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Synthesis and characterization of 2,6-bis-hydrazinopyridine, and its conversion to 2,6-bis-pyrazolylpyridines

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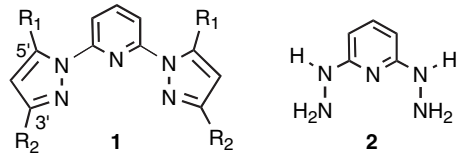
Abstract—2,6-Bis-hydrazinopyridine has been prepared and characterized for the first time. This material is useful for the preparation of a wide variety of 2,6-bis-pyrazolylpyridines. This approach represents the most efficient preparation to date of sterically crowded 2,6-bis-pyrazolylpyridines, and the only method for the preparation of pyrazolylpyridines containing unsymmetrically 3′,5′-disubstituted pyrazoles with the larger groups in the 5′ positions.

1. Introduction

Substituted pyridines have played a remarkably diverse role as chelating ligands in transition metal chemistry.[1] The potentially tridentate 2,6-bis-pyrazolylpyridines (e.g., **1**, Scheme 1) are one such class of ligands that have been recently reviewed.[2] While there are several examples of such ligands with large groups in the 3′ positions,[2–4] including chiral groups,[5] no examples having groups larger than methyl at the 5′ position have been reported, apparently because of difficulties in their preparation. To date, 2,6-bis-pyrazolylpyridines have been made almost exclusively by nucleophilic aromatic substitution reactions of pyrazole anions with 2,6-dihalopyridines.[2–5] Given the low reactivity of aryl halides and the poor nucleophilicity of even unhindered pyrazole anions, these reactions require rather severe conditions. For example, the reaction of 2,6-dibromopyridine with 3,5-dimethylpyrazolyl sodium or potassium required $\geq$110 °C for several days.[3] We have found that these reactions are quite sensitive to steric bulk, with more hindered 3,5-disubstituted pyrazole anions reacting very poorly with pyridyl halides even under forcing conditions. A recent report using similar conditions found that attempted Pd(II) catalysis actually inhibited the reaction.[6] A more efficient preparation of 2,6-bis-pyrazolylpyridines is needed to better explore the chemistry of these ligands.

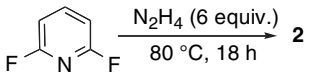


Scheme 1.

Arylhydrazines react readily with 1,3-diketones to provide *N*-arylpyrazoles in high yield.[7] We anticipated that reaction of 2,6-bis-hydrazinopyridine (BHP, **2**, Scheme 1) with 1,3-diketones would efficiently provide the desired 2,6-bis-pyrazolylpyridines. *N*-Arylpyrazoles have been made from 2-hydrazinopyridine[8] and 2-hydrazinoquinoline[9] and 1,3-diketones. However, the literature contains only obscure references to bis-hydrazine **2**,[10] with no details of its preparation or characterization. A recent review has noted both the potential utility of BHP in preparing 2,6-bis-pyrazolylpyridines and the lack of any published routes to it.[2]

2. Results and discussion

The preparation of BHP via reaction of a 2,6-dihalopyridine with hydrazine was studied. The 2,6-dihalopyridines (X=F, Cl, Br) are all commercially available; we chose 2,6-difluoropyridine (Scheme 2) because of its expected higher reactivity and, being the only liquid 2,6-dihalopyridine, it allowed for solvent-free reactions with hydrazine. In addition, ^{19}F coupling to the aryl protons provided



Scheme 2.

Keywords: 2,6-Difluoropyridine; Hydrazine; Hydrazinopyridine; Pyrazolylpyridine.
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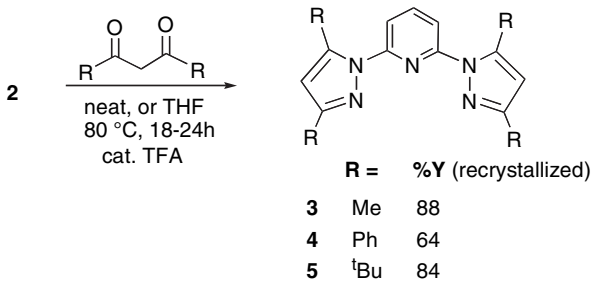
a simple way to monitor the presence of both starting material and the mono-hydrazino intermediate. We employed excess anhydrous hydrazine (6 equiv) to avoid significant amounts of polymer formation.[11] The reaction proceeds readily to the mono-hydrazino stage at room temperature, and disubstitution occurs with moderate warming (70–80°) overnight. Higher temperatures (~100 °C) cause decomposition (darkening) of the product. Surprisingly, these reactions are quite oxygen-sensitive; under argon, the mixtures are colorless to light yellow, while exposure to air rapidly results in extensive brown or black coloration and a dramatic loss in yield. Interestingly, this degradation is not evident by ^{1}H NMR; even largely impure samples are soluble in DMSO-d_6 and exhibit clean proton NMR spectra.

The isolation of pure BHP was not entirely straightforward. Simple recrystallization of the crude reaction mixture directly from deoxygenated water gave feathery yellow plates in an apparent yield of 88%. However, elemental analysis revealed that this material contained only 75–80% BHP, the remainder being $N_2H_4\cdot HF$ and water.[12]

The tendency of HF salts to contaminate BHP led us to study recrystallization from aqueous base, the idea being that neutralization of $N_2H_4\cdot HF$ would eliminate the presence of both hydrazine and fluoride salts. Indeed, neutralization of the HF salts in the crude product with an equimolar amount of aqueous NaOH caused immediate precipitation of the sparingly soluble NaF. After hot filtration (under inert atmosphere), 2,6-bis-hydrazino-pyridine crystallized in 85–95% yield as colorless to brownish rods. Elemental analysis showed no hydrazine, fluoride or water present in this material. These crystals were stable enough to be weighed in air, and appear to be indefinitely stable in the freezer under inert atmosphere. BHP is very soluble in DMSO, somewhat soluble in water and slightly soluble in THF. We have reported the crystal structures of BHP dihydrate, the di-tosylate salt and 2,6-bis-pyrazolylpyridine **5** (described below) elsewhere.[13]



Scheme 3.

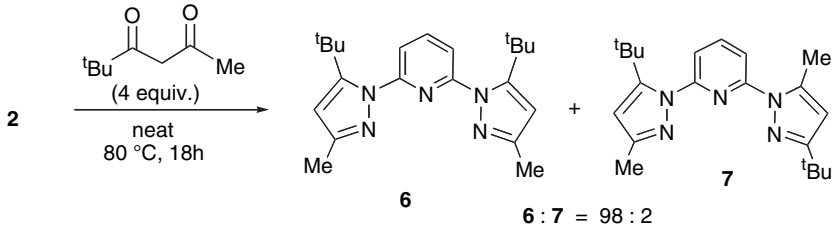
The preparation of 2,6-bis-pyrazoylpyridines from bis-hydrazine **2** is straightforward and generally quite efficient (Scheme 3). Treatment of **2** with an excess (4 equiv) of neat 2,4-pentanedione results in an exothermic reaction, and is easily complete at 80 °C overnight, providing the known[3,14] 2,6-bis-(3′,5′-dimethylpyrazolyl)pyridine (**3**) in 88% yield after recrystallization. More hindered diketones also react efficiently, aided by catalytic amounts of acid. For example, reaction of an excess (4 equiv) of dibenzoylmethane and 0.1 equiv of trifluoroacetic acid with BHP in refluxing THF yielded 64% (recrystallized) of the corresponding 2,6-bis-pyrazolylpyridine **4** after recrystallization. Likewise, neat 2,2,6,6-tetramethyl-3,5-heptanedione (4 equiv) reacted with **2** (80 °C, 0.1 equiv TFA) to yield 84% of 2,6-bis-pyrazolylpyridine **5** after recrystallization. Neither of pyrazolylpyridines **4** or **5** had been reported previously.

BHP also reacts with unsymmetrical 1,3-diketones to provide 2,6-bis-pyrazoylpyridines that are not easily obtained any other way. For example, GC–MS revealed that reaction of 2,2-dimethyl-3,5-hexanedione with BHP (80 °C, 24 h) yielded a 98:2 ratio of pyrazolylpyridines **6** and **7** (Scheme 4), and no detectable amounts (<ca. 0.1%) of the third possible isomer **8** (Scheme 5). Compounds **6** and **8** were easily identified by their proton NMR spectra; both were clearly symmetrical, and the 5′ methyls are more downfield (2.61 ppm) than the 3′ methyls (2.29 ppm), as is commonly observed in pyrazolylpyridines.[6] The regio-chemistry of **6** is easily rationalized by initial reaction of each NH_2 group of BHP with the less-hindered carbonyl group of the diketone, followed by cyclization of the remaining carbonyl onto the NH, placing the larger group immediately adjacent to the pyridine ring. Reactions of mono-amines with 1,3-diketones are known to form imines at the less-hindered carbonyl group.[15]

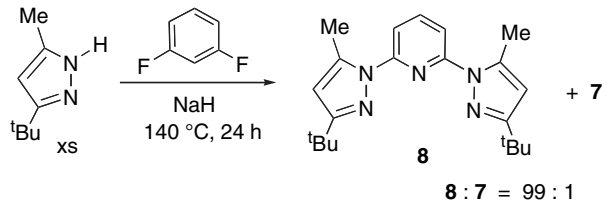
In contrast, unsymmetrical pyrazole anions are well known[5] to undergo arylation selectively at the less-hindered nitrogen, in this case yielding an entirely different isomer than that given by BHP. Reaction of the anion of 3-*tert*-butyl-5-methylpyrazole[16] with 2,6-difluoropyridine (140 °C, 24 h) produced a 99:1 mixture of pyrazolylpyridines **8** and **7** (Scheme 5), and no detectable amounts of **6** by GC–MS.

3. Conclusion

The use of BHP allows the preparation of new 2,6-bis-pyrazoylpyridines, particularly those with large groups at



Scheme 4.



Scheme 5.

the 5′ position of the pyrazole ring. Studies of electronic effects and application of this chemistry to the preparation of chiral non-racemic ligands for possible application in asymmetric synthesis are now in progress. We anticipate that BHP will be useful in several other applications.

4. Experimental

4.1. General

Unless specified otherwise, reagents and solvents were purchased from the Aldrich Chemical Company or from Acros Organics, and were used as received. 2,2-Dimethyl-3,5-heptanedione was obtained from Strem Chemical. NMR spectra were obtained at 300, 360 or 500 MHz for ^{1}H and 75, 90 or 125 MHz for ^{13}C. Spectra obtained in $CDCl_3$ were referenced to TMS (0 ppm) for ^{1}H and to solvent (77.0 ppm) for ^{13}C. Spectra obtained in DMSO-d_6 were referenced to solvent (2.48 ppm for ^{1}H, 39.5 ppm for ^{13}C). Selected IR peaks are reported in cm^{-1}, with the strongest peaks indicated by an (s). GC–MS was done on a Hewlett-Packard GCD using a 30 m×0.25 mm HP-5 capillary column with helium carrier and EI ionization. High-resolution mass spectra were obtained from the University of California, Riverside, mass spectroscopy facility. Elemental analyses were performed by Atlantic Microlabs, Norcross, GA. Melting points were calibrated against accepted standards.

4.1.1. 2,6-Bis-hydrazinopyridine (BHP, 2). Caution: 2,6-difluoropyridine is poorly miscible in hydrazine and the two-phase mixture can react violently if the addition is too fast or the stirring is not vigorous enough, especially on larger scales.

Under inert atmosphere and with vigorous stirring, 2,6-difluoropyridine (0.5 mL, 5.5 mmol) was cautiously added dropwise to anhydrous hydrazine (1.03 mL, 33 mmol). The mixture was heated to 80 °C for 18–24 h, then cooled to yield a yellow solid. This was treated with deoxygenated aqueous NaOH (2.2 M, 5 mL, 11 mmol, 2 equiv), which immediately yielded a white precipitate of sodium fluoride. The suspension was then warmed to 60–70 °C with stirring and, using a cannula, filtered hot through a small amount of Celite under inert atmosphere. Upon cooling, amber plates formed. After cooling to 0 °C, the supernatant was removed by cannula, the crystals were washed once with cold water and dried under vacuum to yield BHP (0.68 g, 89%), mp (sealed tube) 125–127 °C (dec). ^{1}H NMR (DMSO-d_6): 3.99 (4H, br s), 5.95 (2H, d, J=7.8 Hz), 7.01 (2H, s), 7.20 (1H, t, J=7.8 Hz). $^{13}C\{^{1}H\}$ NMR (DMSO-d_6): 94.7, 138.8, 161.6. IR (KBr pellet): 4435, 3295, 3258, 1594 (s), 1465 (s). HRMS: calcd for $C_5H_9N_5$=139.0858, found 139.0853. Anal. Calcd for $C_5H_9N_5$: C, 43.15; H, 6.52; N, 50.33. Found: C, 43.34; H, 6.47; N, 50.33.

4.2. Procedure for the preparation of 2,6-bis-pyrazolyl-pyridines (3–6) from BHP

Under inert atmosphere, BHP (250 mg, 1.8 mmol) was treated with neat 1,3-diketone (7.2 mmol, 4 equiv). Solid diketones were added as a solution in a minimum amount of THF. With hindered diketones, catalytic trifluoroacetic acid (0.18 mmol, 0.1 equiv) was added. The mixture was heated to 80 °C for 18–24 h. Excess diketone was removed by bulb-to-bulb vacuum distillation, and the residue was recrystallized from hexanes or hexanes/ethyl acetate. Column chromatography on silica gel using 20–40% ethyl acetate and 2% triethyl amine in hexanes can also be used. On a smaller scale, the products could be purified by preparative TLC eluted with 5–10% ethyl acetate and 1–2% triethylamine in hexanes.

4.2.1. 2,6-Bis-(3′,5′-diphenylpyrazolyl)pyridine (4). Sixty four percentage yield after recrystallization from ethyl acetate/hexanes, mp 165.5–167 °C. ^{1}H NMR ($CDCl_3$): 6.70 (2H, s), 7.12–7.18 (4H, m), 7.21–7.30 (6H, m), 7.33–7.47 (6H, m), 7.58 (2H, d, J=8 Hz), 7.81–7.91 (5H, m) $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): 106.6, 116.3, 125.9, 127.9, 128.0, 128.2, 128.6, 128.8, 130.7, 132.6, 140.2, 145.3, 150.8, 152.4. IR (KBr pellet): 1584, 1454 (s), 1353, 759, 694. Anal. Calcd for $C_{35}H_{25}N_5$: C, 81.53; H, 4.89; N, 13.58. Found: C, 81.32; H, 4.85; N, 13.55.

4.2.2. 2,6-Bis-(3′,5′-di-*tert*-butylpyrazolyl)pyridine (5). Eighty four percentage yield after recrystallization from hexanes, mp 161–162 °C. ^{1}H NMR ($CDCl_3$): 1.26 (18H, s), 1.32 (18H, s), 6.05 (2H, s), 7.58 (2H, d, J=8.1 Hz), 7.90 (1H, t, J=8.1 Hz). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): 30.4, 30.8, 32.0, 32.4, 102.0, 120.0, 139.8, 153.0, 154.1, 161.5. IR (KBr pellet): 2967 (s), 1592, 1465 (s), 1362, 1246, 820. HRMS: calcd for $C_{27}H_{41}N_5$=435.3362, found 435.3356. Anal. Calcd for $C_{27}H_{41}N_5$: C, 74.44; H, 9.49; N, 16.08. Found: C, 74.50; H, 9.68; N, 16.22.

4.2.3. 2,6-Bis-(5′-*tert*-butyl-3′-methylpyrazolyl)pyridine (6). Reaction was done according to the standard procedure using catalytic trifluoroacetic acid. GC–MS (HP-5, 60–300 °C at 10 °C/min, hold 6 min) of the crude product showed two peaks of mass 351, at 24.8 min (98%) and 25.7 min (2%), each having distinctly different fragmentation patterns, especially with respect to the base peaks. After removing excess diketone by Kugelrohr distillation, the residue was passed through a 3 cm column of silica gel using 50% ethyl acetate in hexanes to give **6** as an amber oil in 90% yield. The major product **6** could also be isolated by preparative TLC. ^{1}H NMR ($CDCl_3$): 1.24 (18H, s), 2.29 (6H, s), 6.02 (2H, s), 7.52 (2H, d, J=7.8 Hz), 7.94 (1H, t, J=7.8 Hz). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): 13.5, 30.7, 32.2, 105.3, 120.7, 140.2, 148.7, 152.9, 154.7. MS (EI): 351, 336, 229 (base), 203, 160, 123. IR (thin film): 2966, 1595, 1579, 1466 (s), 1355, 1014, 814, 792. HRMS: calcd for $C_{21}H_{29}N_5$=351.2423, found 351.2435. The minor isomer **7** gave the following MS: 351, 336 (base), 137.

4.2.4. 2,6-Bis-(3′-*tert*-butyl-5′-methylpyrazolyl)pyridine (8). A conical flask was charged with 3-*tert*-butyl-5-methylpyrazole[16] (112 mg, 0.81 mmol, 2.2 equiv), sodium hydride (43 mg, 1.8 mmol, 5 equiv) and a stir bar. Under inert atmosphere, anhydrous diglyme (0.5 mL) and 2,6-difluoropyridine (33 μL, 0.36 mmol, 1 equiv) were added and the mixture was heated to 140 °C overnight. The crude product was extracted into CH_2Cl_2 and analyzed by GC–MS as for compound **6** above. Two compounds of mass 351 were observed at 25.7 min (1%, **7**) and 27.0 min (99%, **8**), each having very distinct fragmentation patterns. The major isomer was purified by preparative TLC (10% ethyl acetate and 2% triethylamine in hexanes) to yield 29 mg (23%) of **8** as a white solid, mp 131–134 °C. ^{1}H NMR ($CDCl_3$): 1.35 (18H, s), 2.61 (6H, s), 6.08 (2H, s), 7.72 (2H, d, $J=8$ Hz), 7.87 (1H, t, $J=8$ Hz). $^{13}C\{^1H\}$ NMR ($CDCl_3$): 14.3, 30.3, 32.2, 105.7, 113.6, 140.3, 140.6, 151.7, 162.9. MS (EI): 351 (base), 336, 294, 160. IR (KBr pellet): 2964, 1599, 1585, 1487, 1468 (s), 1431, 1363, 1076, 798. HRMS: calcd for $C_{21}H_{29}N_5=351.2423$, found 351.2420.

Acknowledgements

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11. With lesser amounts of hydrazine, increasing amounts of an insoluble white material, considered to be polymer, were observed.
12. In the elemental analysis, given that the reactions had gone to completion, the percent carbon indicated the amount of BHP present, and percent F and O revealed the amounts of HF and H_2O, respectively. The amount of nitrogen in excess of that contributed by BHP was calculated, indicating an equimolar ratio of HF and N_2H_4.
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