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A CONVENIENT SYNTHESIS OF 2,4'-BIPYRIDINE

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Abstract- 2,4'-Bipyridine 6 was synthesized starting from N-ethoxycarbonylpyridinium chloride 1 and 2-benzyloxy-6-bromopyridine 2a or 6-bromo-2-methoxypyridine 2b via 6-benzyloxy-2,4'-bipyridine 3a or 6-methoxy-2,4'-bipyridine 3b and 6-cholro-2,4'-bipyridine 5.

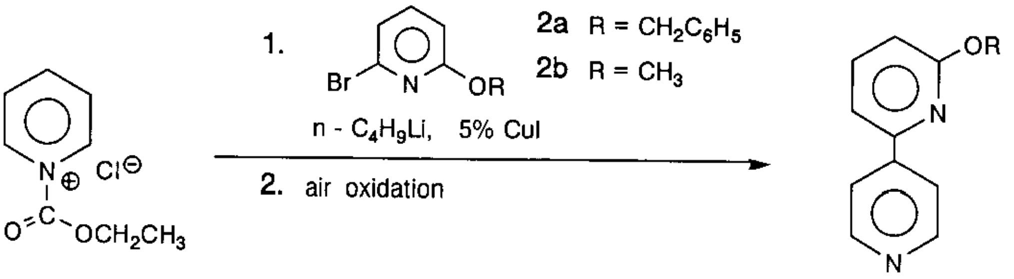
Synthesis of bipyridines has attracted much attention because of their importance as industrial compounds and medicinal compounds, analytical reagents, and ligands for the preparation of metal complexes and catalytic activity.[1,2] Symmetrical bipyridine derivatives have been synthesized by the Ullmann reaction,[3] the best modification being the coupling of halopyridines in the presence of metal catalyst.[4,5] However, literature survey indicated that syntheses of unsymmetrical bipyridines have rarely been reported and the published methods can be classified into condensation of pyridinium salts with unsaturated ketone[6,7] and cross-coupling of halopyridines.[8]

Previously, we reported a convenient synthesis of 3,4'-bipyridine involving the condensation of lithium salts derived from 2-benzyloxy- and 2-methoxy-5-bromopyridine with N-ethoxycarbonylpyridinium chloride to the corresponding 6-alkoxy-3,4'bipyridine.[9] An attempted to synthesize 2,4'-bipyridine **6** directly by Grignard reaction of 2-bromopyridine with N-ethoxycarbonylpyridinium chloride **1**[10] followed by air oxidation using our previously published method[11] gave 6 but in low yield (15%). We now wish to report a convenient synthesis of 2,4'-bipyridine **6** starting from 2-benzyloxy-6-bromopyridine **2a** or 6-bromo-2-methoxypyridine **2b**.

2-Benzyloxy-6-bromopyridine **2a**[12] was treated with n-butyllithium (1.2 eq.) and a catalytic amount of 5% cuprous iodide in THF at -25^{0}C for 1 h. Addition of this solution to a solution of N-ethoxycarbonylpyridinium chloride 1 (1 eq.) in THF gave the corresponding unstable 1,4-dihydropyridine which was readily oxidized in oxygen for 8 h to give the 2,4'-bipyridine 3a, as a crystalline solid, in 62% yield. Similarly, treatment of the lithium salt derived from 6-bromo-2-

methoxypyridine[13] 2b with compound 1 followed by oxidation gave 2,4’-bipyridine **3b**, in 58% yield.

Hydrogenolysis of the benzyl ether **3a** in methanol over 5% palladium on charcoal gave 6-(4-pyridinyl)-2(1H)-pyridone 4, in 86% yield. Compound 4 was transformed into the corresponding 6-chloro-2,4’-bipyridine 5 upon treatment with phosphoryl chloride in N,N-dimethylformamide[14] in 85% yield. Subsequent catalytic dechlorinating 5 with hydrogen over 10% palladium on charcoal afforded the desired 2,4’-bipyridine 6[15] (89% yield). The 6-methoxy-2,4’-bipyridine 3b was directly transformed into compound 5 with phosphoryl chloride in N,N-dimethylformamide (92% yield) as was reported earlier for 2-methoxypyridine.[16] The 2-alkoxy substituent in the pyridine ring presumably enhanced the lithiated metal-halide exchange to afford a better yield products of 3a and 3b after air oxidation.[9] Thus, we found a convenient synthesis of 2,4’-bipyridine 6 starting from 1 and 2a or 2b by a four-step process in 40% yield or by a three-step process in 47% yield, respectively.



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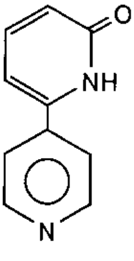
3a R = $CH_2C_6H_5$
3b R = CH_3



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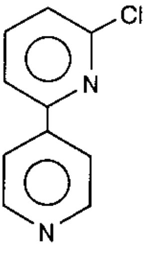

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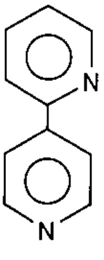

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EXPERIMENTAL

Melting points are uncorrected. The ^{1}H-nmr spectra were recorded on a Bruker AW 80 and MSL 200 spectrometer. The ms spectra were obtained by using a Hewlett-Packard 5995 GC/MS system at 70 ev. The ir spectra were recorded with a Perkin Elmer 882 infrared spectrophotometer. Elemental analyses were performed on a Perkin-Elmer 2400 Elemental Analyzer. All anhydrous solvents were freshly distilled before use.

6-Benzyloxy-2,4'bipyridine **3a**.

To a solution of 2-benzyloxy-6-bromopyridine **2a** (0.28 g, 1 mmol) in 12 ml of dry tetrahydrofuran (THF) was added 1.6 M n-butyllithium solution in hexane (0.77 ml, 1.2 mmol) and 0.11 g of cuprous iodide at -78^{0}C under nitrogen for 1 h. Addition of this solution to a solution of pyridinium chloride 1 (prepared from 0.1 ml (1.2 mmol) of pyridine and 0.13 ml (1.4 mmol) of ethyl chloroformate, 15 ml of THF at -25^{0}C for 10 min) at -25^{0}C for 1 h. The reaction mixture was warmed to room temperature and quenched with 5% sodium bicarbonate solution (6 ml). After evaporation of THF the residue was extracted with dichloromethane (3 x 50 ml). The extract was dried over anhydrous Na_2SO_4 and concentrated. The residue was stirred under an oxygen stream at room temperature for 8 h. The reaction mixture was extracted with dichloromethane, and the organic extracts were washed with water, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was chromatographed on silica gel column (3% hexane-ethyl acetate) to give 0.16 g (62%) of **3a**, mp 20-21^{0}C (hexane-ethyl acetate). ^{1}H Nmr ($CDCl_3$): δ 5.51 (s, 2H, benzylic H); 6.83 (dd, 1H, J = 7.4 Hz, 0.6 Hz, H-5); 7.41 (m, 5H, aromatic 5H); 7.48 (dd, 1H, J = 8.3 Hz, 0.6 Hz, H-3); 7.69 (dd, 1H, J = 8.3 Hz, 7.4 Hz, H-4); 7.89 and 8.68 (AA'BB', 4H, J=8.0 Hz, 2.0 Hz, pyridine 4H). Anal. Calcd for $C_{17}H_{14}N_2O$: C, 77.84; H, 5.38; N, 10.68. Found: C, 77.82; H, 5.41; N, 10.70.

6-Methoxy-2,4'-bipyridine **3b**.

Compound **2b** (0.38 g) was treated under the conditions as above to give 0.16 g (58%) of **3b**, mp 48.5-49^{0}C (ether-hexane). ^{1}H Nmr ($CDCl_3$): δ 4.05 (s, 3H, OCH_3); 6.78 (dd, 1H, J = 8.3 Hz, 0.6 Hz, H-5); 7.40 (dd, 1H, J = 7.5 Hz, 0.6 Hz, H-3); 7.64 (dd, 1H, J = 8.3 Hz, 7.5 Hz, H-4); 7.91 and 8.71 (AA'BB', 4H, J=8.0 Hz, 2.0 Hz, pyridine 4H). Anal. Calcd for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.05.

Found: C, 70.94; H, 5.39; N, 15.07.

6-(4-Pyridinyl)-2(1H)-pyridone 4.

A solution of compound 3a (0.1 g) in 10 ml of methanol was hydrogenated for 3 h over 5% Pd/C (7 mg) then filtered and concentrated in vacuum. The residue was purified by column chromatography on silica gel (5% methanol-dichloromethane) to give 57 mg (86%) of 4. mp 159-160^{0}C(methanol-dichloromethane). ^{1}H Nmr ($CDCl_3$): δ 6.67 (dd, 1H, J = 9.0 Hz, 2.0 Hz, H-5); 7.56 (dd, 1H, J = 9.0 Hz, 8.0 Hz, H-4); 8.04 (dd, 1H, J = 8.0 Hz, 2.0 Hz, H-3); 7.65 and 8.74 (AA'BB', 4H, J=8.0 Hz, 2.0 Hz, pyridine 4H); 11.8 (bs, NH). Anal. Calcd for $C_{10}H_8N_2O$: C, 69.75; H, 4.68; N, 16.27. Found: C, 69.76; H, 4.68; N, 16.28.

6-Chloro-2,4'-bipyridine 5.

To a stirred solution of 4 (1.72 g, 10 mmol) in 6 ml of dry dimethylformamide at 0^{0}C, phosphoryl chloride (2.0 ml, 20 mmol) was added dropwise. The stirring was continued for 2 h and the mixture was heated at 80^{0}C for 1 h. After the solution is cooled to 0^{0}C, the saturated sodium acetate solution was added and the mixture was extracted with dichloromethane. The extract was washed with water, dried over anhydrous Na_2SO_4 and concentrated in vacuum. The residue was chromatographed on silica gel (10% hexane-ethyl acetate) to give 1.61 g (85%) of 5, mp 120.5-121.5^{0}C (dichloromethane). ^{1}H Nmr ($CDCl_3$): δ 7.36 (dd, 1H, J = 7.2 Hz, 1.5 Hz, H-5); 7.71 (dd, 1H, J = 7.6 Hz, 1.5 Hz, H-3); 7.79 (dd, 1H, J = 7.6 Hz, 7.2 Hz, H-4); 7.87 and 8.72 (AA'BB', 4H, J=8.0 Hz, 2.0 Hz, pyridine 4H). Anal. Calcd for $C_{10}H_7N_2Cl$: C, 71.09; H, 6.71; N, 10.36. Found: C, 71.10; H, 6.69; N, 10.30.

From 3b

Compound 3b (1.86 g) was treated in the same way to give 1.75 g (92%) of 5.

2,4'-Bipyridine 6.

A solution of 5 (0.57 g, 3 mmol) and potassium hydroxide (0.12 g) in 15 ml of methanol was hydrogenated at ordinary pressure and temperature for 3 h over 10% Pd/C (0.08 g). The catalyst was removed by filtration and the solvent was evaporated. The residue was extracted with ether. The ether extract was washed with water, and dried over anhydrous Na_2SO_4. Vacuum evaporation gave 0.42 g (89%)

of **6**, mp 60-61°C (ethanol) (lit.,[15] mp 61.5°C). ^{1}H Nmr ($CDCl_3$): δ 7.35 (m, 1H, H-4); 7.82 (m, 2H, H-3 and H-5); 7.90 and 8.73 (AA'BB', 4H, J=8.0 Hz, 2.0 Hz, pyridine 4H); 8.75 (dd, 1H, J = 4.2 Hz, H-6).

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REFERENCES

1 G. R. Newkome, W. E. Puckett, G. E. Kiefer, V. K. Gupta, Y. Xia, M. Coreil, and M. A. Hackney, J. Org. Chem., 1982, 47, 4116.

2 G. Zassinovich, G. Mastroni, and A. Camus, J. Organomet. Chem., 1979, 168.

3 P. E. Fanta, Chem. Rev., 1964, 64, 613; Synthesis, 1974, 9.

4 P. Bamfield and P. M. Ouan, Synthesis, 1978, 537.

5 I. Colon and D. R. Kelsey, J. Org. Chem., 1986, 51, 2627.

6 F. Kröhnke, Synthesis, 1976, 1.

7 S. Hünig, J. Gro, and W. Schenk, Ann., 1973, 324.

8 D. L. Coffen, B. Schaer, F. T. Bizzarro, and J. B. Cheung, J. Org. Chem., 1984, 49, 296.

9 M.-J. Shiao, P. Shieh, and J.-S. Lai, Synth. Commun., 1988, 18, 1397.

10 K. Y. Akiba, Y. Iseki, and M. Wada, Tetrahedron Lett., 1982, 23, 429; Bull. Chem. Soc. Jpn, 1984, 77, 1994; D. L. Comins and A. H. Abdullah, J. Org. Chem., 1982, 47, 4315.

11 W.-P. Fang, P. Shieh, and M.-J. Shiao, Heterocycles, 1986, 24, 1585; M.-J. Shiao, P. Shieh, and J.-S. Lai, J. Chinese Chem. Soc., 1988, 35, 233.

12 2-Benzyloxy-6-bromopyridine was prepared from 2,6-dibromopyridine in DMF with sodium benzyloxide at 80°C under N_2, bp 142°C/2 torr; ^{1}H Nmr ($CDCl_3$): δ 5.36 (s, 2H); 6.73 (dd, 1H, J = 8.0 Hz 1.0 Hz, H-4); 7.24-7.45 (m, 6H, aromatic 5H and H-3).

13 L. Testaferri, M. Tieco, M. Tringoli, D. Bartoli, and A. Massoli, Tetrahedron, 1985, 41, 1373.

14 C. Jutz, Adv. Org. Chem., 1976, 9, 225.

15 P. Krumhotz, J. Am. Chem. Soc., 1951, 73, 4449.

16 T. R. Kasturi, H. R. Y. Jois, and L. Mathew, Synthesis, 1984, 1743.

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