A CONVENIENT SYNTHESIS OF FIVE-MEMBERED HETEROARYL - SUBSTITUTED PYRIDINES

Min- Jen Shiao,[a*] Li- Hua Shih,[a] Win- Long Chia,[a] and Tay-Yuan Chau[b]

[a]Institute of Chemistry, Academia Sinica, Nankang, Taipei, Taiwan 11529 R.O.C. and [b]Department of Chemistry, National Chung-Hsing University, Taichung, Taiwan 40027 R.O.C.

Abstract-- Five-membered heteroarylpyridines (3) or (4) such as furylpyridines, thienylpyridines, imidazolylpyridines and pyrrolylpyridines were obtained regioselectively in appreciable yields (40-67%) by reaction of heteroaryllithium salts with N-ethoxycarbnylpyridinium chloride (1) followed by oxygen oxidation.

Heteroarylpyridines and their salts have been of interests due to their various biological activities.[1,2] Only a few synthesis have been reported.[3-6] 2-Furylpyridines or 3-furylpyridines were prepared by multistep processes either from ethyl pyridincarbonylacetates or from chloroacetylpyridines.[3] Wynberg et al.[4] prepared 3-thienylpyridines by reaction of appropriate lithiopyridines with 3-ketotetrahydrothiophene and subsequent aromatization of the carbinols in low yields.[4] Seki et al.[5] described that photolysis of iodopyridines in the presence of various heteroaromatics leads to the corresponding heteroarylpyridines in appreciable yields. Gronowitz et al.[6] reported that various thiopheneboronic acid coupled with bromopyridines in the presence of catalytic amount of $Pd(PPh_3)_4$ to give the thienylpyridines. Although some procedures[4,5] might be

useful for the synthesis of heteroarylpyridines as above, most of them involve multistage ring syntheses or require difficultly accessible starting materials. In addition, these syntheses gave low yields or were accompanied with several isomers, and thus could not be used as a general method.

In the previous investigations from this laboratory we have developed a method to synthesize series of various unsymmetric bipyridines,[7] 4-arylpyridines,[8] and 4-benzylpyridines[9] in high regioselectivity by addition of Grignard reagents or organolithium compounds derived from bromopyridines, bromobenzenes, and benzyl bromides to N-ethoxycarbonylpyridinium chloride (1)[10] in the presence of cuprous iodide. We wish here to report a convenient preparation of various 2- or 4- heteroarylpyridines (3) or (4) by means of essentially the same procedure.

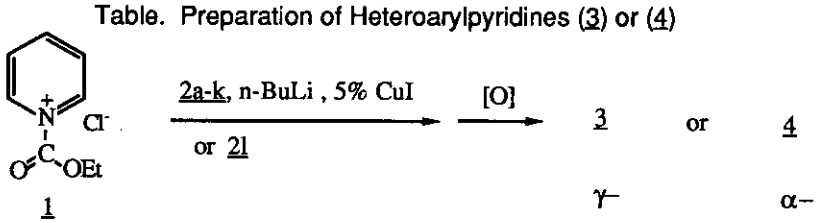
Addition of lithium salts derived from heteroaromatic compounds (2a-k) to 1 at 78°C in THF in the presence of a catalytic amount of 5% cuprous iodide should give the intermediate, 1,4-dihydropyridines or 1,2-dihydropyridines. However, these intermediates were quite unstable[10] and could be easily oxidized under air. The crude intermediate dihydropyridine was not purified but was immediately oxidized by oxygen[7] to provide the corresponding 3 or 4, respectively. Yields are in the range of 40-67% as shown in Table.

We found that reactions of 1 with compounds (2a-d, i, l) proceeded with high γ- selectivity to give the 4-(2-furyl)pyridines (3a), (3b), (3c), (3d), 4-(3-thienyl)-pyridine (3i), and 4-(2-pyrrolyl)pyridine (3l), and those with compounds (2e-h, j, k) to give regioselectively the 2-(2-pyrrolyl)pyridines (4e), (4f), (4g), (4h), 2-(2-imidazolyl)pyridine (4j), and 2-(2-pyrrolyl)pyridines (4k). However, in the case of N-methylpyrrole (2l), its lithium salt was found not to react with 1 in the same way, but instead attack on the carbonyl moiety of 1 took place.[11] Fortunately, we found that N-methylpyrrole itself can react directly with 1 at the C_4 in a yield of 45%. Apparently the π-electrons on pyrrole served as the nucleophile to react with active electrophile, pyridinium salt (1). The explanation suggested by Yamaguchi[12] is the HSAB principle;[13] softer reagents attack more easily at the C_4, while the harder reagents attack at the C_2. The observation in this study seems to imply the 2-anions of furans and pyrroles which attack 1 at C_4 is softer than those of thiophenes which

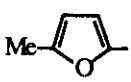
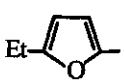
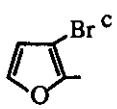
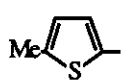
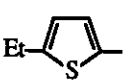
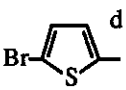
attack 1 preferentially at C_2. From these studies, it demonstrates that the regioselectivity is highly dependent upon the nature of nucleophilic heteroaromatic rings.

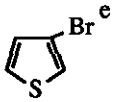
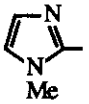
The structural assignments of compounds obtained from above reactions were principally made on the basis of mass spectra, ^{1}H-nmr spectra and elemental analysis. Because of a simple procedure, appreciable yields, and regioselectivity, the present method would provide a convenient synthesis of 2-or 4-heteroarylpyridines.

Table. Preparation of Heteroarylpyridines (3) or (4)



1

2	Reaction Site	3 or 4	Yield(%)[a]	mp(°C)[b]
2a		3a	49	65-66(lit.,[3] mp 69°C) (EA[g] / Hex)
2b		3b	44	68-69 (EA / Hex)
2c		3c	41	160-161 (EA / Hex)
2d		3d	40	63.5-64.5 (EA / Hex)
2e		4e	67	61-62(Lit.,[4] mp 60.5-62°C) (EA / Hex)
2f		4f	47	82-83 (EA / Hex)
2g		4g	45	104-105 (EA / Hex)
2h		4h	49	82.5-83.5

				(EA / Hex)
2i		3i	51	136-137(lit.,[4] mp137.5-138°C) (EA / Hex)
2j		4j	46	164-165(lit.,[5] mp167°C) (Methanol)
2k		4k	54	91-92 (EA / Hex)
2l		3l	45	63.5-64.5(lit.,[5] mp 63-63.5°C) (EA / Hex)

[a]isolated yield. [b]uncorrected. [c]ref. 14. [d]ref. 15. [e]3-lithium generated from 3-bromide. [f]Reaction occurs with I without using n-BuLi and CuI. [g] EA=Ethyl Acetate.

EXPERIMENTAL

Melting points are uncorrocted. The ^{1}H-nmr spectra were recorded on Bruker AC 200 and MSL 200 spectrometers. The ms spectra were obtained by using a VG 7-250 GC-MS system at 70 eV. Elemental analyses were performed on a Perkin-Elmer 2400 Elemental Analyzer. All anhydrous solvents were freshly distilled before use.

General Procedure for the Synthesis of 2-or 4-Heteroarylpyridines (3 or 4).

To a solution of heteroaromatic (2a-k) (5 mmol) in 25 ml of dry tetrahydrofuran (THF) was added 1.6 M n-butyllithium solution in hexane (3.8 ml, 6 mmol) and 0.66 g of cuprous iodide at -78°C under nitrogen for 1 h. The above solution was added to a solution of pyridinium chloride (prepared from 0.5 ml (6 mmol) of pyridine and 0.65 ml (7 mmol) of ethyl choroformate, 20 ml of THF at -30°C for 10 min) at -78°C over 30 min. The reaction mixture was warmed to room temperature and quenched with 5% sodium bicarbonate solution (25 ml). After evaporation of THF the residue was extracted with dichloromethane (3 X 4 ml). The extract was dried over anhydrous Na_2SO_4 and concentrated. The residue was diluted with a small amount of dichloromethane and stirred under an oxygen stream at room temperature for 10 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 (5% hexane-ethyl acetate) to afford 3 or 4. The products were characterized by ir, ^{1}H-nmr and elemental analyses as illustrated below.

4-(2-Furyl)pyridine (3a)

^{1}H-Nmr($CDCl_3$): δ 8.65 (br s, 2H, pyridine $H_{2,6}$), 7.54 (m, 3H, pyridine $H_{3,5}$ and furan H_5), 6.90 (d, J=3.4 Hz, 1H, furan H_3), 6.54 (dd, J=1.8, 3.4 Hz, 1H, furan H_4). Ms m/z: 145 (M^+, 100), 116 (47), 90 (49). Hrms Calcd for C_9H_7NO: 145.0528. Found: 145.0529.

4-(5-Methyl-2-furyl)pyridine (3b)

^{1}H-Nmr($CDCl_3$): δ 8.55 (dd, J=1.6, 4.6 Hz, 2H, pyridine $H_{2,6}$), 7.46 (dd, J= 1.7, 4.6 Hz, 2H, pyridine $H_{3,5}$), 6.78 (d, J=3.3 Hz, 1H, furan H_3), 6.13 (d, J=3.3 Hz, 1H, furan H_4), 2.40 (s, 3H, methyl). Ms m/z: 159 (M^+, 100), 158 (M^+ -1, 66), 130 (18). Anal. Calcd for $C_{10}H_9NO$: C, 75.45; H, 5.70; N, 8.50. Found: C, 75.24; H, 5.69; N, 8.88.

4-(5-Ethyl-2-furyl)pyridine (3c)

^{1}H-Nmr($CDCl_3$): δ 8.84 (d, J= 5.9 Hz, 2H, pyridine $H_{2,6}$), 7.51 (d, J= 5.9 Hz, 2H, pyridine $H_{3,5}$), 6.83 (d, J=3.4 Hz, 1H, furan H_3), 6.14 (d, J=3.4 Hz, 1H, furan H_4), 2.74 (q, J=7.6 Hz, 2H, methylene), 1.30 (t, J=7.6 Hz, 3H, methyl). Ms m/z: 173 (M^+, 70), 158 (100), 130 (14). Hrms Calcd for $C_{11}H_{11}NO$: 173.0840. Found: 173.0841.

4-(3-Bromo-2-furyl)pyridine (3d)

^{1}H-Nmr($CDCl_3$): δ 8.69 (br s, 2H, pyridine $H_{2,6}$), 7.89 (br s, 2H, pyridine $H_{3,5}$), 7.50 (d, J=1.9 Hz, 1H, furan H_5), 6.95 (d, J=1.9 Hz, 1H, furan H_4). Ms m/z: 225 (M^++2, 100), 223 (M^+, 98), 222 (M^+-1, 10), 116 (40). Hrms Calcd for C_9H_6NOBr: 222.9633. Found: 222.9638.

2-(2-Thienyl)pyridine (4e)

^{1}H-Nmr($CDCl_3$): δ 8.56 (dd, J=1.4, 4.9 Hz, 1H, pyridine H_6), 7.67 (m, 2H, pyridine $H_{3,5}$), 7.57 (dd, J=1.2, 3.7 Hz, 1H, thiophene H_5), 7.39 (dd, J=1.2, 5.1 Hz, 1H, pyridine, H_4), 7.12 (m, 2H, thiophene $H_{3,4}$). Ms m/z: 162 (M^++1, 16), 161 (M^+, 100), 116 (18). Anal. Calcd for C_9H_7NS: C, 67.05; H, 4.38; N, 8.69. Found: C, 67.05; H, 4.32; N, 8.72.

2-(5-Methyl-2-thienyl)pyridine (4f)

^{1}H-Nmr($CDCl_3$): δ 8.57 (m, 1H, pyridine H_6), 7.58 (m, 2H, pyridine $H_{3,5}$),7.36 (d, J=3.6 Hz, 1H, thiophene H_3), 7.06 (m, 1H, pyridine H_4), 6.74 (d, J=3.6 Hz, 1H, thiophene H_4), 2.50 (s, 3H, methyl). Ms m/z: 175 (M^+, 46), 174 (M^+-1, 36), 130 (18), 45 (100). Anal. Calcd for $C_{10}H_9NS$: C, 68.54; H, 5.18; N, 8.00. Found: C, 68.33; H, 5.29; N, 7.89.

2-(5-Ethyl-2-thienyl)pyridine (4g)

^{1}H-Nmr($CDCl_3$): δ 8.53 (m, 1H, pyridine H_6), 7.61 (m, 2H, pyridine $H_{3,5}$), 7.39 (d, J=3.7 Hz, 1H, thiophene H_3), 7.09 (m, 1H, pyridine H_4), 6.79 (d, J=3.7 Hz, 1H, thiophene H_4), 2.87 (q, J=7.4 Hz, 2H, methylene), 1.34 (t, J=7.4 Hz, 3H, methyl). Ms m/z: 190 (M^++1, 20), 189 (M^+, 100), 174 (50). Anal. Calcd for $C_{11}H_{11}NS$: C, 69.80; H, 5.86; N, 7.40. Found: C, 69.82; H, 5.86; N, 7.65.

2-(5-Bromo-2-thienyl)pyridine (4h)

^{1}H-Nmr($CDCl_3$): δ 8.52 (m, 1H, pyridine H_6), 7.60 (m, 2H, pyridine $H_{3,5}$), 7.31 (d, J=3.9 Hz, 1H, thiophene H_3), 7.19 (m, 1H, pyridine, H_4), 7.05 (d, J=3.9 Hz, 1H, thiophene H_4). Ms m/z: 241 (M^++2, 29), 239 (M^+, 26), 161 (100), 116 (37). Anal. Calcd for C_9H_6NBrS: C, 45.02; H, 2.52; N, 5.80. Found: C, 45.27; H, 2.42; N, 5.54.

4-(3-Thienyl)pyridine (3i)

^{1}H-Nmr($CDCl_3$): δ 8.61 (br s, 2H, pyridine $H_{2,6}$), 7.67 (dd, J=2.2, 4.3 Hz, 1H, thiophene H_5), 7.48 (d, J=5.1 Hz, 2H, pyridine $H_{3,5}$), 7.45 (m, 2H, thiophene $H_{2,4}$). Ms m/z: 162 (M^++1, 13), 161 (M^+, 100), 117 (20). Anal. Calcd for C_9H_7NS: C, 67.05; H, 4.38; N, 8.69. Found: C, 67.19; H, 4.17; N, 8.67.

2-(1-Methyl-2-imidazolyl)pyridine (4j)

^{1}H-Nmr($CDCl_3$): δ 8.59 (d, J=4.1 Hz, 1H, pyridine H_6) , 8.17 (d, J=4.1 Hz, 1H, pyridine H_5) ,7.77 (m, 1H, pyridine H_4), 7.22 (m, 1H, pyridine H_3), 7.20 (s, 1H, imidazole H_4), 7.06 (s, 1H, imidazole H_5), 4.14 (s, 3H, methyl). Ms m/z: 159 (M^+, 98), 130 (100), 103 (35). Hrms Calcd for $C_9H_9N_3$: 159.0796. Found: 159.0789.

2-(1-Benzsulfonyl-2-pyrrolyl)pyridine (4k)

^{1}H-Nmr($CDCl_3$): δ 8.46 (dd, J=0.8, 4.0 Hz, 1H, pyridine H_6), 7.69 (m, 3H, pyridine $H_{3,4,5}$), 7.50 (m, 5H, phenyl), 7.19 (dd, J=1.7, 3.8 Hz, 1H, pyrrole H_5), 6.48 (dd, J=1.7, 3.0 Hz, 1H, pyrrole H_3), 6.36 (dd, J=3.0, 3.8 Hz, 1H, pyrrole H_4). Ms m/z: 284 (M^+, 24), 219 (90), 143

(100). Anal. Calcd for $C_{15}H_{12}N_2O_2S$: C, 63.14; H, 4.59; N, 9.82. Found: C, 63.24; H, 4.36; N, 9.77.

4-(1-Methyl-2-pyrrolyl)pyridine (3l)

^{1}H-Nmr($CDCl_3$): δ 8.56 (d, J=4.7 Hz, 2H, pyridine $H_{2,6}$), 7.39 (d, J=4.7 Hz, 2H, pyridine $H_{3,5}$), 6.78 (dd, J=1.7, 3.2 Hz, 1H, pyrrole H_5), 6.43 (dd, J=1.7, 3.6 Hz, 1H, pyrrole H_3), 6.22 (dd, J=3.2, 3.6 Hz, 1H, pyrrole H_4), 3.75 (s, 3H, methyl). Ms m/z: 158 (M^+, 100), 157 (M^+-1, 43), 130 (37). Hrms Calcd for $C_{10}H_{10}N_2$: 158.0844. Found: 158.0841.

ACKNOWLEDGEMENT

We thank the financial support of National Science Council of the Republic of China.

REFERENCES AND NOTE

1. G. E. Wiegand, V. J. Bauer, and S. R. Safir, J. Med. Chem., 1971, 14, 214.
2. P. J. Brown, B. B. Buttler, W. B. Cowden, G. W. Grigg, D. Kavulak, and D. M. Podger, Aust. J. Chem., 1981, 34, 2423.
3. P. Ribereau and G. Quequiner, Can. J. Chem., 1983, 61, 334.
4. H. Wynberg, T. T. Van Bergen, and R. M. Kellog, J. Org. Chem., 1969, 34, 3175.
5. K. Seki, K. Ohkura, and M. Terashima, Heterocycles, 1986, 24, 799; K. Seki, K. Ohkura, and M. Terashima, Heterocycles, 1984, 22, 2347.
6. S. Gronowitz and K. Lawitz, Chemical Scripta, 1985, 24, 5.
7. W.-P. Fang, P. Shieh, and M.-J. Shiao, Heterocycles, 1986, 24, 1585; M.-J. Shiao, P. Shieh, and J. S. Lai, Syn. Commun., 1988, 18, 1397; M.-J. Shiao and K.-Y. Tarng, Heterocycles, 1990, 31, 637; M.-J. Shiao, L.-M. Shyu, and C.-F. Chen, Heterocycles, 1990, 31, 523.
8. M.-J. Shiao, C.-Y. Perng, C.-T. Chiu, and D. Liang, J. Chin. Chem. Soc., 1990, 37, 625; M.-J. Shiao, C.-Y. Perng, and C.-C. Shen, J. Chin. Chem. Soc., 1991, 38, 47.
9. M.-J. Shiao and W. L. Chia, Syn. Commun., 1991, 21, 401.
10. K. Akiba, Y. Iseki, and M. Wada, Tetrahedron Lett., 1982, 23, 429; D. L. Comins and A. H. Abdullah, J. Org. Chem., 1982, 47, 4315.

11. We found from the ^{1}H-nmr data that N-methylpyrrol-2-ylcarboxylate was formed in this reaction. Similar result was reported by A. Dondoni, T. Dall'Occo, G. Galliani, A. Mastellari, and A. Medici, Tetrahedron Lett., 1984, 25, 3637.

12. R. Yamaguchi, Y. Nakazono, T. Matsuki, E. Hata, and M. Kawanisi, Bull. Chem. Soc. Japan, 1987, 60, 215.

13. T. L. Ho, "Hard and Soft Acids and Bases Principles in Organic Chemistry," Academic Press, New York, 1977.

14. N. D. Ly and M. Schlosser, Helv. Chim. Acta, 1977, 60, 2085; G. M. Davies and P. S. Davies, Teterhedron Lett., 1972, 3507.

15. P. T. De Sousa Jr. and R. J. K. Taylor, Synlett., 1990, 755; H. W. Gschwend and H. R. Rodriguez, Org. React., 1979, 26, 1.

Received, 5th June, 1991