REACTIONS OF 3-SUBSTITUTED QUINOLINE 1-OXIDES WITH ACYLATING AGENTS

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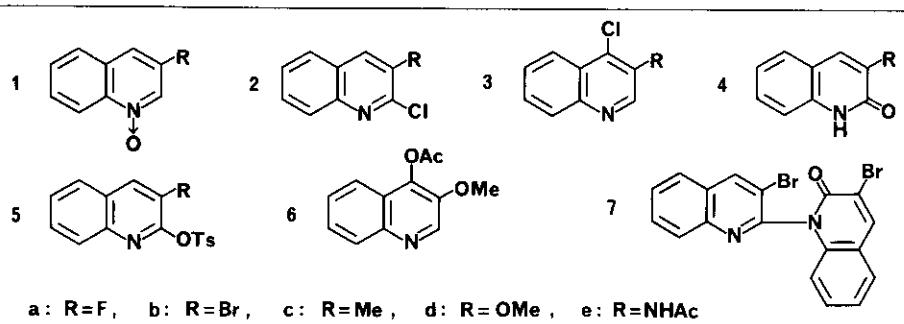
Abstract — Reactions of 3-fluoro- (**1a**), 3-bromo- (**1b**), 3-methyl- (**1c**), 3-methoxy- (**1d**) and 3-acetamidoquinoline 1-oxides (**1e**) with acylating agents ($POCl_3$, Ac_2O, TsCl and PhCOCl) were examined (Table). While only 2-substituted quinolines were obtained from **1a** and **1b**, fair amounts of 4-substituted products were formed in reactions of **1d**, the sole formation of the 4-acetoxyquinoline (**6**) with Ac_2O being the most significant result. 2-Chloroquinolines, 4-chloroquinolines and 2-tosyloxyquinolines were formed (and sometimes predominate) in addition to 2-quinolinones in reactions with TsCl.

In our search for effective medicines for dementia of Alzheimer type, we have synthesized a number of 4-aminopyridine and 4-aminoquinoline derivatives. During the course of this work we examined reactions of 3-substituted quinoline 1-oxides with acylating agents in connection with synthesis of 2,3-disubstituted 4-aminoquinolines. Although there are a few reports on such reactions,[1] no conherent studies have not be done. We chose 3-fluoro- (**1a**), 3-bromo- (**1b**), 3-methyl- (**1c**), 3-methoxy (**1d**), and 3-acetamidoquinoline 1-oxides (**1e**) as 3-substituted quinoline 1-oxide and studied their deoxygenative substitution with phosphoryl chloride ($POCl_3$), acetic anhydride (Ac_2O), tosyl chloride (TsCl), and benzoyl chloride (PhCOCl). The reaction conditions and results are summarized in Table.

Table. Reactions of 3-Substituted Quinoline 1-Oxides (**1**) with Acylating Agents

Reagents and conditions: 1) $POCl_3$, 90°C, 1 h; 2) Ac_2O, reflux, 2 h; 3) TsCl-$CHCl_3$, 10% K_2CO_3, room temperature, 3 h; 4) TsCl, $CHCl_3$, reflux, 1 h; 5) PhCOCl-$CHCl_3$, 10% K_2CO_3, room temperature, 3 h

Run	1	Reaction	2-Substituted Product (%)	4-Substituted Product (%)	Other
1		1)	**2a** (83)	---	
2		2)	**4a** (70)	---	
3	**1a** (R=F)	3)	**2a** (49)	---	
4		4)	**2a** (54)	---	
5		5)	**4a** (48)	---	
6		1)	**2b** (78)	---	
7		2)	**4b** (10)	---	**7** (42)
8	**1b** (R=Br)	3)	**2b** (18), **4b** (36)	---	
9		4)	**2b** (51), **4b** (20)	---	
10		5)	**4b** (58)	---	
11		1)	**2c** (31)	**3c** (34)	
12		2)	**4c** (55)	---	
13	**1c** (R=Me)	3)	**4c** (50)	---	
14		4)	**4c** (20), **5c** (19)	---	
15		5)	**4c** (55)	---	
16		1)	**2d** (43)	**3d** (23)	
17		2)	---	**6** (65)	
18	**1d** (R=OMe)	3)	**2d** (45), **4d** (20)	**3d** (30)	
19		4)	**2d** (25), **4d** (17)	**3d** (21)	
20		5)	---	---	
21		1)	**2e** (16)	---	
22		2)	**4e** (29)	---	
23	**1e** (R=NHAc)	3)	**4e** (40)	---	
24		4)	**2e** (18), **4e** (25) **5e** (37)	---	
25)		5)	**4e** (23)	---	



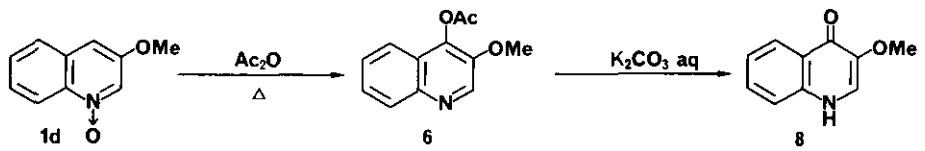
a: R=F, **b**: R=Br, **c**: R=Me, **d**: R=OMe, **e**: R=NHAc

Reactions of 3-fluoroquinoline 1-oxide (**1a**) proceeded regioselectively and afforded exclusively 2-substituted quinolines (**2a** and **4a**) in generally good yields. Thus, the reaction with $POCl_3$ afforded only 2-chloro-3-fluoroquinoline (**2a**) without simultaneous formation of the 4-chloro isomer, and it was found that the reaction with TsCl gave **2a** alone not only under reflux in chloroform but also at room temperature in the presence of 10% potassium carbonate (K_2CO_3), the corresponding 2-quinolinone being not isolated.

The reaction of 3-bromoquinoline 1-oxide (**1b**) gave also only 2-substituted quinolines (**2b**, **4b** and **7**). While Ochiai and Okamoto[1a] reported that 3-bromo-2-quinolinone (**4b**) was formed in 70% yield upon heating **1b** with Ac_2O at 130-140°C in a sealed tube, heating **1b** at reflux with Ac_2O for 2 h resulted in the formation of **4b** in a small yield of 10% with a major formation of N-(3-bromo-2-quinolyl)-3-bromo-2-quinolinone (**7**; 42%). Reactions with TsCl yielded the 2-chloroquinoline (**2b**) and the 2-quinolinone (**4b**) differently from those of **1a**.

Although Lyle and coworkers reported that 3-methylquinoline 1-oxide (**1c**) gave 2-chloro-3-methylquinoline (**2c**) in 87% yield when heated at reflux with $POCl_3$,[1f] we obtained practically the same amounts of **2c** (31%) and the 4-chloro isomer[2] (**3c**; 34%) from the reaction at 90°C for 1 h. Such an inconsistency remains to be explored further. Whereas the reaction of **1c** with TsCl and 10% K_2CO_3 gave 3-methyl-2-quinolinone (**4c**) as the sole product, **4c** and 3-methyl-2-tosyloxyquinoline (**5c**) were obtained under reflux with TsCl in chloroform, no formation of the 2-chloroquinoline (**2c**) being noticed in these cases.

In the reaction of 3-methoxyquinoline 1-oxide (**1d**) the reactivity of the 4-position apparently appeared. Fair amounts of 4-chloro-3-methoxyquinoline (**3d**) were obtained together with the 2-chloro isomer (**2d**) not only in the reaction with $POCl_3$ but also in those with TsCl; the latter reaction gave additionally 2-quinolinone (**4d**) but in rather small yields. Particularly noteworthy is the exclusive formation of 4-acetoxy-3-methoxyquinoline (**6**) in 65% yield in the reaction with Ac_2O. Treatment of **6** with K_2CO_3 solution smoothly led to 3-methoxy-4-quinolinone (**8**). The reaction of **1d** with PhCOCl gave rise to much resinification, no definite products being obtained.



Reactions of 3-acetamidoquinoline 1-oxide (**1e**) gave only 2-substituted products in consistently rather low yields. While the reaction with TsCl in the presence of 10% K_2CO_3 gave only 3-acetamido-2-quinolinone (**4e**), a fair amount of the 2-tosyloxyquinoline (**5e**) was formed together with **4e** and the 2-chloroquinoline (**2e**) in the reaction in boiling chloroform.

The structures of these products were assigned on the basis of elemental analyses and ^{1}H-nmr spectra, and the structure of **6** was further confirmed X-ray diffraction study.

Among the above-mentioned reactions, the exclusive formation of 4-acetoxy-3-methoxyquinoline (**6**) from **1d** and Ac_2O is most significant, because the reaction of Ac_2O with quinoline 1-oxide having no 2-substituent did not produce 4-substitution products, with one exception of the formation of a minute amount of 6-methoxy-4-quinolinol (0.5%) from 6-methoxyquinoline 1-oxide.[3] The reaction of quinoline 1-oxides with TsCl or PhCOCl, especially in the presence of an alkaline solution, has been efficiently applied to the preparation of 2-quinolinones, but some other products have been isolated in some cases.[3-6] In fact, while the reaction with PhCOCl provided only the corresponding 2-quinolinones (**4a,b,c,e**) apart from the resinification in the case of **1d**, the reaction with TsCl gave rise to other products in all cases. Thus, 2-tosyloxyquinolines (**5c** and **5e**) were formed in reactions of **1c** and **1e**, and the deoxygenative chlorination occurred in reactions of **1a**, **1b**, **1d**, and **1e**. The formation of 2-acyloxyquinolines from quinoline 1-oxides and acylating agents has been previously observed in reactions of 6-methoxy-,[3] 6-acetamido-[3] and 4-methylquinoline 1-oxides[5] with TsCl or PhCOCl in the presence of bases, and electron-donating substituent seems to promote this type of reactions but its essential features are not yet clear. The deoxygenative chlorination by means of TsCl has been also described in a few cases.[3,4,6] However, it is very noticeable that the reaction of the **1a** with TsCl afforded exclusively the 2-chloroquinoline (**2a**) independently of the presence or absence of K_2CO_3 solution. We obtained the quinolylquinolinone (**7**) only from the reaction of **1b**

with Ac_2O; similar quinolylquinolinones were shown to be given also from reactions of some quinoline 1-oxides with TsCl and PhCOCl.[3,4]

EXPERIMENTAL

All melting points are uncorrected. ^{1}H-Nmr spectra were recorded on a Hitachi RB-24 spectrometer using tetramethylsilane as an internal standard. X-Ray diffraction data were obtained from a Enraf-Nonius CAD 4 diffractometer.

Reaction with $POCl_3$ — A solution of **1a-e** (2 g) in $POCl_3$ (10 ml) was heated at 90°C for 1 h. Excess $POCl_3$ was distilled off, and the residue was poured into H_2O, neutrallized with 10% K_2CO_3 and extracted with $CHCl_3$. The residue from the $CHCl_3$ extract was chromatographed on silica gel column, and the products were recrystallized from appropriate solvents.

Reaction with Ac_2O — A solution of **1a-e** (2 g) in Ac_2O (10 ml) was heated at relux for 2 h. Excess Ac_2O was evaporated under reduced pressure, and the residue was poured into H_2O, neutrallized with 10% K_2CO_3 and extracted with $CHCl_3$. The residue from the $CHCl_3$ extract was chromatographed on silica gel column, and the products were recrystallized from appropriate solvents.

4-Acetoxy-3-methoxyquinoline (**6**) — A solution of **1d** (2 g) in Ac_2O (10 ml) was heated at reflux for 2 h, and then excess Ac_2O was evaporated under reduced pressure and the residue was dissolved in $CHCl_3$. The $CHCl_3$ solution was washed succesively with aq.$NaHCO_3$ and H_2O. The residue from the $CHCl_3$ solution was recrystallized from $CHCl_3$-ether to give 17 g (69%) of **6**, colorless needles, mp 115-116°C. Anal. Calcd for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.10; N, 6.45. Found: C, 66.34; H, 5.07; N, 6.41. ^{1}H-Nmr ($CDCl_3$) δ: 2.47 (3H, s, $COCH_3$), 4.00 (3H, s, OCH_3), 7.31-8.12 (4H, m, H_{5-8}), 8.80 (1H, s, H_2).

To a solution of **6** (1.65 g) in MeOH (40 ml) was added 10% K_2CO_3 (10 ml), and the whole was stirred at room temperature for 1 h and then treated with anhydrous resin amberlyst. The solvent was evaporated and the residue was recrystallized from $CHCl_3$-MeOH to give 1.3 g (65%) of 3-methoxy-4-quinolinone (**8**), colorless granules, mp 151-152°C. Anal. Calcd for $C_{10}H_9NO_2$: C, 68.17; H, 5.15; N, 7.95. Found: C, 68.35; H, 5.01; N, 8.20. ^{1}H-Nmr ($CDCl_3$) δ: 3.80 (1H, s, OCH_3), 7.15-7.95 (4H, m, H_{5-8}), 8.30-8.55 (1H, dd, J=1.5 and 8.0 Hz, H_2), 11.70 (1H, br s, NH).

Reaction with TsCl-10% K_2CO_3 — A solution of **1a-e** (2 g) and TsCl (2.06-2.80 g, 1.2 equiv.) in $CHCl_3$ (40 ml) was stirred with 10% K_2CO_3 (40 ml) at room temperature for 3 h. The $CHCl_3$ layer was separated, washed with H_2O and concentrated. The residue was chromatographed on silica gel column, and the products were recrystallized from appropriate solvents

Reaction with TsCl — A solution of **1a-e** (2 g) and TsCl (2.06-2.80 g, 1.2 equiv.) in $CHCl_3$ (40 ml) was heated at reflux for 1 h. The reaction mixture was washed with H_2O and concentrated. The residue was chromatographed on silica gel column, and the products were recrystallized from appropriate solvents.

Reaction with PhCOCl-10% K_2CO_3 — A solution of **1a-e** (2 g) and PhCOCl (1.52-2.19 g, 1.2 equiv.) in $CHCl_3$ (40 ml) was stirred with 10% K_2CO_3 (40 ml) at room temperature for 3 h. The precipitate was filtered off, and the $CHCl_3$ layer was washed with H_2O and concentrated. The residue was chromatographed on silica gel column, and the products were recrystallized from appropriate solvents.

2-Chloroquinolines

2a (Runs 1, 3 and 4): Colorless needles, mp 83-84°C (hexane). Anal. Calcd for C_9H_5NFCl: C, 59.53; H, 2.78; N, 7.71. Found: C, 59.50; H, 2.62; N, 7.71. ^{1}H-Nmr ($CDCl_3$) δ: 7.40-8.05 (5H, m, H_{4-8}).

2b (Runs 6, 8 and 9): Colorless needles, mp 91-92°C (hexane). Anal. Calcd for C_9H_5NBrCl: C, 44.58; H, 2.08; N, 5.78. Found: C, 44.87; H, 2.03; N, 5.68. ^{1}H-Nmr ($CDCl_3$) δ: 7.30-8.01 (4H, m, H_{5-8}), 8.28 (1H, s, H_4).

2c[1f] (Run 11); Colorless scales, mp 80-81°C (hexane). Anal. Calcd for $C_{10}H_8NCl$: C, 67.62; H, 4.54; N, 7.89. Found: C, 67.86; H, 4.43; N, 7.85. ^{1}H-Nmr ($CDCl_3$) δ: 2.43 (3H, s, CH_3), 7.20-8.00 (5H, m, H_{4-8}).

2d (Runs 16, 18 and 19): Colorless needles, mp 80-81°C (hexane). Anal. Calcd for $C_{10}H_8NCl$: C, 62.03; H, 4.16; N, 7.23. Found: C, 62.23; H, 4.09, N, 7.25. ^{1}H-Nmr ($CDCl_3$) δ: 3.95 (3H, s, OCH_3), 7.30-8.10 (5H, m, H_{4-8}).

2e (Runs 21 and 24): Orange needles, mp 168-169°C (EtOH). Anal. Calcd for $C_{11}H_9N_2OCl$: C, 59.88; H, 4.11; N, 12.70. Found: C, 59.94; H, 4.07; N, 12.60. ^{1}H-Nmr ($CDCl_3$) δ: 2.30 (3H, s, $COCH_3$), 7.10-7.90 (5H, m, H_{5-8}, NHAc), 8.91 (1H, s, H_4).

4-Chloroquinolines

3c[2] (Run 11): Colorless needles, mp 52-53°C (hexane). Anal. Calcd for $C_{10}H_8NCl$:

C, 67.62; H, 4.54; N, 7.89. Found: C, 67.66; H, 4.44; N, 7.85. ^{1}H-Nmr ($CDCl_3$) δ: 2.50 (3H, s, CH_3), 7.40 (4H, m, H_{5-8}), 8.61 (1H, s, H_2).

3d (Runs 16, 18 and 19): Colorless needles, mp 73-74°C (hexane). Anal. Calcd for $C_{10}H_8NOCl$: C, 63.03; H, 4.16; N, 7.23. Found: C, 62.15; H, 4.06; N, 7.10. ^{1}H-Nmr ($CDCl_3$) δ: 4.10 (3H, s, OCH_3), 7.40-8.25 (4H, m, H_{5-8}), 8.75 (1H, s, H_2).

2-Quinolinones

4a (Runs 2 and 5): Colorless needles, mp 244°C ($CHCl_3$-MeOH). Anal. Calcd for C_9H_6NOF: C, 66.26; H, 3.71; N, 8.59. Found: C, 66.39; H, 3.69; N, 8.56. ^{1}H-Nmr ($CDCl_3$) δ: 6.99-7.85 (5H, m, H_{4-8}), 12.31 (1H, br s, NH).

4b[1a] (Runs 7, 8, 9 and 10): Colorless prisms, mp 250-251°C ($CHCl_3$-MeOH). Anal. Calcd for C_9H_6NOBr: C, 48.25; H, 2.70; N, 6.25. Found: C, 48.27; H, 2.61; N, 6.36. ^{1}H-Nmr ($CDCl_3$) δ: 6.96-7.65 (4H, m, H_{5-8}), 8.25 (1H, s, H_4), 12.25 (1H, br s, NH).

4c (Runs 12, 13, 14 and 15): Yellow needles, mp 240-242°C ($CHCl_3$). Anal. Calcd for $C_{10}H_9NO$: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.55; H, 5.70; N, 8.75. ^{1}H-Nmr ($CDCl_3$) δ: 2.14 (3H, s, CH_3), 6.90-7.73 (5H, m, H_{4-8}), 12.10 (1H, br s, NH).

4d (Runs 18 and 19): Colorless needles, mp 189-190°C ($CHCl_3$-MeOH). Anal. Calcd for $C_{10}H_9NO_2$: C, 68.15; H, 5.15; N, 7.95. Found: C, 68.68; H, 5.04; N, 8.01. ^{1}H-Nmr ($CDCl_3$) δ: 3.83 (3H, s, OCH_3), 6.95-7.60 (5H, m, H_{4-8}), 12.02 (1H, br s, NH).

4e (Runs 22, 23, 24 and 25): Colorless crystals, mp 230°C ($CHCl_3$-MeOH). Anal. Calcd for $C_{11}H_{10}N_2O_2$: C, 65.34; H, 4.98; N, 13.85. Found: C, 65.40; H, 4.83; N, 13.76. ^{1}H-Nmr ($CDCl_3$) δ: 2.17 (3H, s, $COCH_3$), 6.95-7.65 (5H, m, H_{4-8}), 9.30 (1H, br s, NHAc), 12.15 (1H, br s, NH).

2-Tosyloxyquinolines

5c (Run 14): Colorless needles, mp 193-195°C (MeOH-ether). ^{1}H-Nmr ($CDCl_3$) δ: 2.30 (3H, s, 3-CH_3), 2.70 (3H, s, CH_3-Ph-), 7.09-7.81 (4H, ABq, J=8.0 Hz, Ph-$H_{2,3,5,6}$), 7.93-8.60 (4H, m, H_{5-8}), 9.37 (1H, s, H_4).

5e (Run 24): Colorless needles, mp 157-158°C (MeOH-ether). ^{1}H-Nmr ($CDCl_3$) δ: 2.24 (3H, s, CH_3-Ph-), 2.27 (3H, s, $COCH_3$), 6.96-7.37 (4H, ABq, J=8.0 Hz, Ph-$H_{2,3,5,6}$), 7.55-8.45 (4H, m, H_{5-8}), 9.60 (1H, s, H_4), 10.15 (1H, br s, NHAc).

Quinolylquinolinone **7** (Run 7) : Brown prisms, mp 249-250°C ($CHCl_3$-ether). Anal. Calcd for $C_{18}H_{10}N_2OBr_2$: C, 50.27; H, 2.34; N, 6.51. Found: C, 50.43; H, 2.29; N, 6.71. ^{1}H-Nmr ($CDCl_3$) δ: 7.20-8.35 (9H, m, Ar-H), 8.65 (1H, s, H_4).

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