SYNTHESIS OF 4-ALKOXYQUINOLINES FROM QUINOLINE REISSERT COMPOUNDS

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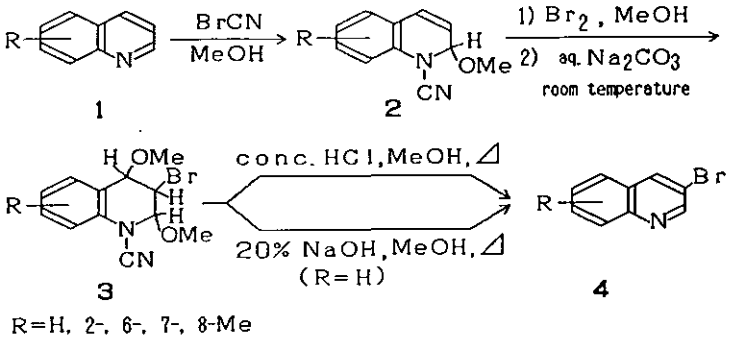
Abstract —— The quinoline Reissert compound (5a) was converted to 1-benzoyl-3-bromo-2-cyano-1,2,3,4-tetrahydro-4-methoxyquinoline (6a) by successive treatment in methanol with bromine and aq. sodium carbonate. Hydrolysis of 6a with hydrochrolic acid gave 3-bromoquinoline (4; R=H), but that with aq. sodium hydroxide afforded 4-methoxyquinoline (7a). Reissert compounds derived from some quinoline derivatives (5) gave the corresponding 4-methoxyquinolines (7) through tetrahydroquinolines (6) in a similar way.

We have previously reported that 1-cyano-1,2-dihydro-2-methoxyquinolines (2) derived from quinolines (1) and cyanogen bromide in methanol are converted to 3-bromo-1-cyano-1,2,3,4-tetrahydro-2,4-dimethoxyquinolines (3) by successive treatment in methanol with bromine and aq. sodium carbonate (Na_2CO_3) at room temperature, and 3 affords 3-bromoquinolines (4) in high yields upon heating with conc. hydrochloric acid in methanol[1] or with 20% sodium hydroxide (NaOH) in methanol[2] as illustrated in Scheme 1.

As an extension of this work, we chose 1-benzoyl-2-cyano-1,2-dihydroquinoline (5a), the quinoline Reissert compound, as a 1,2-dihydroquinoline in place of 2 and investigated its behavior towards the above processes.

The quinoline Reissert compound (5a) was treated with bromine in methanol at room temperature for 3 h followed by stirring with 20% Na_2CO_3 at room

temperature for 2 h to give 1-benzoyl-3-bromo-2-cyano-1,2,3,4-tetrahydro-4-methoxyquinoline (6a), corresponding to 3, in 63.1% yield (Scheme 2). The ir spectrum of 6a exhibited a CN band at 2380 cm^{-1}, an amidocarbonyl band at 1651 cm^{-1} and two ether bands at 1288 and 1076 cm^{-1}. Its empirical formula, $C_{18}H_{15}N_2O_2Br$, and ^1H-nmr and mass spactra (Table I) were fully consistent with the proposed structure.



1 2 3 4

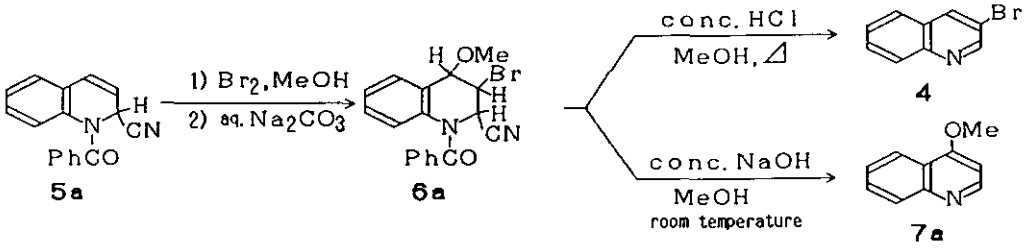
R=H, 2-, 6-, 7-, 8-Me

Scheme 1

Hydrochrolic acid hydrolysis of 6a was carrid out under the same conditions as that of 3 to 4. Thus, a solution of 6a in methanol was heated under reflux with conc. hydrochloric acid for 24 h to afford 3-bromoquinoline (4, R=H) but in a rather low yield of 20.9%. Such a low yield of 4 might be ascribed to the fact that acid catalyzed hydrolysis of Reissert compounds follows a somewhat complicated courses.[3] Accordingly this route from 5a to 4 appears to be less useful as compared with that starting from 1-cyano-1,2-dihydro-2-methoxyquinoline(2), in which hydrochloric acid hydrolysis of 3 gave rise to 3-bromoquinolines (4) consistently in high yields.

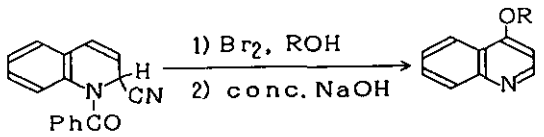
Next we tried basic hydrolysis of 6a. It has been known that 3 does not undergo hydrolysis upon treatment with aq. Na_2CO_3 in methanol at room temterature[1a] but is hydrolyzed to 4 (R=H) by heating with aq. NaOH in methanol,[2] and quinoline Reissert compounds smoothly aromatize to quinolines by the action of aq. NaOH in alcohol.[4] Taking into account these facts, we explored the reaction of 6a with NaOH. When conc. NaOH solution was added to a solution of 6a in methanol with stirring at room temperature and the reaction mixture was

kept at room temperature for 4 h until no peak of 6a could be detected on gas chromatogram, 4-methoxyquinoline (7a) was obtained in 56.4% yield, 4 being not isolated at all (Scheme 2). This result is very surprising in view of the alkaline hydrolysis of 3 to 4, and seems to provide a convenient method for synthesis of 4-alkoxyquinolines.



Scheme 2

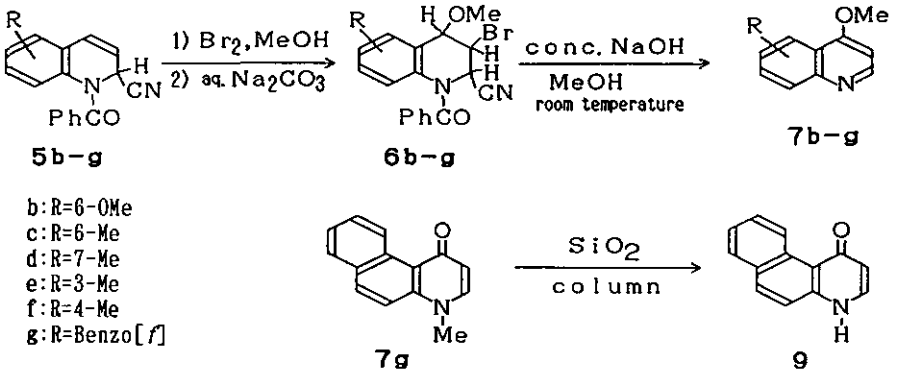
From the synthetic viewpoint, one-pot procedure was tried. When bromine was added to a solution of 5a in methanol and the mixture was kept at room temperature for 2 h, and then conc. NaOH was directly added and the resultant mixture was kept at room temperature for 20 h, 4-methoxyquinoline (7a) was obtained in a better yield of 65.4% than that of the two-step procedure (ca. 35.6%) (Scheme 3). Further this one-pot procedure was carried out under the same conditions using ethanol, propanol, isopropanol and butanol. The corresponding 4-alkoxyquinolines (8a-d) were also formed, but their yields were much lower ranging from 18 to 6.6% yields (Scheme 3).



Scheme 3

In further exploring the scope of the reaction, the two-step procedure was attempted with Reissert compounds of some quinoline derivatives (5b-f) and that of benzo[*f*]quinoline (5g) (Scheme 4, Tables I and II). 6-Methoxy- and 6-methylquinoline Reissert compounds (5b and 5c) reacted in a similar way and provided the corresponding tetrahydroquinolines (6b:48.2%, 6c:58.5%) and the 4-methoxy-

quinolines (7b:21.8%, 7c:44.2%). Reactions of Reissert compounds derived from 7-methyl- and 3-methylquinolines (5d and 5e) were accompanied by an additional bromination at the first step, leading to x-bromo-4-methoxyquinolines (7d and 7e).



Scheme 4

They seems likely to be 6-bromoquinoline derivatives, though their structural elucidation was not done. It is interest that the 3-methyl substituent in 5e did not disturb the reaction. The Reissert compound of lepidine (5f) also gave the tetrahydroquinoline (6f) in 75.5% yield, but its alkaline hydrolysis afforded complicated mixture, no definite product being isolated. While the reaction of benzo[*f*]quinoline derivative (5g) afforded the corresponding tetrahydro compound (6g) in 80.2% yield, the NaOH hydrolysis of 6g gave not 1-methoxybenzo[*f*]-quinoline but instead 4-methyl-1-one derivative (7g) in 80.5% yield. Further 7g was found to undergo demethylation to give 1,4-dihydrobenzo[*f*]quinolin-1-one (9) by means of silica gel column chromatography.

It may be concluded that the above reaction sequence is a more convenient route to 4-alkoxyquinolines as compared with the hitherto reported ones.[5]

EXPERIMENTAL

General comments

Melting points were measured on a Yanagimoto Micromelting Point Apparatus and

are uncorrected. The ^{1}H-nmr spectra were recorded on a JEOL JNM GX-270(270 MHz) or JEOL JNM GX-400(400 MHz) spectrometer with tetramethylsilane as an internal standerd. Chemical shifts are given in ppm(δ), and signals are expressed as s(singlet), d(doublet), dd(doublet of doublet), t(triplet), q(quartet), m(multiplet) or br(broad). Mass spectra(ms) were taken with a Hitachi M-80B GC-MS spectrometer. Gas chromatography was carried out using Hitachi G-3000 Gas Chromatograph. (3% silicone GE-SE30 on chromosorb-W 60-80 mesh; 3mmϕ × 2m stainless column) Silica gel used for column chromatography was Merck Silica Gel 60(70-230 mesh).

1-Benzoyl-3-bromo-2-cyano-4-methoxy-1,2,3,4-tetrahydroquinolines (6a-g) from 1-benzoyl-2-cyano-1,2-dihydroquinoline (5a-g)

To a stirred solution of 5a-g (0.5 g) in MeOH(200 ml) was added bromine (2 ml, 38.8 mmol)at room temperature and the whole was kept at room temperature for 3 h, then 20% Na_2CO_3 (50 ml) was added at room temperature, and the resulting mixture was stirred at room temperature for 2 h. The reaction mixture was poured into water and extracted with CH_2Cl_2, and the CH_2Cl_2 solution was dried over $MgSO_4$, filtered and coccentrated. The crystalline residue was recrystallized from hexane-benzene (10:1) to give 6a-g (Table I).

Table I. Yields and physical properties of 6a-g.

Starting material		Product		mp	Ir ν_{max}^{KBr} cm^{-1}			Nmr($CDCl_3$)				
No.	Substituent	No.	Yield(%)	°C	-CN	>C=O	-O-	1-H (s)	2-H (d)	3-H (t)	4-H (d)	4-OCH_3 (s)
5a	H	6a[a)p)]	63.1	154-157	2380	1651	1288,1076	-	5.87	4.55	4.53	3.75
5b	6-CH_3O	6b[q)]	48.2	148-154	2400	1660	1278,1080	-	5.86	4.81	4.76	3.72[d)]
5c	6-CH_3	6c[r)]	58.5	127-130	2380	1641	1292,1077	-	5.87	4.54	4.51	3.76[e)]
5d	7-CH_3	6d[b)s)]	53.9	121-123	2400	1662	1289,1073	-	5.82	4.57	4.48	3.72[f)]
5e	3-CH_3	6e[c)t)]	65.4	120-127	2300	1654	1283,1075	-	5.76[g)]	-[h)]	4.50[g)]	3.76
5f	4-CH_3	6f[u)]	75.5	168-171	2350	1654	1067	-	5.38	4.43[i)]	-[k)]	3.40
5g	Benzo[*f*]	6g[v)]	80.2	218-225	2400	1671	1063	5.13[j)]	4.96[k)]	6.03[j)]	-	-[j)]

a)m/z 371(M^+). b)m/z 464(M^+). c)m/z 464(M^+). d)3.78(6-OCH_3). e)2.23(6-CH_3). f)2.11(7-CH_3). g)singlet. h)2.10(3-CH_3). i)doublet. j)1.67(4-CH_3). k)double doublet. p)Anal. Calcd for $C_{18}H_{15}N_2O_2Br$:C,58.24;H,4.07;N,7.55. Found:C,58.51;H,3.86;N,7.71. q)Anal. Calcd for $C_{19}H_{17}N_2O_3Br$: C,56.87;H,4.27;N,6.98. Found:C,56.51;H,4.03;N,7.11. r)Anal. Calcd for $C_{19}H_{17}N_2O_2Br$:C,59.24; H,4.45;N,7.27. Found:C,59.46;H,4.20;N,7.51. s)Anal. Calcd for $C_{18}H_{16}N_2O_2Br_2$:C,49.17;H,3.47;

N, 6.04. Found: C, 48.96; H, 3.62; N, 6.25. t) Anal. Calcd for $C_{10}H_{16}N_2O_2Br_2$: C, 49.17; H, 3.47; N, 6.04. Found: C, 49.35; H, 3.66; N, 5.87. u) Anal. Calcd for $C_{10}H_{17}N_2O_2Br$: C, 59.24; H, 4.45; N, 7.27. Found: C, 59.51; H, 4.31; N, 7.42. v) Anal. Calcd for $C_{22}H_{17}N_2O_2Br$: C, 62.72; H, 4.07; N, 6.65. Found: C, 62.53; H, 4.20; N, 6.81. w) Anal. Calcd for $C_{16}H_{15}N_2O_2Br$: C, 58.24; H, 4.07; N, 7.55. Found: C, 58.46; H, 3.85; N, 7.69. x) Anal. Calcd for $C_{10}H_{17}N_2O_2Br$: C, 59.24; H, 4.45; N, 7.27. Found: C, 59.37; H, 4.26; N, 7.49.

Alkaline hydrolysis of 6a-g

To a stirred solution of 6a-g (1.0 g) in MeOH (20 ml) was added conc. NaOH solution (4 ml, 50 mmol), and the whole was kept at room temperature for 4 h while being monitored by gas chromatography. The reaction mixture was poured into water and extracted with CH_2Cl_2, and the extract was dried over $MgSO_4$, filtered and concentrated. The product obtained from 6a was chromatographed on silica gel column with benzene to give 7a. Products obtained from 7b-g were chromatographed on alumina column with benzene to give 7b-g (Table II).

Table II. Yields and physical properties of 7a-g.

Starting material		Product		mp	Ir	Nmr($CDCl_3$)		
No.	Substituent	No.	Yield(%)	°C	$\nu_{max}^{KBr}cm^{-1}$ -O-	2-H (d)	3-H (d)	4-OCH_3 (s)
6a	H	7a[a]	50.4	oil	1074, 1112	8.74	6.72	4.03
6b	6-CH_3O	7b[f]	21.8	oil	1099, 1071	8.59	6.67	3.91
6c	6-CH_3	7c[g]	44.2	oil	1109, 1071	8.64	6.62	3.96
6d	7-CH_3	7d[a,h]	46.3	96-101	1124, 1071	8.62	6.54	3.91
6e	3-CH_3	7e[b,i]	68.7	66-68	1111	8.71[k]	2.44[l]	4.02
6f	4-CH_3	7f	-	—	—	—	—	—
6g	Benzo[*f*]	7g[c,j]	80.5	148-158	1646	8.10	9.03	—[d]

a) m/z 252(M^+). b) m/z 252(M^+). c) m/z 209(M^+). d) 4.12(4-N-CH_3). e) Anal. Calcd for $C_{10}H_9NO$: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.32; H, 5.55; N, 8.70. f) Anal. Calcd for $C_{11}H_{11}NO_2$: C, 69.83; H, 5.86; N, 7.40. Found: C, 69.62; H, 5.51; N, 7.55. g) Anal. Calcd for $C_{10}H_{11}NO$: C, 76.28; H, 6.40; N, 8.09. Found: C, 76.47; H, 6.39; N, 8.23. h) Anal. Calcd for $C_{10}H_{10}NOBr$: C, 52.41; H, 4.00; N, 5.56. Found: C, 52.49; H, 3.77; N, 5.71. Nmr: 8.24(1H, s, 5-H), 7.80(1H, s, 8-H). i) Anal. Calcd for $C_{10}H_{10}NOBr$: C, 52.41; H, 4.00; N, 5.56. Found: C, 52.53; H, 3.86; N, 5.79. Nmr: 8.21(1H, d, $J_{5,7}$=2 Hz, 5-H), 7.91(1H, d, $J_{7,8}$=9 Hz, 8-H), 7.69(1H, dd, $J_{7,8}$=9 Hz, $J_{5,7}$=2 Hz, 7-H). j) Anal. Calcd for $C_{14}H_{11}NO$: C, 80.36; H, 5.30; N, 6.69. Found: C, 80.05; H, 5.52; N, 6.91. k) singlet. l) 3-CH_3.

Acid hydrolysis of 6a

To a solution of 6a (2.0 g, 5.4mmol) in MeOH (100 ml) was added conc. HCl (6 ml) and the whole was refluxed for 24 h. After cooling, the reaction mixture was poured into water and extracted with CH_2Cl_2, and the CH_2Cl_2 extract was dried over $MgSO_4$, filtered and concentrated. The residue was chromatographed on silica gel column with benzene to give 4 (R=H) in 20.9% yield. It was identified by comparison of its ir spectrum with that of an authentic sample.

One-pot synthesis of 4-alkokyquinolines (7a, 8a-d)

To a solution of 5a (2.0 g) in an alcohol (MeOH, EtOH, PrOH, isoPrOH and BuOH, 100 ml) was added bromine (1 ml, 19.4 mmol) at room temperature, and the mixture was allowed to stand for 2 h. Then, 50% NaOH solution (2 ml) was added to this solution, and the whole was kept at room temperature for 20 h while being monitored by gas chromatography. The reaction mixture was poured into water and extracted with CH_2Cl_2, and the extract was dried over $MgSO_4$ and concentrated to give a oily residue. This was purified by chromatography on alumina with benzene to give 7a, 8a-d (Table III).

Table III. Yields and physical properties of 7a, 8a-d.

Entry	ROH R	Product No.	Yield(%)	Ir $\nu_{max}^{KBr}cm^{-1}$ -O-	Nmr($CDCl_3$) 2-H (d)	3-H (d)	Formula	Anal.(%) Found(Calcd) C	H	N
1	CH_3	7a[a)]	65.4							
2	C_2H_5	8a	18.0	1114, 1074	8.72	6.70	$C_{11}H_{11}NO$	76.02 (76.28	6.33 6.40	8.05 8.09)
3	n-C_3H_7	8b	13.2	1111, 1073	8.71	6.67	$C_{12}H_{13}NO$	76.79 (76.98	6.85 7.00	7.32 7.48)
4	i-C_3H_7	8c	6.6	1111, 1061	8.70	6.71	$C_{12}H_{13}NO$	76.76 (76.98	7.01 7.00	7.55 7.48)
5	n-C_4H_9	8d	14.0	1110, 1074	8.71	6.70	$C_{13}H_{15}NO$	77.51 (77.58	7.25 7.51	6.61 6.96)

a) Identified by ir spectrum.

1,4-Dihydrobenzo[*f*]quinolin-1-one(9) from 1,4-dihydro-4-methylbenzo[*f*]quinolin-1-one(7g)

Chromatography of 7g on silica gel column with benzene-MeOH(10:1) gave 9 in 60.42% yield.

mp 232-234°C[6]; ir: ν_{max}^{KBr} cm^{-1}: 1707(CO), 3440(NH); nmr($CDCl_3$): 9.17(1H, d, J=8.7 Hz, 3-H), 8.42(1H, d, J=8.7 Hz, 2-H), 4.21(1H, s, N-H); ms: m/z 195(M^+). *Anal.* Calcd for $C_{13}H_9NO$: C, 79.98; H, 4.65; N, 7.17. Found: C, 79.74; H, 4.85; N, 7.37.

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