Nitration of Quinoline 1-Oxide: Mechanism of Regioselectivity

Akihiro YOKOYAMA, Tomohiko OHWADA, Shinichi SAITO, and Koichi SHUDO*

Faculty of Pharmaceutical Sciences, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113, Japan.

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The acidity dependence of orientation in the nitration of quinoline 1-oxide was investigated by using the trifluoromethanesulfonic acid (TFSA)–trifluoroacetic acid (TFA) system and the antimony pentafluoride (SbF₅)–TFSA system. These systems provide a wider range of acidity than that of aqueous sulfuric acid. Comparison of the behavior of quinoline 1-oxide and 1-methoxyquinolinium triflate in acidic and neutral media demonstrated that *O*-protonated quinoline 1-oxide is nitrated at the 5- and 8-positions, and the free (unprotonated) molecule is nitrated at the 4-position. This result is consistent with theoretical expectation. It was also discovered that nitration at the 5-position increasingly predominates over that at the 8-position as the acidity is increased.

Key words nitration; quinoline 1-oxide; regioselectivity; superacid; protonation; dication

Nitration of quinoline 1-oxide (**1**) in acid is a complex reaction which yields 4-(**2**), 5-(**3**), and 8-nitroquinoline 1-oxides (**4**) (Chart 1). The isomer ratio depends on the reaction conditions. Ochiai and Okamoto¹⁾ showed that nitration of **1** in concentrated sulfuric acid at 0 °C gave **3** and **4**, but at above 60 °C the predominant product was **2**. Ochiai and Satake found that nitration of quinaldine 1-oxide in 86% sulfuric acid gave a higher ratio of the 4-nitro isomer than did nitration in 96% sulfuric acid.²⁾ Hamana and Nagayoshi³⁾ observed a similar effect of sulfuric acid concentration in the nitration of **1**. In a study of the nitration of 6-substituted quinoline 1-oxides, they investigated the effects of reaction temperature and concentration of sulfuric acid on the nitrated isomer ratio, and concluded that the concentration of sulfuric acid was a more important factor than the reaction temperature in determining the position of nitration.

In order to examine the reactive species which is nitrated in acid, Schofield and co-workers⁴⁾ measured the rates of nitration of **1** in sulfuric acid of various concentrations. They showed that the relationship between the acidity and the rates of 5- and 8-nitration was very similar to those of quinoline and isoquinoline, which are supposed to be nitrated in the protonated form, and suggested that 5- and 8-nitration of **1** involved the *O*-protonated cation, the 1-hydroxyquinolinium ion. It seems to be made clear that the protonation state of the substrate is important. However, generally the reactions were not very clean, and the concept of acidity was not well defined, so the nature of the regioselectivity of the nitration remains to be properly clarified.

In this work, we investigated the acidity dependence of orientation in the nitration of **1** to determine unambiguously the factors which control the position of nitration. Instead of sulfuric acid, we used trifluoromethanesulfonic acid (TFSA), TFSA–trifluoroacetic acid (TFA) and SbF₅–TFSA systems as the acid. These acid systems are stable, non-aqueous, non-oxidative and only weakly nucleophilic, and can cover a wider range of acidity than can aqueous sulfuric acid. In this paper, the acidities of acid systems are represented by the reported values of

Hammett's acidity function (H_0).^{5a)} As a nitrating reagent, a nitronium salt NO₂BF₄ was used, which is of great advantage in analyzing complex reactions, because it can nitrate less reactive substrates in neutral or weakly acidic media.⁶⁾

Results and Discussion

Acidity-Dependence Nitration of quinoline 1-oxide (**1**) with 3 eq of KNO₃ in excess acid gave 4-nitro- (**2**), 5-nitro- (**3**), and 8-nitroquinoline 1-oxides (**4**), and the isomer distribution was reproducibly dependent on the acidity of the medium (Table 1, entries 1–4). When the acid catalyst was TFA ($H_0 = -2.7$) or 10% TFSA–TFA ($H_0 = -9.6$), **2** was the sole product. As the ratio of TFSA was increased, the 5- and 8-nitrations became increasingly predominant over the 4-nitration, and in TFSA ($H_0 = -14.1$) **3** and **4** were the major products. This result shows that the 4-position of **1** is nitrated under weakly acidic conditions and the 5- and 8-positions under strongly acidic conditions, which is consistent with the reported results obtained by the use of aqueous sulfuric acid.³⁾ The period required for completion of the reaction indicates that nitration at the 4-position is much faster than at the 5- and 8-positions (Table 1, entries 1–4).

While nitration of **1** in 50% TFSA–TFA ($H_0 = -11.8$) gave **3** and **4** in approximately equal yields, in TFSA ($H_0 = -14.1$) the yield of **3** is twice that of **4**. This result suggests that the ratio of 5- and 8-products is also sensitive to the acidity.

Ochiai and Okamoto reported that the position of nitration of **1** was influenced by reaction temperature.¹⁾ They used about 9 eq of concentrated sulfuric acid as the acid. When **1** was nitrated with KNO₃ (3 eq) at 0 °C and 60 °C in the presence of 100 eq of TFA, 11% TFSA–TFA, TFSA or concentrated sulfuric acid (Table 1, entries 5–12), no significant change in the orientation ratio was

Chart 1

This paper is dedicated to the late Prof. Toshihiko Okamoto who deceased on Nov. 28, 1996.

* To whom correspondence should be addressed.

Table 1. Nitration of Quinoline 1-Oxide (1)

Entry	Reaction conditions					Yield of products (%)			
	Acid	Acidity (H_0) ⁵⁾	Reagent	Temp. (°C)	Time (h)	2	3	4	Recovery (1)
1	TFA (500 eq)	-2.7	KNO ₃	60	0.5	85	0	0	0
2	10% TFSA-TFA (500 eq)	-9.6	KNO ₃	60	0.6	54	1	0	0
3	50% TFSA-TFA (500 eq)	-11.8	KNO ₃	60	20	2	31	24	0
4	TFSA (500 eq)	-14.1	KNO ₃	60	20	<1	54	25	0
5	TFA (100 eq)	-2.7	KNO ₃	0	24	22	0	0	74
6	TFA (100 eq)	-2.7	KNO ₃	57	1	90	0	0	0
7	11% TFSA-TFA (100 eq)	-9.7	KNO ₃	0	25	92	<1	<1	0
8	11% TFSA-TFA (100 eq)	-9.7	KNO ₃	60	0.8	82	0	0	0
9	TFSA (100 eq)	-14.1	KNO ₃	0-10	24	<1	25	27	32
10	TFSA (100 eq)	-14.1	KNO ₃	60	2	0	46	37	0
11	97% H ₂ SO ₄ (100 eq)	-10.0	KNO ₃	0	10	1	38	55	<1
12	97% H ₂ SO ₄ (100 eq)	-10.0	KNO ₃	60	0.4	5	34	35	0
13	50% TFSA-TFA (500 eq)	-11.8	NO ₂ BF ₄	60	20	1	36	27	0
14	TFSA (500 eq)	-14.1	NO ₂ BF ₄	60	20	0	55	21	7
15	1.6% SbF ₅ -TFSA (500 eq)	< -16	NO ₂ BF ₄	60	20	0	61	7	0

Chart 2

Table 2. Nitration of 1-Methoxyquinolinium Triflate (6) at 60 °C

Reaction conditions				Yield of products (%)			
Acid	H_0	Reagent	Time (h)	7	8	9	Recovery (6)
TFA	-2.7	KNO ₃	20	0	0	0	100
TFA	-2.7	NO ₂ BF ₄	20	0	36	18	44
TFSA	-14.1	KNO ₃	20	0	59	15	7
TFSA	-14.1	NO ₂ BF ₄	20	0	52	11	19

observed: nitration in TFA and 11% TFSA-TFA gave only **2**, and that in TFSA and concentrated sulfuric acid gave **3** and **4**. This result reveals that the orientation in the nitration of **1** is determined only by the acidity of the medium, but not by the reaction temperature, when a large quantity of the acid is used.

Nitration of 1-Methoxyquinolinium Ion Since the orientation in nitration is influenced by the acidity of the medium, it seems very likely that protonation of the oxygen atom of the *N*-oxide group plays an important role, as suggested previously.⁴⁾ The fact that the pK_a of the 1-hydroxyquinolinium ion (**5**) is 0.7,⁷⁾ however, indicates that **1** is almost completely protonated even in TFA ($H_0 = -2.7$), which is the weakest acid catalyst among the acid systems we used. In order to examine the involvement of **5** we prepared 1-methoxyquinolinium triflate (**6**) which is considered as an isostere of **5**. This salt can be isolated as a stable, pure compound, which enabled us to test the nitration of the quaternary salt. Thus, **6** was nitrated with 3 eq of KNO₃ or NO₂BF₄ in 500 eq of TFA and TFSA (Chart 2, Table 2).

When TFA was used as the acid catalyst, **6** was not

nitrated by KNO₃, as expected: no trace of the 4-nitro compound (**7**) was detected. With NO₂BF₄, however, 5- and 8-nitration of **6** occurred to a significant degree. This result, that the 4-position of **6** is not nitrated by KNO₃-TFA, implies that the 1-hydroxyquinolinium ion (**5**) is not nitrated by KNO₃-TFA. The substrate for the 4-nitration is not *O*-protonated **1**, but the free *N*-oxide. The experiment also indicates that (1) the active nitrating agent in KNO₃-TFA which can nitrate the 4-position of the free *N*-oxide is not NO₂⁺, but a less reactive electrophile, (2) the active species in KNO₃-TFA can not nitrate the salt **6** or, therefore, the 5- and 8-positions of protonated **1** (**5**), and (3) NO₂⁺ can nitrate the salt **6** and therefore the protonated **1** (**5**) at the 5- and 8-positions. The active species formed in KNO₃-TFA may be a species such as CF₃COONO₂⁸⁾ or the nitrate of *N*-oxide, which is electrophilic enough to nitrate the free *N*-oxide.

Nitration of **6** in the strong acid TFSA with KNO₃ or NO₂BF₄, on the other hand, gave the 5-nitro (**8**) and 8-nitro (**9**) isomers. This result indicates that, in the nitration in a strongly acidic medium, the electrophilic species formed from KNO₃ is the same as or equivalent to that from NO₂BF₄. Though the isomer distribution in the nitration of **6** in TFSA was somewhat different from that in the nitration of **1** in KNO₃-TFSA, the observations suggest that the *O*-protonated ion (1-hydroxyquinolinium ion, **5**) is the substrate for the 5- and 8-nitration in TFSA.

Because a superacid such as TFSA can diprotonate some substrates⁹⁾ and is suggested to protonate nitronium ion¹⁰⁾ too, it is difficult to determine unambiguously the reactive species based solely on the results of nitration in strong acids. In order to exclude such effects, we examined nitration of **1** and **6** by NO₂BF₄ in a neutral solvent. Sulfolane was chosen as the neutral solvent because it is inert to nitration and is able to dissolve a sufficient quantity of NO₂BF₄.⁶⁾ Under the neutral condition, nitration of **1** gave the 4-nitro isomer, and that of **6** gave the 5- and 8-nitro isomers (Table 3). The latter nitration does not require further activation of the nitronium ion by protonation to the protonated nitronium ion, a dication. It is natural that in the neutral condition NO₂⁺ preferentially

Table 3. Nitration of Quinoline 1-Oxide (**1**) and 1-Methoxyquinolinium Triflate (**6**) with NO_2BF_4 in Sulfolane at 60°C

Reaction conditions		Yield of products (%)			
Substrate	Time (h)	4- NO_2 (2 or 7)	5- NO_2 (3 or 8)	8- NO_2 (4 or 9)	Recovery (1 or 6)
1	0.4	44	0	0	0
6	1	0	57	41	0

Chart 3

nitrate the 4-position of the free *N*-oxide.

Based on the results of nitration of **1** and **6** in TFA-TFSA and a neutral solvent, it can be concluded that the 4-nitration of **1** proceeds through the action of a weak nitrating agent on the non-protonated **1**, while the nitration of protonated **1** occurs at the 5- and 8-positions with a stronger nitrating agent, nitronium ion (Chart 3).

Nitration in More Acidic Media Entries 1–4 of Table 1 suggest that the distribution of **3** and **4** is also dependent on the acidity of the medium. In order to confirm this, **1** was subjected to nitration in 500 eq of stronger acids (Table 1, entries 13–15). We used 3 eq of NO_2BF_4 as the nitrating reagent rather than KNO_3 (this weakens the acidity of the medium). The ratio of **3** to **4** in 50% TFSA-TFA ($H_0 = -11.8$) was 1.3. The ratio increased as the acidity of the medium increased, and reached nearly 9 when 1.6% SbF_5 -TFSA ($H_0 < -16$) was used as the acid; thus, nitration in a stronger acid tends to give the 5-nitro product.

The selectivity toward the 5-nitration under highly acidic conditions may be interpreted in two ways: a protonated nitronium ion¹⁰⁾ contributes to this regioselectivity, or the diprotonated quinoline 1-oxide (**10**) participates (Chart 4). The involvement of protonated NO_2^+ (NO_2H^{2+}) in the nitration of monoprotonated *N*-oxide is not likely, because the 5-nitration occurs even with NO_2BF_4 in sulfolane, where protonation of NO_2^+ is very unlikely to occur. In the latter case, the regioselectivity might be brought about by the electrostatic repulsion between the electrophile and the positive charge of the oxonium ion of the *N*-oxide: that is, if such a dicationic species contributes to the nitration, the electrostatic repulsion which arises from the approach of the electrophile to the 8-position of the quinoline ring would be much

Chart 4

greater than that in the case of the 5-position, and therefore, 5-nitration might be predominant over 8-nitration in a highly acidic medium. The diprotonated *N*-oxide is more deactivated than the monoprotonated *N*-oxide, so in this case the nitrating agent might be more activated. The participation of the protonated nitronium ion NO_2H^{2+} can not be completely ruled out.

Nitration by NO_2BF_4 in TFSA or 1.6% SbF_5 -TFSA gave a by-product, the yield being 14% or 15%, respectively. Its molecular formula was $\text{C}_9\text{H}_5\text{N}_3\text{O}_6$, which suggested that this compound was dinitrohydroxyquinoline 1-oxide. By comparison of the melting point and ^1H -NMR and IR spectra, it was proved to be identical with an authentic sample of 6,8-dinitro-5-hydroxyquinoline 1-oxide (**11**) prepared by nitration of 5-hydroxyquinoline 1-oxide. Bennett and Grove reported that the 6,8-dinitro-5-hydroxyquinoline was obtained in the nitration of quinoline.¹¹⁾

A possible mechanism of formation of **11** is illustrated in Chart 5. The σ -complex (**12**) formed from the attack of NO_2^+ at the 8-position undergoes nucleophilic attack of $\text{CF}_3\text{SO}_3\text{H}$ (this is a very weak nucleophile, but may be stronger than TFA). Under the strongly acidic conditions, the NO_2 moiety at the 8-position can be the leaving group, and 5-trifluoromethylsulfoxyquinoline 1-oxide is formed by elimination of HNO_2 . The sulfoxy compound can be nitrated at the 6- and 8-positions. For the formation of **11** to occur *via* this mechanism, deprotonation of **12** should be slow enough to compete with the attack of the triflic acid (or triflic anion) at the 5-position of **12**. Since formation of **11** requires very strong acids, the rate of deprotonation of **12** might become slower as the acidity increases. If this is the case, this deprotonation step could become the rate-determining step of the 8-nitration when the acidity of the catalyst is high enough, and the rate of the 8-nitration might become slower than that of the 5-nitration.

Theoretical Interpretation The highest occupied molecular orbitals (HOMO) and the charges of **1** and **5** were calculated by the PM3 method¹²⁾ (Fig. 1) in order to examine the idea that protonation of **1** determines the position of nitration. Because the total electron densities and the coefficients of HOMO are the largest at the 2- and 4-positions of **1**, it is reasonable that nitration of **1** occurs

Chart 5

Fig. 1. Total Electron Densities (Net Charges, Left) and HOMO (Right) of Quinoline 1-Oxide (1) and Hydroxyquinolinium Ion (5) Calculated by PM3

at the 4-position, though this calculation does not explain why the 2-nitro product is not formed. Some other factors may prevent nitration at the 2-position, for example the nitrating agent may be too bulky (e.g., $\text{CF}_3\text{COONO}_2$) and the rate-determining transition state may be late. On the other hand, the total electron densities of the protonated form are lower than those of **1**, particularly at the 4-position, and this is consistent with the fact that the nitration of **6** is much slower than that of **1**. The coefficients of HOMO of **5** are the largest at the 5- and 8-positions, which explains why **5** tends to be nitrated at these positions.

Experimental

General Methods All melting points were measured with a Yanagimoto hot-stage melting point apparatus (MP-500) and are uncorrected. ^1H -NMR spectra were measured on a JEOL GX-400 MHz NMR spectrometer with tetramethylsilane and the midpoint of dimethyl sulfoxide ($\text{DMSO}-d_6$, 2.50 ppm) as an internal reference in CDCl_3 at 23°C and in $\text{DMSO}-d_6$ at 30°C , respectively, or with CH_2Cl_2 (5.30 ppm) as an internal reference in acid or sulfolane solution. IR spectra were measured on a Shimadzu IR-408 for KBr tablets. Flash column chromatography was performed on silica gel (Kieselgel 60, 230–400 mesh, Merck) with the specified solvent unless otherwise noted. The combustion analyses were carried out in the microanalytical center of this Faculty.

Materials TFSA was purchased from Central Glass Co. (Japan) and was purified as reported.^{5a)} TFA and antimony pentafluoride were also purified as reported.^{5a)} Sulfuric acid (97%) was purchased from Wako Pure Chemical Industries, Ltd. (Japan), and used as concentrated sulfuric acid without additional purification. Sulfolane was purified by distillation under reduced pressure. Nitronium tetrafluoroborate was purchased from Aldrich Co., and used without additional purification. Quinoline 1-oxide

(**1**)¹³⁾ and methyl triflate¹⁴⁾ were prepared as reported.

Nitration of Quinoline 1-Oxide (1) in Acid. General Procedure A solution of **1** (102 mg, 0.70 mmol) in 53 g of TFSA (500 eq) was stirred at 60°C , and 3 eq of KNO_3 (212 mg) was added all at once. The mixture was stirred at 60°C for 20 h, and poured dropwise into ice-water (200 ml). The solution was basified with saturated K_2CO_3 and extracted with CH_2Cl_2 (200, 100, 100 ml). The combined organic layer was washed with brine, dried over anhydrous K_2CO_3 , and evaporated to give a mixture of products. The mixture was separated by flash column chromatography ($\text{CH}_3\text{CN}:\text{CH}_2\text{Cl}_2 = 1:4$ to $1:1$, then $\text{MeOH}:\text{AcOEt} = 1:10$). In the case of nitration with NO_2BF_4 in TFSA and 1.6% SbF_5 -TFSA, the ^1H -NMR spectrum of the reaction mixture was observed directly before quenching, and the yields of **10** were estimated from the integrals of the peak areas.

2: Yellow needles, mp 157°C (from acetone, lit.¹³⁾ 153 – 154°C . ^1H -NMR (CDCl_3) δ : 8.88–8.84 (1H, m), 8.80–8.76 (1H, m), 8.52 (1H, d, $J = 7.0$ Hz), 8.21 (1H, d, $J = 7.0$ Hz), 7.93–7.86 (2H, m). *Anal.* Calcd for $\text{C}_9\text{H}_6\text{N}_2\text{O}_3$: C, 56.85; H, 3.18; N, 14.73. Found: C, 57.15; H, 3.06; N, 14.67.

3: Yellow needles, mp 165°C (from methanol, lit.¹⁾ 160 – 161°C . ^1H -NMR (CDCl_3) δ : 9.15 (1H, d, $J = 8.8$ Hz), 8.61 (1H, d, $J = 6.2$ Hz), 8.50 (1H, d, $J = 8.8$ Hz), 8.46 (1H, dd, $J = 7.7$, 1.1 Hz), 7.86 (1H, dd, $J = 8.8$, 7.7 Hz), 7.53 (1H, dd, $J = 8.8$, 6.2 Hz). *Anal.* Calcd for $\text{C}_9\text{H}_6\text{N}_2\text{O}_3$: C, 56.85; H, 3.18; N, 14.73. Found: C, 56.61; H, 3.17; N, 14.95.

4: Lemon-yellow prisms, mp 184 – 185°C (from acetone, lit.¹⁵⁾ 180 – 181°C . ^1H -NMR (CDCl_3) δ : 8.50 (1H, d, $J = 6.2$ Hz), 8.05 (1H, dd, $J = 8.1$, 1.5 Hz), 7.83 (1H, d, $J = 8.8$ Hz), 7.75 (1H, dd, $J = 7.7$, 1.5 Hz), 7.69 (1H, dd, $J = 8.1$, 7.7 Hz), 7.46 (1H, dd, $J = 8.4$, 6.2 Hz). *Anal.* Calcd for $\text{C}_9\text{H}_6\text{N}_2\text{O}_3$: C, 56.85; H, 3.18; N, 14.73. Found: C, 56.65; H, 3.23; N, 15.01.

Preparation of 1-Methoxyquinolinium Triflate (6) Methyl triflate (3.6 ml) was added dropwise to a stirred solution of **1** (3.52 g, 24.3 mmol) in dry Et_2O (150 ml) over a period of 2 min at room temperature. The precipitates were collected by filtration, and washed with dry Et_2O to give 7.23 g (23.4 mmol, 96%) of **6** as colorless crystals. This product was recrystallized repeatedly from acetone prior to use. Colorless cubes, mp 132 – 133°C (from acetone). ^1H -NMR ($\text{DMSO}-d_6$) δ : 10.00 (1H, dd, $J = 6.2$, 1.1 Hz), 9.31 (1H, d, $J = 8.4$ Hz), 8.57 (1H, d, $J = 8.8$ Hz), 8.56 (1H, d, $J = 9.2$ Hz), 8.37–8.33 (1H, m), 8.26 (1H, dd, $J = 8.4$, 6.2 Hz), 8.12 (1H, t, $J = 8.1$ Hz), 4.55 (3H, s). *Anal.* Calcd for $\text{C}_{11}\text{H}_{10}\text{F}_3\text{NO}_4\text{S}$: C, 42.72; H, 3.26; N, 4.53. Found: C, 42.55; H, 3.10; N, 4.38.

Preparation of 1-Methoxy-5-nitroquinolinium Triflate (8) A solution of **3** (55 mg, 0.29 mmol) in methyl triflate (1.0 ml) was stirred at room temperature for 16.5 h. Then methyl triflate (1.0 ml) was added and the mixture was stirred at room temperature for an additional 3 h. The precipitates were collected by suctional filtration to give 22 mg of **8**. The filtrate was concentrated by evaporation under reduced pressure and the residue gave 31 mg of **8** after recrystallization from $\text{AcOEt}-\text{Et}_2\text{O}$. Total yield of **8** was 53 mg (57%). Lemon-yellow prisms, mp 88 – 89°C (from $\text{AcOEt}-\text{Et}_2\text{O}$). ^1H -NMR ($\text{DMSO}-d_6$) δ : 10.20 (1H, d, $J = 6.2$ Hz), 9.56 (1H, d, $J = 9.2$ Hz), 8.97 (1H, d, $J = 8.8$ Hz), 8.85 (1H, d, $J = 7.0$ Hz), 8.50–8.45 (2H, m), 4.58 (3H, s). *Anal.* Calcd for $\text{C}_{11}\text{H}_9\text{F}_3\text{N}_2\text{O}_6\text{S}$: C, 37.29; H, 2.56; N, 7.91. Found: C, 37.18; H, 2.46; N, 8.17.

Preparation of 1-Methoxy-8-nitroquinolinium Triflate (9) Methyl triflate (0.3 ml) was added to a stirred solution of **4** (248 mg, 1.31 mmol) in CHCl_3 (15 ml) and the mixture was stirred at room temperature for

5.5 h. Then the precipitates were collected by suctional filtration to give **9** (408 mg, 88%). Colorless prisms, mp 139–140 °C (from AcOEt–Et₂O). ¹H-NMR (DMSO-*d*₆) δ : 10.23 (1H, d, *J*=6.2 Hz), 9.47 (1H, d, *J*=7.7 Hz), 8.82 (1H, d, *J*=7.7 Hz), 8.79 (1H, d, *J*=8.4 Hz), 8.47 (1H, dd, *J*=8.4, 6.6 Hz), 8.25 (1H, t, *J*=8.1 Hz), 4.46 (3H, s). *Anal.* Calcd for C₁₁H₉F₃N₂O₆S: C, 37.29; H, 2.56; N, 7.91. Found: C, 37.29; H, 2.55; N, 7.68.

Nitration of 1-Methoxyquinolinium Triflate (6) in Acid. General Procedure A solution of **6** (218 mg, 0.70 mmol) in 500 eq of TFSA (53 g) was stirred at 60 °C, then 3 eq of NO₂BF₄ (279 mg) was added. The mixture was stirred at 60 °C for 20 h, cooled to room temperature, and transferred into an NMR tube. The yields of the products were determined from the ¹H-NMR spectrum of the reaction mixture. Chemical shifts were assigned by comparison with those of an authentic sample prepared as described above.

Nitration of Quinoline 1-Oxide (1) in Sulfolane To a stirred solution of **1** (103 mg, 0.71 mmol) in sulfolane (7.34 g) at 60 °C was added 3 eq of NO₂BF₄ (290 mg) all at once, and the solution was stirred at 60 °C for 0.4 h. The reaction mixture was poured into water (10 ml), and the solution was neutralized with several drops of saturated K₂CO₃. The mixture was subjected to reversed-phase column chromatography (Senshu Scientific Co., Ltd., Japan, ODS-SS-1020T) with H₂O, 20% acetone–H₂O, and then acetone as eluents. The fractions containing the products were combined, acetone was removed by evaporation under reduced pressure, and the products were extracted with CH₂Cl₂ (200, 100, 100 ml). The combined organic layer was washed with brine (50 ml), dried over anhydrous K₂CO₃, and evaporated. Column chromatography (AcOEt : *n*-hexane = 1 : 2, CH₃CN : CH₂Cl₂ = 1 : 4, then MeOH : AcOEt = 1 : 10) of the residue gave 58 mg (0.31 mmol, 44%) of **2**.

Nitration of 1-Methoxyquinolinium Triflate (6) in Sulfolane To a stirred solution of **6** (210 mg, 0.68 mmol) in sulfolane (7.00 g) at 60 °C was added 3 eq of NO₂BF₄ (270 mg) all at once, and the solution was stirred at 60 °C for 1 h. A portion of the reaction mixture was transferred into an NMR tube, and the yields of the products were determined from the ¹H-NMR spectrum.

Isolation of the By-product in Nitration of Quinoline 1-Oxide (1) A solution of **1** (1.45 g, 10 mmol) in 10 eq of TFSA (15 g) was stirred at 60 °C, and 1.5 eq of NO₂BF₄ (2.0 g) was added all at once. The mixture was stirred at 60 °C for 1 h, and poured dropwise into ice-water (30 ml). The solution was neutralized with anhydrous Na₂CO₃ (6.18 g) and extracted with CH₂Cl₂ (50, 50, 50 ml). The aqueous layer was basified with 2 N Na₂CO₃ (5 ml), and both the aqueous and organic layers were left at room temperature for 2 d. Then the precipitates were collected from both layers by suctional filtration and washed with H₂O, MeOH, and CH₂Cl₂ successively, to give 70 mg of a light yellow powder. Recrystallization of the crude product from TFA–H₂O gave 6,8-dinitro-5-hydroxyquinoline 1-oxide (**11**) as yellow crystals, 212–213 °C (dec.). ¹H-NMR (DMSO-*d*₆) δ : 8.53–8.51 (2H, m), 8.21 (1H, dd, *J*=8.2, 1.1 Hz), 7.45 (1H, dd, *J*=8.2, 6.2 Hz). IR (KBr) cm⁻¹: 1610, 1555 (NO₂), 1535 (NO₂), 1505, 1420, 1395, 1375, 1320, 1280, 1260 (*N*-oxide), 1205, 1165, 1140, 1080, 1005, 895, 840, 805, 790, 760, 745. *Anal.* Calcd for C₉H₅N₃O₆: C, 43.04; H, 2.01; N, 16.73. Found: C, 42.97; H, 1.82; N, 16.83.

5-Hydroxyquinoline 1-Oxide 3-Chloroperoxybenzoic acid (863 mg) was added all at once to a stirred solution of 5-hydroxyquinoline (510 mg, 3.5 mmol) in MeOH (50 ml) at 0 °C and the mixture was stirred at room temperature for 1 h. Further 3-chloroperoxybenzoic acid (864 mg) was added, and the reaction mixture was stirred at room temperature for 1 h. This operation was repeated again. The reaction mixture was cooled in an ice bath and the precipitates were collected by filtration to give 328 mg of crude product. The filtrate was concentrated by evaporation

under reduced pressure, and CH₂Cl₂ (50 ml) was added to the residue. The mixture was refluxed for 30 h, then cooled in an ice bath. The precipitates were collected by filtration to give 110 mg of the crude product. The precipitates were combined and recrystallized from MeOH to give 5-hydroxyquinoline 1-oxide as yellow crystals, 215 °C (dec.). ¹H-NMR (DMSO-*d*₆) δ : 10.86 (1H, s), 8.53 (1H, dd, *J*=6.0, 0.8 Hz), 8.01 (1H, d, *J*=8.8 Hz), 7.95 (1H, d, *J*=8.8 Hz), 7.59 (1H, dd, *J*=8.6, 7.7 Hz), 7.36 (1H, dd, *J*=8.6, 6.0 Hz), 7.05 (1H, dd, *J*=7.7, 0.8 Hz). IR (KBr) cm⁻¹: 1620, 1570, 1490, 1455, 1385, 1355, 1295 (*N*-oxide), 1240 (*N*-oxide), 1210, 1190, 1145, 1080, 950, 870, 775. *Anal.* Calcd for C₉H₇NO₂: C, 67.08; H, 4.38; N, 8.69. Found: C, 66.85; H, 4.31; N, 8.39.

Synthesis of 6,8-Dinitro-5-hydroxyquinoline 1-Oxide (11) from 5-Hydroxyquinoline 1-Oxide To a stirred solution of 5-hydroxyquinoline 1-oxide (194 mg, 1.20 mmol) in TFSA (3.3 g) was added all at once 6 eq of NO₂BF₄ (953 mg) at room temperature and the mixture was stirred at 60 °C for 2 h. It was poured dropwise into ice-water (20 ml), and the precipitates were collected by suctional filtration, then washed with H₂O, acetone and Et₂O to give 266 mg of **10** (1.06 mmol, 88%) as yellow crystals. Recrystallization from TFA–H₂O gave yellow crystals; the decomposition point, IR and ¹H-NMR spectra were identical with those of the by-product obtained from nitration of **1** in TFSA.

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