One-Step Synthesis of Symmetrically Substituted 2,6-Bis(pyrazol-1-yl)pyridine Systems

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A one-pot synthetic route that allows functionalization of the 2,6-bis(pyrazol-1-yl)pyridine backbone in the 4- and 4″-pyrazole positions by direct H(4)-pyrazole halogen exchange is described. The diiodo derivative in particular provides easy access to additional functionalities through both Sonogashira and Grignard exchange reactions. These synthons represent optimal building blocks for the extension of the chelating core and for the assembly of rigid organic and metalloorganic nanostructures.

Introduction

The classes of tridentate nitrogen donor ligands based on 2,6-bis(pyrazol-1-yl)pyridine[1] and 2,2′:6′,2″-terpyridine systems[2] (Figure 1) are known for their rich coordination chemistry[3–9] and have therefore been used widely in supramolecular assemblies,[10–14] molecular biology,[15] optical devices,[16] spin-crossover compounds[17–25] and even in photochemistry.[26]

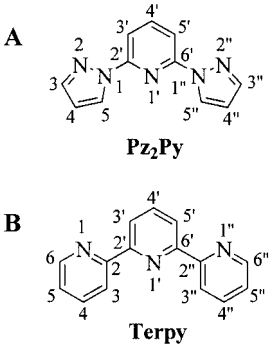

Figure 1. The tridentate nitrogen core in the 2,6-bis(pyrazol-1-yl)-pyridine (**A**) and in the terpyridine (**B**) systems, with ring substitution numbering.

The 2,6-bis(pyrazol-1-yl)pyridine core (**Pz_2Py**) is particularly attractive in comparison with the terpyridine scaffold, because both its electronic and its steric properties are readily altered by varying the substitution pattern on the pyrazole moiety. As a result, the synthesis of functionalized **Pz_2Py** compounds requires less effort than that of similarly substituted 2,2′:6′,2″ terpyridine synthons.[27–34] There are, however, some exceptions. While access to 3,5-functionalization in pyrazoles is fairly easy, since they are readily generated by sequential Claisen condensation to form 1,3-dicarbonyl precursors, followed by treatment with hydrazine for the heterorings closure,[1,35–37] those with substituents in position 4 are much less common, and often involve tedious multi-step approaches. For that reason several 3,3″-, 5,5″- or 3,3″,5,5″-**Pz_2Py** derivatives have been synthesized over the years, while there is still a need for an easy methodology for those featuring the 4,4″ pattern. This prompted us to seek such a procedure.

There are two possible synthetic routes towards a flexible 4,4″-**Pz_2Py** model. One method would rely on firstly assembling the pyrazole-4 derivative, followed by its nucleophilic reaction with 2,6-dibromopyridine, whereas the second would consist of the synthesis of the entire **Pz_2Py** backbone and subsequent functionalization of the core selectively at the 4- and 4″-positions. In the first approach, the synthetic methodology would include treatment of 4-lithiopyrazoles with electrophiles.[38] Such lithiated species are generated by N(H)-protection followed by electrophilic halogenation[39,40] or nitration[41] and subsequent lithium exchange. However, there are only few examples of pyrazole C-4 lithiation.[42–45] Such reactions proceed with low selectivity, due to competing deprotonation at C-5[42] or isomerization of the 4-lithiopyrazole to the corresponding 5-lithiopyrazole.[46] This problem can be circumvented through the introduction of a second protecting group at C-5,[47] but the overall multi-step synthesis makes such an option not very attractive, in our opinion. Here we describe a *one-pot* reaction that allows functionalization of the **Pz_2Py** backbone in the 4- and 4″-positions by direct H(4)-pyrazole halogen

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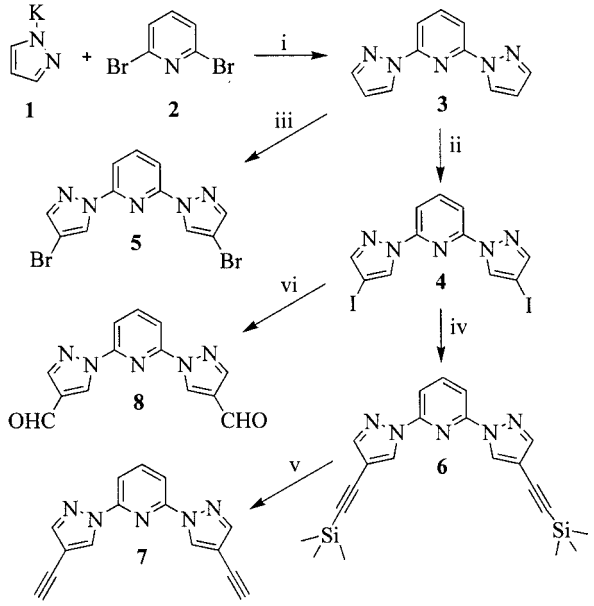
(iodine or bromine) exchange. These derivatives represent flexible building blocks for extending the nitrogen-containing chelating core through both Sonogashira and Grignard coupling reactions, affording new synthons for assembling rigid scaffolds.

Results and Discussion

The synthetic pathway towards the 4,4″-**Pz_2Py** derivatives begins with **3**, the unsubstituted **Pz_2Py** core, as shown in Scheme 1. Compound **3** is readily generated through nucleophilic reaction between pyrazole anion (**1**) and 2,6-dibromo-pyridine (**2**).[1] Although slow (≈ 72 hours) due to the inactivation of the second bromine group, once the first is replaced, the process always affords **3** in high yield. The reaction can also be carried out on large scale (grams).



Scheme 1. Synthetic route to 4,4″-pyrazole-functionalized 2,6-bis-(pyrazol-1-yl)pyridines: (**i**) (a) K metal, pyrazole, 70 °C, argon; (b) **2**, 110 °C, 72 h in argon. (**ii**) (a) CH_3COOH, H_2SO_4, **3**, 60 °C in argon; (b) $HIO_3/I_2/H_2SO_4$, 60 °C, 3 h. (**iii**) (a) CH_3COOH, H_2SO_4, **3**, 60 °C; (b) Br_2, 80 °C, 1 h. (**iv**) (a) dioxane, Et_3N, Pd^{II}, CuI, **4**, TMS, in argon, 80 °C, 30 min; (b) room temp., 1 h. (**v**) **6**, MeOH/THF, K_2CO_3, 3 h, room temp. (**vi**) (a) EtMgBr, THF, 90 min, 0–4 °C; (b) DMF, 60 min, 4 °C.

With the core **3** to hand, direct H→halogen exchange is very easy. A previous report described some electrophilic reactions (e.g., bromination, chlorination, nitration) performed on various 2-(pyrazol-1′-yl)pyridines,[48] but to the best of our knowledge there is no precedent for similar reactions with **3** as starting material. Direct halogenation of **3** affords the symmetrical 2,6-bis(4-iodopyrazol-1-yl)pyridine (**4**) and 2,6-bis(4-bromopyrazol-1-yl)pyridine (**5**) in very good (**4**: >80%) to good (**5**: 57%) yields. The key to the regiospecific introduction of the electrophile lies in slow addition of the iodinating or brominating agent to an acetic acid solution of **3**. In fact we found that only the 4-position was favoured kinetically when the *N*-protonation of pyrazole was carried out in an acid medium.[49] Since the 4,4″-substituted **Pz_2Py** species are not very soluble even in acetic acid, precipitation either drives the reaction to near completion, as found for compound **4**, or at least minimizes the extend of side products, in the case of **5**. Compound **4** is thus regarded as the ideal derivative for Sonogashira coupling reactions, since it is obtained both on gram scales and in high purity without the need for chromatographic separation on a column. The trimethylsilylacetylene (TMSA) reaction in the presence of base (Et_3N) and catalysts [$PdCl_2(PPh)_3$, CuI] takes place rapidly (<2 h) and affords 2,6-bis[4-(trimethylsilanylethynyl)pyrazol-1-yl]pyridine (**6**) in almost quantitative yield (91%). Comparable yields are obtained upon subsequent desilylation of **6** in the presence of base (K_2CO_3) to give 2,6-bis(4-ethynylpyrazol-1-yl)pyridine (**7**). Compound **7** can therefore be regarded as an alternative building block with respect to 5,5″-diethynyl-2,2′:6′,2″-terpyridine for the generation of large macrocyclic structures based on phenylethynyl nanoarchitectures.[50]

We explored the extent to which **4** is sensitive towards halogen–Grignard exchange reactions by taking 2,6-bis(4-formylpyrazolyl)pyridine (**8**) as a target molecule. We had previously reported the synthesis of **8**[51] by nucleophilic substitution between the potassium anion of pyrazole-4-carboxaldehyde and 2,6-dibromopyridine in diethylene glycol dimethyl ether. However, since the syntheses of pyrazole-4-carboxaldehyde via triformylmethane[52] (two steps) or pyrazole[49] (four steps) were both synthetically demanding, the efficiency of Grignard reactions carried out directly on **4** should provide an easier and much more flexible route. Surprisingly, though, compound **4** did not react with magnesium wire, either in THF or in glyme, even upon prolonged heating (glyme) up to 90 °C in the presence of CuI as initiator. There is literature precedent for similar behaviour, however, since it had also occurred with another 4-substituted pyrazole.[53] Nonetheless, on treatment of **4** with ethylmagnesium bromide (EtMgBr) as a stronger Grignard reagent in THF, the successful formation of the magnesiate derivative proceeded very smoothly. This derivative, as would be expected, is not very stable and needs to be kept below 4 °C under inert atmosphere. Furthermore, it is not soluble in THF and it forms a solid paste once the iodine–magnesium exchange is completed. This behaviour can be used to monitor the progress of the reaction directly. Nonetheless, slow addition of the electrophile initially results in the resolubilization of the solid, followed by formation of a dense flocculate. The carboxyaldehyde derivative **8** is then obtained in good yield (72%) after hydrolysis, in just three steps. Figure 2 shows the ^1H NMR spectra of the derivatives **4**–**7** (Figure 2, parts B–E) compared with the unsubstituted bispyrazolylpyridine backbone **3** (Figure 2, part A). After bromination or iodination of **3** the signal at δ = 6.48 ppm (dd, J = 4.2, 0.9 Hz, 2 H), representing the fingerprint of the 4,4″ hydrogens of the pyrazolyl moieties, disappears in **4** and **5**. Consequently this signal can be used to monitor the progresses of the electrophilic reactions.

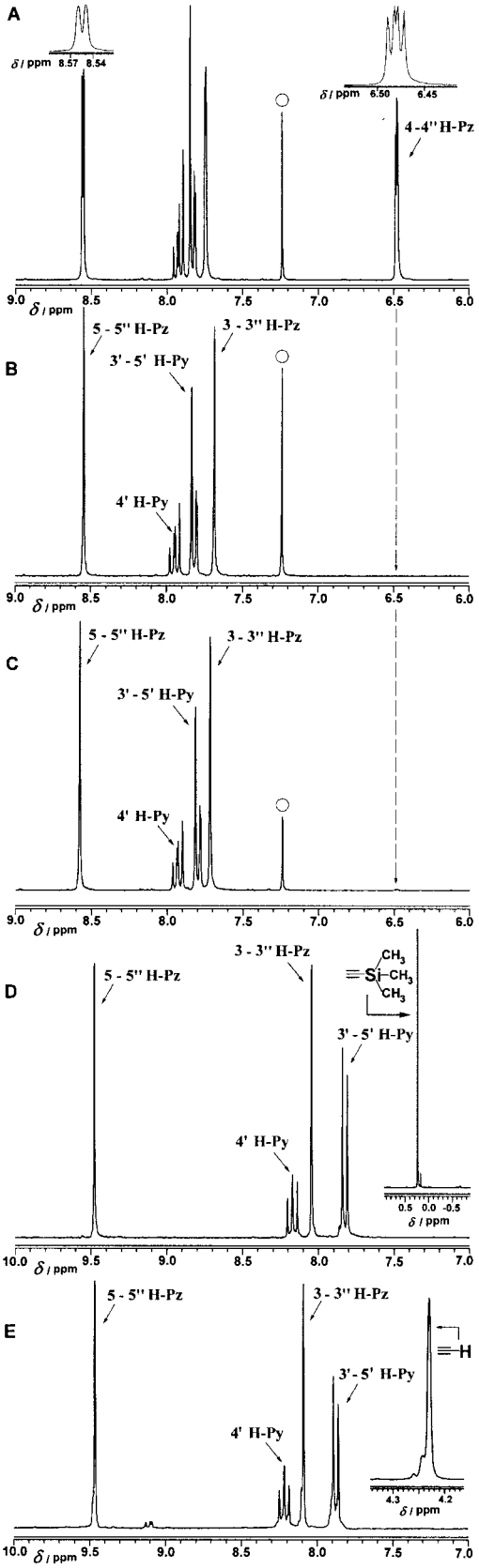


Figure 2. ^{1}H NMR spectra of compounds **3** (**A**), **5** (**B**), **4** (**C**), **6** (**D**) and **7** (**E**). The open circles (○) in (**A**), (**B**) and (**C**) indicate the solvent peak ($CDCl_3$). The spectra **D** and **E** were recorded in ([D_6]-DMSO).

Conclusion

In conclusion, a simple and efficient methodology for the straightforward halogen bisfunctionalization of the **Pz_2Py** core in the 4- and 4″-positions is described. The diiodo derivative in particular shows promising reactivity towards both Sonogashira and Grignard-exchange reactions. The utility of these synthons for assembling nanosized metallo-organic scaffolds and spin-crossover complexes is presently under investigation.

Experimental Section

General Methods: All the solvents (THF, Et_3N) were distilled before use and kept dry over molecular sieves. All the other reagents (2,6-dibromopyridine, pyrazole) were used as received. UV/Vis spectra were recorded with a Perkin–Elmer Spectrometer (UV/Vis/NIR Lambda 900) in a 1 cm optical path quartz cell at room temperature. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AMX 250 spectrometer. IR spectra were measured in KBr pellets (Nicolet 730 FT-IR spectrometer) at room temperature. Mass spectra were obtained on a VG ınstuments ZAB-2 FD-MS mass spectrometer. Elemental analyses were performed on a Foss Heraeus Varieo EL machine. Melting points were measured on a Büchi B-545 apparatus (uncorrected) in open-ended capillaries. Compound **3** was synthesized by the published procedures[1] but was purified in a different way, by column chromatography with a $CHCl_3$/hexane/ethyl acetate mixture (6:2:1). The unreacted 2,6-dibromopyridine (**2**) was eluted first (R_f = 0.9), followed by a small fraction of monocoupled impurity (2-bromo-6-pyrazol-1-yl)pyridine, (R_f = 0.8), and finally the product **3** (R_f range: 0.1–0.5).

2,6-Bis(4-iodopyrazol-1-yl)pyridine (4): 2,6-Bis(pyrazol-1-yl)pyridine (**3**, 0.3 g, 1.42 mmol) in a round-bottomed flask was treated under argon with acetic acid (4 mL) and H_2SO_4 (30% in water, 0.5 mL) and heated to 60 °C. A separately prepared deep violet aqueous solution (H_2O, 10 mL) containing HIO_3 (0.1 g, 0.57 mmol), I_2 (0.29 g, 1.14 mmol) and two drops of concentrated H_2SO_4 was slowly added to the solution of **3** in such way that the iodine was consumed before addition of the next drop. Only when half of this solution (5 mL) had been added were the remaining 5 mL dropped into the reaction mixture, which appeared heterogeneous due to the presence of a white flocculate. This was then left under argon at 60 °C for a further 3 h. After the mixture had cooled to room temperature, just enough $Na_2S_2O_3$ to quench the pale rose colour was added. A $NaHCO_3$/Na_2CO_3 (1:1 in H_2O) solution was used to neutralize the acetic acid/H_2SO_4 mixture (pH = 7–8) and the product 2,6-bis(4-iodopyrazol-1-yl)pyridine (**4**) was extracted with portions of $CHCl_3$ and air-dried. Recrystallization from benzene gave pure **4** (white sponge, 0.64 g, yield 97%). The product obtained was monitored by TLC (SiO_2) with a $CHCl_3$/hexane/ethyl acetate mixture (4:2:1). In this solvent mixture the starting material **3** exhibited R_f = 0.6, while **4** had R_f = 0.85. A very small amount of monoiodo derivative could be detected, with its R_f exactly in between (R_f = 0.72) those for **3** and **4**. However, no trace of the starting material **3** was detected in the crystalline product. When the TLC was run in the presence of Et_3N (5%) the small amount of impurity was not observed, so a part of **4** presumably decomposed on silica. The reaction can easily be scaled up by the same procedure, but it was optimized by working in more dilute solution, with the following proportions: 2,6-bis(pyrazol-1-yl)pyridine (1.2 g, 5.68 mmol) dissolved in acetic acid/H_2O/H_2SO_4 (16 mL/2 mL/2 mL 30%), then HIO_3 (0.408 g, 2.32 mmol), I_2 (1.18 g, 4.64 mmol), both dissolved in H_2O/H_2SO_4 mixture (60 mL/

4 drops). The heating was increased from 60 °C to 70 °C for only 1 h after complete addition of the iodinating agent. The yield after workup was a little lower, however (2.2 g, 82%). M.p. 188–189 °C. ^{1}H NMR (250 MHz, $CDCl_3$, 298 K): δ = 8.57 (s, 2 H, –CH), 7.96–7.90 [dd, $^3J_{H,H}$ = 6.95 Hz, 1.90 Hz, 1 H, –CH], 7.81–7.78 ($d_{asymmetric}$, $^3J_{H,H}$ = 7.27 Hz, 2 H, –CH), 7.72 (s, 2 H, –CH) ppm. ^{13}C NMR (63 MHz, $CDCl_3$, 298 K): δ = 150.0, 148.1, 142.7, 132.4, 110.4, 61.2 ppm. FT-IR (KBr): $\tilde{\nu}$ = 3149 (w), 3096 (w), 2874 (w), 1611 (m), 1586 (s), 1514 (m), 1466 (vs), 1422 (m), 1372 (s), 1314 (m), 1198 (m), 1145 (m), 963 (m), 950 (s), 801 (s), 601 (s) cm^{-1}. UV/Vis (CH_2Cl_2): λ_{max} (ε, mol^{-1} × cm^{-1}) = 262 (17020), 279 (sh, 13250), 286 (14590), 314 (23650). MS-FD ($CHCl_3$, 70 eV): *m*/*z* (%) = found 463.1 (100%) $[M]^+$, calcd. for $C_{11}H_7I_2N_5$ (463.02). $C_{11}H_7I_2N_5$ (463.02): calcd. C 28.53, H 1.52, N 15.13; found C 28.74, H 1.65, N 14.98.

2,6-Bis(4-bromopyrazol-1-yl)pyridine (5): 2,6-Bis(pyrazol-1-yl)pyridine (**3**, 1.0 g, 4.73 mmol) in a round-bottomed flask was charged with acetic acid (15 mL) and H_2SO_4 (10%, v/v in water, 2.0 mL) and was heated up to 60 °C. A separately prepared solution of Br_2 (d = 3.11 g·mL^{-1}, 0.364 mL, 7.102 mmol) diluted in acetic acid (10 mL) was slowly added dropwise to the 2,6-bis(pyrazol-1-yl)pyridine solution. When half of the bromine had been added, a dense inhomogeneous orange-yellowish mixture formed, showing the presence of a white flocculate. The Br_2 was then added more rapidly, and the temperature was increased to 85 °C and the mixture was left stirring for 1 h. After cooling to room temperature the mixture was quenched with aqueous $NaHCO_3$ and then Na_2CO_3 solutions until pH ≈ 9 was reached. Just enough $Na_2S_2O_3$ powder to destroy the excess of bromine was added. The white precipitate was extracted with $CHCl_3$ and the solvent was evaporated under reduced pressure. The 2,6-bis(4-bromopyrazol-1-yl)pyridine (**5**) was purified by column chromatography (SiO_2) and first eluted with a ethyl acetate/$CHCl_3$/hexane (1:1:6) mixture (R_f = 0.6). The impurities run after (R_f <0.5). Recrystallization from ethyl acetate/hexane (1:1) afforded pure **5** (1.0 g, yield 57%) as a white powder. ^{1}H NMR (250 MHz, $CDCl_3$, 298 K): δ = 8.55 (s, 2 H, –CH), 7.98–7.91 (dd, ^3J = 6.95 Hz, 2.21 Hz, 1 H, –CH), 7.84–7.80 ($d_{asymmetric}$, $^3J_{H,H}$ = 8.53 Hz, 2 H, –CH), 7.68 (s, 2 H, –CH) ppm. ^{13}C NMR (63 MHz, 298 K, $CDCl_3$): δ = 147.6, 141.3, 140.1, 125.5, 107.8, 95.2 ppm. FT-IR (KBr): $\tilde{\nu}$ = 3157 (w), 3097 (w), 2954 (w), 2923 (ws, ν_{CH} aliphatic), 2852 (w), 1735 (m), 1612 (vs), 1587 (vs), 1525 (m), 1471 (vs), 1428 (s), 1378 (vs), 1325 (s), 1273 (m), 1198 (ms), 1145 (s), 1032 (ms), 958 (vs), 848 (ms), 796 (vs), 775 (ms), 646 (m), 598 (s) cm^{-1}. MS-FD ($CHCl_3$, 70 eV) *m*/*z* (%) = found 369.2 (100%) $[M]^+$, calcd. for $C_{11}H_7Br_2N_5$ (369.01). $C_{11}H_7Br_2N_5$ (369.01): calcd. C 35.80, H 1.91, N 18.98; found C 35.64, H 2.02, N 18.74.

2,6-Bis(4-trimethylsilanylethynyl-pyrazol-1-yl)pyridine (6): 2,6-Bis(4-iodopyrazol-1-yl)pyridine (**4**, 0.36 g, 0.78 mmol) in a round-bottomed flask was charged with freshly distilled and anhydrous triethylamine (Et_3N, 10 mL) and dioxane (2 mL), together with dichlorobis(triphenylphosphane)palladium(II) $[Pd(PPh)_2Cl_2$, 55 mg, 0.078 mmol], triphenylphosphane (41 mg, 0.156 mmol) and CuI (20 mg, 0.1 mmol) as additional catalyst. The flask was evacuated and filled with argon. Trimethylsilylacetylene (0.71 g·mL^{-1}, 0.33 mL, 2.35 mmol) was added under argon by syringe, and the resulting mixture was heated to 80 °C for 30 min until it became dark-green/black. It was then cooled to room temperature and left stirring for one additional hour. The mixture was neutralized in an ice-bath with dilute HCl (20% in H_2O, v/v, added dropwise) and the product was extracted with portions of CH_2Cl_2 (3 × 20 mL). The orange-yellow organic phase was collected and washed with a saturated solution of NH_4Cl. The organic phase was collected and dried over $MgSO_4$, and the CH_2Cl_2 was evaporated under an air stream to afford a pale yellowish powder. The product, 2,6-bis(4-trimethylsilanylethynylpyrazol-1-yl)pyridine (**6**), was purified on a silica column (SiO_2) with a $CHCl_3$/hexane (5:3) mixture in the presence of Et_3N (5%) (R_f = 0.55). The impurities were eluted first (R_f = 0.8–0.9). After recrystallization from Et_2O, compound **6** was obtained as a fine yellowish powder (285 mg, yield 91%). The reaction can be scaled up to a gram of the starting material **4** without loss of yield. Compound **6** can be stored at room temperature for long time without decomposition. M.p. 132–133 °C (decomposed from yellow to dark brown powder before melting). ^{1}H NMR (250 MHz, [D$_6$]DMSO, 298 K): δ = 9.47 (s, 2 H, –CH), 8.16 (t, $^3J_{H,H}$ = 8.2 Hz, 1 H, –CH), 8.04 (s, 2 H, –CH), 7.83–7.80 (d, $^3J_{H,H}$ = 7.9 Hz, 2 H, –CH), 0.23 (s, 18 H, –CH_3) ppm. ^{13}C NMR (63 MHz, [D$_6$]DMSO, 298 K): δ = 148.7, 144.7, 143.0, 131.4, 128.7, 109.7, 105.1, 96.4, –0.1 [–Si(CH_3)$_3$] ppm. FT-IR (KBr): $\tilde{\nu}$ = 3139 (w), 3056 (w), 2958 (s, ν_{CH} aliphatic), 2896 (w), 2164 [vs, C≡C–Si(CH_3)$_3$], 1608 (s), 1582 (s), 1554 (m), 1471 (vs), 1435 (s), 1402 (s), 1348 (m), 1249 (s), 1180 (m), 1010 (vs), 966 (m), 952 (m), 858 (vs), 800 (s), 759 (m), 657 (m) cm^{-1}. MS-FD (CH_2Cl_2, 70 eV): *m*/*z* (%) = 404.8 (100%) $[M + H]^+$, calcd. for $C_{21}H_{26}Si_2N_5$ (404.64, $[M + H]^+$) $C_{21}H_{25}Si_2N_5$ (403.63): calcd. C 62.49, H 6.24, N 17.35; found C 62.16, H 6.42, N 17.10.

2,6-Bis(4-ethynylpyrazol-1-yl)pyridine (7): 2,6-Bis(4-trimethylsilanylethynylpyrazol-1-yl)pyridine (**6**, 150 mg, 0.372 mmol) was initially dissolved in a MeOH (99% dry)/THF mixture (5 mL/5 mL), and the reaction vessel was evacuated and filled with argon. Solid K_2CO_3 (52 mg, 0.376 mmol) was then added, and the mixture was left under argon at room temperature whilst stirring for 3 hours. Initially the organic mixture appeared bright yellow, and then became very dark. The organic solution was evaporated under an air stream, and the brown-yellowish residue was dissolved in CH_2Cl_2 (10 mL). A saturated solution of $NaHCO_3$ (5 mL) was added and the organic phase was extracted with portions of CH_2Cl_2 (2 × 10 mL). Collection of the organic layer, followed by drying over $MgSO_4$ and solvent evaporation under reduced pressure, afforded a pale yellowish residue containing 2,6-bis(4-ethynylpyrazol-1-yl)-pyridine (**7**). The residue was dissolved in the minimum amount of CH_2Cl_2 and loaded onto a column packed with neutral alumina (CH_2Cl_2/hexane/ethyl acetate 6:4:1). The first eluted yellowish fraction contained **7**. After solvent evaporation and recrystallization from ethyl acetate, compound **7** was collected as a pale yellowish powder (92 mg, yield 95%). When starting from **6** (0.60 g), **7** was obtained in 92% yield (0.36 g). The product **7** is stable at room temp. under air for days. M.p. >390 °C. ^{1}H NMR (250 MHz, [D$_6$]-DMSO, 298 K): δ = 9.41 (s, 2 H, –CH), 8.16 (t, $^3J_{H,H}$ = 8.2 Hz, 1 H, –CH), 8.04 (s, 2 H, –CH), 7.84–7.81 (d, $^3J_{H,H}$ = 8.2 Hz, 2 H, –CH), 4.23 (s, 2 H, ≡–CH) ppm. ^{13}C NMR (63 MHz, [D$_6$]DMSO, 298 K): δ = 149.1, 145.2, 143.4, 132.1, 110.0, 104.8, 83.3, 75.1 ppm. FT-IR (KBr): $\tilde{\nu}$ = 3280 (s, ν C≡C–H), 3157 (w), 3097 (w), 2962 (w, νCH aliphatic), 2921 (w), 1604 (s), 1581 (m), 1552 (m), 1479 (vs), 1434 (m), 1400 (m), 1346 (w), 1261 (m), 1207 (mw), 1095 (m), 1005 (s), 952 (s), 871 (m), 798 (vs), 671 (m) cm^{-1}. UV/Vis (CH_2Cl_2): λ_{max} (ε, mol^{-1} × cm^{-1}) = 263 (9810), 279 (sh, 9080), 286 (9570), 319 (12480), 351 (sh, 4100), 379 (broad, 850). MS-FD ($CHCl_3$, 70 eV): *m*/*z* (%) = 260.4 (100%) $[M + H]^+$, calcd. for $C_{15}H_{10}N_5$ (260.27, $[M + H]^+$). $C_{15}H_9N_5$ (259.27) calcd. C 69.49, H 3.50, N 27.01; found C 69.62, H 3.66, N 26.88.

1,1′-(Pyridine-2,6-diyl)bis(pyrazole)-4,4′-dicarboxaldehyde (8): 2,6-Bis(4-iodopyrazol-1-yl)pyridine (**4**, 300 mg, 0.648 mmol) was placed in dry THF (15 mL) in a round-bottomed Schlenk flask, evacuated and kept under argon while stirring. The solution was then cooled in an ice bath (0–4 °C). Through the rubber septum, a

cold solution of Grignard reagent (EtMgBr in diethyl ether, 1.43 mmol, 0.47 mL) was slowly added under argon (10 min) by syringe. After its complete addition the reaction mixture became heterogeneous and very pale pink. The mixture was left at 0 °C for a further 90 min. Then, dry DMF (0.12 mL, 1.6 mmol) was added slowly and the system was left to react at this temperature for 60 min. The ice bath was removed and the solution was allowed to warm up to room temperature. A milky mixture was obtained, showing the presence of a fine precipitate. Half of the THF solvent (≈ 7 mL) was removed under reduced pressure, and the residue was filtered. The collected precipitate was suspended into a solution of EDTA in water (10%, 10 mL), left whilst stirring for 3 min, collected by filtration in a Buchner funnel and further washed with cold portions of acetone (2×2 mL). Compound **8** was obtained as a fine yellowish powder (125 mg, yield 72%) which did not require further purification. The physical properties of **8** (^{1}H, ^{13}C, FT-IR, FD-MS, m.p.) were reported previously.[51]

Acknowledgments

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