Bull. Chem. Soc. Jpn., **78**, 2235–2237 (2005)

Electrophilic Arylation of Phenols: Construction of a New Family of 1-Methyl-2-quinolones

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1-Methyl-3,6,8-trinitro-2-quinolone was found to be a suitable substrate for electrophilic arylation on benzene rings leading to (1,2-dihydro-4-quinolyl)phenols. The resultant products constitute a new family of 1-methyl-2-quinolones, which is often found in biologically active compounds as a partial structure.

The Friedel–Crafts reaction is one of the fundamental methods for C–C bond formation on the benzene ring, however, electrophilic arylation is not easily performed.[1] In order to overcome this difficulty, significantly electron-deficient compounds showing less aromaticity should be used as the electrophile. From this viewpoint, 1-methyl-3,6,8-trinitro-2-quinolone (**1**)[2] is considered to be a suitable substrate for the present purpose because of its low aromaticity. The steric repulsion between 1-methyl and 8-nitro groups distorts the quinolone framework, and the pyridone moiety cannot achieve coplanarity with the benzene moiety.[3] Consequently, trinitroquinolone **1** displays high reactivity to give various kinds of functionalized 1-methyl-2-quinolone (MeQone) derivatives.[4]

The MeQone framework has been found in more than 300 quinoline alkaloids that are mostly isolated from the Rutaceae family.[5] Since these alkaloids show physiological activity, many researchers have energetically studied the isolation, structural determination, and total syntheses of quinoline alkaloids containing the MeQone skeleton.[5] Unnatural MeQone derivatives have attracted recent attention in regards to the design of a new drug,[6] thus it is highly demanded to develop convenient methods for modification of the MeQone skeleton. In the present paper, we provide a preparative method for arylated MeQones, which includes electrophilic substitution of phenoxides **2** by trinitroquinolone **1**.

To a solution of potassium phenoxide **2a** in acetonitrile, trinitroquinolone **1** was added, and the mixture was heated at 60 °C for 3 days. In the ^{1}H NMR spectrum of the product isolated after acidification of the reaction mixture, signals of the 1,2,4-trisubstituted benzene skeleton and two dinitroquinolone rings were observed. This result means double substitution proceeded at the 2- and 4-positions of **2a**. The product was determined as 2,4-bis(quinolyl)phenol **3a** (30% yield based on **1**), and the mass spectrum and elemental analysis supported this structure. The 3-nitro group of the quinolone ring was eliminated during the substitution, which is called *cine*-substitution. The yield of **3a** was improved up to 51% when the reaction was conducted for a prolonged time.

Double substitution of *o*-methylphenoxide **2b** by **1** effectively proceeded to afford **3b**. In the case of the highly electron-rich *p*-methoxyphenoxide **2c**, a couple of quinolone rings were introduced at both vicinal positions of the hydroxy group despite steric hindrance. On the other hand, reactions of **1** with *m*- and *p*-methylphenoxides **2d** and **2e** furnished single substitution products **5d** and **5e**. The phenoxides **2f** and **2g** derived from *p*-nitrophenol and 2-naphthol were also applicable, giving **5f** and **5g** (Fig. 1).

In the reaction of **1** with **2b**, no single substitution product **5b** was detected. Furthermore, the yield of **3b** was reduced by half without formation of **5b** when the molar ratio of **1**:**2b** was changed from 1:1 to 2:1 (Table 1). These experimental facts indicated the second substitution proceeded much faster than the first one, and a half amount of phenoxide was consumed as the base.

On the basis of these results, a plausible mechanism is illustrated in the Scheme 1. The phenoxide **2** attacks at the 4-position of the quinolone **1** giving adduct **6**, and another phenoxide **2** assists aromatization of the benzene ring. In the quinolone ring, proton transfer also occurs from the 4-position to the

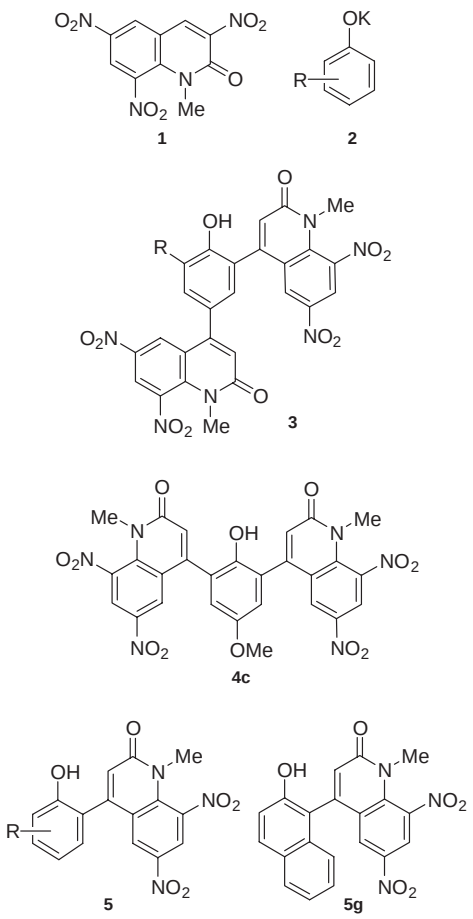
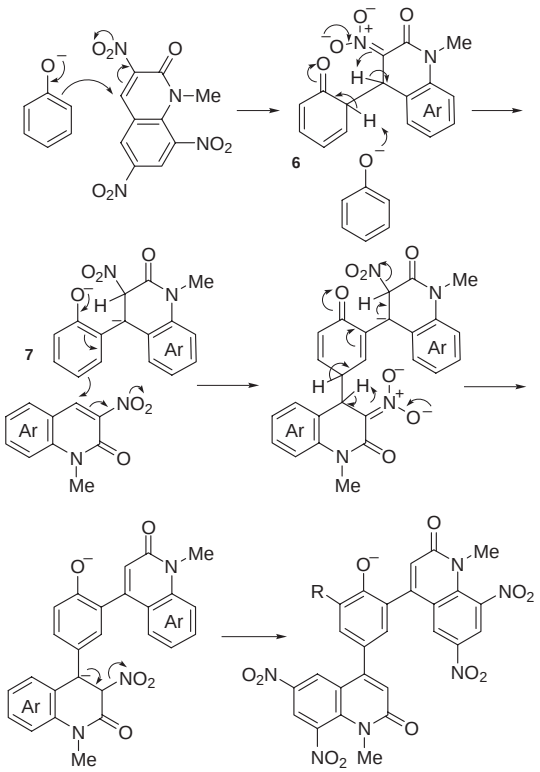


Fig. 1. Arylated phenols.

Published on the web December 9, 2005; DOI 10.1246/bcsj.78.2235

Table 1. Reactions of Quinolone **1** with Phenoxides **2**

R	Temp/°C	Time	Product	Yield/%
H	60	3 d	**3a**	51
2-Me	60	3 h	**3b**	91
4-MeO	60	3 h	**4c**	67
3-Me	60	3 h	**5d**	35
4-Me	80	3 h	**5e**	82
4-NO_2	80	1 d	**5f**	36
o-Phenylene	60	3 h	**5g**	75



Scheme 1. A plausible mechanism for the present reaction.

3-position affording the phenoxide **7**. Since the resultant dianionic phenoxide **7** is more reactive than **2**, the second substitution readily proceeds. The final product is formed by aromatization of the quinolone ring with a loss of nitrous acid.

In summary, trinitroquinolone **1** was found to be an excellent substrate for electrophilic arylation. The present reaction enables the synthesis of several kinds of 1,2-dihydro-4-quinolylphenols, which are novel unnatural MeQone derivatives. These results are also valuable information in the benzene chemistry.

Experimental

General. The melting points were determined on a Yanaco micro-melting-points apparatus, and were uncorrected. All of the reagents and solvents were commercially available and used as received. ^{1}H NMR and ^{13}C NMR spectra were measured on a Bruker DPX-400 at 400 MHz and at 100 MHz with TMS as an internal standard. ^{13}C NMR assignments (s, d, and q) were made from DEPT experiments. Mass spectra were recorded on a JEOL JMS-AX505HA. Elemental microanalyses were performed using a Yanaco MT-3 CHN corder.

1-Methyl-3,6,8-trinitro-2-quinolone (1).[2] According to the procedure described for 1-methyl-2-pyridone,[7] MeQone was prepared by the oxidation of the 1-methylquinolinium ion using potassium hexacyanoferrate(III) under alkaline conditions after methylation of quinoline with dimethyl sulfate using a three times diluted solution. Nitration of MeQone with fuming nitric acid ($d = 1.52$) afforded **1** in 90% yield.

General Procedure. To a solution of phenol (94 mg, 1.0 mmol) in methanol (10 mL), potassium hydroxide (56 mg, 1.0 mmol) was added, and the solution was stirred at room temperature for 1.5 h. After removal of the solvent, the residue was dissolved into acetonitrile (10 mL), and then trinitroquinolone **1** (294 mg, 1 mmol) was added. The mixture was heated at 60 °C for 3 days. White precipitates were collected by filtration, and washed with 1 M hydrochloric acid (1 mL, 1 mmol) and with water (2 mL) to afford the analytically pure product **3a** (150 mg, 0.26 mmol, 51% yield based on **1**). When other phenoxides were employed, their reactions were similarly conducted.

2,4-Bis(1-methyl-6,8-dinitro-2-oxo-1,2-dihydro-4-quinolyl)-phenol (3a): White powder; mp >300 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.39 (s, 3H), 3.41 (s, 3H), 7.01 (s, 1H), 7.02 (s, 1H), 7.30 (d, $J = 8.5$ Hz, 1H), 7.58 (d, $J = 2.1$ Hz, 1H), 7.67 (dd, $J = 8.5$, 2.1 Hz, 1H), 8.31 (d, $J = 2.5$ Hz, 1H), 8.59 (d, $J = 2.5$ Hz, 1H), 8.96 (d, $J = 2.5$ Hz, 2H), 10.75 (s, 1H). MS (FAB): $m/z = 589$ ($M^+ + 1$, 20), 497 (60), 232 (100). Anal. Found: C, 52.87; H, 2.57; N, 14.02%. Calcd for $C_{26}H_{16}N_6O_{11}$: C, 53.06; H, 2.72; N, 14.29%.

6-Methyl-2,4-bis(1-methyl-6,8-dinitro-2-oxo-1,2-dihydro-4-quinolyl)phenol (3b): White powder; mp 293–296 °C (dec.). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.39 (s, 3H), 3.39 (s, 3H), 3.42 (s, 3H), 6.97 (s, 1H), 6.99 (s, 1H), 7.38 (d, $J = 2.0$ Hz, 1H), 7.59 (d, $J = 2.0$ Hz, 1H), 8.24 (d, $J = 2.5$ Hz, 1H), 8.61 (d, $J = 2.5$ Hz, 1H), 8.95 (d, $J = 2.5$ Hz, 1H), 8.97 (d, $J = 2.5$ Hz, 1H), 9.58 (brs, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 15.6 (q), 33.3 (q), 33.3 (q), 121.1 (d), 121.3 (d), 121.5 (s), 121.6 (s), 122.0 (s), 123.5 (d), 124.3 (s), 124.5 (d), 124.9 (d), 124.9 (d), 125.9 (s), 127.7 (s), 131.9 (d), 136.4 (d), 136.8 (s), 137.5 (s), 137.5 (s), 138.6 (s), 138.7 (s), 146.3 (s), 147.9 (s), 152.4 (s), 160.1 (s), 160.3 (s). MS (FAB): $m/z = 603$ ($M^+ + 1$, 44), 192 (100). Anal. Found: C, 53.74; H, 2.63; N, 13.94%. Calcd for $C_{27}H_{18}N_6O_{11}$: C, 53.82; H, 2.99; N, 13.95%.

4-Methoxy-2,6-bis(1-methyl-6,8-dinitro-2-oxo-1,2-dihydro-4-quinolyl)phenol (4c): Yellow granules; mp 213–215 °C (dec.). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.41 (s, 6H), 3.42 (s, 6H), 3.81 (s, 3H), 3.82 (s, 3H), 6.99 (s, 2H), 7.04 (s, 2H), 7.18 (d, $J = 2.4$ Hz, 4H), 8.25–8.27 (m, 4H), 8.94–8.96 (m, 5H), 9.04 (s, 1H). In the ^{1}H NMR, signals assigned for two kinds of **4c** were observed. Since a recent report[8] describes that 2-quinolone forms a complex with phenol derivatives, **4c** is considered to form a complex with another molecule of **4c**. MS (FAB): $m/z = 619$ ($M^+ + 1$, 100), 238 (84). Anal. Found: C, 52.43; H, 2.91; N, 13.59%. Calcd for $(C_{27}H_{18}N_6O_{12})_2$: C, 52.44; H, 2.93; N, 13.59%.

5-Methyl-2-(1-methyl-6,8-dinitro-2-oxo-1,2-dihydro-4-quinolyl)phenol (5d): Pale yellow powder; mp 274–285 °C (dec.). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.35 (s, 3H), 3.39 (s, 3H), 6.80 (s, 1H), 6.84 (d, $J = 7.7$ Hz, 1H), 6.88 (s, 1H), 7.17 (d, $J = 7.7$ Hz, 1H), 8.24 (d, $J = 2.6$ Hz, 1H), 8.91 (d, $J = 2.6$ Hz, 1H), 9.95 (s, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 21.9 (q), 35.4 (q), 117.3 (d), 119.8 (s), 121.5 (d), 123.1 (d), 123.6 (s), 124.4 (d), 127.2 (d), 131.2 (d), 138.3 (s), 139.6 (s), 140.6 (s), 142.1 (s), 149.5 (s), 154.9 (s), 162.4 (s). MS (FAB): $m/z = 356$ ($M^+ + 1$,

100). Anal. Found: C, 57.38; H, 3.68; N, 12.08%. Calcd for $C_{17}H_{13}N_3O_6$: C, 57.46; H, 3.66; N, 11.83%.

4-Methyl-2-(1-methyl-6,8-dinitro-2-oxo-1,2-dihydro-4-quinolyl)phenol (5e): Brown oil. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.28 (s, 3H), 3.40 (s, 3H), 6.82 (s, 1H), 6.96 (d, $J = 8.2$ Hz, 1H), 7.10 (s, 1H), 7.23 (d, $J = 8.2$ Hz, 1H), 8.21 (d, $J = 2.1$ Hz, 1H), 8.92 (d, $J = 2.1$ Hz, 1H), 9.81 (s, 1H). MS (FAB): $m/z = 356$ ($M^+ + 1$, 100). The crude product was pure based on NMR results, however, satisfactory analytical and other spectral data were not obtained since further purification could not be performed.

2-(1-Methyl-6,8-dinitro-2-oxo-1,2-dihydro-4-quinolyl)-4-nitrophenol (5f): Pale yellow powder; mp >300 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.42 (s, 3H), 7.01 (s, 1H), 7.24 (d, $J =$ 9.1 Hz, 1H), 8.12 (d, $J = 2.6$ Hz, 1H), 8.25 (d, $J = 2.9$ Hz, 1H), 8.35 (dd, $J = 9.1$, 2.9 Hz, 1H), 8.94 (d, $J = 2.6$ Hz, 1H), 11.75 (brs, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 34.6 (q), 116.4 (d), 122.1 (s), 122.4 (s), 122.4 (d), 124.7 (d), 125.7 (d), 127.1 (d), 127.4 (s), 137.4 (d), 138.7 (s), 139.8 (s), 139.9 (s), 146.1 (s), 160.8 (s), 161.3 (s). MS (FAB): $m/z = 387$ ($M^+ + 1$, 40), 176 (100). Anal. Found: C, 49.96; H, 2.44; N, 14.44%. Calcd for $C_{16}H_{10}N_4O_8$: C, 49.74; H, 2.59; N, 14.51%.

1-(1-Methyl-6,8-dinitro-2-oxo-1,2-dihydro-4-quinolyl)-2-naphthol (5g): Yellow powder; mp 272–274 °C (dec.). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.46 (s, 3H), 6.91 (s, 1H), 7.34–7.45 (m, 4H), 7.87 (d, $J = 2.6$ Hz, 1H), 7.94–7.96 (m, 1H), 8.04 (d, $J = 8.9$ Hz, 1H), 8.92 (d, $J = 2.6$ Hz, 1H), 10.17 (brs, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 33.4 (q), 112.1 (s), 117.0 (d), 121.3 (d), 122.2 (d), 122.4 (d), 123.7 (d), 124.4 (s), 124.8 (d), 126.2 (d), 126.6 (s), 127.1 (d), 130.1 (d), 131.3 (s), 136.9 (s), 137.6 (s), 138.7 (s), 145.2 (s), 151.2 (s), 160.5 (s). MS (FAB): $m/z =$ 392 ($M^+ + 1$, 100). Anal. Found: C, 61.35; H, 3.11; N, 10.55%. Calcd for $C_{20}H_{13}N_3O_6$: C, 61.38; H, 3.32; N, 10.74%.

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