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A FACILE SYNTHESIS OF BROMO-2-ALKOXYPYRIDINES

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Abstract- Several bromo-2-methoxypyridines **2a-2e** and bromo-2-benzyloxypyridines **2a'-2e'** were synthesized by the reaction of bromo-substituted 2-pyridones **1** which were reacted with alkyl halides in the presence of silver carbonate in benzene.

Bromo-2-alkoxypyridines are usable as starting materials for syntheses of steroids,[1] bipyridine derivatives,[2,3] and other medicinally interesting compounds.[4-6] As for syntheses of bromo-2-alkoxypyridines, the following two general methods are well known: (I) the mono-displacement reaction of dibromopyridines or bromochloropyridines using alcohol or dimethylformamide as solvent;[7-9] (II) bromination of 2-alkoxypyridines.[6-8] In the former case, some of their starting materials are either not conveniently prepared[10] or not available. In addition, disubstituted derivatives are consistently formed as minor by-products.[8,9] The second method is limited only to the preparation of 3-bromo-, 5-bromo- or 3,5-dibromo-2-alkoxypyridines, other bromo congeners being not obtainable.[11]

Hopkin et al.[12] have reported that the ambident anion of 2-pyridone generated by silver carbonate can be selectively O-alkylated with alkyl halides in nonpolar solvent such as benzene. In this paper we wish to report the successful application of this method to the preparation of several bromo-2-methoxypyridines (**2a-2e**) and bromo-2-benzyloxypyridines (**2a'-2e'**) from the corresponding bromopyridines (1a-1e).

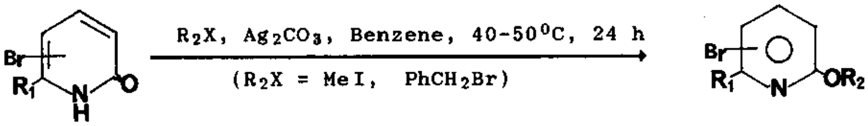
3-Bromo-2-pyridone (**1a**),[13] 5-bromo-2- pyridone (**1b**)[14,15] and 3,5-dibromo-2-pyridone (1d),[15] 6-bromo-2-pyridone (1c),[16] and 5-bromo-6-methyl-2-pyridone (1e)[17] were prepared from 3-bromopyridine, 2-pyridone, 2,6-dibromopyridine, and 6-amino-2-picoline, respectively, according to the published methods. The alkyl halides used for these reactions were methyl iodide and benzyl bromide.

The reaction was carried out by the following general procedure: a mixture of a bromo-2-pyridone (1) (21 mmol), silver carbonate (14 mmol) and alkyl halide (25 mmol) in benzene (35 ml) was stirred at 40-50°C for 24 h in the dark. The product was purified by chromatography on silica gel with hexane-ethyl acetate (2:1) and vacuum distillation.

The yields of O-alkylation of 1 were found to be very high (93-99%) (Table I), and superior to those obtained by other methods; the reported yields from other routes are also shown in Table I. The preparation of bromo-2-benzyloxypyridines (2a'-2e') from the corresponding (1a-1e) and benzyl bromide also was achieved in high yields (95-99%) (Table I).

In conclusion, this paper has described a convenient and high yield method for the synthesis of brominated 2-alkoxypyridines.

Table I. O-Alkylation of Bromo-2-pyridones (1a-1e)



1	2 (yield)	2' (yield)
R_1= H	R_1 =H, R_2 = Me	R_1 = H, R_2 = CH_2Ph
1a 3-Br	2a: 3-Br (96%)[a]	2a': 3-Br (95%)
1b: 5-Br	2b: 5-Br (95%)[b]	2b': 5-Br (95%)
1c: 6-Br	2c: 6-Br (93%)	2c': 6-Br (99%)
1d: 3,5-Br_2	2d: 3,5-Br_2 (96%)[c]	2d':3,5-Br_2 (98%)
R_1 = Me	R_1 = Me, R_2 = Me	R_1 = Me, R_2 =CH_2Ph
1e: 5-Br	2e: 5-Br (90%)	2e': 5-Br (96%)

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a) Reported yield from 3-bromo-2-chloropyridine:[10] 63%

b) Reported yield from 2-methoxypyridine:[8] 49%

c) Reported yield from 3,5-dibromo-2-chloropyridine[8] and 2-methoxypyridine:[6] 75 and 71%, respectivelly.

Table II. Some Physical Properties of Bromo-2-alkoxypyridines (2 and 2')

2, 2')	mp(^{0}C)$^{a)}$ or bp(^{0}C)/torr	Ms(70eV) m/z(%)	Molecular formula or lit. mp(^{0}C)	Analysis(%) Found(Calcd) C	H	N	^{1}H-Nmr(CDCl$_3$/TMS) δ, J(Hz)
2a	140-143/9	189(M$^+$+2,66);188 (100);187(M$^+$,79);186 (90);159(53);157(56); 79(90)	C_6H_6BrON	38.14 (38.32)	3.20 (3.22)	7.68 (7.45)	3.91(s,3H); 6.60(dd,J=8.0 and 4.8 Hz,1H,H-5); 7.74(dd, J=8.0 and 2.0 Hz,1H,H-4); 8.02 (dd,J=4.8 and 2.0 Hz,1H,H-6)
2b	194-194.5/760	189(M$^+$+2,76);188 (100);187(M$^+$,76);186 (98);159(50);157(47); 78(80)	C_6H_6BrON	38.36 (38.32)	3.04 (3.22)	7.42 (7.45)	3.86(s,3H); 6.60(d,J=8 Hz,1H, H-3); 7.57(dd,J=8.0 and 4.0 Hz,1H,H-4); 8.17(d,J=4.0 Hz,1H,H-6).
2c	75-78/12	189(M$^+$+2,70);188 (100);187(M$^+$,65);159 (46);157(40);78(70)	C_6H_6BrON	38.30 (38.32)	3.16 (3.22)	7.59 (7.45)	3.84(s,3H); 6.56(dd,J=8.0 and 1.0 Hz,1H,H-5); 6.93(dd, J=7.4 and 1.0 Hz,1H,H-3); 7.27 (dd,J=7.4 and 8.0 Hz,1H,H-4)
2d	46.5-48.5	269(M$^+$+4,40);267(M$^+$ +2,82);265(M$^+$,38); 186(25);184(23);79 (40)	48.5-49^8 49-51^6				3.94(s,3H); 7.89(d,J=2.0 Hz,1H, H-4); 8.12(d,J=2.0 Hz,1H,H-6)
2e	95-96/6	203(M$^+$+2,37);201(M$^+$, 39);173(27);171(30); 119(30);117(30);92 (100)	C_7H_8BrON	41.34 (41.61)	3.78 (3.99)	6.81 (6.93)	2.51(s,3H); 3.89(s,3H); 6.45 (d,J=8.6 Hz,1H,H-3); 7.60(d, J=8.6 Hz,1H,H-4)
2a'	175-178/6	265(M$^+$,12);263(M$^+$-2, 14);159(10);157(9); 91(100)	$C_{12}H_{10}BrON$	54.51 (54.57)	3.74 (3.82)	5.46 (5.30)	5.44(s,2H); 6.64(dd,J=8.0 and 4.8 Hz, 1H,H-5); 7.20-7.60(m, 5H,aromatic H); 7.78(dd,J= 8.0 and 2.0 Hz,1H,H-6)
2b'	55-57	265(M$^+$,11);263(M$^+$-2, 10);91(100)	56-58^5				5.34(s,2H); 6.73(d,J=8.0 Hz,1H, H-3); 7.38(m,5H,aromatic H); 7.66(dd,J=8.0 and 2.0 Hz, 1H,H-4); 8.21(d,J=2.0 Hz,1H,H-6)
2c'	13-15	265(M$^+$,7.3);263(M$^+$-2, 7.1);159(4.9);157 (5.2);91(100)	$C_{12}H_{10}BrON$	54.43 (54.57)	3.96 (3.82)	5.21 (5.30)	5.36(s,2H); 6.73(dd,J=8.0 and 1.0 Hz,1H,H-5); 7.07(dd,J=8.0 and 1.0 Hz,1H,H-3); 7.24-7.45 (m,6H,aromatic H and H-4)

2d'	84-86	345(M^++4,23);343(M^++2,47);341(M^+,25);264(14);262(16);91(100)	$C_{12}H_9Br_2ON$	42.26 (42.01)	2.48 (2.64)	4.36 (4.08)	5.32(s,2H); 7.83(d,J=2.0 Hz,1H,H-4); 7.31-7.48(m,5H,aromatic H); 8.10(d,J=2.0 Hz,1H,H-6)
2e'	185-187/6	279(M^++2,9.3);277(M^+,9.8);202(4.4);200(4.6);173(7.6);171(8.4);119(5.9);117(5.4);91(100)	$C_{13}H_{12}BrON$	56.03 (56.13)	4.47 (4.35)	5.18 (5.04)	2.53(s,3H); 5.32(s,2H); 6.48(d,J=8.6 Hz,1H,H-3); 7.30-7.45(m,5H,aromatic H); 7.57(d,J=8.6 Hz,1H,H-4)

a) Not corrected.

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EXPERIMENTAL

Melting points are uncorrected. The ^{1}H-nmr spectra were recorded on a Bruker AW80 and MSL 200 spectrometer. Mass spectra were obtained from a Hewlett-Packard 5995 GC/MS system at 70ev. Elemental analyses were performed on a Perkin-Elmer 2400 Elemental Analyzer. 2-Pyridone and 2-methoxypyridine were obtained from the Aldrich Chemical Company. Silver carbonate was prepared by known procedures.[18]

Bromo-2-alkoxypyridines 2(2'): General Procedure:
2-Pyridone 1 (21 mmol), silver carbonate (14 mmol), and alkyl halide (25 mmol) were stirred for 24 h in 35 ml of benzene at 40-50 °C in the dark. The mixture was cooled in an ice bath and silver salt was removed by filtration. The filtrate was washed with 50 ml of 2% sodium bicarbonate solution and then twice with 25 ml portions of water. The benzene was removed by evaporation at atmospheric pressure. The remaining liquid was chromatographed on silica gel (hexane/ethyl acetate, 2/1). The pure product was obtained by bulb-to-bulb distillation. Their structures were determined by ir, nmr, ms, and elemental analysis (see Table II).

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