL). The organic phases were combined, dried with anhydrous Na_2SO_4, and the solvent was evaporated *in vacuo* to afford the crude product. Further purification was conducted by column chromatography on silica gel with eluent of CH_2Cl_2/MeOH (40:1, v/v) to give a milk white solid, 171mg (98%), mp 191-192 °C; ms: *m/z* 349.0 ($[M+H]^+$); ir (KBr): ν (NH) 3229 cm^{-1}; ^1H nmr ($CDCl_3$): δ 8.72 (d, $^3J_{6,5}$ = 4.4 Hz, 2H, pyridyl H_6), 8.29 (d, $^3J_{3,4}$ = 7.6 Hz, 2H, pyridyl H_3), 7.84 (td, $^3J_{4,3}$ = $^3J_{4,5}$ = 7.8 Hz, $^4J_{4,6}$ = 1.6 Hz, 2H, pyridyl H_4), 7.34 (t, *J* = 6.0 Hz, 2H, pyridyl H_5); ^{13}C nmr ($CDCl_3$): δ 149.8, 149.4, 147.9, 136.9, 123.5, 122.4, 56.4.

Anal. Calcd. for $C_{13}H_9IN_4$: C, 44.85; H, 2.61; N, 16.09. Found: C, 44.99; H, 2.71; N, 16.02.

4-Nitro-3, 5-bis(2-pyridyl)-1*H*-pyrazole (**5**).

Compound **1** (222 mg, 1 mmol) was dissolved in H_2SO_4 (80%, 6 mL) at 0 °C. To this solution, a mixture solution of HNO_3 (65%, 3 mL) and H_2SO_4 (80%, 3 mL) was added dropwise over a period of 20 minutes. After the reaction mixture had been heated to 100 °C for 6 hours, it was cooled to room temperature. Then it was poured into ice (100 g) and carefully neutralized with Na_2CO_3. The resulting green precipitate was collected by filtration as crude product. The aqueous phase was extracted with dichloromethane (2×30 mL). The organic phase were combined and dried with anhydrous Na_2SO_4, and the solvent was evaporated *in vacuo* to afford more product. Further purification was conducted by column chromatography on silica gel with eluent of CH_2Cl_2/MeOH (40:1, v/v) to give a colorless solid, 213 mg (80%), mp 163-165 °C; ir (KBr): ν (NH) 3271 cm^{-1}, ν $(N=O)_{as}$ 1522 cm^{-1}, ν $(N=O)_{sym}$ 1376 cm^{-1}; ^1H nmr ($CDCl_3$): δ 8.69 (d, $J_{6,5}$ =3.3 Hz, 2H, pyridyl H_6), 7.95 (d, $^3J_{3,4}$ = 7.2 Hz, 2H, pyridyl H_3), 7.84 (t, $^3J_{4,3}$ = $^3J_{4,5}$ = 8.0 Hz, 2H, pyridyl H_4), 7.38 (t, *J* = 6.0 Hz, 2H, pyridyl H_5); ^{13}C nmr ($CDCl_3$): δ 149.7, 149.4, 137.3, 123.2, 123.0, 120.5, 102.2; TOF MS ES-: Calcd. 266.0678; Measured: 266.0686 [M-H]/1.

4-Diazo-3, 5-bis(2-pyridyl)pyrazole (**6**).

Compound **1** (222 mg, 1 mmol) was dissolved in acetic acid (20 mL). Acetic anhydride (0.5 mL, 5 mmol) was added, followed immediately by the addition of sodium nitrite (345 mg, 5 mmol). The solution was set aside at room temperature. After 24 hours and again after 48 hours, similar portions of acetic anhydride and sodium nitrite were added. At the end of the reaction, the mixture was poured into a stirred solution of sodium nitrite (345 mg) and HCl (2 *N*, 2 mL) in ice-water (30 mL). After stirring at 0-5 °C for 0.5 hour, additional sodium nitrite (175 mg) was added and stirred continually for another 1 hour. Then, the solution was neutralized with NaOH (4 *N*). A yellow solid was isolated as crude product. Further purification was conducted by column chromatography on silica gel with eluent of CH_2Cl_2/MeOH (40:1, v/v) to afford a yellow solid, 196 mg (79%), mp 194-196 °C; ir (KBr): ν (N=N) 2177 cm^{-1}; ^1H nmr ($CDCl_3$): δ 8.62 (d, $^3J_{6,5}$ = 4.8 Hz, 2H, pyridyl H_6), 8.40 (d, $^3J_{3,4}$ = 7.6 Hz, 2H, pyridyl H_3), 7.86 (td, $^3J_{4,3}$ = $^3J_{4,5}$ = 7.8 Hz, $^4J_{4,6}$ = 1.6 Hz, 2H, pyridyl H_4), 7.37-7.34 (m, 2H, pyridyl H_5); ^{13}C nmr ($CDCl_3$): δ 156.8, 150.5, 149.3, 137.0, 124.3, 120.9; TOF MS EI+: Calcd. 248.0810; Measured: 248.0820.

1-[3,5-Bis(2-pyridyl)pyrazol-4-yl-azo]-2-naphthol (**7**).

Compound **6** (50 mg, 0.2 mmol) and β-naphthol (45 mg, 0.3 mmol) were dissolved in 10 mL of benzene and five drops of NaOH (1 *N*) were added. The solution was refluxed for 2 hours and the solvent was removed *in vacuo*. The resulting deep red residue was purified on silica gel with eluent of CH_2Cl_2/MeOH (40:1, v/v) to afford a red solid, 66 mg (84%), mp 232-233 °C; ir (KBr): ν (OH) 3434 cm^{-1}, ν (NH) 3209 cm^{-1}, ν (N=N) 2188 cm^{-1}; uv-vis (CH_2Cl_2): [λ_{max} /(ε_{max}/dm^3 mol^{-1} cm^{-1})] 312 (13962), 492 (10396); ^1H nmr ($(CD_3)_2CO$): δ 8.79 (brs, 2H, pyridyl H_6), 8.25-8.15 (m, 2H, pyridyl H_3), 7.96 (t, $^3J_{4,3}$ = $^3J_{4,5}$ = 7.2 Hz, 2H, pyridyl H_4), 7.86 (d, $^3J_{4',3'}$ = 9.6 Hz, 1H, naphthol $H_{4'}$), 7.79 (d, *J* = 8.0 Hz, 1H, $H_{5'}$ or $H_{8'}$), 7.74 (d, *J* = 8.0 Hz, 1H, naphthol $H_{8'}$ or $H_{5'}$), 7.53 (brs, 1H, pyridyl H_5), 7.46 (brs, 1H, pyridyl H_5), 7.37-7.29 (m, 2H, naphthol $H_{6'}$, $H_{7'}$), 7.03 (d, $^3J_{3',4'}$ = 9.2 Hz, 1H, naphthol $H_{3'}$); ^{13}C nmr (DMSO-D_6): δ 160.7, 152.1, 149.3, 148.7, 148.0, 143.4, 136.7, 136.2, 134.0, 132.2, 129.2, 128.8, 127.9, 127.3, 124.4, 123.3, 123.1, 122.5, 122.4, 121.3, 120.7; TOF MS EI+: Calcd. 392.1386; Measured: 392.1387.

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