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DEVELOPMENT OF A FACILE AND INEXPENSIVE ROUTE FOR THE PREPARATION OF α-HALOBENZOPYRIDINES FROM α-UNSUBSTITUTED BENZOPYRIDINES

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Abstract – A facile and inexpensive route for the preparation of α-halobenzopyridines from α-unsubstituted benzopyridines *via* *N*-methylbenzopyridin-α-ones was developed. α-Unsubstituted benzopyridines were converted easily into the corresponding *N*-methylbenzopyridin-α-ones, which were halogenated using PPh_3-TCICA or PPh_3-DBICA without using solvent to give α-halobenzopyridines.

Syntheses of benzopyridine (quinoline and isoquinoline) derivatives are important because their derivatives possess bioactivity.[1] α-Halobenzopyridines, such as 2-haloquinolines and 1-haloisoquinolines, are useful intermediates because they can be converted into the corresponding α-substituted benzopyridines *via* nucleophilic aromatic substitution (S_NAr) reactions,[2] palladium-catalyzed coupling reactions,[3] and halogen exchange reactions.[4] The α-halobenzopyridines can be synthesized by reaction of the corresponding benzopyridin-α-ones with phosphorus oxyhalide (POX_3). For example, reaction of quinolin-2(1*H*)-ones/isoquinolin-1(2*H*)-ones with $POCl_3$ gave 2-chloroquinolines/1-chloroisoquinolines, respectively.[5] However, this protocol required two problems to be solved: the poor availability of benzopyridin-α-ones and the intractability of POX_3. Although several routes for the preparation of benzopyridin-α-ones from benzene derivatives *via* ring closure have been reported,[6] these syntheses require many steps. Furthermore, many benzopyridin-α-ones are expensive or not commercially available. In addition, POX_3 is so reactive with water that careful handling is required during the post-treatment process. Thus, a new route for the preparation of α-halobenzopyridines would be useful.

In this study, a facile and inexpensive route for the preparation of α-halobenzopyridines from *N*-methylbenzopyridin-α-ones (which are easily prepared from α-unsubstituted benzopyridines) was

investigated using an easily prepared and safe halogenating reagent, PPh_3-TCICA,[7] as a substitute for the conventional chlorinating reagents $POCl_3$ and PCl_5.[8] Furthermore, PPh_3-DBICA, prepared from PPh_3 and dibromoisocyanuric acid (DBICA), was used for bromination (Figure 1 and Scheme 1).

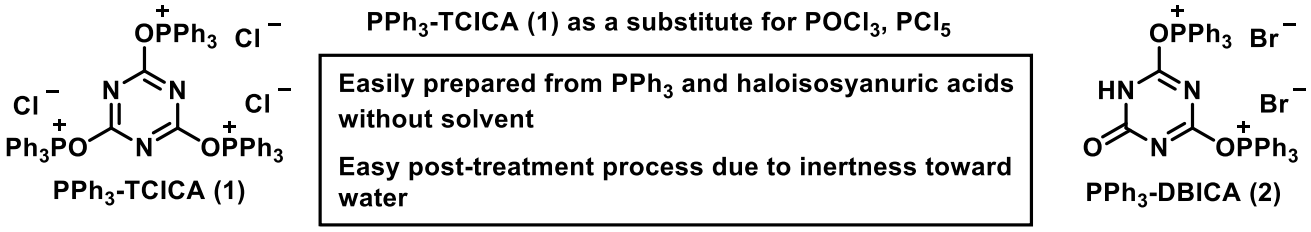
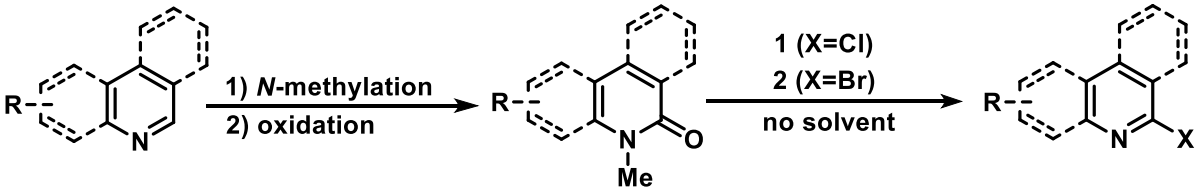


Figure 1. Phosphonium salts (**1**, **2**)

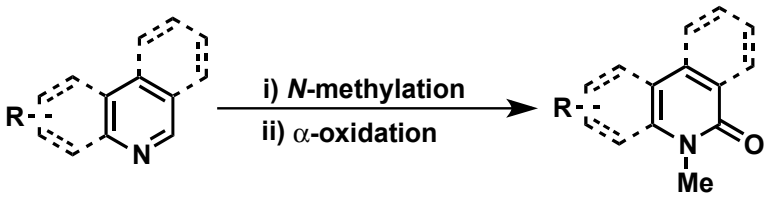


Scheme 1. Overview of α-halobenzopyridine synthesis

Prill *et al.* reported that reaction of pyridine with dimethyl sulfate gave 1-methylpyridinium salt followed by oxidation at the α-position using $K_3[Fe(CN)_6]$ and NaOH at 0-10 °C to afford 1-methylpyridin-2(1*H*)-one in 65-70% yield.[9] Using this method, substrates for the preparation of α-halobenzopyridines, *N*-methylbenzopyridin-α-ones, were synthesized from the corresponding α-unsubstituted benzopyridines in 44-66% yield (Method A, Table 1, entries 1-3). Interestingly, reaction using a simplified method (Method B: without $K_3[Fe(CN)_6]$) gave similar yields (28-55% yield, Table 1, entries 4-9). In the reaction using Method B, the air oxidation proceeded during the reaction or the work-up process to give the product, *N*-methylbenzopyridin-α-ones. Similar reaction is reported that 2-hydroxy-1,2-dihydropyridines undergo the air oxidation to afford 2(1*H*)-pyridinones.[10] Although product yields were poor, this synthetic route has the advantage of inexpensive and easily available substrates.

Previous studies demonstrated that the reaction of quinolin-2(1*H*)-one with PPh_3-TCICA (**1**) in toluene[7] or in no solvent[11] gave the chlorinated product, 2-chloroquinoline (Table 2, entries 1-4). In contrast, chlorination of 1-methylquinolin-2(1*H*)-one using **1** in toluene or xylene did not proceed (entries 5 and 6). These results indicate that halogenation of *N*-methylbenzopyridin-α-ones using **1** requires more drastic conditions than those used for conventional halogenation using toluene or xylene with reflux.

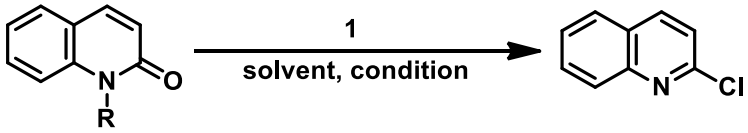
Table 1. Preparation of *N*-methylbenzopyridin-α-ones



Method A: i) MeI, THF, reflux; ii) $K_3[Fe(CN)_6]$, NaOH, H_2O, 0-10 °C.
Method B: i) MeI, dioxane, reflux; ii) NaOH, H_2O, rt.

Entry	Substrate	Method	Product	Yield (%)
1	Isoquinoline	A	2-Methylisoquinolin-1(2*H*)-one	66
2	Quinoline	A	1-Methylquinolin-2(1*H*)-one	37
3	3-Methylquinoline	A	1,3-Dimethylquinolin-2(1*H*)-one	44
4	Isoquinoline	B	2-Methylisoquinolin-1(2*H*)-one	47
5	Quinoline	B	1-Methylquinolin-2(1*H*)-one	32
6	3-Methylquinoline	B	1,3-Dimethylquinolin-2(1*H*)-one	55
7	6-Methylquinoline	B	1,6-Dimethylquinolin-2(1*H*)-one	28
8	6-Methoxyquinoline	B	6-Methoxy-1-methylquinolin-2(1*H*)-one	37
9	7-Methylquinoline	B	1,7-Dimethylquinolin-2(1*H*)-one	33

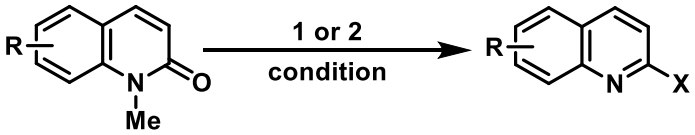
Table 2. Chlorination of quinolin-2(1*H*)-ones using **1** with and without solvent



Entry	R	Cl^- / substrate Molar ratio [Ref12]	Solvent	Condition	Yield (%)
1 [Ref7]	H	2.0	toluene	reflux, 4 h	73
2 [Ref11]	H	1.0	no solvent	140-150 °C, 2 h	54
3 [Ref11]	H	1.5	no solvent	140-150 °C, 2 h	79
4 [Ref11]	H	2.0	no solvent	140-150 °C, 2 h	86
5	Me	3.0	toluene	reflux, 4 h	0
6	Me	3.0	xylene	reflux, 8 h	0

Halogenation of 1-methylquinolin-2(1*H*)-one derivatives using **1** (chlorination) or **2** (bromination) without solvent then was performed according a previously described protocol[11] (Table 3).

Table 3. Halogenation of 1-methylquinolin-2(1*H*)-ones without solvent



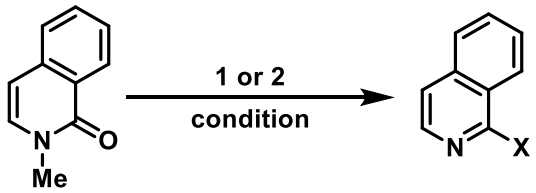
Entry	R	X^- / substrate Molar ratio Ref12	X	Condition	Yields (%)	
					Product	Recovery
1	H	**1** 2.0	Cl	160-170 °C, 22 h	42	44
2	H	**1** 2.7	Cl	160-170 °C, 2.5 h	71	0
3	H	**1** 2.7	Cl	160-170 °C, 7 h	73	0
4	H	**1** 3.0	Cl	130-140 °C, 3 h	82	0
5	H	**1** 3.0	Cl	130-140 °C, 31 h	81	0
6	H	**1** 3.0	Cl	160-170 °C, 24 h	65	0
7	3-Me	**1** 3.0	Cl	160-170 °C, 17 h	54	0
8	6-Me	**1** 3.0	Cl	160-170 °C, 14 h	87	0
9	7-Me	**1** 3.0	Cl	160-170 °C, 18 h	77	0
10	6-OMe	**1** 2.6	Cl	160-170 °C, 15 h	57	0
11	H	**2** 2.0	Br	130-140 °C, 18 h	58	22
12	H	**2** 3.0	Br	130-140 °C, 19 h	58	0
13	H	**2** 3.0	Br	160-170 °C, 16 h	78	0
14	3-Me	**2** 3.0	Br	130-140 °C, 15 h	45	10
15	6-Me	**2** 3.0	Br	130-140 °C, 18 h	41	0
16	7-Me	**2** 3.0	Br	130-140 °C, 17 h	27	0
17	6-OMe	**2** 2.6	Br	130-140 °C, 10 h	23	0

Reaction of quinolin-2(1*H*)-one (Table 3) with a slight excess amount of **1** without solvent gave 2-chloroquinoline in good yield (entries 2-6), whereas a stoichiometric amount of **1** resulted in recovery of a significant amount of starting material substrate (entry 1). To clarify the generality of this reaction, 3-methyl, 6-methyl, 7-methyl, and 6-methoxy derivatives of quinolin-2(1*H*)-ones were chlorinated using 1.4-1.5 equiv. of **1** at 160-170 °C. The corresponding substituted 2-chloroquinoline products were

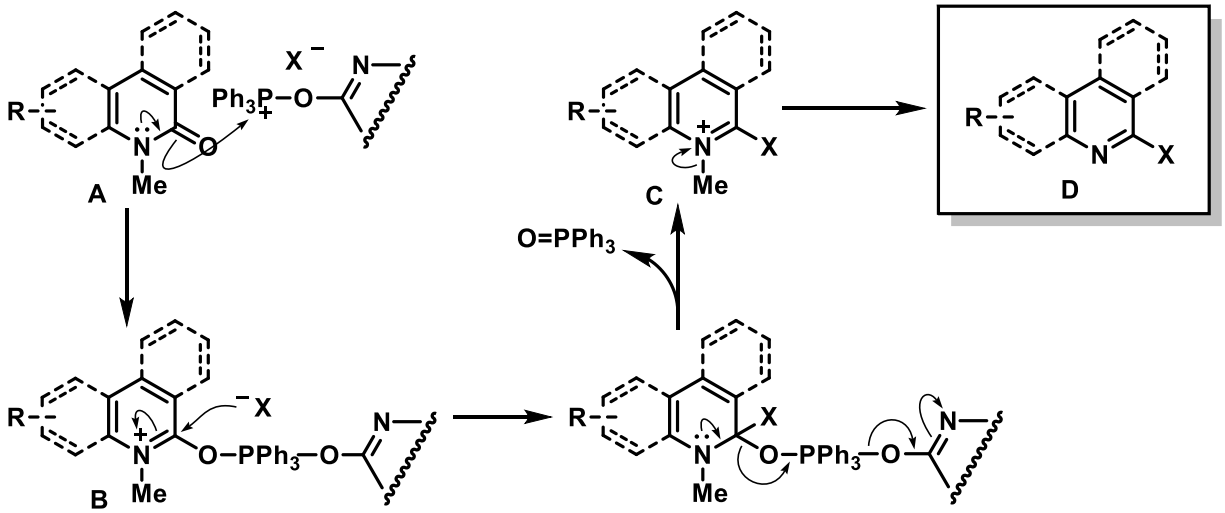
obtained in 54-87% yield (entries 7-10). The bromination of the substrates using **2** also gave 2-bromoquinolines (entries 11-16).

Next, 1-haloisoquinolines were prepared by reaction of 2-methylisoquinolin-1(2*H*)-one with **1** or **2** (Table 4). The 1-chloroisoquinoline and 1-bromoisoquinoline products were obtained in good to moderate yield.

Table 4. Halogenation of 2-methylisoquinolin-1(2*H*)-one without solvent



Entry	X^- / substrate Molar ratio [Ref12]	X	Condition	Yields (%)	
				Product	Recovery
1	**1** 2.0	Cl	160-170 °C, 25 h	37	45
2	**1** 3.0	Cl	130-140 °C, 28 h	41	36
3	**1** 3.0	Cl	160-170 °C, 4 h	45	29
4	**1** 3.0	Cl	160-170 °C, 15 h	60	0
5	**1** 4.0	Cl	130-140 °C, 21 h	63	0
6	**1** 4.0	Cl	160-170 °C, 15 h	70	0
7	**2** 4.0	Br	160-170 °C, 17 h	53	0



Scheme 2. Proposed mechanism for the halogenation of *N*-methylbenzopyridin-α-ones

The proposed mechanism for the halogenation of *N*-methylbenzopyridin-α-ones is shown in Scheme 2. The oxygen atom in **A** and the phosphorus atom in **1** or **2** reacted to form intermediate **B** due to a high affinity of oxygen for phosphorus. Subsequent addition of X^- and elimination of $O=PPh_3$ formed the α-halobenzopyridinium salt **C**. The final step, elimination of a methyl group from **C** proceeded to give the product **D**.

In summary, a facile and inexpensive route for the preparation of α-halobenzopyridines from α-unsubstituted benzopyridines *via* *N*-methylbenzopyridin-α-ones was developed.

EXPERIMENTAL

The melting points were not corrected. ^{1}H-NMR (90 MHz) spectra were obtained using a Hitachi R-90H spectrometer with tetramethylsilane (TMS) as an internal standard.

Preparation of 2-methylisoquinolin-1(2*H*)-one (general procedure for preparing *N*-methylbenzopyridin-α-ones)

Method A (Prill *et al.*[9]): In a flask (100 mL) equipped with a magnetic stirrer bar, a mixture of isoquinoline (776 mg, 6.01 mmol) and iodomethane (1306 mg, 9.20 mmol) in THF (10 mL) was heated to reflux for 1.5 h. Resulting solids were filtered, washed with EtOAc, and dried. The solids were dissolved in water (6 mL) and the solution cooled to 0-10 °C. Then, $K_3[Fe(CN)_6]$ (2884 mg, 8.76 mmol) in water (6 mL) and NaOH (1428 mg, 35.7 mmol) in water (3 mL) were added simultaneously dropwise to keep the temperature below 10 °C. After an additional amount of $K_3[Fe(CN)_6]$ (2887 mg, 8.77 mmol) in water (6 mL) was added, the reaction mixture was allowed to cool to rt and then stirred for 1.5 h. The mixture was neutralized with HCl and extracted with EtOAc. The organic layer was dried over sodium sulfate and separated using silica gel column chromatography eluted with hexane-EtOAc (1:2) to give 2-methylisoquinolin-1(2*H*)-one (632 mg, 66%).

Method B (simplified method, without $K_3[Fe(CN)_6]$): In a flask (100 mL) equipped with a magnetic stirrer bar, a mixture of isoquinoline (788 mg, 6.10 mmol) and iodomethane (4251 mg, 29.9 mmol) in dioxane (15 mL) was heated to reflux for 2 h. Resulting solids were filtered, washed with Et_2O, and dried. A mixture of the solids and 1 N NaOH (12 mL) was stirred at rt for 20 h. The mixture was neutralized with HCl and extracted with EtOAc. The organic layer was dried over sodium sulfate and separated using silica gel column chromatography eluted with hexane-EtOAc (1:3) to give 2-methylisoquinolin-1(2*H*)-one (455 mg, 47%).

1-Methylquinolin-2(1*H*)-one:[13] brown oil. ^{1}H-NMR ($CDCl_3$) δ: 3.71 (3H, *s*), 6.70 (1H, *d*, *J*=9.4 Hz),

7.07-7.70 (4H, *m*), 7.69 (1H, *d*, *J*=9.4 Hz).

1,3-Dimethylquinolin-2(1*H*)-one: yellow solid. Mp. 67-68 °C (lit.[14] 74 °C). ^{1}H-NMR ($CDCl_3$) δ: 2.26 (3H, *d*, *J*=0.9 Hz), 3.73 (3H, *s*), 7.05-7.65 (5H, *m*).

1,6-Dimethylquinolin-2(1*H*)-one: brown solid. Mp 74-75 °C (lit.[15] 83-84 °C). ^{1}H-NMR ($CDCl_3$) δ: 2.42 (3H, *s*), 3.70 (3H, *s*), 6.67 (1H, *d*, *J*=9.5 Hz), 7.10-7.50 (2H, *m*), 7.33 (1H, *s*), 7.60 (1H, *d*, *J*=9.5 Hz).

1,7-Dimethylquinolin-2(1*H*)-one: brown solid. Mp 105-106 °C (lit.[16] 105-107 °C). ^{1}H-NMR ($CDCl_3$) δ: 2.50 (3H, *s*), 3.70 (3H, *s*), 6.63 (1H, *d*, *J*=9.3 Hz), 7.04 (1H, *d*, *J*=8.0 Hz), 7.15 (1H, *s*), 7.43 (1H, *d*, *J*=8.0 Hz), 7.61 (1H, *d*, *J*=9.3 Hz).

6-Methoxy-1-methylquinolin-2(1*H*)-one:[17] yellow solid. ^{1}H-NMR ($CDCl_3$) δ: 3.70 (3H, *s*), 3.86 (3H, *s*), 6.70 (1H, *d*, *J*=9.4 Hz), 6.99 (1H, *d*, *J*=2.3 Hz), 7.14 (1H, *d*, *J*=9.1 Hz), 7.30 (1H, *d*, *J*=9.1 Hz), 7.59 (1H, *d*, *J*=9.4 Hz).

2-Methylisoquinolin-1(2*H*)-one:[18] brown oil. ^{1}H-NMR ($CDCl_3$) δ: 3.59 (3H, *s*), 6.46 (1H, *d*, *J*=7.3 Hz), 7.04 (1H, *d*, *J*=7.3 Hz), 7.30-7.75 (3H, *m*), 8.41 (1H, *d*, *J*=7.7 Hz).

Preparation of 2-chloroquinoline (general procedure for preparation of α-chlorobenzopyridine): In a flask (50 mL) equipped with a magnetic stirrer bar and balloon, a mixture of triphenylphosphine (1191 mg, 4.54 mmol) and trichloroisocyanuric acid (360 mg, 1.55 mmol) was heated under an argon atmosphere. During the heating process, triphenylphosphine melted, and trichloroisocyanuric acid vigorously reacted at 130-140 °C to form a dark brown oil, followed by further heating for 10 min. 1-Methylquinolin-2(1*H*)-one (242 mg, 1.50 mmol) was added to the mixture followed by heating at 130-140 °C for 3 h. Then, the reaction mixture was dissolved in CH_2Cl_2 and basified with triethylamine followed by silica gel column chromatography using hexane-EtOAc (6:1) as an eluate. The product 2-chloroquinoline (204 mg, 82%) was obtained.

2-Chloroquinoline:[19] pale yellow liquid. ^{1}H-NMR ($CDCl_3$) δ: 7.37 (1H, *d*, *J*=8.5 Hz), 7.50-7.70 (1H, *m*), 7.70-7.91 (2H, *m*), 8.09 (2H, *d*, *J*=8.5 Hz).

2-Chloro-3-methylquinoline: white solid. Mp 81-82 °C (lit.[20] 84 °C). ^{1}H-NMR ($CDCl_3$) δ: 2.53 (3H, *s*), 7.35-7.85 (3H, *m*), 7.85-8.10 (1H, *m*), 7.95 (1H, *s*).

2-Chloro-6-methylquinoline: white solid. Mp 112-113 °C (lit.[21] 111-114 °C). ^{1}H-NMR ($CDCl_3$) δ: 2.53 (3H, *s*), 7.33 (1H, *d*, *J*=8.7 Hz), 7.42-7.70 (2H, *m*), 7.75-8.15 (2H, *m*).

2-Chloro-7-methylquinoline: white solid. Mp 79-80 °C (lit.[22] 83-84 °C). ^{1}H-NMR ($CDCl_3$) δ: 2.55 (3H, *s*), 7.20-7.50 (2H, *m*), 7.70 (1H, *d*, *J*=8.4 Hz), 7.79 (1H, *s*), 8.03 (1H, *d*, *J*=8.6 Hz).

2-Chloro-6-methoxyquinoline: white solid. Mp 94-95 °C (lit.[23] 106-107 °C). ^{1}H-NMR ($CDCl_3$) δ: 3.92 (3H, *s*), 7.06 (1H, *d*, *J*=2.7 Hz), 7.32 (1H, *d*, *J*=8.5 Hz), 7.37 (1H, *dd*, *J*=9.1 Hz, 2.7 Hz), 7.91 (1H, *d*, *J*=9.1 Hz), 7.98 (1H, *d*, *J*=8.5 Hz).

1-Chloroisoquinoline:[24] pale yellow liquid. ^{1}H-NMR ($CDCl_3$) δ: 7.47-7.98 (4H, *m*), 8.15-8.48 (2H, *m*).

Preparation of 2-bromoquinoline (general procedure for preparation of α-bromobenzopyridine): In a flask (50 mL) equipped with a magnetic stirrer bar and a balloon, a mixture of triphenylphosphine (1186 mg, 4.52 mmol) and dibromoisocyanuric acid (652 mg, 2.27 mmol) was heated under an argon atmosphere. Dibromoisocyanuric acid vigorously reacted at 115 °C, and the mixture heated for an additional 10 min. 1-Methylquinolin-2(1*H*)-one (239 mg, 1.50 mmol) was added to the mixture, which was heated at 160-170 °C for 16 h. Then, the reaction mixture was dissolved in CH_2Cl_2 and basified with triethylamine, followed by separation using silica gel column chromatography. The use of hexane-EtOAc (6:1) as an eluate resulted in isolation of 2-bromoquinoline (244 mg, 78%).

2-Bromoquinoline:[19] yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 7.51 (1H, *d*, *J*=8.4 Hz), 7.51-8.20 (4H, *m*), 7.98 (1H, *d*, *J*=8.4 Hz).

2-Bromo-3-methylquinoline: light yellow powder (recryst. from hexane). Mp 90-91 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.55 (3H, *d*, *J*=0.5 Hz), 7.35-7.85 (3H, *m*), 7.85-8.15 (2H, *m*). *Anal*. Calcd for $C_{10}H_8BrN$: C, 54.08; H, 3.63; N, 6.31. Found: C, 54.03; 3.85; N, 6.40.

2-Bromo-6-methylquinoline: white solid. Mp 109-111 °C (lit.[25] 117-118 °C). ^{1}H-NMR ($CDCl_3$) δ: 2.52 (3H, *s*), 7.30-7.70 (3H, *m*), 7.75-8.10 (2H, *m*).

2-Bromo-7-methylquinoline: yellow solid. Mp 79-80 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.55 (3H, *s*), 7.25-7.55 (2H, *m*), 7.55-8.15 (3H, *m*).

2-Bromo-6-methoxyquinoline: white solid. Mp 122-127 °C (lit.[26] 110 °C). ^{1}H-NMR ($CDCl_3$) δ: 3.92 (3H, *s*), 7.05 (1H, *d*, *J*=2.8 Hz), 7.36 (1H, *dd*, *J*=9.1 Hz, 2.8 Hz), 7.45 (1H, *d*, *J*=8.6 Hz), 7.87 (1H, *d*, *J*=8.6 Hz), 7.93 (1H, *d*, *J*=9.1 Hz).

1-Bromoisoquinoline:[27] yellow liquid. ^{1}H-NMR ($CDCl_3$) δ: 7.50-7.90 (4H, *m*), 8.15-8.45 (2H, *m*).

REFERENCES AND NOTES

1. For example, procaterol (an intermediate-acting β_2-adrenergic receptor agonist), quinine, primaquine, chloroquine (antimalarials), chinoiodine, chinoform (antiamebic agents), and papaverine (an opium alkaloid antispasmodic drug) are known as bioactive quinolineandisoquinoline derivatives.
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