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REGIOSELECTIVE NITROALKYLATION OF THE 1-METHYL-2-QUINOLONE FRAMEWORK

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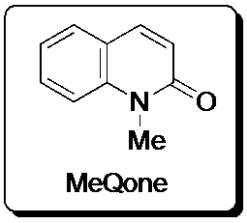
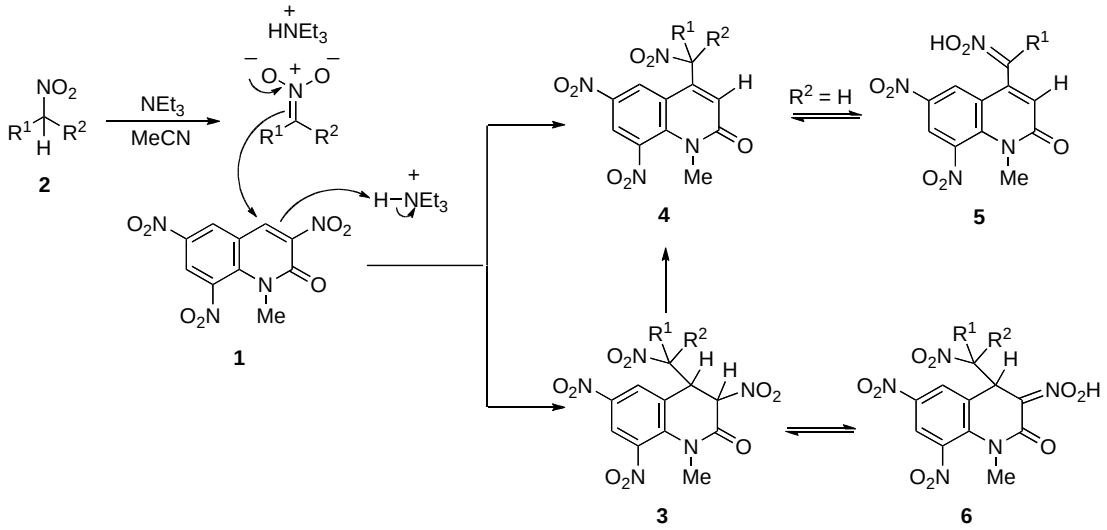
Abstract – Regioselective introduction of an (α-nitro)alkyl group to the 1-methyl-2-quinolone framework was performed upon treatment of 1-methyl-3,6,8-trinitro-2-quinolone with nitroalkanes in the presence of triethylamine, in which a nitronate anion attacks at the 4-position and the subsequent aromatization by elimination of nitrous acid lead to 4-(α-nitro)alkylated 6,8-dinitro-1-methyl-2-quinolones.



The 1-methyl-2-quinolone (MeQone) framework is seen in more than 300 quinoline alkaloids isolated from the Rutaceae family, and the isolation, the structural determination and total syntheses of new quinoline alkaloids concerning MeQone are still active area.[1] From the viewpoint of biochemical and pharmacological interests, researcher's attention is recently turned to not only study on natural products but also preparation of unnatural compounds having the MeQone framework as the partial structure.[2] However, the pyridone moiety is not so reactive because of somewhat aromatic property, which prevents functionalization of the MeQone.[2] Thus, development of a facile method for modifying the MeQone framework is one of the highly demanded projects.

Among less reactive MeQones, 1-methyl-3,6,8-trinitro-2-quinolone (**1**)[3a] has peculiar reactivity caused by steric repulsion between the 1-methyl and the 8-nitro groups,[3e] which enables functionalization of the MeQone framework. Indeed, a new ring is easily constructed on the [*c*]-face by cycloaddition with electron-rich diene or electron-rich alkenes,[4] and functionalization at the 4-position is also performed by reaction with nucleophiles.[3] In this paper, we demonstrate a new method for regioselective C-C bond formation on the MeQone framework by *cine*-substitution using nitroalkanes (**2a-c**) as nucleophiles.

Table Synthesis of nitroalkylated MeQones



run	R^1	R^2	Nitroalkane	Temp. / °C	Time / h	Product	Yield / %
1	Me	H	**2a**	rt	3	**4a**/**5a**	41
2	Me	H	**2a**	80	3	**4a**/**5a**	80
3	Et	H	**2b**	rt	3	**4b**	41
4	Et	H	**2b**	80	3	**4b**	98
5	Me	Me	**2c**	rt	24	**3c**/**6c**	50
6	Me	Me	**2c**	80	24	**4c**	77

When trinitroquinolone (**1**) was allowed to react with nitroethane (**2a**) in the presence of triethylamine at room temperature, *cine*-substituted product (**4a**) was isolated in 41% yield as a mixture with its tautomer (**5a**) (Table, run 1). Higher temperature was effective for the present reaction increasing the yield of **4a** up to 80% (run 2). 1-Nitropropane (**2b**) also reacted with **1** to give **4b** effectively (runs 3 and 4). On the other hand, a mixture of adduct (**3c**) and its tautomer (**6c**) was formed in the reaction of **1** with 2-nitropropane (**2c**) at room temperature (run 5). At high temperature, further aromatization accompanying elimination of nitrous acid proceeded to afford *cine*-substituted product (**4c**) in 77% yield (run 6). Consequently, an (α-nitro)alkyl group was introduced to the MeQone framework regioselectively upon treatment of trinitroquinolone (**1**) with nitroalkanes (**2**). Constructing a new family of unnatural MeQones will contribute to the research of biologically active compounds.

EXPERIMENTAL

Melting points were measured on a Yanaco micro melting point apparatus and are uncorrected. The IR spectra were recorded on a JASCO FT/IR-4200 infrared spectrophotometer. The ^{1}H and ^{13}C NMR spectra

were measured using a dimethyl sulfoxide-d_6 (DMSO-d_6) solution on a Brucker DPX-400 at 400 MHz and at 100 MHz respectively with tetramethylsilane (TMS) as an internal standard. ^{13}C NMR assignments were made from DEPT experiments. MS spectra were recorded on a JEOL JMS-AX505HA, and elemental microanalyses were performed using a Yanaco MT-3 CHN corder. All reagents and solvents were commercially available and used as received.

6,8-Dinitro-1-methyl-4-(1-nitroethyl)-2-quinolone (4a) and 1-(1,2-Dihydro-6,8-dinitro-1-methyl-2-oxoquinoline-4-yl)ethanenitronic acid (5a)

To a solution of quinolone **1** (294 mg, 1.0 mmol) in acetonitrile (10 mL), nitroethane (216 μL, 3.0 mmol) and triethylamine (167 μL, 1.2 mmol) were added. After heating under reflux, solvent was removed under reduced pressure. The residue was treated with column chromatography on silica gel to afford *cine*-substituted quinolone **4a** (258 mg, 0.8 mmol, 80% yield, eluted with hexane-EtOAc = 1/1) that contains a small amount of tautomer **5a**. After recrystallization from EtOH, all products were converted to nitronic acid **5a**. In cases of other nitroalkanes **2b** and **2c**, reactions were conducted in the same way.

4a including a trace amount of **5a**: Yellow powder; mp 165-167 ˚C (decomp). IR (KBr) 1290, 1350, 1469, 1535, 1607, 1679 cm^{-1}; ^{1}H NMR δ 1.96 (d, J = 6.7 Hz, 3H), 3.35 (s, 3H), 6.86 (q, J = 6.7 Hz, 1H), 7.20 (s, 1H), 9.00 (d, J = 2.4 Hz, 1H), 9.02 (d, J = 2.4 Hz, 1H); ^{13}C NMR δ 17.4 (CH_3), 34.9 (CH_3), 79.7 (CH), 121.4 (C), 122.7 (CH), 123.4 (CH), 123.8 (CH), 137.8 (C), 138.9 (C), 140.2 (C), 143.3 (C), 161.1 (C). **5a**: Pale yellow needles; mp 256-258 (decomp). ^{1}H NMR δ 2.67 (s, 3H), 3.35 (s, 3H), 7.08 (s, 1H), 8.93 (d, J = 2.5 Hz, 1H), 9.17 (d, J = 2.5 Hz, 1H), 12.18 (s, 1H); ^{13}C NMR δ 13.3 (CH_3), 33.6 (CH_3), 119.9 (C), 121.2 (CH), 121.6 (CH), 125.5 (CH), 137.1 (C), 137.7 (C), 139.7 (C), 144.0 (C), 150.3 (s), 160.3 (C). Anal. Calcd for $C_{12}H_{10}N_4O_7$: C 44.73, H 3.13, N 17.39. Found: C 45.11, H 2.81, N 17.51.

6,8-Dinitro-1-methyl-4-(1-nitropropyl)-2-quinolone (4b)

Pale yellow powder; mp 132-133 ˚C (decomp). IR (KBr) 1341, 1531, 1559, 1606, 1682 cm^{-1}; ^{1}H NMR δ 1.20 (dd, J = 7.3, 7.3 Hz, 3H), 2.24 (ddq, J = 16.2, 7.3, 5.5 Hz, 1H), 2.67 (ddq, J = 16.2, 9.2, 7.3 Hz, 1H), 3.50 (s, 3H), 5.95 (dd, J = 9.2, 5.5 Hz, 1H), 7.16 (s, 1H), 8.78 (d, J = 2.3 Hz, 1H), 8.93 (d, J = 2.3 Hz, 1H); ^{13}C NMR δ 10.7 (CH_3), 26.0 (CH_2), 35.3 (CH_3), 86.5 (CH), 121.8 (C), 122.6 (CH), 122.7 (CH), 124.7 (CH), 138.2 (C), 139.6 (C), 140.7 (C), 141.0 (C), 161.0 (C). Anal. Calcd for $C_{13}H_{12}N_4O_7$: C 46.44, H 3.60, N 16.66. Found: C 46.73, H 3.32, N 16.65.

3,4-Dihydro-1-methyl-4-(2-nitro-2-propyl)-3,6,8-trinitro-2-quinolone (3c) and 6,8-Dinitro-1-methyl-4-(2-nitro-2-propyl)-2-oxo-1,2,3,4-tetrahydroquinoline-3-nitronic acid (6c)

3c: Yellow plates; mp 220-225 °C (decomp). ^{1}H NMR δ 1.62 (s, 3H), 1.75 (s, 3H), 3.04 (s, 3H), 4.96 (d, J = 1.2 Hz, 1H), 6.37 (d, J = 1.2 Hz, 1H), 8.75 (d, J = 2.6 Hz, 1H), 8.78 (d, J = 2.6 Hz, 1H); ^{13}C NMR δ 21.8 (CH_3), 23.0 (CH_2), 33.3 (CH_3), 45.7 (CH), 81.8 (CH), 87.4 (C), 121.5 (CH), 124.2 (C), 128.6 (CH), 137.3 (C), 138.9 (C), 141.6 (C), 158.3 (C); MS (FAB) m/z = 384 (M^++1, 42), 368 (100), 350 (73). Anal.

Calcd for $C_{13}H_{13}N_5O_9$: C 40.74, H 3.42, N 18.27. Found: C 40.62, H 3.57, N 18.65. **6c** including a trace amount of **3c**: Yellow powder; mp 190-195 °C (decomp). IR (KBr) 1342, 1412, 1528, 1605, 1682, 3569 cm^{-1}; ^1H NMR δ 1.36 (s, 3H), 1.59 (s, 3H), 2.77 (s, 3H), 8.22 (d, J = 2.4 Hz, 1H), 8.59 (d, J = 2.4 Hz, 1H), A hydroxy proton was not observed presumably due to overlapping with a signal of water; ^{13}C NMR δ 21.5 (CH_3), 24.0 (CH_2), 33.6 (CH_3), 47.7 (CH), 92.7 (C), 101.5 (C), 120.9 (CH), 126.3 (CH), 130.0 (C), 137.6 (C), 139.8 (C), 139.9 (C), 160.8 (C). It was found that conversion from **3c** to **6c** predominantly occurred upon treatment with triethylamine, and reverse conversion from **6c** to **3c** occurred with hydrochloric acid.

6,8-Dinitro-1-methyl-4-(2-nitro-2-propyl)-2-quinolone (4c)

Yellow plates; mp 230-232 °C (decomp). IR (KBr) 1299, 1332, 1348, 1541, 1603, 1683 cm^{-1}; ^1H NMR δ 2.16 (s, 6H), 3.36 (s, 3H), 7.24 (s, 1H), 8.22 (d, J = 2.4 Hz, 1H), 8.94 (d, J = 2.4 Hz, 1H); ^{13}C NMR δ27.0 (CH_3), 35.0 (CH_2), 89.4 (C), 119.8 (C), 122.2 (CH), 122.4 (CH), 123.6 (CH), 138.2 (C), 139.4 (C), 139.9 (C), 145.4 (C), 161.0 (C); MS (FAB) m/z = 337 (M^++1, 82), 291 (100). Anal. Calcd for $C_{13}H_{12}N_4O_7$: C 46.44, H 3.60, N 16.66. Found: C 46.66, H 3.42, N 16.68.

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