Pergamon

Tetrahedron, Vol. 52, No. 46, pp. 14469-14474, 1996

0040-4020/96 $15.00 + 0.00

PII: S0040-4020(96)00892-7

INTER-RING DIRECTED *ORTHO* LITHIATION BY THE 2-PYRIDYL GROUP IN BIPYRIDINES

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Key words:
Lithiation, bipyridines, Pd-catalyzed coupling, terpyridines.

Abstract: *Kinetically enhanced metallation by the 2-pyridyl group of 2,2'-bipyridine or 2,4'-bipyridine (BPY) in the presence of lithium 2,2,6,6-(tetramethyl)piperidide directs lithiation to the ortho position of the adjacent ring. Representative electrophiles convert the lithiated material to a number of substituted products. The stannylated BPY products were coupled with 3-iodopyridine in the presence of $Pd(PPh_3)_4$ to give two novel terpyridines.*

INTRODUCTION

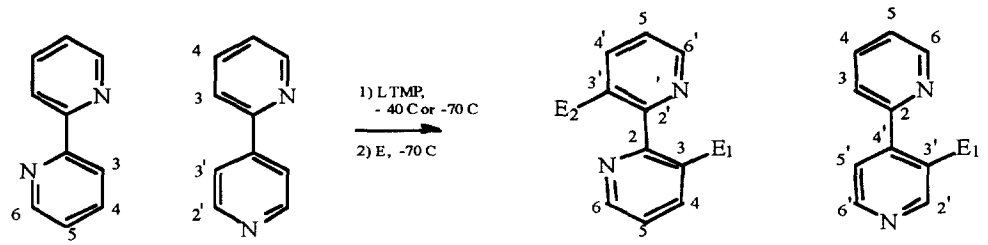
Heteroatom-containing substituents on an aromatic ring can direct lithiation to an *ortho* position and may have a strong rate accelerating effect on deprotonation.[1] The phenomenon has been called a "directed *ortho* metallation"[2,3] and a "complex induced proximity effect".[4] Initial coordination of a lithium atom to the lone electron pair of the heteroatom brings the metallating agent into close proximity of the *ortho* hydrogen atom that is removed. Often this is said to be a ground state effect but the results of recent computations suggest the phenomenon to be a transition state effect, more adequately described as "kinetically enhanced metalation."[5] Stronger stabilization of the transition state than the ground state accounts for the directing and accelerating capabilities of such substituents.

We wish to report the use of the 2-pyridyl group in bipyridines to direct lithiation and subsequent electrophilic substitution to the adjacent ring and thereby provide a facile route to the synthesis of 3- or 3'-substituted bipyridines. Two of the newly formed stannyl products were cross-coupled under Stille conditions[6] in the presence of $Pd(PPh_3)_4$ to afford two novel terpyridines.

The lithiation chemistry of pyridine rings has largely been concerned with substituents that direct metallation to an *ortho* site on the same ring.[2-4] The use of a 2-pyridyl substituent to effect inter-ring kinetically enhanced metallation is far less common.[4]

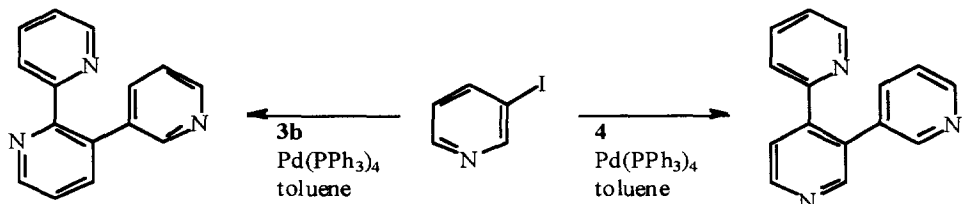
Results

Lithiation and Electrophilic Substitution: 2,2'-BPY (**1**) or 2,4'-BPY (**2**) was mono lithiated with lithium 2,2,6,6-(tetramethyl)piperidide (LTMP)[7] at -40 °C or -70 °C and then quenched with several illustrative electrophiles. Bu_3SnCl, Et_2BOMe, I_2, or CH_3CHO and **1** gave substituted 2,3'-BPYs **3a-e** and Bu_3SnCl with **2**



1 **2** **3 a-e** **4**

3a: $E_1 = SnBu_3$, $E_2 = SnBu_3$ (14%)
3b: $E_1 = SnBu_3$, $E_2 = H$ (50%)
3c: $E_1 = BEt_2$, $E_2 = H$ (50%)
3d: $E_1 = I$, $E_2 = H$ (11%)
3e: $E_1 = CH(OH)CH_3$, $E_2 = H$ (41%)
4: $E_1 = SnBu_3$ (64%)



5 (21%) **6** (80%)

gave 2,4'-BPY **4**. Mixtures of mono- (**3b**) and distannylated (**3a**) BPYs resulted from the same reaction but were easily separated by column chromatography, the latter in low yield (14%).

To demonstrate the utility of the stannylated BPYs for cross-coupling reactions, **3b** and **4** were treated with 3-iodopyridine in the presence of $Pd(PPh_3)_4$ under Stille coupling conditions[8] to yield 2,2':3',3"-terpyridine (**5**) and 2,4':3',3"-terpyridine (**6**), respectively. While **6** was formed in high yield (80%), various attempts to improve the outcome (21%) for **5** consistently failed. The proton spectrum of **6** (DMSO-d_6) was deceptive in that accidental signal overlap at two low field positions appeared to indicate the presence of an unsubstituted 4-pyridyl ring. However, a COSY analysis confirmed that simple cross-coupling did occur to give the expected product **6**.

Structure Determinations: To verify that the site of lithiation and therefore electrophilic substitution was indeed the 3 or 3' position, the structures of the BPY products were established by NMR analysis. For 2,2'-BPYs **3a-e**, the absence of a singlet in the aromatic region easily excluded positions 4 and 5 as sites of lithiation. The same spin-spin coupling patterns arise from substitution at either the 3 or 6 positions but these are easily distinguished. If substitution were to occur at position 3, H-5 would couple with H-4 and H-6, thus giving a dd splitting pattern with coupling constants of about 8 and 5 Hz, respectively, with signals appearing at approximately 7.3-7.4 ppm. This was observed. Had substitution occurred at position 6, H-4 would be coupled with H-3 and H-5 and a similar dd (or t) splitting pattern would be found but with coupling constants of

about 8 Hz for both sites.[9] This was not the case. Also, the typical shift of H-4 is downfield compared to H-5 as is found here, providing further confirmation.

The simple three proton spectrum of the aromatic portion of disubstituted BPY **3a** due to its symmetry indicates that substitution took place at the same site on each ring, again at the 3 (3') positions as ascertained above. Moreover, the presence of small side bands associated with the 4 and 4' positions in **3a** and **3b** resulting from the coupling of ^{117}Sn and ^{119}Sn isotopes identifies the adjacent proton and further supports the structures.[10]

The ethyl chains of borane **3c** show diastereotopic protons for the methylene groups; these are present as *two* sets of multiplets at 0.81 and 0.57 ppm thus indicating the presence of a BN inter-ring bond and restricted rotation of the boryl group, as observed by others.[11]

In the case of product **4** from 2,4'-BPY, the absence of two multiplets, each containing two protons typically associated with a symmetrical 4-substituted pyridyl ring, indicates that substitution occurred on the 4'-pyridyl ring. However, the proton spectrum was not especially informative about the two possible reaction sites but the ^{13}C spectrum was useful.[12] Knowing that an *ipso* carbon is deshielded by tin, as are the *ortho* carbons but to a lesser degree, the reaction site could be identified.[10] An APT experiment indicated the signals at 146.5 (C4') and 154.8 (C2) ppm to be those of the proton-free carbons of starting material **2** while the APT spectrum of **4** contained proton-free signals at three sites, 150.8 (C4'), 155.7 (C2) and 136.4 (C3') ppm. The high field position of this latter signal identifies it as a 3' and not a 2' carbon atom, having been shifted from 121.2 ppm in the starting material.

The preparation of 3- and 3'-substituted BPYs directly from the parent BPY has not been common.[13,14] The approach presented here allows this deficiency to be remedied.

Experimental

Lithium 2,2,6,6-(Tetramethyl)piperidide (LTMP).[7] n-Butyllithium and 2,2,6,6-tetramethylpiperidine were added with stirring to THF at -30 °C under nitrogen. The solution was warmed to 0 °C, stirred for 30 min. and then cooled prior use.

General Procedure for the Preparation of 3- or 3'- Substituted Bipyridines. With the LTMP at -40 °C or -70 °C, 2,2'-BPY (**1**) or 2,4'-BPY (**2**) dissolved in THF (15 mL) was added over 15 min. The reaction was stirred for 45 min, followed by slow addition of the electrophile (Bu_3SnCl, Et_2BOCH_3, I_2, or CH_3CHO). After stirring at -70 °C for 1h, the mixture was then warmed to rt and stirred for several hours. Distilled water (5mL) was added along with diethyl ether (30 mL). The ether phase was washed with saturated NaH_2PO_4 (2 x 50 mL), water (50 mL) and brine (50 mL, 1 M), then dried over Na_2SO_4 and evaporated to the crude product. For **3a**, **3b** and **3c**, the crude product mixtures were redissolved in ether and washed several times with a satd. solution of $FeSO_4$ until the red color of a complex with 2,2'-BPY was no longer observed, after which the ether phase was collected, dried over Na_2SO_4 and evaporated to crude product. Column chromatography gave the pure product.

3,3'-Bis(tributylstannyl)-2,2'-bipyridine (3a) and 3-(Tributylstannyl)-2,2'-bipyridine (3b). Starting materials: LTMP (4.80 mmol, -70 °C), 2,2'-BPY (**1**) (0.300 g, 1.92 mmol), and tributyltin chloride (1.35 mL, 4.99 mmol). First, a silica gel column of the orange oil was eluted with hexanes: EtOAc (95:5) to remove excess tributyltin and then an alumina column was eluted with hexanes, which afforded (**3a**). BPY (**3b**) was eluted from the alumina with hexanes: EtOAc (90:10). After solvent evaporation both products were isolated as clear oils: (**3a**) 190 mg (0.20 mmol, 14% yield): (**3b**) 430 mg (0.97 mmol, 50% yield). (**3a**): ^{1}H NMR ($CDCl_3$): δ 8.47 (2H, dd, J = 2 and 5 Hz), 8.06 (2H, dd, J = 2 and 7 Hz; Sn, J = 35 and 50 Hz) 7.28 (2H, dd, J = 5 and 7 Hz), 0.83-1.43 (54 H, m). Anal. Calcd. For $C_{34}H_{60}N_2Sn_2$: C, 55.62; H, 8.24; N, 3.82. Found C, 55.87; H, 8.49; N, 4.16. (**3b**): ^{1}H NMR (CD_3OD): δ 8.55 (2H, dd, J = 2 and 5 Hz), 8.45 (1H, d, J = 8 Hz), 8.05 (1H, dd, J = 2 and 7 Hz; Sn, J = 33 and 48 Hz), 7.90 (1H, td, J = 2 and 8 Hz), 7.40 (1H, ddd, J = 1, 5, and 8 Hz), 7.33 (1H, dd, J = 5 and 8 Hz), 0.80-1.14 (27H, m). Anal. Calcd. For $C_{22}H_{34}N_2Sn$: C, 59.35; H, 7.70; N, 6.29. Found: C, 59.72; H, 8.01; N, 6.58.

3-Diethylboryl-2,2'-bipyridine (3c). Starting materials: LTMP (4.80 mmol, -40 °C), 2,2'-BPY (0.500 g, 3.20 mmol) and diethylmethoxyborane (0.63 mL, 5.0 mmol) were added over 30 min. An alumina column of the dark oil was eluted first with hexanes, then with increasing EtOAc up to 30%. The product was isolated as a yellow oil (362 mg, 1.62 mmol, 50% yield). ^{1}H NMR ($CDCl_3$): δ 8.54 (1H, dd, J = 2 and 5 Hz), 8.40 (2H, m), 8.08 (1H, td, J = 2 and 8 Hz), 7.95 (1H, dd, J = 2 and 8 Hz), 7.50 (1H, td, J = 2 and 6 Hz), 7.28 (1H, dd, J = 5 and 7 Hz), 0.81 (2H, m), 0.57 (2H, m), 0.43 (6H, t, J = 8 Hz). Anal. Calcd. For $C_{14}H_{17}N_2B$i1/2 H_2O: C, 72.01; H, 7.72; N, 12.01. Found: C, 72.40; H, 7.97; N, 11.93.

3-Iodo-2,2'-bipyridinium Diperchlorate (3d). Starting materials: LTMP (9.28 mmol, -40 °C), 2,2'-BPY (1.00 g, 6.40 mmol) and iodine (1.62 g, 6.40 mmol) in THF (15 mL). An alumina column of the dark oil was eluted first with hexanes, then with increasing EtOAc up to 30%. The material was isolated as the pale solid diperchlorate salt (199 mg, 0.70 mmol, 11 % yield) by dissolving the oil product in a solution of AcOH (2 mL), EtOAc (2 mL), and $NaClO_4$ (20 mg) and adding perchloric acid (70%) dropwise to afford the solid. ^{1}H NMR ($CDCl_3$): δ 8.89 (1H, d, J = 5 Hz), 8.75 (1H, dd, J = 1 and 5 Hz), 8.56 (1H, dd, J = 1 and 8 Hz), 8.40 (1H, td, J = 2 and 8 Hz), 8.12 (1H, d, J = 8 Hz), 7.88 (1H, ddd, J = 1, 5 and 8 Hz), 7.38 (1H, dd, J = 5 and 8 Hz). Anal. Calcd. For $C_{10}H_9N_2ICl_2O_8$i1/2 H_2O: C, 24.41; H, 2.05; N, 5.69. Found: C, 24.18; H, 1.64; N, 5.51.

3-(1-Hydroxyethyl)-2,2'-bipyridine (3e). Starting materials: LTMP (4.80 mmol, -70 °C), 2,2'-BPY (0.500 g, 3.20 mmol) and acetaldehyde (0.25 mL, 4.45 mmol). An alumina column of the dark oil was eluted first with hexanes, then with increasing EtOAc up to 30%. The product was isolated as a yellow oil (218 mg, 1.09 mmol, 34% yield). ^{1}H NMR ($CDCl_3$): δ 8.62 (2H, m), 8.14 (1H, dd, J = 1 and 7 Hz), 7.91 (2H, m),

7.32 (2H, m), 6.97 (1H, d, J = 5 Hz), 4.89 (1H, q, J = 6 Hz), 1.54 (3H, d, J = 7 Hz). Anal. Calcd. For $C_{12}H_{12}N_2O.1/3H_2O$: C, 69.88; H, 6.19; N, 13.58. Found: C, 69.78; H, 6.21 ; N, 13.20.

3-(Tributylstannyl)-2,4'-bipyridine (4). Starting materials: LTMP (9.60 mmol, -70 °C), 2,4'-BPY (1.00 g, 6.40 mmol) and tributyltin chloride (2.10 mL, 7.68 mmol). A silica gel column was eluted sequentially with 100 mL of hexanes: EtOAc (90:10), 100 mL of hexanes: EtOAc (70:30), 100 mLof hexanes: EtOAc (50:50) and finally with 100 mL hexanes: EtOAc (30:70). The product eluted with the latter solvent. Evaporation afforded 1.82 g of the clear oil product (4.09 mmol, 64% yield). ^{1}H NMR ($CDCl_3$): δ 8.81 (1H, d, J = 1 Hz; Sn, J = 24 Hz), 8.59 (2H, d, J = 5 Hz), 7.83 (1H, d, J = 8 Hz), 7.78 (1H, td, J = 2 and 8 Hz), 7.66 (1H, dd, J = 1 and 5 Hz), 7.30 (1H, ddd, J = 2, 5 and 7 Hz), 0.80-1.14 (27H, m). ^{13}C NMR ($CDCl_3$): 157.3, 155.7, 150.8, 149.3, 147.3, 137.1, 136.4 (Sn, ^1J = 393 Hz), 123.3, 120.6, 28.9, 27.2, 13.4, 12.3. Anal. Calcd. For $C_{22}H_{34}N_2Sn$ï1/2 H_2O: C, 58.17; H, 7.77; N, 6.17. Found: C, 58.34; H, 7.93; N, 5.81.

General Procedure for the Palladium-Catalyzed Cross-Coupling to Give Terpyridines 5 and 6. 3-Iodopyridine and $Pd(PPh_3)_4$ in degassed toluene (50 mL) were stirred under nitrogen for 15 min and heated at gentle reflux. **3b** or **4** dissolved in toluene (5 mL) was added in three equal portions over 30 min. After refluxing (**4** for 18 h and **3b** for 6 days followed by the addition of CuI (5 mg) and another day) the reaction was cooled with ice and diluted with EtOAc (30 mL). Insolubles were filtered away, and the filtrate was concentrated to a yellow oil which was dissolved in a solution of AcOH (2 mL), EtOAc (2 mL), and $NaClO_4$ (20 mg). Perchloric acid (70%) was added dropwise to this solution affording a white precipitate that was collected and washed with EtOAc and hexanes. Recrystallized from EtOH and EtOAc gave the white solid terpyridinium diperchlorate.

2,2': 3',3"-Terpyridinium Diperchlorate (5). Starting materials: 3-Iodopyridine (0.230 g, 1.12 mmol), $Pd(PPh_3)_4$ (0.130 g, 0.112 mmol), and **3b** (0.500 g, 1.12 mmol). The solid was recrystallized from EtOH and EtOAc yielding 131 mg of the white solid terpyridinium diperchlorate (0.30 mmol, 21% yield, m. p. > 280 °C). ^{1}H NMR (CD_3OD): δ 8.96 (1H, d, J = 5 Hz), 8.90 (1H, s), 8.85 (1H, d, J = 6 Hz), 8.71 (1H, d, J = 5 Hz), 8.47 (1H, dt, J = 2 and 8 Hz), 8.23 (2H, m), 8.04 (1H, dd, J = 6 and 8 Hz) 7.87 (1H, dd, J = 5 and 8 Hz), 7.81 (2H, m). Anal. Calcd. For $C_{15}H_{13}Cl_2N_3O_8$: C, 41.49; H, 3.02; N, 9.68. Found: C, 41.53; H, 2.89; N, 9.54.

2,4': 3',3"-Terpyridinium Diperchlorate (6). Starting materials: 3-Iodopyridine (0.300 g, 1.46 mmol), $Pd(PPh_3)_4$ (0.170 g, 0.146 mmol), and **4** (0.700 g, 1.57 mmol). The solid was recrystallized from EtOH and EtOAc yielding 508 mg of the white solid terpyridinium diperchlorate (1.17 mmol, 80% yield, m. p. > 280 °C). ^{1}H NMR (DMSO): δ 9.04 (2H, m), 8.87 (2H, m), 8.52 (1H, d, J = 5 Hz), 8.24 (1H, dd, J = 2 and 8 Hz), 8.12 (1H, d, J = 6 Hz), 7.95 (2H, m), 7.67 (1H, d, J = 8 Hz), 7.49 (1H, dd, J = 5 and 7 Hz). Anal. Calcd. For $C_{15}H_{13}Cl_2N_3O_8$: C, 41.49; H, 3.02; N, 9.68. Found: C, 41.49; H, 2.81; N, 9.39.

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(*Received in USA* 13 *August* 1996; *revised* 19 *September* 1996; *accepted* 23 *September* 1996)