DEOXYGENATIVE 2-ALKOXYLATION OF QUINOLINE 1-OXIDE[1]

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Abstract —— Treatment of quinoline 1-oxide (**1**) with ethyl chloroformate or tosyl chloride and triethylamine in some lower alcohols affords the corresponding 2-alkoxyquinolines (**2a-f**) in generally satisfactory yields. Reactions of 2-methylpyridine and 2-methylquinoline 1-oxides lead to the corresponding 2-ethoxycarbonyloxymethyl (**3** and **5**) and 2-ethoxymethyl derivatives (**4** and **6**).

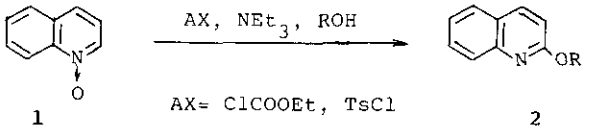
One of the authors (M.H.) and coworkers have carried out an extensive study of reactions of aromatic N-oxides of pyridine and benzopyridine series with a number of nucleophiles in the presence of acylating agents and obtained a variety of interesting results.[3] This paper mainly deals with the deoxygenative 2-alkoxylation of quinoline 1-oxide by the reaction with alcohol in the presence of acylating agents and triethylamine.

In exploring the applicability of ethyl chloroformate (ECF) as an acylating agent to the reaction of quinoline 1-oxide (**1**) with nucleophiles, it was found that, while no reaction was observed upon treatment of **1** with ECF in ethanol, a reaction readily occurred in the presence of triethylamine. Thus, when triethylamine (2 eq.) was added to an ice-cooled solution of **1** and ECF (1.3 eq.) in ethanol with stirring, an exothermic reaction occurred. After the reaction mixture was stirred at room temperature for 12 h, the product mixture was purified by chromatography on silica gel to afford 2-ethoxyquinoline (**2b**) in 75.5% yield accompanied with small amounts of carbostyril and recovered **1**.

It was consecutively found that the reaction proceeded in the same way with meth-

anol, 1-propanol, 2-propanol, allyl alcohol, and 1-butanol to give the corresponding 2-alkoxyquinolines (**2a**, **2c-f**) in generally good yields except for the reaction with 1-butanol. Further, some examinations of reaction conditions revealed that the reaction similarly proceeded by using tosyl or benzoyl chloride instead of ECF and also by means of ECF and sodium alkoxides.[4] Table summarizes the results obtained from the reactions using ECF and tosyl chloride. These reactions are typical examples of the deoxygenative α-substitution reaction of aromatic N-oxide by the addition-elimination mechanism shown in Scheme 1.[3]

Table. Deoxygenative 2-Alkoxylation of Quinoline 1-Oxide (1)



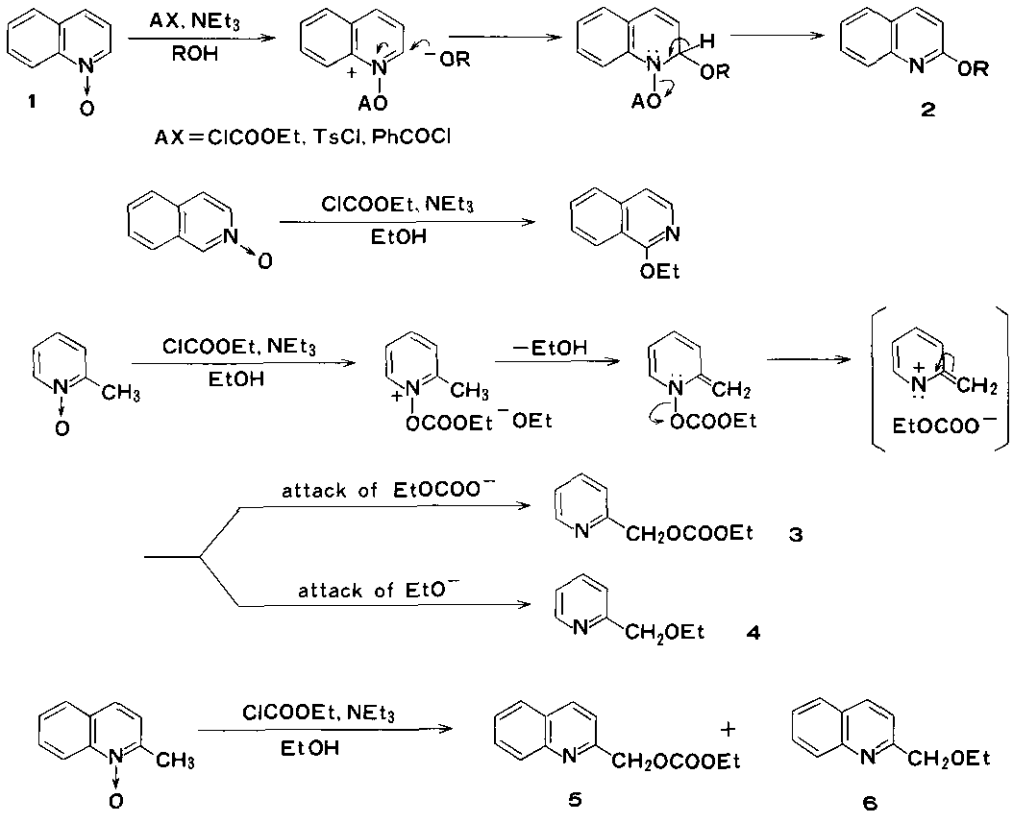
1 **2**

ROH	AX	Product[1] (%)
MeOH	ClCOOEt	**2a**: 81.0
	TsCl	**2a**: 85.5
EtOH	ClCOOEt	**2b**: 75.5
	TsCl	**2b**: 84.8
PrOH	ClCOOEt	**2c**: 44.7
	TsCl	**2c**: 73.7
Me_2CHOH	ClCOOEt	**2d**: 65.9
		2d: 55.6
$CH_2=CH-CH_2OH$	ClCOOEt	**2e**: 55.9
	TsCl	**2e**: 63.5
BuOH	ClCOOEt	**2f**: 5.0
	TsCl	**2f**: 28.5

1) **2a**: R=Me, **2b**: R=Et, **2c**: R=Pr, **2d**: R=Me_2CH
2e: R=allyl, **2f**: R=Bu

In contrast to the above cases, the reaction with 2-butanol, 3-methyl-1-butanol or cyclohexanol gave not the corresponding 2-alkoxyquinolines but only a minute amount of 2-ethoxyquinoline **2b**. An attempt to improve the reaction by using dichloromethane as a solvent was unsuccessful, practically the same results being obtained. Such a discontinous difference depending on the number of carbon atoms of alcohols is remarkable, but the details remain to be explored.

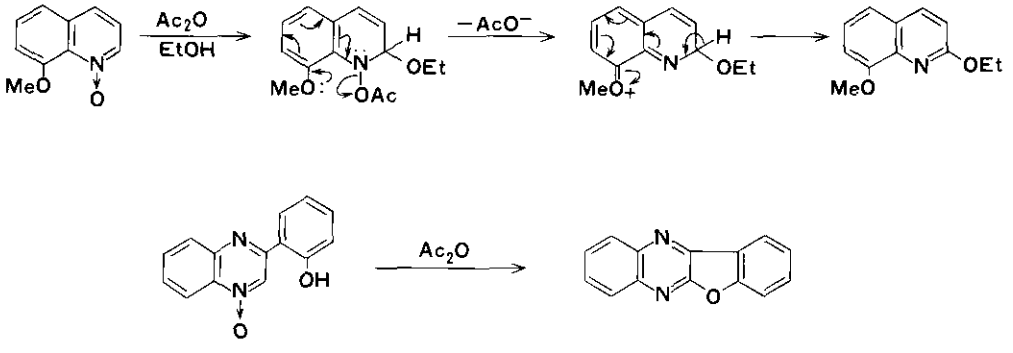
The reaction of isoquinoline 2-oxide occurred also readily, and 1-ethoxyisoquinoline was obtained in 73% yield when treated with ethanol in the presence of ECF and triethylamine, but pyridine 1-oxide resisted the reaction. However, 2-methylpyridine 1-oxide reacted with ethanol under the same conditions to afford ethyl 2-pyridylmethyl carbonate (**3**) in 67% yield with a minute amount of 2-ethoxymethylpyridine (**4**) being detected by ir and nmr spectra. This reaction is evidently different from those of quinoline and isoquinoline N-oxides, but is one of the deoxygenative α-substitution through an anhydrobase[3,5] as illustrated in Scheme 1. Similarly from the reaction of 2-methylquinoline 1-oxide, ethyl 2-quinolylmethyl carbonate (**5**) and 2-ethoxymethylquinoline (**6**) were isolated in 20.7 and 10.8% yields, respectively. It is very interesting that **4** and **6** were formed by nucleophilic attack of ethoxy anion instead of ethoxycarbonate anion.[6]



Scheme 1

Dimsdale[7] described that 8- and 6-methoxyquinoline 1-oxides gave the corresponding 2-ethoxyquinolines when treated with acetic anhydride in ethanol, whereas quinoline and 7-methoxyquinoline 1-oxides were recovered unchanged. He explained the formation of these 2-ethoxyquinolines in terms of the mesomeric effect of the methoxy groups, which facilitate the elimination of acetoxy anion from the 1,2-dihydroquinoline intermediate as illustrated in Scheme 2 with 8-methoxyquinoline 1-oxide. These observations are of interest in that the substituent effect promoted the reaction, but our procedure might be more favorable for the practical synthetic utility.

Issidorides et al.[8] found that 3-(2'-hydroxyphenyl)quinoxaline 1-oxide was readily transformed into benzofuro[2,3-b]quinoxaline in good yield by refluxing with acetic anhydride alone (Scheme 2). Apparently, the favorable steric environment facilitated the reaction in this case. We have also observed that some quinoline 1-oxide derivatives bearing a relevant hydroxyalkyl side chain easily undergo the intramolecular 2-alkoxylation upon treatment with acetic anhydride alone, which will be published shortly.



Scheme 2

EXPERIMENTAL

All melting points are uncorrected. Ir spectra were recorded on JASO DS-301, IR-S, and IR-E spectrophotometers, and ^{1}H-nmr spectra were measured with JNM-3H-60 spectrometer at 60 MHz using trimethylsilane as an internal reference.

Formation of 2-Alkoxyquinoline (**2**) from Quinoline 1-Oxide (**1**)—General Procedure: To an ice-cooled solution of **1** (0.72 g) and ECF (0.7 g, 1.3 eq.) or TsCl (1.2 g, 1.3 eq.) in an alcohol (30 ml) was added NEt_3 (1.1 g, 2 eq.) with stirring. The reaction mixture was stirred at room temperature for 12 h, then concentrated under reduced pressure and the residue was extracted with 10% HCl. The HCl solution was made alkaline with aq. Na_2CO_3 and extracted with $CHCl_3$, and the residue from the extract was chromatographed on silica gel. Elution with hexane gave **2**.

2a[9]: a colorless oil, 0.64 g (81%) or 0.68 g (85.8%). Ir (neat): 1275, 1255, 1240, 1110, 1025, 1015 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 4.05 (3H, s, CH_3), 6.87 (1H, d, J=9.0 Hz, Q-H_3), 7.33 (1H, d, J=9.0 Hz, Q-H_4), 7.15-8.0 (4H, m, Q-H_{5-8}). Picrate, yellow scales, mp 170-171°C (EtOH). Anal. Calcd for $C_{10}H_9NO \cdot C_6H_3N_3O_7$: C, 49.47; H, 3.12; N, 14.43. Found: C, 49.24; H, 3.21; N, 14.48.

2b[10]: a colorless oil, 0.65 g (75.5%) or 0.73 g (84.8%). Picrate, yellow needles, mp 148-149°C (EtOH), undepressed on admixture with an authentic sample. Further elution with AcOEt and then MeOH gave 30 mg of recovered **1** and a minute amount of carbostyril, colorless needles, mp 190-192°C (MeOH).

2c: a colorless oil, 0.42 g (44.7%) or 0.68 g (73.7%). Ir (neat): 1275, 1255, 1240, 1115, 1015, 990 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 1.70 (3H, t, J=7.0 Hz, CH_3), 1.85 (2H, m, J=7.0 Hz, $-OCH_2-\underline{CH_2}-Me$), 4.45 (2H, t, J=7.0 Hz, $-O\underline{CH_2}-$), 6.87 (1H, d, J=9.0 Hz, Q-H_3), 7.94 (1H, d, J=9.0 Hz, Q-H_4), 7.18-8.0 (4H, m, Q-H_{5-8}). Picrate, yellow scales, mp 144-145°C (EtOH). Anal. Calcd for $C_{12}H_{13}NO \cdot C_6H_3N_3O_7$: C, 51.92; H, 3.87; N, 13.46. Found: C, 51.98; H, 3.76; N, 13.42.

2d: a colorless oil, 0.62 g (65.9%) or 0.52 g (55.6%). Ir (neat): 1275, 1255, 1240, 1110, 1105, 985 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 1.40 [6H, d, J=6.0 Hz, $-CH(\underline{CH_3})_2$], 5.61 (1H, m, J=6.0 Hz, $O-\underline{CH}Me_2$), 6.84 (1H, d, J=9.0 Hz, Q-H_3), 7.92 (1H, d, J=9.0 Hz, Q-H_4), 7.1-8.0 (4H, m, Q-H_{5-8}). Picrate, yellow scales, mp 152-153°C (EtOH). Anal. Calcd for $C_{12}H_{13}NO \cdot C_6H_3N_3O_7$: C, 51.92; H, 3.87; N, 13.46. Found: C, 52.04; H, 3.92; N, 13.47.

2e[11]: a colorless oil, 0.52 g (55.9%) or 0.58 g (63.5%). Ir (neat): 1275, 1255, 1240, 1110, 1025, 1005, 900 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 4.49 (2H, m, $-O-\underline{CH_2}-$), 5.1-5.65 (2H, m, $=CH_2$), 5.85-6.5 (1H, m, -CH=), 6.85 (1H, d, J=9.0 Hz, Q-H_3), 7.95 (1H, d, J=9.0 Hz, Q-H_4), 7.15-7.9 (4H, m, Q-H_{5-8}). Picrate, yellow prisms, mp 141-142°C

(EtOH). Anal. Calcd for $C_{12}H_{11}NO \cdot C_6H_3N_3O_7$: C, 52.18; H, 3.41; N, 13.52. Found: C, 52.26; H, 3.24; N, 13.71.

2f: a colorless oil, 0.05 g (5%) or 0.28 g (28.5%). Ir (neat): 1275, 1255, 1240, 1105, 1035, 1015 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 1.01 (3H, t, J=6.0 Hz, CH_3), 1.2-2.1 (4H, m, -O-CH_2-CH_2CH_2-Me), 4.47 (2H, t, J=6.0 Hz, -O-CH_2-), 6.85 (1H, d, J=9.0 Hz, Q-H_3), 7.91 (1H, d, J=9.0 Hz, Q-H_4), 7.2-7.9 (4H, m, Q-H_{5-8}). Picrate, yellow scales, mp 137-138°C (EtOH). Anal. Calcd for $C_{13}H_{15}NO \cdot C_6H_3N_3O_7$: C, 53.02; H, 4.45; N, 13.02. Found: C, 53.21; H, 4.41; N, 12.98.

Reaction of Isoquinoline 2-Oxide ——Isoquinoline 2-oxide (0.72 g) was treated with ECF (0.7 g, 1.3 eq.) and NEt_3 (1.1 g, 2 eq.) in EtOH (30 ml) as mentioned above to give 0.64 g (73%) of 1-ethoxyisoquinoline as a colorless oil. Ir (neat): 1155, 1100, 1070, 1020 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 1.49 (3H, t, J=7.0 Hz, CH_3), 4.52 (2H, q, J=7.0 Hz, CH_2), 7.15 (1H, d, J=6.0 Hz, isoQ-H_4), 7.95 (1H, d, J=6.0 Hz, isoQ-H_3), 8.25 (1H, m, isoQ-H_8), 7.3-7.8 (3H, m, isoQ-H_{5-7}). Picrate, yellow powder, mp 158-159°C (EtOH). Anal. Calcd for $C_{11}H_{11}NO \cdot C_6H_3N_3O_7$: C, 50.75; H, 3.51; H, 13.93. Found: C, 50.55; H, 3.68; N, 13.85.

Reaction of 2-Methylpyridine 1-Oxide — To an ice-cooled solution of the N-oxide (1.1 g) and ECF (1.4 g, 1.3 eq.) in EtOH (30 ml) was added NEt_3 (2.2 g, 2 eq.) with stirring. The reactants were stirred at room temperature for 12 h, and worked up as mentioned above. Elution with hexane-ether (5:1) gave a minute amount of 2-ethoxymethylpyridine (**4**) and 1.2 g (67%) of ethyl 2-pyridylmethyl carbonate (**3**) as a colorless oil.

3: Ir (neat): 1750, 1270, 1010 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 1.35 (3H, t, J=7.0 Hz, CH_3), 4.27 (2H, q, J=7.0 Hz, -O-CH_2-), 5.30 (2H, s, Py-CH_2-), 8.60 (1H, m, Py-H_6), 7.1-7.9 (3H, m, Py-H_{3-5}). Picrate, yellow needles, mp 121-122°C (EtOH). Anal. Calcd for $C_9H_{11}NO_3 \cdot C_6H_3N_3O_7$: C, 43.91; H, 3.44; N, 13.66. Found: C, 43.87; H, 3.21; N, 13.48.

4: ^{1}H-Nmr ($CDCl_3$) δ: 1.31 (3H, t, CH_3), 3.65 (2H, q, -O-CH_2Me), 4.65 (2H, s, PyCH_2-).

Reaction of 2-Methylquinoline 1-Oxide— The N-oxide (0.8 g) was treated with ECF (0.7 g, 1.3 eq.) and NEt_3 (1.1 g, 2 eq.) in EtOH (30 ml) in the same way. Elution with hexane-ether (20:1) gave 0.1 g (10.8%) of 2-ethoxymethylquinoline (**6**) as a colorless oil and subsequent elution with hexane-ether (10:1) gave 0.24 g (20.7%)

of ethyl 2-quinolylmethyl carbonate (**5**) as a colorless oil.

5: Ir (neat): 1745, 1250, 1015 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 1.35 (3H, t, J=7.0 Hz, CH_3), 4.28 (2H, q, J=7.0 Hz, -O-CH_2-), 5.48 (2H, s, Q-CH_2-), 7.4-8.3 (6H, m, Q-H_{3-8}). Picrate, yellow scales, mp 122-123°C (MeOH). Anal. Calcd for $C_{12}H_{13}NO_3 \cdot C_6H_3N_3O_7$: C, 49.57; H, 3.50; N, 12.17. Found: C, 49.27; H, 3.49; N, 11.84.

6: Ir (neat): 1120, 1105, 1070 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 1.31 (3H, t, J=7.0 Hz, CH_3), 3.68 (2H, q, J=7.0 Hz, -O-CH_2-), 4.82 (2H, s, Q-CH_2-), 7.4-8.3 (6H, m, Q-H_{3-8}). Picrate, yellow needles, mp 128-129°C (EtOH). Anal. Calcd for $C_{12}H_{13}NO \cdot C_6H_3N_3O_7$: C, 51.92; H, 3.87; N, 13.46. Found: C, 51.62; H, 3.67; N, 13.10.

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