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Use of Pyridine N-Oxide and Pyridinium Ion Synthons in the Preparation of Oligopyridines. Two New Unsymmetrical Quaterpyridines with 2,2'-Bipyridine Units

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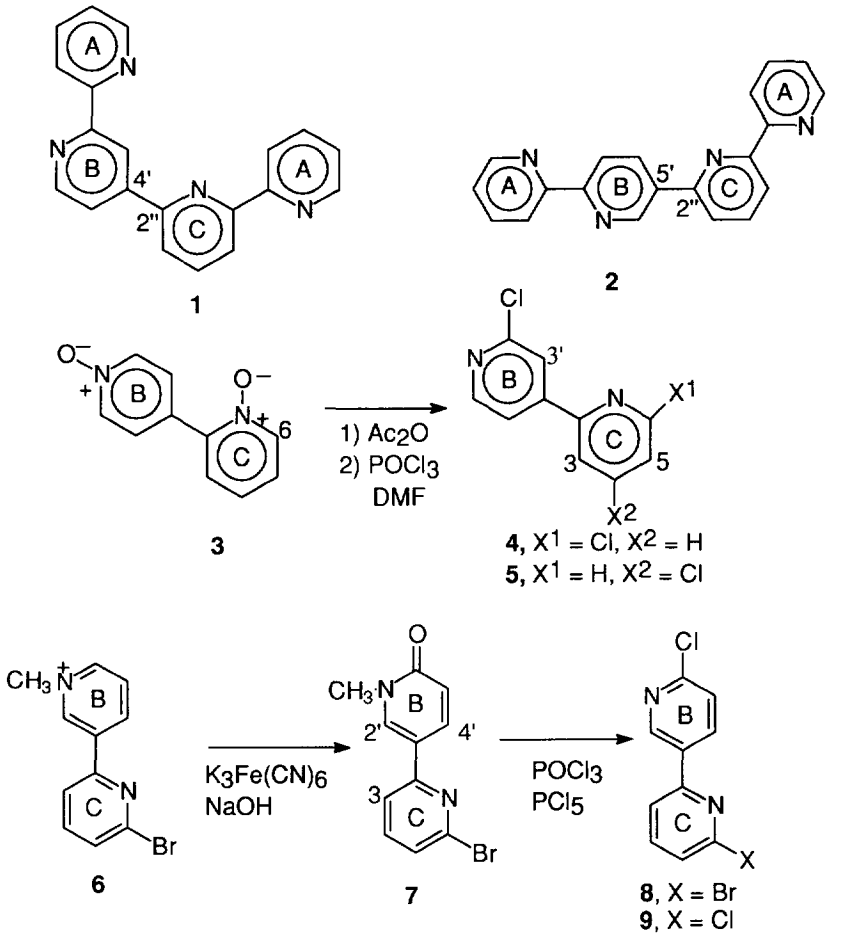
Abstract: Isomeric quaterpyridines **1** and **2** were prepared. They formally represent the coupling of two 2,2'-bipyridine units at their 4' and 5' positions of the B ring to the 2'' position of the C ring. N-Oxidized and N-methylated bipyridine synthons served to introduce halogen regiospecificially prior to Pd(0)-catalyzed cross-coupling with a 2-pyridylstannane.

Unsymmetrical polycarbocyclic and polyheterocyclic ring systems are readily made today by palladium(0)-catalyzed cross coupling reactions between an aromatic halide and either an aromatic organoborane or boronic acid (Suzuki coupling) or organostannane (Stille coupling).[1,2]

Pyridyl halides may be prepared readily by the judicious choice of an N-oxide or N-methylated pyridine synthon. We report the facile preparation of dihalogenated bipyridines using such synthons. An unsymmetrically substituted bipyridine di-N-oxide was easily transformed into the corresponding bipyridine in which chlorine atoms are located alpha to the nitrogen atom in each ring. An N-methylated bipyridinium ion was converted into its neutral unquaternized state with the halide atom situated at the less hindered alpha site. The dihalides then were cross-coupled to a 2-pyridylstannane in the presence of a Pd(0) catalyst. Others have used such synthons,[3-6] but the current literature concerning the regiochemistry of both conversions is confusing.[7,8]

The preparations of two new unsymmetrically substituted quaterpyridines **1** and **2** of type A-B-C-A, each letter representing a pyridyl ring, have been selected to illustrate the use of the two synthons. They formally represent the union of two 2,2'-bipyridine (2,2'-BPY) units at two different positions, 4' and 5', of the B-ring and the same 2'' site of the C-ring. Of the six possible ways of joining together two 2,2'-BPY's to give an A-B-C-A QTPY, **1** and **2** now are now added to the third such reported structure which



has the B- and the C-rings attached at the 3′ and 2′′ positions, respectively.[9]

The parent 2,2′-BPY has been a favored ligand because of its ability to chelate various metal ions.[10] More recently, 2,2′-BPY oligomers, especially unsymmetrical oligomers, have become of intense interest because they possess multiple binding sites that allow the formation of mixed metal complexes.[11,12] Such assemblies have interesting electrochemical and fluorescence properties that find potential use in many practical devices.[13]

RESULTS AND DISCUSSION

2,2′;4′,2′′;6′′,2′′′-Quaterpyridine (1). This heretofore unknown QTPY was selected because it was incorrectly claimed to be prepared by the two-step oxidative dimerization of 2,2′-BPY initiated by lithium diethylamide.[9,14] Using a di-N-oxide synthon, we have prepared this QTPY in a simple, three-step synthesis starting from the commercially available 2,4-BPY.

2,4-BPY was di-N-oxidized with MCPBA to give the known **3**[6] (54%). Conversion of **3** into 2',6-dichloride **4** (33%) was achieved by formation of the dipyridone with Ac_2O followed by treatment with $POCl_3$/DMF. Direct conversion of **3** into dichloride **4** with $POCl_3$/DMF was unsatisfactory. A 1:1 mixture of **4** and isomeric 2',4-dichloride **5** resulted. Since both isomers represented chlorination at the 4 and 6 positions of the 2-pyridyl ring, identification of each was easy. The desired 6-chloro compound **4** showed a characteristic triplet for H-4 partially overlapped by H-5' at δ 7.8 ($CDCl_3$). Addition of both A rings by Pd-catalyzed cross-coupling with 2-(tributylstannyl)-pyridine[15,16] completed the synthesis of **1** (57%).

The proton NMR spectrum of **1** and its chemical shift assignments given in the Experimetal Section are based on COSY and NOE difference spectra. This spectrum differs markedly from that of the QTPY made by the oxidative dimerization of 2,2'-BPY and erroneously claimed to be **1**.[14]

2,2';5',2'';6'',2'''-Quaterpyridine (2) was prepared using a pyridone synthon in five steps starting from commercially available 2,6-dibromopyridine and diethyl(3-pyridyl)borane to make the known 6-bromo-2,3'-bipyridine[17] by Pd-catalyzed cross-coupling.

Following quaternization of this latter bromide with MeI (94%) at the less sterically hindered and more basic nitrogen atom,[18] **6** was prepared. Ready oxidation with alkaline ferricyanide at room temperature gave 6-bromo-1'-methyl-2,3'-bipyrid-6'-one (82%) (**7**) along with a minor amount of the corresponding isomeric 4'-pyridone. Since the oxidation involves the formation of a pseudo-base[19] intermediate by the hydration of the more electrophilic α and/or γ positions of the ring prior to the rate limiting step,[20,21] the observed mixture of isomers is expected. The structure of the 6'-pyridone was confirmed by NOE difference NMR; irradiation of the N-methyl group provided only one enhanced signal (H2') while irradiation of the proton at H3 (δ 7.43) enhanced both the low field H2' and H4' signals. These observations eliminated both the 2'- and 4'-pyridones from consideration.

Conversion of the 6'-pyridone to 6-bromo-6'-chloro-2,3'-bipyridine (**8**) free of the N-methyl group was achieved on heating **7** with $POCl_3$ and PCl_5. A small amount of 6,6'-dichloro material **9** was formed during the conversion. The mixture was directly cross-coupled with 2-(tributylstannyl)-pyridine[15,16,22] in the presence of Pd(0) to give **2** (13%). The proton NMR spectrum of **2** is remarkably different from that of **1**, the former consisting largely of overlapped multiplets.

EXPERIMENTAL SECTION

Palladium tris(dibenzylidene)acetone, phosphorus oxychloride, 2,6-dibromopyridine, triphenylphosphine, 2,4'-bipyridine, acetic anhydride

(Ac_2O), tetrakis-(triphenylphosphine)palladium(0) ($Pd(PPh_3)_4$), diethyl(3-pyridyl)borane and 57-80% m-chloroperbenzoic acid (MCPBA) were purchased from Aldrich or Acrõs. Flash chromatography was carried out using alumina 80-200 mesh or Kieselgel 60 230-400 mesh. 2-(Tributylstannyl)-pyridine[16] was prepared by trapping the Grignard derivative of 2-bromopyridine with tributyltin chloride. All coupling constants (J) are in Hz.

2,4'-Bipyridine-1,1'-dioxide (3): The following represents a considerable improvement over the literature preparation[6] in terms of yield. To a solution of 2,4'-bipyridine (1.60 g, 10.2 mmol) in $CHCl_3$ (50 mL) was added 57-80% MCPBA (6.63 g, 38.1 mmol). The solution was stirred overnight at room temperature and then washed twice with 25 mL of H_2O. The aqueous extracts were combined and concentrated to give 1.40 g of a white solid. The solid was washed with 25 mL of diethyl ether and then recrystallized with 2-propanol/H_2O to give 1.04 g (5.53 mmol, 54%) of a white solid (mp > 200 °C, lit[6] mp 240-242 °C). δ_H (DMSO-d_6) 8.38 (1H, dd, J = 2 and 5, H6), 8.32 (2H, d, J = 7, H2',6'), 8.05 (2H, d, J = 7, H3',5'), 7.81 (1H, dd, J = 5 and 6 Hz, H4), 7.54 (2H, m, H3, 5).

2',6-Dichloro-2,4'-bipyridine (4) and 2',4-dichloro-2,4'-bipyridine (5): A suspension of 2,4'-bipyridine-1,1'-dioxide (**3**) (1.00 g, 5.31 mmol) in Ac_2O (30 mL) was heated at reflux for 8 h. The mixture was concentrated to a brown oil and dissolved in 50 mL of MeOH which was decolorized with charcoal and filtered through a bed of Celite. The filtrate was concentrated to a brown solid that was washed with 50 mL of diethyl ether to give 600 mg of the dipyridone. This dipyridone, suspended in $POCl_3$ (15 mL) and DMF (2 mL), was heated at reflux for 8 h under N_2. The mixture was concentrated to a brown oil and cold aqueous Na_2CO_3 was added until the aqueous phase was basic to pH paper. The aqueous phase was extracted with 50 mL of $CHCl_3$ that was dried and concentrated to a brown oil. Column chromatography with Kieselgel and 90/10 hexanes/EtOAc gave 400 mg (1.78 mmol, 33%) of **4** as a yellow solid (mp 145-147 °C). $C_{10}H_6N_2Cl_2$ requires: C, 53.35; H, 2.69; N, 12.45. Found: C, 53.52; H, 2.43; N, 12.28. δ_H ($CDCl_3$) 8.50 (1H, dd, J = 1 and 5, H6'), 7.96 (1H, dd, J = 1 and 2, H3'), 7.81 (1H, t, H4, J = 7), 7.81(1H, dd, J = 1 and 6, H5') 7.72 (1H, dd, J = 1 and 8, H3), 7.42 (1H, dd, J = 1 and 8, H5).

In addition, 50 mg (0.22 mmol, 4%) of slightly less polar **5**, a yellow solid (mp 116-120 °C), was isolated from the column in an early fraction. $C_{10}H_6N_2Cl_2$ requires: C, 53.35; H, 2.69; N, 12.45. Found: C, 53.65; H, 2.37; N, 12.39. δ_H ($CDCl_3$) 8.64 (1H, d, J = 5), 8.51 (1H, d, J = 5), 7.95 (1H, d, J = 1), 7.79 (2H, m), 7.39 (1H, dd, J = 2 and 5).

2,2':4',2'':6'',2'''-Quaterpyridine (1): A solution of 2',6-dichloro-2,4'-bipyridine **(4)** (100 mg, 0.444 mmol) and $Pd(PPh_3)_4$ (51 mg, 0.044 mmol) in degassed toluene was stirred at reflux for 15 min under N_2. 2-

(Tributylstannyl)pyridine[15] (654 mg, 1.78 mmol) was added in three equal portions over 1 h. The reaction was stirred at reflux for 48 h and then concentrated to an oil. Column chromatography with alumina and 80/20 EtOAc/hexanes gave 95 mg of a white solid. The product was washed with 30 mL of diethyl ether to give 78 mg of **1** (0.25 mmol, mp 134-141 °C, 57% yield). $C_{20}H_{14}N_4$ requires: C, 77.40; H, 4.55; N, 18.05. Found: C, 77.38; H, 4.64; N, 18.21. δ_H ($CDCl_3$) 9.07 (1H, dd, J = 1 and 2, H3'), 8.84 (1H, dd, J = 1 and 5, H6',), 8.75 (1H, dt, J = 1, 2 and 5, H6 or H6'''), 8.72 (1H, dt, J = 1, 2 and 5, H6 or H6'''), 8.68 (1H, dd, J = 1 and 9, H3), 8.50 (2H, m, H5'' and H3'''), 8.20 (1H, dd, J = 2 and 5, H5'), 8.40 (1H, dd, J = 1 and 7, H3''), 7.98 (1H, t, J = 7, H4''), 7.89 (2H, m, H4 and H4''), 7.36 (2H, ddd, J = 1, 5 and 7, H5 and H5''').

6-Bromo-1'-methyl-2,3'-bipyridinium Iodide (6). A mixture of 1.00 g (4.25 mmol) of 6-bromo-2,3'-bipyridine,[17] 2 mL of diethyl ether and 3 mL (5 mmol) of methyl iodide was allowed to stand at room temperature for several hours. The solid mass was filtered and washed with ether to give 1.5 g (4.0 mmol, 94%) of the iodide, mp. > 200 °C. $C_{11}H_{10}N_2BrI$ requires: C, 35.04; H, 2.67; N, 7.43. Found: C, 34.85; H, 2.44; N, 7.22. δ_H (DMSO-d_6) 9.60 (1H, s); 9.13 (1H, d, J = 8); 9.04 (1H, d, J = 6); 8.27 (1H, d, J = 8); 8.24 (1H, dd, J = 6 and 8); 8.05 (1H, t, J = 8); 7.86 (1H, d, J = 8); 4.45 (3H, s, Me).

6-Bromo-1'-methyl-2,3'-bipyrid-6'-one (7). The method is similar to that reported for the oxidation of a 2,2'-bipyridinium salt.[4] To 10 mL of a saturated solution of $K_3Fe(CN)_6$ saturated with aqueous KOH was added 1.13 g (3.00 mmol) of bipyridinium ion **6**. The mixture was stirred for 1.5 h at room temperature and then extracted twice with 20 mL of $CHCl_3$ which then was concentrated to a yellow oil. Chromatography on silica gel with EtOAc and then EtOAc/5% EtOH gave 650 mg (2.45 mmol, 82 %) of slightly orange product, mp 179-182 °C, dec. Other fractions were contaminated with the 4'-pyridone isomer. Recrystallization from water-ethanol gave the analytical sample, mp 183-186 °C, (dec.). $C_{11}H_9N_2BrO$ requires: C, 49.84; H, 3.41; N, 10.57. Found: C, 49.70; H, 3.26; N, 10.48. δ_H ($CDCl_3$) 8.23 (1H, d, J = 2, H2'); 7.86 (1H, dd, J = 3 and 10, H4'); 7.56 (1H, td, J = 1 and 8, H4); 7.43 (1H, dd, J = 1 and 8, H3); 7.36 (1H, dd, J = 1 and 8, H5), 6.65 (1H, dd, J = 10, H5'), 3.66 (3H, s, Me).

Conversion of 6-Bromo-1'-methyl-2,3'-bipyrid-6'-one (7) to a Mixture of 6-Bromo-6'-chloro- (8) and 6,6'-Dichloro-2,3'-bipyridine (9). To 350 mg (1.40 mmol) of pyridone **7** was added 0.2 g of PCl_5 and 5 mL of $POCl_3$; the solution was heated at reflux for 1 h. After concentrating to an oil, a mixture of ice and aqueous carbonate was added until the solution was basic. The aqueous phase was extracted twice with $CHCl_3$; the extracts were combined, dried and concentrated to an oil. Chromatography on silica gel (1/1

hexane/EtOAc) gave 0.180 g of a white solid which was washed with hexanes to give 0.140 g of the mixture, mp 154-158 °C, which was used directly in the following coupling reaction. Combustion analysis indicated a composition of about 72% of **8** and 28% of **9**.

2,2′:5′,2″:6″,2‴-Quaterpyridine (2). Cross-coupling of the dihalide mixture (62 mg, 0.24 mmol) with 2-(tributylstannyl)pyridine[15] (18 mg, 0.49 mmol), palladium tris(dibenzylidene)acetone (30 mg, 0.033 mmol) and triphenylphosphine (20 mg, 0.76 mmol) at reflux in 30 mL of toluene for 60 h gave the QTPY following filtration, removal of the solvent and chromotography on alumina. The column was eluted initially with hexanes and then gradually with ethyl acetate to a final 1.5/1 mixture of hexanes/ethyl acetate. Removal of the solvent gave a yellow oil that gradually solidified (10 mg, 0.032 mmol, 13%) mp 148-150 °C. $C_{20}H_{14}N_4.0.25H_2O$ requires C, 76.71; H, 4.40. Found: C, 76.33; H, 4.64. δ_H ($CDCl_3$) 9.46 (1H, dd, J = 1 and 2); 8.73 (2H, m), 8.66 (1H, dt, J = 1 and 8), 8.5 (4H, m), 7.96 (1H, t, J = 8), 7.86 (3H, m), 7.36 (2H, m).

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