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REACTION OF QUINOLINE 1-OXIDES WITH SODIUM METHOXIDE IN THE PRESENNCE OF LEAD(IV) ACETATE

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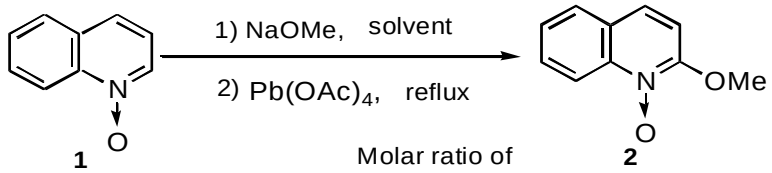
Abstract - In the presence of lead(IV) acetate, the reaction of quinoline 1-oxide with methoxide anion under various reaction conditions gives 2-methoxyquinoline 1-oxide without deoxygenation of *N*-oxide group. Reaction of 4-substituted quinoline 1-oxides with methoxide anion also resulted in the corresponding 4-substituted 2-methoxyquinoline 1-oxides under the same reaction conditions. As the reaction mechanism, ionic pathway is suggested rather than radical pathway through the investigation using radical initiators.

Formerly in 1962, Ochiai and Ohta reported that 1-hydroxy-2(1*H*)-quinolinones were obtained in good yields upon treatment of quinoline 1-oxides with lead(IV) acetate or lead(IV) benzoate in benzene.[1] These reactions seem likely to proceed *via* 2-acetoxy- or 2-benzoyloxyquinoline 1-oxides and then1-acetoxy- or 1-benzoyloxy -2(1*H*)-quinolinones as the intermediates.

In general the reaction of aromatic *N*-oxide with nucleophile, in particular in the presence of an acylating agent, smoothly occurrs to give deoxygenated α- or γ-substituted product through 1-acyloxy-1, 2- or -1, 4-dihydro intermediate.[2] Apparently, the α- or γ-substituted *N*-oxides are much more versatile for further transformations than the corresponding deoxygenated products due to the various reactivities of *N*-oxide function, but *N*-reoxidation, for instance, of deoxygenated α-substituted products is sometimes very difficult, in particular for the compounds having the substituents vulnerable to peracid owing to the possible occurrence of hydrolysis, oxidation or rearrangement.[3]

Thus, the establishment of the general way of the the reaction of aromatic *N*-oxides with nucleophiles not accompanying with deoxygenation is theoretically interesting and highly desirable. In connection with this project, we previously described the reactions of quinoline 1-oxides with alkyl- and aryllithiums in the presence of oxidant.[4] The present paper deals with the reactions of quinoline 1-oxides with methoxide anion in the presence of lead(IV) acetate, giving the corre-

Table 1 Reaction of quinoline 1-oxide with sodium methoxide in the presence of lead(IV) acetate



1 **2**

Solvent	Reflux time (h)	Molar ratio of **1** : NaOMe : $Pb(OAc)_4$	Yield (%)
PhH	2	1 : 1.2 : 0	0
$CHCl_3$	2	1 : 1.2 : 1.2	23
$CHCl_3$	2	1 : 2 : 1.2	18
$CHCl_3$	2	1 : 4 : 1.2	7
$CHCl_3$	2	1 : 0.5 : 1.2	7
$CHCl_3$	2	1 : 1 : 0.5	12
$CHCl_3$	5min	1 : 1 : 1.2	25
THF	2	1 : 1 : 1.2	9
CH_3CN	2	1 : 1 : 1.2	25
MeOH	2	1 : 1 : 1.2	18
MeOH	2	1 : 0.5 : 1.2	0
MeOH	5min	1 : 1 : 1.2	12
MeOH	6	1 : 1 : 1.2	55
MeOH	24	1 : 1 : 1.2	40

sponding 2-methoxyquinoline 1-oxides in moderate yields.

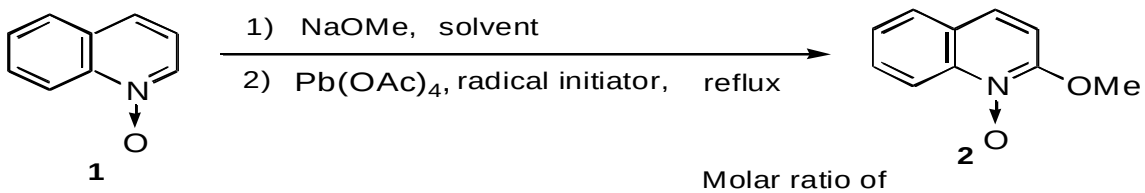
At first, the conditions of the reaction of quinoline 1-oxide (**1**) were explored in terms of solvent, reflux time and molar ratio (Table 1).

Thus it was found that 2-methoxyquinoline 1-oxide (**2**) was obtained in the highest yield of 55% when refluxed with 1 equivalent NaOMe and 1.2 equivalent $Pb(OAc)_4$ in MeOH for 6 h. Although only one example was shown in Table 1, the reaction did not proceed without lead(IV) acetate, the presence of lead(IV) acetate being indispensable in this reaction.

As for the reaction mechanism of this reaction the possibility of a radical mechanism should be taken into consideration, since some reactions using lead(IV) acetate are noticed to follow radical processes[5] rather than ionic ones. In order to explore this aspect we attempted the reactions in the presence of radical initiators, benzoyl peroxide (BPO) and 2, 2'-azobisisobutyronitrile(AIBN) (Table 2). As shown in Table 2 the promotion by means of radical initiators was not practically noticed and this reaction seems likely to follow principally an ionic path. We tentatively suggest the following ionic mechanism involving the initial formation of the adduct of $Pb(OAc)_4$ to the *N*-oxide oxygen followed by nucleophilic addition of methoxy anion and the oxidation of so-formed 1, 2-dihydroquinoline 1-oxide intermediate (Scheme 1).

Subsequently we extended this procedure to reaction of 4-substituted quinoline 1-oxide with methoxide anion and found that this procedure is fairly useful for preparation of 4-substituted 2-

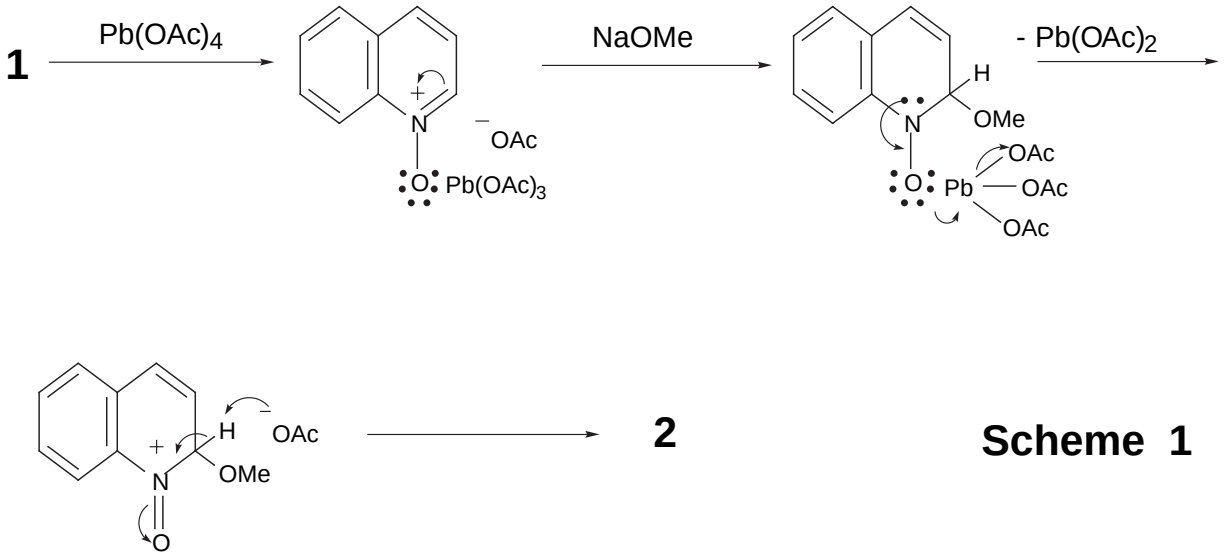
Table 2 Effect of radical initiator on the yield of **2**



1 **2**

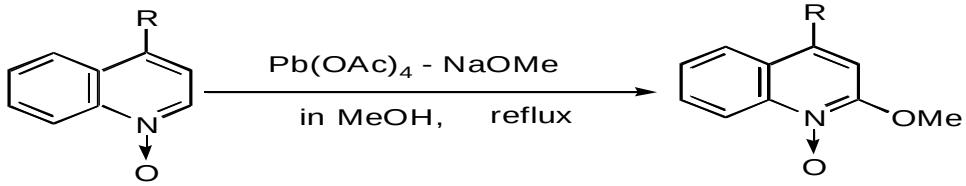
Radical initiator	Solvent	Reflux time (h)	Molar ratio of **1** : NaOMe : $Pb(OAc)_4$: initiator	Yield (%)
———	PhH	2	1 : 1.2 : 1.2 : 0	7
BPO	PhH	2	1 : 1.2 : 1.2 : 1	12
AIBN	PhH	2	1 : 1.2 : 0.01 : 1	0
AIBN	PhH	2	1 : 1.2 : 0.1 : 1	0
AIBN	PhH	2	1 : 1.2 : 1.0 : 1	12
AIBN	PhH	2	1 : 1.2 : 1.2 : 1	10
BPO	PhH	6	1 : 1.2 : 1.2 : 1	2
BPO	PhH	1	1 : 1.2 : 1.2 : 1	10
BPO	$CHCl_3$	2	1 : 1.2 : 1.2 : 1	26

BPO : benzoyl peroxide AIBN : 2,2'-azobisisobutyronitrile



Scheme 1

Table 3 Reaction of 4-substituted quinoline 1-oxide with sodium methoxide in the presence of lead(IV) acetate in MeOH



3 (a-f) **4 (a-f)**

Product No.	R	Reflux Time (h)	Molar ratio of **1** : NaOMe : $Pb(OAc)_4$	Yield (%)
3a	NO_2	2	1 : 1 : 1.2	12
3b	Cl	2	1 : 1 : 1.2	51
3c	CH_3	2	1 : 1 : 1.2	39
3d	CHO	2	1 : 1 : 1.2	23
3e	OCH_3	2	1 : 1 : 1.2	22
3f	CN	2	1 : 1 : 1.2	23

methoxyquinoline 1-oxide (Table 3).

Although the difference of the reactivity between the compounds having electron-releasing groups (OMe, Me and Cl) and those having electron- withdrawing ones (NO_2, CHO and CN) was not observed apparently in this reaction, the compounds with electron-releasing group afforded the corresponding products in somewhat better yields.

This procedure was investigated using other alkoxides (EtONa, sodium 2-phenylphenoxide and *t*-BuOK), however the formation of carbon-oxygen bond was not observed so far in the case of these reactions. Moreover, in the presence of lead(IV) acetate the reaction of quinoline *N*-oxide with ethyl cyanoacetate as a C-nucleophile was also tried, but the expected product was not obtained at all under the present reaction conditions as yet. To form carbon-oxygen bond and carbon-carbon bond in better yields the continuous research is under way.

EXPERIMENTAL

Melting points were measured on a Yanagimoto micro melting points apparatus and are uncorrected. Spectal data were recorded in the following spectrometers: IR spectra, JASCO FT/IR -470 Plus ; ^{1}H-NMR spectra, JEOL GX-400 (400 MHz) and JEOL A-500 (500 MHz) ; ^{13}C-NMR spectra, JEOL GX-400 (100 MHz) and JEOL A-500 (125 MHz) ; MS spectra, Shimadzu GC-MS QP5050 for EI-MS and JMS-HX100 for FAB-MS. The H-COSY, DEPT and HMQC experiments were also used for the assignments of the structures. The chemical shifts are given in the δ scale. Elemental analyses were performed on a Yanaco CHN CORDER MT-6 instrument. Medium pressure liquiud chromatography (MPLC) was carried out with Yamazen 540 FMI-C pump and Wakogel FC-40 (20-40 μm, Wako). Column chromatography was carried out with Kieselgel 60 (70-230 mesh, Merck). High-performance thin layer chromatography (HPTLC) for the yields shown in Table1 was conducted on Shimadzu high speed thin layer chromatoscanner (CS-9300PC) with the detector set at uv 254 nm.

General procedure for the reaction of quinoline 1-oxide (1) with sodium methoxide in the presence of lead(IV) acetate

To a solution of sodium methoxide in a solvent, which was prepared from sodium and MeOH and then MeOH was removed *in vacuo*, were added **1**(1.0 g, 6.9 mmol) and lead(IV) acetate, and the resulting mixture was refluxed under nitrogen with stirring according to Table1.

The resulting solution was filtered and after the solvent of the filtrate was evaporated, the residue was extracted with organic solvent and water. The residure from water extract was chromatographed with the mixed solvent of $CHCl_3$: MeOH = 30 : 1 to give 2-methoxyquinoline 1-oxide (**2**). The exact yields as shown in Table 1 were determined using chromatoscanner (CS-9300 PC) . HPTLC conditions: HPTLC plate, silica gel $60F_{254}$ precoated (Merck); solvent system, $CHCl_3$: MeOH = 10: 1.

General procedure for the reaction of 1 with sodium methoxide in the presence of lead(IV) acetate using radical initiator

Reaction was carried out as described in general procedure for the reaction of **1** with sodium methoxide in the presence of lead(IV) acetate but using BPO or AIBN as a radical initiator with a molar ratio as shown in Table 2. The residue from water extract was purified by MPLC to give starting material (ethyl acetate) and **2** ($CHCl_3$: MeOH = 30 : 1) with the yields shown in Table 2 in turn.

General procedure for the reaction of 4-substituted quinoline 1-oxide with sodium methoxide in the presence of lead(IV) acetate

Reaction was carried out as described in general procedure for the reaction of **1** with sodium methoxide (0.32 g, 6 mmol) in the presence of lead(IV) acetate (3.2 g, 7.2 mmol) under reaction conditions shown on Table 3 but using 4-substituted quinoline 1-oxide (6 mmol) instead of **1**. MeOH was evaporated off from the resulting solution after the reaction and the residue was worked up in the manner as shown below.

Reaction of 4-nitroquinoline 1-oxide (3a)

The residue was purified by MPLC to give starting material (*n*-hexane : ehtyl acetate = 1 : 1) and 2-methoxy-4-nitroquinoline 1-oxide (**4a**) (ethyl acetate)(0.16 g, 12%). This compound was re-crystallized from ether-acetone to give brown powder, mp 146-148 ℃. *Anal.* Calcd for $C_{10}H_8N_2O_4$: C, 54.55 ; H, 3.66 ; N, 12.72. Found: C, 54.46 ; H, 3.87 ; N, 12.44. IR (KBr) : 3095, 1606, 1530, 1498, 1298, 1119, 772 cm^{-1}. ^{1}H-NMR($CDCl_3$): δ 4.29 (3H, s, CH_3), 7.75 (1H, ddd, J= 8.6, 7.0 and 1.2 Hz, H-6), 7.86 (1H, ddd, J= 8.7, 7.0 and 1.4 Hz, H-7), 8.05(1H, s, H-3), 8.75 (1H, d, J= 7.9 Hz, H-5), 8.78(1H, d, J= 8.9 Hz, H-8). ^{13}C-NMR($CDCl_3$): δ58.4 (q, CH_3), 105.9 (d, C-3), 117.7(s, Ar), 119.5 (d, C-8), 124.3(d, C-5), 129.7(d, C-6), 131.9(d, C-7), 140.5 (s, Ar), 142.9 (s, Ar), 154.9 (s, Ar). MS (FAB^+); 221 (M^++H).

Reaction of 4-chloroquinoline 1-oxide (3b)

The residue was purified by column chromatography to give 2-methoxy-4-chloroquinoline 1-

oxide ($CHCl_3$: MeOH = 30 : 1)(**4b**) (0.60 g, 51%). This compound was recrystallized from ether to give colorless prisms, mp 91-93 ℃(decomp). *Anal.* Calcd for $C_{10}H_8NO_2Cl \cdot 0.2H_2O$: C, 56.33; H, 3.97 ; N, 6.57. Found: C, 56.38 ; H, 4.09 ; N, 6.54. IR (KBr) : 3060, 1667, 1586, 846, 758 cm^{-1}. ^{1}H-NMR($CDCl_3$): δ 4.23 (3H, s, CH_3), 7.27 (1H, s, H-3), 7.64 (1H, ddd, J= 8.5, 6.9 and 1.2 Hz, H-6), 7.83 (1H, ddd, J= 8.5, 7.2 and 1.2 Hz, H-7), 8.14 (1H, d, J= 8.1 Hz, H-5), 8.79 (1H, d, J= 8.2 Hz, H-8). ^{13}C-NMR($CDCl_3$): δ 58.0 (q, CH_3), 108.9 (d, C-3), 119.6 (d, C-8), 123.3 (s, Ar), 124.9 (d, C-5), 127.4 (d, C-6), 131.5 (s, Ar), 131.8 (d, C-7), 142.0 (s, Ar), 155.2 (s, Ar). MS (FAB^+); 210 (M^++H).

Reaction of 4-methylquinoline 1-oxide (3c)

The residue was purified by MPLC to give starting material (*n*-hexane : ehtyl acetate = 10 : 1) and 2-methoxy-4-methylquinoline 1-oxide ($CHCl_3$: MeOH = 50 : 1)(**4c**) (0.44 g, 39%). This compound was recrystallized from ether-acetone to give colorless prisms, mp 136-137 ℃. *Anal.* Calcd for $C_{11}H_{11}NO_2 \cdot 1.6H_2O$: C, 60.60 ; H, 6.56 ; N, 6.42. Found: C, 60.48 ; H, 6.48 ; N, 6.25. IR (KBr) : 3378, 1613, 1484, 1376, 1253, 1117, 1053, 778 cm^{-1}. ^{1}H-NMR($CDCl_3$): δ 2.69 (3H, s, CH_3), 4.22 (3H, s, OCH_3), 6.99 (1H, s, H-3), 7.56 (1H, ddd, J= 9.5, 7.0 and 1.2 Hz, H-6), 7.77 (1H, ddd, J= 9.5, 7.0 and 1.2 Hz, H-7), 7.91 (1H, d, J= 8.4 Hz, H-5), 8.81 (1H, d, J= 8.4 Hz, H-8). ^{13}C-NMR($CDCl_3$): δ 18.7 (q, CH_3), 57.6 (q, OCH_3), 108.9 (d, C-3), 119.6 (d, C-8), 124.4 (d, C-5), 125.0 (s, Ar), 126.3 (d, C-6), 130.7 (d, C-7), 136.6 (s, Ar), 141.2 (s, Ar), 154.9 (s, Ar). MS (FAB^+); 190 (M^++H).

Reaction of 4-formylquinoline 1-oxide (3d)

The residue was purified by MPLC to give starting material (*n*-hexane : ehtyl acetate = 50 : 1) and 2-methoxy-4-formylquinoline 1-oxide (*n*-hexane : ehtyl acetate = 1 : 1)(**4d**) (0.28 g, 23%). This compound was recrystallized from ether-acetone to give yellow needles, mp 176-178 ℃.

Anal. Calcd for $C_{11}H_9NO_3$: C, 65.02 ; H, 4.46 ; N, 6.89. Found: C, 64.92 ; H, 4.59 ; N, 6.76. IR (KBr) : 3060, 1686, 1514, 1336, 1115, 1060, 756 cm^{-1}. ^{1}H-NMR($CDCl_3$): δ 4.29 (3H, s, CH_3), 7.63 (1H, s, H-3), 7.69 (1H, ddd, J= 8.4, 7.0 and 1.2 Hz, H-6), 7.81 (1H, ddd, J= 8.4, 7.0 and 1.2 Hz, H-7), 8.73 (1H, d, J= 8.9 Hz, H-5), 8.97 (1H, d, J= 7.0 Hz, H-8), 10.42 (1H, s, CHO). ^{13}C-NMR($CDCl_3$): δ 58.0 (q, CH_3), 113.3 (d, C-3), 119.2 (d, C-5), 122.7 (s, Ar), 124.5 (d, C-8), 128.8 (d, C-6), 131.3 (d, C-7), 142.6 (s, Ar), 155.9 (s, Ar), 188.7 (s, CHO). MS (FAB^+); 204 (M^++H).

Reaction of 4-methoxyquinoline 1-oxide (3e)

The residue was purified by MPLC to give starting material ($CHCl_3$: MeOH = 50 : 1) and 2, 4-dimethoxyquinoline 1-oxide ($CHCl_3$: MeOH = 20 : 1)(**4e**) (0.27 g, 22%). This compound was recrystallized from ether-acetone to give colorless prisms, mp 123-125 ℃. *Anal.* Calcd for $C_{11}H_{11}NO_3 \cdot 2H_2O$: C, 54.77 ; H, 6.27 ; N, 5.81. Found: C, 54.62 ; H, 6.05 ; N, 5.74. IR (KBr) : 3206, 1609, 1387, 1234, 1106, 969, 840 cm^{-1}. ^{1}H-NMR($CDCl_3$): δ 4.08 (3H, s, OCH_3-4), 4.25 (3H, s, OCH_3-2), 6.46 (1H, s, H-3), 7.51 (1H, ddd, J= 8.2, 7.0 and 1.2 Hz, H-6), 7.79(1H, ddd, J= 8.7, 7.0 and 1.2 Hz, H-7), 8.12 (1H, d, J= 9.2 Hz, H-5), 8.74 (1H, d, J= 8.2 Hz, H-8). ^{13}C-NMR($CDCl_3$):

δ 56.3 ((q, 4-OCH_3), 57.9 (q, 2-OCH_3), 88.4 (d, C-3), 118.3 (s, Ar), 119.1 (d, C-8), 122.3 (d, C-5), 125.9 (d, C-6), 131.7 (d, C-7), 141.0 (s, Ar), 156.1 (s, Ar). MS (FAB$^+$); 206 (M^++H).

Reaction of 4-cyanoquinoline 1-oxide (3f)

The residue was purified by MPLC to give starting material (ehtyl acetate) and 2-methoxy-4-cyanoquinoline 1-oxide (**4f**)($CHCl_3$: MeOH = 50 : 1) (0.28 g, 23%). This compound was recrystallized from ether-acetone to give , mp 100 ℃. *Anal*. Calcd for $C_{11}H_8N_2O_2$ ・0.1H_2O : C, 65.41 ; H, 4.09 ; N, 13.87. Found: C, 65.31 ; H, 4.18 ; N, 13.63. IR (KBr) : 2853, 1670, 1442, 750 cm^{-1}. ^{1}H-NMR($CDCl_3$): δ 4.25 (3H, s, CH_3), 7.50 (1H, s, H-3), 7.73 (1H, ddd, J= 9.5 , 7.2 and 1.2 Hz, H-6), 7.87(1H, ddd, J= 9.5 , 7.3 and 1.2 Hz, H-7), 8.15 (1H, d, J= 7.6 Hz, H-5), 8.74(1H, d, J= 8.9 Hz, H-8). ^{13}C-NMR($CDCl_3$): δ 58.3 (q, CH_3), 107.0 (s, Ar), 113.1 (d, C-3), 115.3 (s, CN), 119.6 (d, C-8), 124.5 (s, Ar), 125.7(d, C-5), 128.8 (d, C-6), 132.1 (d, C-7). MS(FAB$^+$); 201 (M^++H).

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