Pergamon

Tetrahedron Vol. 51, No. 42, pp. 11393-11400, 1995

0040-4020/95 $9.50+0.00

0040-4020(95)00699-0

Strategies for the Synthesis of Unsymmetrical Quaterpyridines Using Palladium-Catalyzed Cross-Coupling Reactions

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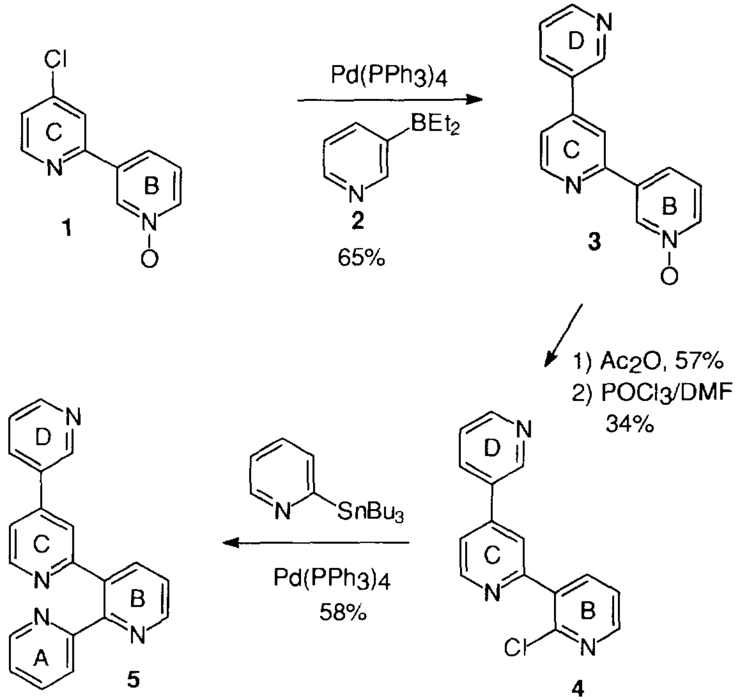
Key Words
Pd cross-coupling, bipyridine, quaterpyridine, N-oxide synthon

Abstract: Model, unsymmetrical quaterpyridines were prepared by Pd(0)-catalyzed cross-coupling of a pyridyl borane or stannane to a chlorinated bipyridine. A pyridyl N-oxide synthon was used to introduce regioselectively the required α-chloro group.

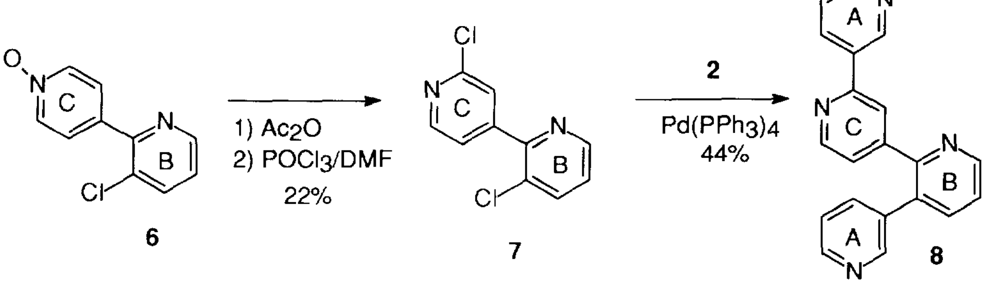
Unsymmetrical and unsubstituted quaterpyridines (QTPY) of the type A-B-C-D where the letters represent individual pyridine rings are largely unknown substances. Of the 426 theoretically possible structures, just seven were reported prior to the start of our investigations. Many contain the 2,2′-bipyridine unit because of the interesting ability of this bipyridine (BPY) to coordinate various metal ions. Five are symmetrical structures of the type A-B-B-A; they are easily prepared by homocoupling the A-B portions under a variety of conditions. Of the two unsymmetrical QTPYs, both[7,8] originally were assigned incorrect structures that have been corrected.[9,10]

We now demonstrate a strategy that has considerable generality for the synthesis of unsymmetrical QTPYs of the types A-B-C-D and A-B-C-A. Individual pyridine rings are joined together in the presence of a Pd(0) catalyst using a pyridyl halide and an organometallic reagent such as a stannane (Stille coupling) or a pyridyl borane (Suzuki coupling[12]). We start with two different model BPYs that comprise the central B-C portion, one linked 2,4′ and the other 2,3′ and show how to functionalize selectively one pyridine ring at a time in order to achieve selective cross-coupling. Liberal use is made of a pyridine N-oxide synthon and its specific conversion into an α-chloro pyridine suitable for the metal-catalyzed cross-coupling.[2] In one instance the N-oxide atom was introduced onto the preformed BPY by controlled N-oxidation while in another example a stannylated pyridine N-oxide directly gave N-oxidized BPY on cross-coupling with a chloropyridine.

Scheme 1



Scheme 2



Results and Discussion

The A-B-C-D Geometry of 2,2′:3′,2′′:4′′,3′′′-Quaterpyridine (5). The known B-C precursor, 4-chloro-2,3′-bipyridine 1′-oxide[13] (**1**) in Scheme 1, was made from 2,4-dichloropyridine and diethyl(3-pyridyl)borane (**2**) by Pd(0) coupling followed by regioselective N-oxidation at the sterically less hindered nitrogen atom. To this was added the D-ring in the form of **2** in the presence of Pd(0) to yield terpyridine **3**. The presence of the N-oxide group in **3** allowed the specific conversion of the B-ring to chloride **4**. It was advantageous to carry out this conversion in a two-step rather than a one-step sequence, first making with acetic anhydride the pyridone and then converting it into the chloride with $POCl_3$/DMF. With the two-step approach the more sterically hindered α position was specifically functionalized. Direct conversion of the N-oxide with $POCl_3$/DMF was not attempted because often a mixture of both the α and γ chlorinated products is produced.[14] Proof that the conversion of N-oxide **3** to the more hindered α-chloride actually took place to give terpyridine **4** was easily demonstrated by the coupling pattern of the B-ring which contained three highly coupled protons and not just two as would have resulted from the undesired α′ or γ chloro isomers. Eight of the ten different proton signals in **4** ($CDCl_3$) are clearly resolved making their assignment quite easy. Addition of the A-ring by means of 2-(tributylstannyl)pyridine[15] with Pd(0) completed the synthesis to give **5**.

Clearly in our synthesis the bonding site of the A and D pyridyl rings easily could have been varied by using an isomerically metallated pyridine starting material. In this way and by keeping the same bonding pattern of the original B and C rings a total of nine quaterpyridines could easily have been prepared.

The A-B-C-A Geometry of 3,3′:2′,4′′:2′′,3′′′-Quaterpyridine (8). 3-Chloro-2,4′-bipyridine 1′-oxide (**6**) in Scheme 2 was easily prepared from 2,3-dichloropyridine and 4-(tributylstannyl)pyridine N-oxide[16] by the palladium route. We assume that coupling took place at the 2 and not the 3 position as expected from a consideration of the mechanism of oxidative addition of palladium which usually takes place at the site more easily undergoing nucleophilic attack.[17-19] Again, the N-oxide was converted to the α chloro derivative by the two-step acetic anhydride-$POCl_3$ method to give dichloride **7** which then with **2** and Pd(0) gave the quaterpyridine **8** having the same two 3-pyridyl terminal rings. Others have used a similar approach first making the B-B portion followed by coupling to form an A-B-B-A QTPY having methyl groups.[20] Had our assumption been wrong about the site of coupling in the first cross-coupling step to prepare **6** in Scheme 2, the final product would have been an isomeric QTPY natural product called nemertelline that we have independently prepared by a convergent synthesis.[9]

Clearly, chloro N-oxide **6** could have been cross-coupled to some other pyridine ring and then the N-oxide of the resultant terpyridine could have been converted to a new chloride as we have done. This new terpyridine, in turn, could have been cross-coupled to a different fourth ring to give a family of nine isomeric QTPYs of the A-B-C-D type.

Chemical shift assignments for the QTPYs found in the Experimental Section are based on COSY and NOE difference spectra of samples in $CDCl_3$. Because there is less signal overlap for these compounds when dissolved in CD_3OD, it is useful to record spectra with both solvents.

Overview of QTPY Preparations. All three isomers of the potential stannyl pyridine[15] starting materials are known as well as the three corresponding boranes.[21] However, the 2-pyridyl borane has never been cross-coupled in a reaction with Pd because it forms an unusually stable cyclic dimer resembling a dihydroanthracene.[22] The 3- and 4-stannylated pyridine N-oxides are easily prepared but the 2 isomer is still unknown.[16]

A large number of mono and dihalogenated pyridines are commercially available for the preparation of BPYs by coupling routes. Still other dihalides may now be prepared by direct lithiation of a suitably activated pyridine with LDA followed by halogenation of this lithiated material.[23,24]

Cross-couplings of dihalopyridines may be made to be selective by the choice of the halogen where the reactivity order is I > Br > Cl and by the realization that the α and γ positions are more reactive than a β position when the halides are the same. Thus, considerable control in the preparation of the crucial central BPYs is possible.

Experimental Section

Diethyl(3-pyridyl)borane, phosphorus oxychloride, 2,3-dichloropyridine, 57-80% m-chloroperbenzoic acid (MCPBA), tributyltin chloride, 2.5 M n-BuLi tetrakis(triphenylphosphine)palladium(0), and 2-bromopyridine were purchased from Aldrich Chemical Company. Flash chromatography made use of Kieselgel 60 230-400 mesh or alumina 80-200 mesh. Grignard reactions were initiated with I_2 or 1,2-dibromoethane. Solvents were freshly distilled in most cases and degassed by bubbling N_2 through them for 15-30 min. All melting points are uncorrected. The drying agent was either sodium or magnesium sulfate.

3,2′:4′,3′′-Terpyridine 1-oxide (3): A solution of 4-chloro-2,3′-bipyridine-1′-oxide[13] (**1**) (500 mg, 2.42 mmol), diethyl(3-pyridyl)borane (**2**) (427 mg, 2.90

mmol), and $(PPh_3)_4Pd(0)$ (140 mg, 0.121 mmol) in degassed THF (30 mL) was stirred at room temperature for 0.25 h under N_2. Potassium carbonate (669 mg, 4.84 mmol) in H_2O (10 mL) was then added and the mixture was heated at reflux for 36 h. Following concentrated to a slurry, 50 mL of MeOH was added. The insoluble K_2CO_3 was removed and the filtrate was concentrated onto Kieselgel (2 g). Column chromatography with 80/20 EtOAc/MeOH gave 390 mg (1.56 mmol) of a white solid (mp > 200 °C, 65% yield). ^1H NMR ($CDCl_3$) δ 9.00 (1H, s), 8.95 (1H, d, J = 2 Hz), 8.83 (1H, d, J = 5 Hz), 8.75 (1H, dd, J = 2 and 5 Hz), 8.31 (1H, dd, J = 2 and 6 Hz), 8.00 (2H, m), 7.91 (1H, s), 7.58 (1H, d, J = 5 Hz), 7.50 (1H, dd, J = 5 and 9 Hz), 7.44 (1H, dd, J = 6 and 9 Hz). Anal. Calcd. for $C_{15}H_{11}N_3O.1/2H_2O$: C, 69.75; H, 4.68; N, 16.27. Found: C, 69.42; H, 4.34; N, 16.07.

2-Chloro-3,2′:4′,3′′-terpyridine (4): A suspension of 3,2′:4′,3′′-terpyridine 1-oxide (**3**) (350 mg, 1.40 mmol) in acetic anhydride (10 mL) was heated at reflux for 24 h. The mixture was concentrated to a brown oil and dissolved in 30 mL of MeOH which was decolorized with charcoal and then filtered through Celite. The filtrate was concentrated to a yellow solid and washed with 30 mL of diethyl ether to give 200 mg (0.802 mmol) of the pyridone (mp 168–172 °C decomp., 57% yield). ^1H NMR ($DMSO-d_6$) δ 8.98 (1H, d, J = 2 Hz), 8.95 (1H, d, J = 1 Hz), 8.70 (2H, m), 8.50 (1H, dd, J = 2 and 8 Hz), 8.18 (1H, dt, J = 2, 2 and 9 Hz), 7.69 (1H, dd, J = 2 and 6 Hz), 7.59 (2H, m), 6.44 (1H, dd, J = 6 and 9 Hz). This material was not further purified and was used as such in the next step.

A suspension of this 3,2′: 4′,3′′-terpyrid-2-one (200 mg, 0.812 mmol) in $POCl_3$ (5 mL) and DMF (1 mL) was heated at reflux for 8 h under N_2. The mixture was concentrated to a brown oil and Na_2CO_3/ice/H_2O was added until basic to pH paper. The aqueous phase was extracted with 50 mL of EtOAc and the organic phase was dried and concentrated to an oil. Column chromatography with Kieselgel and 80/20 EtOAc/MeOH gave 75 mg (0.28 mmol, 34% yield) of a yellow solid (mp 147–149 °C). ^1H NMR ($CDCl_3$) δ 8.96 (1H, dd, J = 1 and 2 Hz), 8.84 (1H, dd, J = 1 and 6 Hz), 8.73 (1H, dd, J = 2 and 5 Hz), 8.50 (1H, dd, J = 2 and 5 Hz), 8.07 (1H, dd, J = 2 and 8 Hz), 8.01 (2H, m), 7.57 (1H, J = dd, 2 and 6 Hz), 7.48 (1H, ddd, J = 1, 5 and 9 Hz), 7.43 (1H, dd, J = 5 and 8 Hz). Anal. Calcd. for $C_{15}H_{10}N_3Cl.1/2\ H_2O$: C, 65.10; H, 4.01; N, 15.19: Found: C, 65.40; H, 3.73; N, 15.18.

2,2′:3′,2′′:4′′,3′′′-Quaterpyridine (5): A solution of 2-chloro-3,2′: 4′,3′′-terpyridine (**4**) (70 mg, 0.26 mmol) and $(PPh_3)_4Pd(0)$ (15 mg, 0.013 mmol) in degassed toluene (20 mL) was stirred at reflux for 15 min under N_2. 2-(Tributylstannyl)pyridine[illegible] (100 mg , 0.261 mmol) was added in three equal portions over 1 h. The mixture was stirred at reflux for 48 h and then concentrated to an oil. Column chromatography with alumina and 80/20 EtOAc/hexanes gave 45 mg (0.15 mmol, 58% yield) of a clear oil. ^{1}H NMR ($CDCl_3$) δ 8.80 (H6′, 1H, dd, J = 2 and 5 Hz), 8.70 (H6′′, 1H, d, J = 6 Hz), 8.63 (H6′′′, 1H, dd, J = 1 and 5 Hz), 8.58 (H2′′′, 1H, d, J = 2 Hz), 8.49 (H6, 1H, dt, J = 1, 2 and 6 Hz), 8.14 (H4′, 1H, dd, J = 2 and 9 Hz), 7.77-7.65 (H3, H4 and H4′′′, 3H, m), 7.50 (H5′, 1H, dd, J = 5 and 9 Hz), 7.39 (H5′′, 1H, dd, J = 2 and 6 Hz), 7.35 (H5′′′, 1H, dd, J = 5 and 9 Hz), 7.27-7.22 (H3′′ and H5, 2H, m). ^{13}C NMR ($CDCl_3$) δ for CH: 119.78, 122.71, 122.86, 123.26, 123.74, 124.58, 134.21, 136.53, 138.69, 148.02, 148.99, 149.31, 150.09, 150.24. The following quaternary carbons are less certain due to low intensity: 133.74, 135.61, 144.96, 156.28, 158, 158. Anal. Calcd. for $C_{20}H_{14}N_4$: C, 77.40; H, 4.55; N, 18.05. Found: C, 77.12; H, 4.56; N, 18.03.

3-Chloro-2,4′-bipyridine 1′-oxide (6): A degassed toluene (5 mL) solution of 2,3-dichloropyridine (400 mg, 2.70 mmol) and $(PPh_3)_4Pd(0)$ (156 mg, 0.0135 mmol) was heated at reflux under N_2 for 1 h. A toluene (5 mL) solution of 4-(tributylstannyl)pyridine N-oxide[25] (1.04 g, 2.70 mmol), prepared by N-oxidation of 4-stannylpyridine,[16] was added in 1 mL portions over the next 5 h. The mixture was stirred at reflux for 24 h and then cooled to room temperature. The mixture was filtered through Celite to remove catalyst and the filtrate was concentrated to an oil. Column chromatography with Kieselgel and 80/20 EtOAc/MeOH gave 290 mg (1.40 mmol) of a yellow solid (mp, 135-139 °C, 52% yield). ^{1}H NMR ($CDCl_3$) δ 8.62 (1H, dd, J = 2 and 6 Hz), 8.28 (2H, d, J = 7 Hz), 7.84 (3H, m), 7.31 (1H, dd, J = 6 and 8 Hz). Anal. Calcd. for $C_{10}H_7ClN_2O.1/2H_2O$: C, 55.69; H, 3.74; N, 12.99. Found: C, 55.77; H, 3.68; N, 13.35.

2′,3-Dichloro-2,4′-bipyridine (7): A suspension of 3-chloro-2,4′-bipyridine 1′-oxide (**6**) (210 mg, 1.02 mmol) in acetic anhydride (10 mL) was heated at reflux for 6 h. The mixture was concentrated to an oil and dissolved in 10 mL of MeOH which was decolorized with charcoal, filtered through Celite, and concentrated to give 170 mg (0.832 mmol, 81% yield) of a slightly yellow oil. The material was dissolved in $POCl_3$ (5 mL) and DMF (1 mL) and heated at reflux for 24 h. Following concentration, Na_2CO_3/ice/H_2O was added until slightly basic to pH paper. The aqueous phase was extracted with 50 mL of EtOAc and the organic phase was dried and concentrated to an oil. Column chromatography with Kieselgel and 100% EtOAc gave 40 mg (0.18 mmol, 22% yield, mp 162-167 °C) of a yellow solid . ^{1}H NMR ($CDCl_3$) δ 8.63 (1H, dd, J = 2 and 5 Hz), 8.50 (1H, dd, J = 1 and 6 Hz), 7.85 (1H, dd, J = 2 and 9 Hz), 7.73 (1H, dd, J = 1 and 2 Hz), 7.62 (1H, dd, J = 2 and 5 Hz), 7.33 (1H, dd, J = 5 and 9 Hz). Anal. Calcd. for $C_{10}H_6N_2Cl_2$: C, 53.36; H, 2.69; N, 12.45. Found: C, 53.55; H, 2.60; N, 12.44.

3,3′:2′,4′′:2′′,3′′′-Quaterpyridine (8): A degassed THF (10 mL) solution of 2′,3-dichloro-2,4′-bipyridine (**7**) (40 mg, 0.18 mmol), diethyl(3-pyridyl)borane (**2**) (65 mg, 0.44 mmol), and $(PPh_3)_4Pd(0)$ (21 mg, 0.018 mmol) was stirred at room temperature under N_2 for 15 min. Sodium bicarbonate (60 mg, 0.711 mmol) in degassed H_2O (5 mL) was added and the mixture was heated at reflux for 48 h. After cooling to room temperature and dilution with 30 mL of EtOAc, the organic phase was dried and concentrated to an oil. Column chromatography with Kieselgel and 80/20 EtOAc/MeOH gave 25 mg (0.081 mmol, 44% yield) of an oil. δ ^{1}H NMR ($CDCl_3$) δ 9.00 (H2′′′, 1H, d, J = 2 Hz), 8.83 (H6′, 1H, dd, J = 2 and 5 Hz), 8.68-8.56 (H6′′, H6′′′, H2 and H6, 4H, m), 8.18 (H4′′′, 1H, dt, J = 2, 2 and 9 Hz), 7.87-7.77 (H4′ and H4, 2H, m), 7.56 (H3′′, 1H, dd, J = 1 and 2 Hz), 7.50 (H5′, 1H, dd, J = 5 and 9 Hz), 7.37 (H5′′′, 1H, ddd, J = 2, 5 and 9 Hz), 7.29 (H5, 1H, ddd, J = 2, 5 and 9 Hz), 7.14 (H5′′, 1H, dd, J = 2 and 6 Hz). Anal. Calcd. for $C_{20}H_{14}N_4$: C, 77.40; H, 4.55; N, 18.05. Found: C, 77.10; H, 4.56; N, 18.05.

References

1. Constable, E. C. *Tetrahedron* **1992**, *48*, 10013.
2. Downard, A. J.; Honey, G. E.; Phillips, L. F.; Steel, P. J. *Inorg. Chem.* **1991**, *30*, 2259.
3. Honey, G. E.; Steel, P. J. *Acta Crystallogr.* **1991**, *C47*, 2247.
4. Kauffmann, T.; Otter, R.; Greving, B.; König, J.; Mitschker, A.; Wienhöfer, E. *Chem. Ber.* **1983**, *116*, 479.
5. Constable, E. C.; Elder, S. M.; Healy, J.; Tocher, D. A. *J. Chem. Soc., Dalton Trans.* **1990**, 1669.
6. Morgan, R. J.; Baker, A. D. *J. Org. Chem.* **1990**, *55*, 1986.
7. Kem, W. R.; Scott, K. N.; Duncan, J. H. *Experientia* **1976**, *32*, 684.
8. Ward, M. D. *J. Chem. Soc. Dalton Trans.* **1993**, 1321.
9. Cruskie, M. P.,Jr.; Zoltewicz, J. A.; Abboud, K. A. *J. Org. Chem.* in press.
10. Ward, M. D. *J. Chem. Soc. , Dalton Trans.* **1994**, 3095.
11. Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508.
12. Suzuki, A. *Pure Appl. Chem.* **1994**, *66*, 213.
13. Zoltewicz, J. A.; Cruskie, M. P.,Jr. *Tetrahedron* in press.
14. Katritzky, A.R.; Lagowski, J.M. *Chemistry of the Heterocyclic N-Oxides;* Academic Press: New York, 1971.
15. Yamamoto, Y.; Yanagi, A. *Chem. Pharm. Bull.* **1982**, *30*, 1731.

16. Zoltewicz, J. A.; Cruskie, M. P.,Jr. *J. Org. Chem.* **1995**, *50*, 3487.
17. Portnoy, M.; Milstein, D. *Organometallics* **1993**, *12*, 1665.
18. Undheim, K.; Benneche, T. *Heterocycles* **1990**, *30*, 1155.
19. Undheim, K.; Benneche, T. *Adv. Heterocycl. Chem.* **1995**, *62*, 305.
20. Baxter, P.; Lehn, J. M.; DeCian, A.; Fischer, J. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 69.
21. Terashima, M.; Ishikura, M. *Adv. Heterocycl. Chem.* **1989**, *46*, 143.
22. Ishikura, M.; Mano, T.; Oda, I.; Terashima, M. *Heterocycles* **1984**, *22*, 2471.
23. Queguiner, G.; Marsais, F.; Snieckus, V.; Epsztajn, J. *Adv. Heterocycl. Chem.* **1991**, *52*, 189.
24. Rewcastle, G. W.; Katritzky, A. R. *Adv. Heterocycl. Chem.* **1993**, *56*, 157.
25. The NMR spectrum of 4-stanylpyridine N-oxide ($CDCl_3$): δ 8.35 (2H, d, J = 5 Hz, Sn side-bands J = 6 Hz), 7.42 (2H, d, J = 5 Hz, Sn side-bands J = 18 Hz), 0.8-1.6 (27H, m).

(*Received in USA* 7 *July* 1995; *accepted* 28 *August* 1995)