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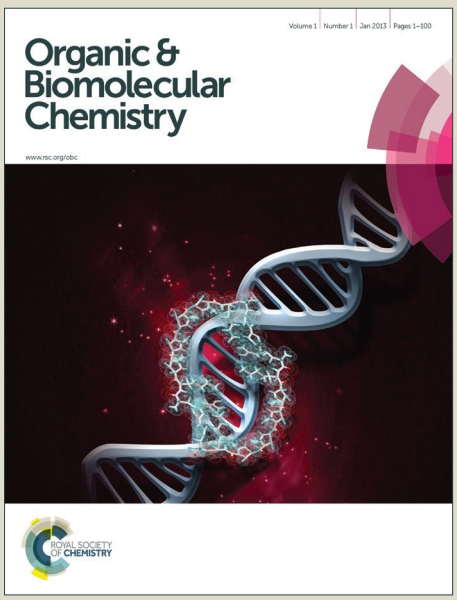

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ARTICLE

A Direct and Vicinal Functionalization of the 1-Methyl-2-quinolone Framework: 4-Alkoxylation and 3-Chlorination

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Feiyue Hao,[a] Haruyasu Asahara*[a,b] and Nagatoshi Nishiwaki*[a,b]

Bis(functionalization), 4-alkoxylation and 3-chlorination, of the 1-methyl-2-quinolone framework were achieved under mild conditions by the sequential treatment of 3-nitrated 1-methyl-2-quinolones with sodium alkoxide and *N*-chlorosuccinimide. Moreover, a succinimide group instead of an alkoxy group was introduced at the 4-position, affording a masked form of the 4-amino-3-chloro-2-quinolone derivative. Furthermore, the prepared vicinally functionalized quinolones thus obtained were subjected to Suzuki-Miyaura coupling reaction, arylating the 3-position.

Introduction

The 1-methyl-2-quinolone (**MeQone**) framework is present in more than 300 quinoline alkaloids exhibiting versatile biological activities.[1] In addition to the synthesis of naturally occurring **MeQone**s, the synthesis of unnatural **MeQone** derivatives has attracted much attention as it allows access to new biologically active compounds,[2] among which **MeQone** derivatives possessing a hydroxy/an alkoxy group at the 4-position are important.[3] Moreover, the enol partial structure is a useful scaffold for the modification of the **MeQone** framework.[3] Despite their usefulness, 4-alkoxylated **MeQone**s have not been prepared by the direct alkoxylation of **MeQone** because of the inertness caused by the aromaticity.[4] Instead, an alkoxy group has been introduced into **MeQone** by the alkylation[5] of 4-hydroxylated **MeQone**s constructed from anthranilic acid derivatives[6] or *N*-methylanilines.[7] However, it is difficult to modify the **MeQone** framework because of the low availability of the corresponding starting materials. Hence, the development of a direct alkoxylation method for the **MeQone** framework is in high demand.

We have shown that 1-methyl-3,6,8-trinitro-2-quinolone (**TNQ**) is highly reactive among **MeQone**s to form either a C–C or C–N bond at the 4-position regioselectively or to undergo cycloaddition reaction readily.[8-11] Inspired by these results, we envisioned that direct C–O bond formation at the 4-position of **MeQone** would be possible by the treatment of 3-nitrated **MeQone**s including **TNQ** with an alkoxide ion. In this case, it is necessary to trap the anionic adduct intermediate by an electrophile because a heteronucleophile is easily eliminated even though it adds to **TNQ**.[10] We focused on the halogenation because **MeQone**s bearing both an alkoxy and a halo group serve as important precursors for various types of compounds.[12,13]

Halogenation at the 3-position of the **MeQone** framework is usually achieved by the treatment of 4-hydroxylated **MeQone** with halogenating agents such as thionyl chloride,[14] *N*-bromosuccinimide (NBS),[15] bromine,[16] *N*-iodosuccinimide (NIS)[13] and iodine.[17] However, only a few examples of the halogenation of 4-alkoxylated **MeQone** have been reported,[12,13] and there is no report on 3-chlorination. Hence, direct bis(functionalization), 4-alkoxylation and 3-halogenation, using 3-nitrated **MeQone**s would afford a new synthetic intermediate for the construction of a new compound library of **MeQone** derivatives.

Results and discussion

To evaluate the potential for vicinal functionalization, **TNQ** was chosen as a model substrate. When **TNQ** was treated with sodium methoxide in methanol at room temperature, the color of the solution immediately became reddish yellow, and a yellow solid precipitated in the reaction mixture (Scheme 1). In the ^{1}H NMR of solid **1a** collected by filtration, two new singlet signals appeared at 3.15 and 5.96 ppm instead of the disappearance of the singlet at 9.26 ppm assigned to the proton at the 4-position of **TNQ**. This spectral change indicated that a methoxide ion was added to the 4-position of **TNQ**, as confirmed by the correlations of the methoxy group with H-4 and H-5 in the ^{1}H–^{1}H NOESY 2D spectrum. Furthermore, a signal for C-4 was observed at 73 ppm in the ^{13}C NMR spectrum, indicating the change from the sp^2 carbon to the sp^3 carbon. Although **1a** was confirmed to have a methoxylated structure, **TNQ** was reproduced by the treatment of **1a** with

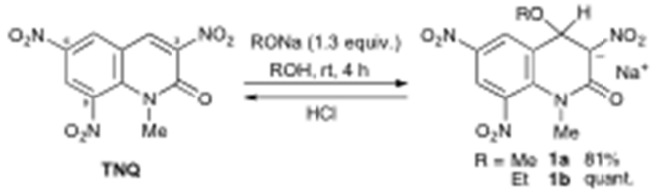
[a]*School of Environmental Science and Engineering, Kochi University of Technology, Miyanokuchi, Tosayamada, Kami, Kochi 782-8502, Japan*
[b]*Research Center for Material Science and Engineering, Kochi University of Technology, Miyanokuchi, Tosayamada, Kami, Kochi 782-8502, Japan*
Email: nishiwaki.nagatoshi@kochi-tech.ac.jp; Fax: +81 887 57 2520; Tel: +81 887 57 2517

Electronic Supplementary Information (ESI) available: Copies of ^{1}H and ^{13}C NMR spectra data for all new products.

[details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

hydrochloric acid. Moreover, **1a** was highly soluble into water. Hence, product **1a** exists in an anionic form stabilized by the adjacent nitro and carbonyl groups.

Sodium ethoxide caused a similar reaction, affording **1b** quantitatively. On the other hand, precipitates were not observed during the reaction in other alcohols; however, the formation of **1** was confirmed by the ^{1}H NMR spectrum of the residue after the removal of the solvent.

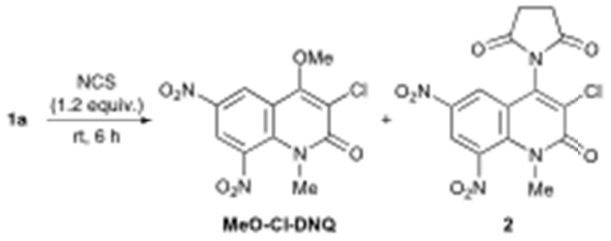


Scheme 1 4-Alkoxylation of **TNQ**

Next, adduct **1a** was reacted with *N*-chlorosuccinimide (NCS) in dichloromethane, affording the 3-chlorinated product, 4-methoxy-3-chloro-1-methyl-6,8-dinitro-2-quinolone (**MeO-Cl-DNQ**), in 45% yield (Table 1, entry 1). The structure was confirmed from the following spectral data. In the MS spectrum, the molecular ion peaks (313 and 315) were observed in a 3:1 intensity ratio, indicating that a chlorine atom was introduced. Although the H-4 signal disappeared, the signal of the methoxy group remained in the ^{1}H NMR. Furthermore, the signal assigned to C-4 shifted from 73 to 160 ppm in the ^{13}C NMR spectrum.

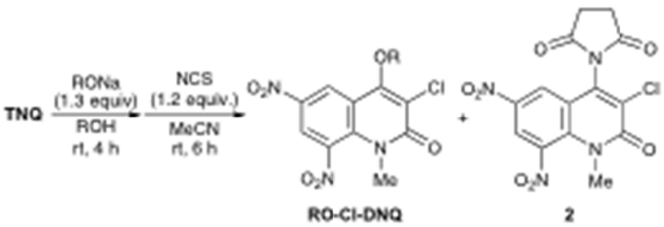
Polar solvents were suitable for this reaction; the yield was increased up to 85% when acetonitrile was used (entries 2–5). The methoxy group of **1a** did not exchange with an ethoxy group even though the reaction was carried out in ethanol (entry 3). In each case, 4-imidated product **2** was also obtained and became the major product when DMF was used as the solvent (entry 4). Under these optimized reaction conditions, **EtO-Cl-DNQ** was obtained similarly as a yellow solid in 73% yield along with **2** in 21% yield.

Table 1 Solvent effect on the chlorination and imidation



		Yield/%	
Entry	Solvent	**MeO-Cl-DNQ**	**2**
1	CH_2Cl_2	45	trace
2	THF	83	11
3	EtOH	76	7
4	DMF	35	40
5	MeCN	85	10

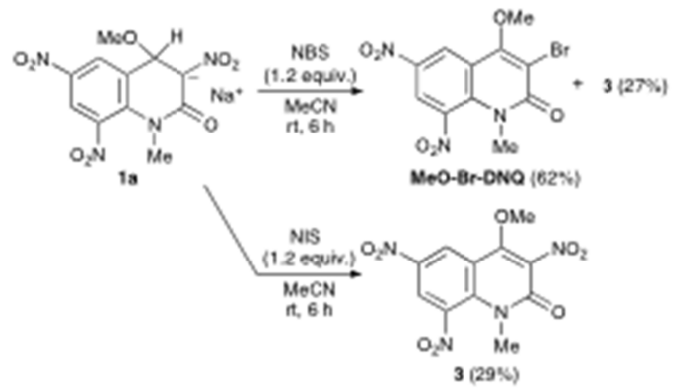
Table 2 One-pot alkoxy-chlorination



		Yield/%	
Entry	R	**RO-Cl-DNQ**	**2**
1	Bu	42	10
2	*i*-Bu	46	0
3	*i*-Pr	45	0
4	$PhCH_2CH_2$ (Phet)	55	0
5	Allyl	51	0
6	Propargyl (Prg)	29	20

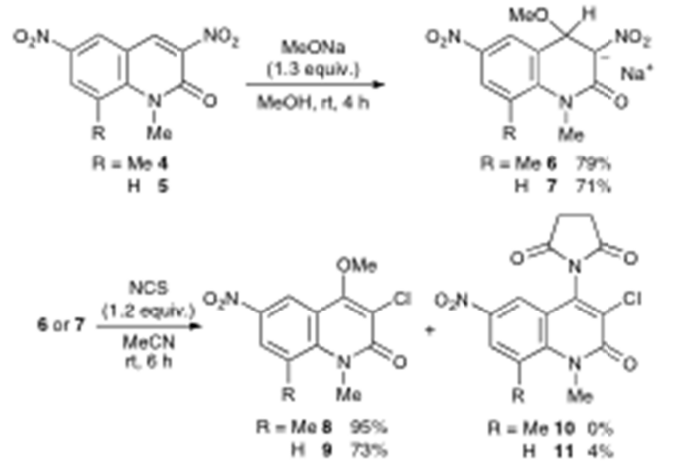
In the cases of other chloroalkoxylation, a one-pot method was used to simplify the experimental operations (Table 2, entries 1–6). Namely, after a solution of **TNQ** and sodium alkoxide in alcohol was stirred at room temperature for 4 h, a solution of NCS in acetonitrile was added, and the resulting mixture was stirred at room temperature for further 6 h. Then, the solvent was removed, and the residue was purified to afford **RO-Cl-DNQ** in a moderate yield. Moreover, an allyloxy or a propargyloxy group was introduced at the 4-position (entries 5 and 6), facilitating further chemical transformations.

To expand the substrate scope of this protocol, sodium salt **1a** was reacted with other *N*-halosuccinimides. Bromination using NBS afforded the corresponding **MeO-Br-DNQ** in 62% yield (Scheme 2). In this reaction, 4-methoxylated trinitroquinolone **3** was also obtained in 27% yield, probably because of the higher leaving ability of bromide than chloride. Indeed, product **3** was obtained without detectable **MeO-I-DNQ** in the reaction of **1a** with NIS. On the other hand, neither the alkoxylated product nor halogenated product was formed in the reactions using Br_2, ICl, and I_2 as the halogenating agent.



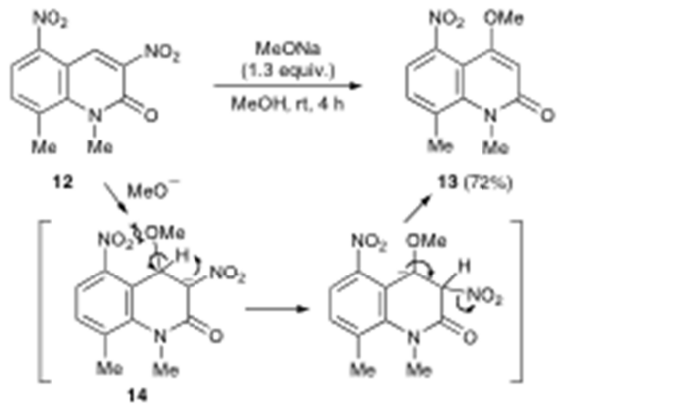
Scheme 2 Reactions of **1a** with other *N*-halosuccinimide

In our previous work, we clarified the high reactivity of **TNQ** was caused by the steric repulsion between the 1-methyl and 8-nitro groups, distorting the **MeQone** framework to reduce the aromaticity.[9] To the contrary, such steric repulsion was not crucial for this reaction because of the high nucleophilicity of the alkoxide anion. 1,8-Dimethyl-3,6-dinitro-2-quinolone (**4**) and 1-methyl-3,6-dinitro-2-quinolone (**5**) underwent the 4-alkoxylation efficiently under the same conditions to afford adducts **6** and **7** without observation of the considerable decrease of the yield, respectively (Scheme 3). Subsequent chlorination of **6** and **7** also proceeded upon treatment with NCS leading to **8** and **9** in high yields, respectively.



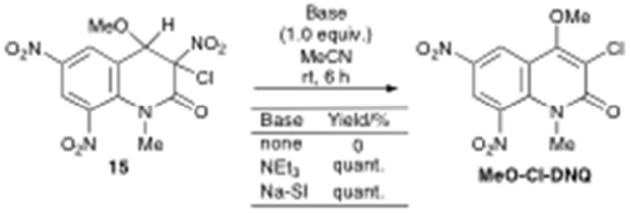
Scheme 3 Effect of the substituent at the 8-position

On the other hand, when 1,8-dimethyl-3,5-dinitro-2-quinolone **12** was employed as the substrate, *cine*-substituted product **13** was obtained without any detectable adduct intermediate **14**. In this reaction, addition of a methoxide surely occurred to afford **14**, however, it is not stable because of steric repulsion with *peri*-substituent. In order to release this repulsion, proton transfer to the 3-position is considered to occur, which undergoes the elimination of nitrite ion accompanied by aromatization to afford *cine*-substituted product **13** (Scheme 4).



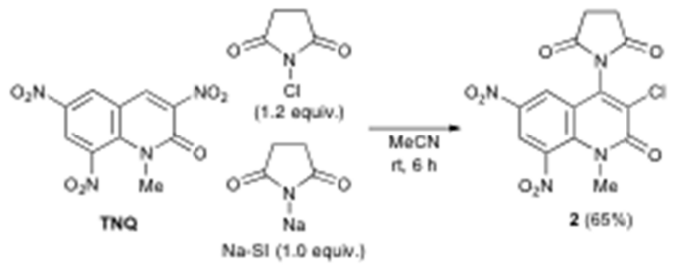
Scheme 4 Reaction of 3,5-dinitroquinolone **12** with methoxide ion

To elucidate the mechanism of the reaction, several experiments were carried out. This reaction should proceed via 3,4-dihydroquinoline intermediate **15** from which nitrous acid is eliminated, affording **RO-X-DNQ**. Although all other attempts to isolate **15** were unsuccessful, the reaction of **1a** with NCS in CH_2Cl_2 in a short reaction time (0.5 h) successfully produced **15** in 45% yield. Dihydroquinoline **15** remained unreacted when a solution of **15** in acetonitrile was stirred at room temperature for 6 h. In contrast, the same solution in the presence of triethylamine furnished **MeO-Cl-DNQ** quantitatively (Scheme 5). In this reaction, sodium succinimide (Na-SI) may have acted as a base. Indeed, the addition of Na-SI facilitated the elimination of nitrous acid from **15**, affording **MeO-Cl-DNQ** quantitatively without any detectable imidation product **2** (Scheme 5).



Scheme 5 Elimination of nitrous acid from intermediate **15**

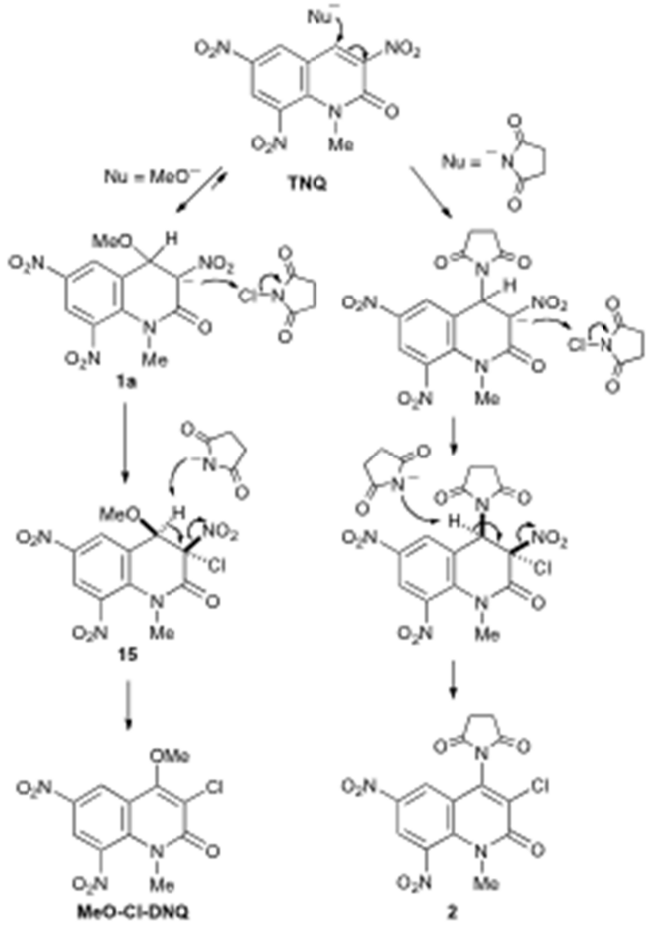
Next, some experiments were carried out to obtain insights into the imidation. When **MeO-Cl-DNQ** was reacted with equimolar Na-SI, no reaction occurred, indicating that product **2** was not formed from **MeO-Cl-DNQ**. On the other hand, chloroimidation occurred by the treatment of **TNQ** with NCS and Na-SI (Scheme 6). Hence, imidation proceeds competitively with the alkoxylation of **TNQ**.



Scheme 6 Chloro-imidation of **TNQ**

Based on the abovementioned results, a plausible mechanism of

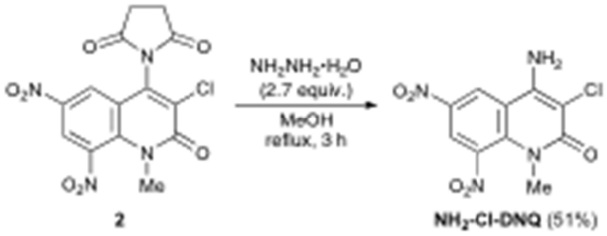
this transformation is illustrated in Scheme 7. The reaction is initiated with the nucleophilic addition of an alkoxide at the 4-position of **TNQ**, furnishing **1a** as a relatively stable sodium salt. The reaction of **1a** with NCS facilitates chlorination at the 3-position by nucleophilic substitution, affording 3,4-dihydroquinoline **15**. Then a nitrous acid molecule is eliminated, leading to the formation of bis(functionalized) product **MeO-Cl-DNQ**. In some cases, **TNQ** was regenerated under equilibrium and then underwent nucleophilic addition with Na-SI followed by chlorination and rearomatization, affording imidated product **2**.



Scheme 7 A plausible mechanism for formation of **MeO-Cl-DNQ** and **2**

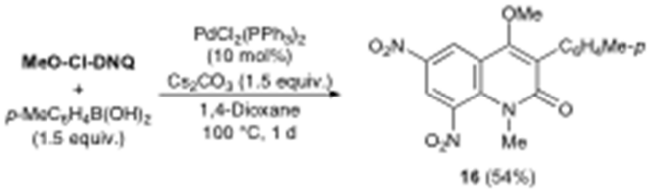
In the chlorination step of **1a**, NCS approaches from the *trans* direction to avoid the steric hindrance of the methoxy group. Hence, nitrous acid is preferentially eliminated over hydrogen chloride in the next rearomatization step because a hydrogen atom and a nitro group are antiperiplanar.[18]

As shown in Scheme 6, **TNQ** also underwent the chloroimidation, affording product **2** in a moderate yield. This can be regarded as a masked form of aminated quinolone, **NH_2-Cl-DNQ**. Indeed, **NH_2-Cl-DNQ** was isolated in 51% yield by the hydrazinolysis of compound **2** (Scheme 8). Aminated **MeQone**s are usually synthesized by chemical conversion from hydroxy derivatives via chloro derivatives.[19] As an alternative approach, a ring is also constructed on an aniline derivative.[20] However, no direct amination method for the **MeQone** framework has been reported, except for our report.[11] Hence, this imidation is a useful method for the direct aminochlorination of the **MeQone** framework.



Scheme 8 Hydrazinolysis of imidated product **2**

Finally, to illustrate the synthetic potential of our protocol, compound **MeO-Cl-DNQ** was subjected to Suzuki–Miyaura coupling reaction[21] because **MeQone**s possessing an alkoxy group and an aryl group at the vicinal positions serve as α4 integrin inhibitors.[22] When **MeO-Cl-DNQ** was reacted with 4-methylphenylboronic acid in the presence of a Pd catalyst, arylated product **16** was successfully obtained in a moderate yield (Scheme 9).



Scheme 9 Suzuki-Miyaura coupling reaction using **MeO-Cl-DNQ**

Conclusions

In conclusion, we have developed a direct and vicinal functionalization of the **MeQone** framework under mild conditions by the treatment of **TNQ** with sodium alkoxides followed by treatment with NCS. This procedure facilitates the regioselective haloalkoxylation readily with simple experimental manipulations. Moreover, chloroimidation proceeded, leading to 4-imidated product **2** which is an equivalent of aminated **MeQone**. The prepared vicinally functionalized **MeQone**s will serve as key synthetic intermediates for versatile **MeQone**s. As one example, the palladium-catalyzed arylation at the 3-position was demonstrated. Hence, this protocol will be used as a powerful tool for constructing a compound library of **MeQone**s.

Experimental

Experimental Section

The melting points were determined on a Yanaco micro-melting-points apparatus, and are uncorrected. All the reagents and solvents were commercially available and used as received. The ^{1}H NMR spectra were measured on a Bruker Ascend-400 at 400 MHz with tetramethylsilane as an internal standard. The ^{13}C NMR spectra were measured on a Bruker Ascend-400 at 100 MHz, and assignments of ^{13}C NMR spectra were performed by DEPT experiments. The IR spectra were recorded on a JASCO FT/IR-4200 spectrometer. The mass spectra and high-resolution mass spectra were measured on an AB SCIEX Triple TOF^{TM} 4600. The gas

chromatography mass spectrum was measured on a JEOL JMS-Q1050GC Ultra Quad GC/MS.

Preparation of 3-nitrated quinolones

1-Methyl-2-quinolone was prepared from quinoline by methylation with Me_2SO_4 followed by oxidation with $K_3[Fe(CN)_6]$ under alkaline conditions. Nitration of 1-methyl-2-quinolone with fuming HNO_3 afforded **TNQ** in 86% total yield.[23]

Other nitroquinolones **4**, **5** and **12** were also prepared in a similar way. Dinitroquinolones were obtained when milder reaction conditions were used in the nitration step.[9]

General procedure for synthesis of 1a and 1b

To a solution of **TNQ** (500 mg, 1.70 mmol) in MeOH (5.5 mL), was added a solution of NaOMe (119 mg, 2.21mmol) in MeOH (0.6 mL), and the resultant mixture was stirred at room temperature for 4 h. The precipitated solid was collected by filtration to afford **1a** (474 mg, 1.36 mmol, 81%) as a yellow powder. The reaction of **TNQ** with NaOEt was performed to prepare **1b** in a similar way.

(6,8-Dinitro-4-methoxy-1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)sodium (1a). Yellow powder (474 mg, 1.36 mmol, 81%); mp 218–220 °C (dec.); ^{1}H NMR (DMSO-d_6, 400 MHz) δ = 2.97 (s, 3H), 3.15 (s, 3H), 5.96 (s, 1H), 8.55 (d, *J* = 2.4 Hz, 1H), 8.60 (d, *J* = 2.4 Hz, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 33.6 (CH_3), 53.9 (CH_3), 73.0 (CH), 106.6 (C), 121.1 (CH), 126.9 (CH), 129.8 (C), 137.2 (C), 139.0 (C), 139.2 (C), 159.9 (C); IR: ν (cm^{-1}) 1634, 1531, 1520, 1335; HRMS (ESI): Calcd for $C_{11}H_{10}N_4NaO_8$ [(M+H)$^+$]: 349.0391, found 349.0386.

(6,8-Dinitro-4-ethoxy-1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)sodium (1b). Yellow powder (615 mg, 1.70 mmol, quant.); mp 213–215 °C (dec.); ^{1}H NMR (DMSO-d_6, 400 MHz) δ = 1.02 (t, *J* = 6.8 Hz, 3H), 2.97 (s, 3H), 3.47 (q, *J* = 6.8 Hz, 2H), 6.03 (s, 1H), 8.53 (d, *J* = 2.8 Hz, 1H), 8.59 (d, *J* = 2.8 Hz, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ = 15.4 (CH_3), 33.6 (CH_3), 61.7 (CH_2), 71.7 (CH), 107.1 (C), 121.0 (CH), 126.7 (CH), 130.5 (C), 137.2 (C), 138.9 (C), 139.2 (C), 160.0 (C); IR: ν (cm^{-1}) 1633, 1537, 1531, 1334; HRMS (ESI) Calcd for $C_{12}H_{12}N_4NaO_8$ [(M+H)$^+$]: 363.0547, found 363.0541.

General procedure for synthesis of MeO-Cl-DNQ and EtO-Cl-DNQ

To a solution of **1a** (70 mg, 0.20 mmol) in MeCN (1.0 mL), NCS (32 mg, 0.24 mmol) was added, and the resultant mixture was stirred at room temperature for 6 h. Then, the solvent was evaporated to afford a reaction mixture as a yellow residue, from which **MeO-Cl-DNQ** was isolated through SiO_2 column chromatography (eluted with CH_2Cl_2/hexane = 4/1), respectively. **EtO-Cl-DNQ** was prepared in a similar way.

3-Chloro-4-methoxy-1-methyl-6,8-dinitroquinolin-2(*1H*)-one (MeO-Cl-DNQ). Yellow powder (53 mg, 0.17 mmol, 85%); R_f = 0.21 (CH_2Cl_2/hexane = 4/1); mp 170–171 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 3.54 (s, 3H), 4.35 (s, 3H), 8.73 (d, *J* = 2.4 Hz, 1H), 8.99 (d, *J* = 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 35.7 (CH_3), 62.1 (CH_3), 116.0 (C), 121.2 (C), 122.4 (CH), 122.7 (CH), 135.2 (C), 139.0 (C), 140.8 (C), 157.9 (C), 160.0 (C); IR: ν (cm^{-1}) 1667, 1537, 1531, 1358, 1307; MS (EI): 315 (M$^+$+2, 21), 313 (M+, 66), 283 (100), 149 (67); HRMS (ESI) Calcd for $C_{11}H_9ClN_3O_6$ [(M+H)$^+$]: 314.0174, found 314.0165.

3-Chloro-4-ethoxy-1-methyl-6,8-dinitroquinolin-2(*1H*)-one (EtO-Cl-DNQ). Yellow powder (46 mg, 0.14 mmol, 73%); R_f = 0.21 (CH_2Cl_2/hexane = 4/1); mp 161–163 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.59 (t, *J* = 6.8 Hz, 3H), 3.54 (s, 3H), 4.62 (q, *J* = 6.8 Hz, 2H), 8.72 (d, *J* = 2.8 Hz, 1H), 8.99 (d, *J* = 2.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 15.7 (CH_3), 35.7 (CH_3), 71.2 (CH_2), 116.4 (C), 121.7 (C), 122.3 (CH), 122.7 (CH), 135.2 (C), 139.0 (C), 140.8 (C), 157.2 (C), 160.0 (C); IR: ν (cm^{-1}) 1682, 1537, 1531, 1352, 1335; HRMS (ESI) Calcd for $C_{12}H_{10}ClN_3O_6$ [(M-H)$^-$]: 326.0185, found 326.0201.

General procedure for one-pot method of synthesis of RO-Cl-DNQ

To a solution of Na (7 mg, 0.31 mmol) in alcohol (0.3 mL), **TNQ** (70 mg, 0.24 mmol) was added, and the resultant mixture was stirred at room temperature for 4 h. Then, a solution of NCS (38 mg, 0.29 mmol) in MeCN (1.0 mL) was added, and the resultant mixture was stirred at room temperature for further 6 h. Then, the solvent was evaporated to afford a reaction mixture as a yellow residue, from which **RO-Cl-DNQ** was isolated through SiO_2 column chromatography (eluted with CH_2Cl_2/hexane = 4/1).

4-Butoxy-3-chloro-1-methyl-6,8-dinitroquinolin-2(*1H*)-one (BuO-Cl-DNQ). Yellow powder (35 mg, 0.10 mmol, 42%); R_f = 0.25 (CH_2Cl_2/hexane = 4/1); mp 135–136 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.05 (t, *J* = 7.6 Hz, 3H), 1.59 (tq, *J* = 7.6, 7.6 Hz, 2H), 1.94 (tt, *J* = 6.8, 6.8 Hz, 2H), 3.54 (s, 3H), 4.53 (t, *J* = 6.8 Hz, 2H), 8.72 (d, *J* = 2.8 Hz, 1H), 8.98 (d, *J* = 2.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 13.7 (CH_3), 19.0 (CH_2), 32.1 (CH_2), 35.7 (CH_3), 75.1 (CH_2), 116.3 (C), 121.6 (C), 122.3 (CH), 122.7 (CH), 135.2 (C), 139.0 (C), 140.8 (C), 157.4 (C), 160.1 (C); IR: ν (cm^{-1}) 1682, 1537, 1531, 1354; HRMS (ESI) Calcd for $C_{14}H_{15}ClN_3O_6$ [(M+H)$^+$]: 356.0644, found 356.0639.

3-Chloro-4-isobutoxy-1-methyl-6,8-dinitroquinolin-2(*1H*)-one (*i*-BuO-Cl-DNQ). Yellow powder (38 mg, 0.11 mmol, 46%); R_f = 0.30 (CH_2Cl_2/hexane = 4/1); mp 146–147 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.16 (d, *J* = 6.4 Hz, 6H), 2.28 (m, 1H), 3.54 (s, 3H), 4.29 (d, *J* = 6.4 Hz, 2H), 8.72 (d, *J* = 2.4 Hz, 1H), 9.01 (d, *J* = 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 19.0 (CH_3), 29.4 (CH), 35.6 (CH_3), 81.3 (CH_2), 116.2 (C), 121.5 (C), 122.2 (CH), 122.6 (CH), 135.3 (C), 139.0 (C), 140.8 (C), 157.4 (C), 160.1 (C); IR: ν (cm^{-1}) 1674, 1537,1531, 1354; HRMS (ESI) Calcd for $C_{14}H_{15}ClN_3O_6$ [(M+H)$^+$]: 356.0644, found 356.0639.

3-Chloro-4-isopropoxy-1-methyl-6,8-dinitroquinolin-2(*1H*)-one (*i*-PrO-Cl-DNQ). Yellow powder (37 mg, 0.11 mmol, 45%); R_f = 0.25 (CH_2Cl_2/hexane = 4/1); mp 168–170 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.50 (d, *J* = 6.0 Hz, 6H), 3.55 (s, 3H), 5.28 (septet, *J* = 6.0 Hz, 1H), 8.72 (d, *J* = 2.4 Hz, 1H), 9.02 (d, *J* = 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 22.7 (CH_3), 35.7 (CH_3), 78.7 (CH), 116.9 (C), 122.2 (CH), 122.7 (C), 123.0 (CH), 135.2 (C), 139.0 (C), 140.7 (C), 156.5 (C), 160.0 (C); IR: ν (cm^{-1}) 1678, 1537, 1531, 1346; HRMS (ESI) Calcd for $C_{13}H_{11}ClN_3O_6$ [(M-H)$^-$]: 340.0342, found 340.0348.

3-Chloro-6,8-dinitro-1-methyl-4-(2-phenylethoxy)quinolin-2(*1H*)-one (PhetO-Cl-DNQ). Yellow powder (53 mg, 0.13 mmol, 55%); R_f = 0.22 (CH_2Cl_2/hexane = 4/1); mp 142–144 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 3.23 (t, *J* = 6.4 Hz, 2H), 3.51 (s, 3H), 4.82 (t, *J* = 6.4 Hz, 2H), 7.21–7.34 (m, 5H), 8.65 (d, *J* = 2.8 Hz, 1H), 8.73 (d, *J* = 2.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 35.7 (CH_3), 36.5 (CH_2), 75.3 (CH_2), 115.7 (C), 121.4 (CH), 122.2 (C), 122.8 (CH), 127.1 (CH), 128.8 (CH), 128.9 (CH), 135.1 (C), 136.6(C), 138.9 (C), 140.7 (C), 157.0 (C), 160.0 (C); IR: ν (cm^{-1}) 1681, 1537, 1531, 1352, 1301; HRMS (ESI) Calcd for $C_{18}H_{13}ClN_3O_6$ [(M-H)$^-$]: 402.0498, found 402.0512.

3-Chloro-1-methyl-6,8-dinitro-4-(prop-2-enyloxy)quinolin-2(*1H*)-one (AllylO-Cl-DNQ). Yellow powder (41 mg, 0.12 mmol, 51%); R_f = 0.22 (CH_2Cl_2/hexane = 4/1); mp 130–131 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 3.54 (s, 3H), 5.04 (dt, *J* = 6.0, 1.2 Hz, 2H), 5.43 (dd, *J* = 1.2, 10.4 Hz, 1H), 5.52 (ddt, *J* = 16.8, 1.2, 1.2 Hz, 1H), 6.13 (ddt, *J* = 10.4,

16.8, 6.0 Hz, 1H), 8.72 (d, *J* = 2.8 Hz, 1H), 9.00 (d, *J* = 2.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 35.7 (CH_3), 75.4 (CH_2), 117.1 (C), 121.4 (CH_2), 121.8 (C), 122.3 (CH), 122.9 (CH), 131.2 (CH), 135.2 (C), 139.0 (C), 140.8 (C), 157.0 (C), 159.9 (C); IR: ν (cm^{-1}) 1674, 1536, 1530, 1350; HRMS (ESI) Calcd for $C_{13}H_9ClN_3O_6$ [$(M-H)^-$]: 338.0185, found 338.0178.

3-Chloro-1-methyl-4-(prop-2-ynyloxy)-6,8-dinitroquinolin-2(*1H*)-one (PrgO-Cl-DNQ). Yellow powder (23 mg, 0.07 mmol, 29%); R_f = 0.20 (CH_2Cl_2/hexane = 4/1); mp 153–155 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.61 (t, *J* = 2.4 Hz, 1H), 3.56 (s, 3H), 5.23 (d, *J* = 2.4 Hz, 2H), 8.74 (d, *J* = 2.8 Hz, 1H), 9.12 (d, *J* = 2.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 35.8 (CH_3), 61.5 (CH_2), 76.4 (CH), 78.7 (C), 118.4 (C), 121.9 (C), 122.5 (CH), 123.6 (CH), 135.0 (C), 139.0 (C), 140.8 (C), 156.4 (C), 159.7 (C); IR: ν (cm^{-1}) 1682, 1537, 1531 1352; HRMS (ESI) Calcd for $C_{13}H_7ClN_3O_6$ [$(M-H)^-$]: 336.0029, found 336.0038.

3-Bromo-4-methoxy-1-methyl-6,8-dinitroquinolin-2(*1H*)-one (MeO-Br-DNQ). Yellow solid (43 mg, 62%) R_f = 0.21 (CH_2Cl_2/hexane = 4/1); mp 155–157 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 3.55 (s, 3H), 4.28 (s, 3H), 8.75 (d, *J* = 2.4 Hz, 1H), 8.97 (d, *J* = 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 35.9 (CH_3), 62.1 (CH_3), 108.7 (C), 121.4 (C), 122.5 (CH), 122.6 (CH), 135.9 (C), 139.1 (C), 140.8 (C), 160.1 (C), 160.6 (C); IR: ν (cm^{-1}) 1667, 1537, 1531, 1358; HRMS (ESI) Calcd for $C_{11}H_7BrN_3O_6$ [$(M-H)^-$]: 355.9524, found 355.9538.

4-Methoxy-1-methyl-3,6,8-trinitroquinolin-2(*1H*)-one (3). Yellow solid, R_f = 0.21 (CH_2Cl_2/hexane = 4/1); m.p. 204–207 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ = 3.43 (s, 3H), 4.25 (s, 3H), 9.01 (d, *J* = 2.8 Hz, 1H), 9.13 (d, *J* = 2.8 Hz, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ = 34.8 (CH_3), 60.4 (CH_3), 118.9 (C), 124.0 (CH), 124.6 (CH), 129.0 (C), 136.1 (C), 138.8 (C), 140.8 (C), 152.7 (C), 156.8 (C); IR: ν (cm^{-1}) 1672, 1537, 1531, 1352; HRMS (ESI) Calcd for $C_{11}H_9N_4O_8$ [$(M+H)^+$]: 325.0415, found 325.0401.

(4-Methoxy-1,8-dimethyl-6-nitro-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)sodium (6). Yellow powder (423 mg, 1.33 mmol, 79%); mp 214–216 °C (dec.); ^{1}H NMR (DMSO-d_6, 400 MHz) δ = 2.47 (s, 3H), 3.14 (s, 3H), 3.28 (s, 3H), 5.73 (s, 1H), 8.02 (d, *J* = 2.8 Hz, 1H), 8.06 (d, *J* = 2.8 Hz, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ = 21.3 (CH_3), 35.9 (CH_3), 53.8 (CH_3), 74.0 (CH), 107.5 (C), 121.5 (CH), 126.9 (CH), 127.2 (C), 127.9 (C), 140.8 (C), 146.4 (C), 162.6 (C); IR: ν (cm^{-1}) 1634, 1520, 1514, 1337. Satisfactory analytical data were not given despite several attempts.

(4-Methoxy-1-methyl-6-nitro-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)sodium (7). Yellow powder (382 mg, 1.26 mmol, 75%); mp 217–220 °C (dec.); ^{1}H NMR (DMSO-d_6, 400 MHz) δ = 3.10 (s, 3H), 3.28 (s, 3H), 5.87 (s, 1H), 7.15 (d, *J* = 9.2 Hz, 1H), 8.17 (dd, *J* = 2.4, 9.2 Hz, 1H), 8.23 (d, *J* = 2.4 Hz, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ = 29.1 (CH_3), 53.6 (CH_3), 73.7 (CH), 107.6 (C), 113.7 (CH), 123.2 (C), 124.2 (CH), 124.3 (CH), 139.9 (C), 145.5 (C), 159.4 (C); IR: ν (cm^{-1}) 1682, 1537, 1520, 1344. Satisfactory analytical data were not given despite several attempts.

3-Chloro-1,8-dimethyl-4-methoxy-6-nitroquinolin-2(*1H*)-one (8). Yellow powder (53.6 mg, 0.19 mmol, 95%); R_f = 0.28 (CH_2Cl_2); mp 185–188 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.80 (s, 3H), 3.88 (s, 3H), 4.23 (s, 3H), 8.22 (d, *J* = 2.4 Hz, 1H), 8.66 (d, *J* = 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 24.1 (CH_3), 37.9 (CH_3), 61.6 (CH_3), 115.1 (C), 118.0 (CH), 119.6 (C), 126.8 (C), 129.4 (CH), 142.4 (C), 143.3 (C), 159.1 (C), 161.7 (C); IR: ν (cm^{-1}) 1659, 1597, 1522, 1341; HRMS (ESI) Calcd for $C_{12}H_{12}ClN_2O_4$ [$(M+H)^+$]: 283.0480, found 283.0482.

3-Chloro-4-methoxy-1-methyl-6-nitroquinolin-2(*1H*)-one (9). Yellow powder (39 mg, 0.15 mmol, 73%); R_f = 0.27 (CH_2Cl_2); mp 197–199 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 3.82 (s, 3H), 4.27 (s, 3H), 7.47 (d, *J* = 9.6 Hz, 1H), 8.43 (dd, *J* = 2.4, 9.6 Hz, 1H), 8.83 (d, *J* = 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 31.3 (CH_3), 61.7 (CH_3), 115.0 (CH), 115.7 (C), 117.7 (C), 120.2 (CH), 125.8 (CH), 141.6 (C), 142.7 (C), 158.8 (C), 159.9 (C); IR: ν (cm^{-1}) 1651, 1537, 1524, 1347; HRMS (ESI) Calcd for $C_{11}H_{10}ClN_2O_4$ [$(M+H)^+$]: 269.0324, found269.0322.

3-Chloro-1-methyl-6-nitro-4-(2,5-dioxopyrrolidino)quinolin-2(1*H*)-one (11). Yellow powder (2.7 mg, 0.01 mmol, 4%); R_f = 0.48 (CH_2Cl_2/MeOH = 20/1); mp 283–285 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ = 2.98–3.19 (m, 4H), 3.83 (s, 3H), 7.92 (d, *J* = 9.2 Hz, 1H), 8.50 (dd, *J* = 2.8, 9.2 Hz, 1H), 8.64 (d, *J* = 2.8 Hz, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ = 29.5 (CH_2), 31.8 (CH_3), 116.8 (C), 117.4 (CH), 120.7 (CH), 126.2 (CH), 127.7 (C), 137.4 (C), 141.7 (C), 142.7 (C), 157.0 (C), 175.4 (C); IR: ν (cm^{-1}) 1651, 1537, 1520, 1337; HRMS (ESI) Calcd for $C_{14}H_{11}ClN_3O_5$ [$(M+H)^+$]: 336.0382, found 336.0387.

Synthesis of 4-methoxy-1,8-dimethyl-5-nitroquinolin-2(*1H*)-one (13)

To a solution of **12** (25 mg, 0.10 mmol) in MeOH (0.5 mL), was added MeONa (7 mg, 0.13 mmol), and the resultant mixture was stirred at room temperature for 4 h. Then, the solvent was evaporated to afford a mixture as a yellow residue, from which **13** was isolated as a yellow powder by SiO_2 column chromatography (eluted with CH_2Cl_2, 16.8 mg, 0.07 mmol, 72%); R_f = 0.10 (CH_2Cl_2); mp 134–136 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ = 2.73 (s, 3H), 3.76 (s, 3H), 3.94 (s, 3H), 6.76 (d, *J* = 9.6 Hz, 1H), 8.06 (s, 1H), 8.12 (d, *J* = 9.6 Hz, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ = 23.0 (CH_3), 35.7 (CH_3), 63.9 (CH_3), 116.6 (C), 121.8 (CH), 122.2 (C), 130.0 (CH), 133.5 (CH), 135.6 (C), 145.6 (C), 149.4 (C), 162.7 (C); IR: ν (cm^{-1}) 1667, 1566, 1556, 1339; HRMS (ESI) Calcd for $C_{12}H_{12}N_2O_4Na$ [$(M+Na)^+$]: 271.0689, found 271.0693.

Synthesis of 3-chloro-3,4-dihydro-4-methoxy-1-methyl-6,8-dinitroquinolin-2(*1H*)-one (15)

To a solution of **1a** (100 mg, 0.29 mmol) in CH_2Cl_2 (2.0 mL), was added NCS (46 mg, 0.34 mmol), and the resultant mixture was stirred at room temperature for 0.5 h. Then, the solvent was evaporated to afford a mixture as a yellow residue, from which **15** was isolated as a yellow powder by silica gel column chromatography (eluted with CH_2Cl_2/hexane = 2/1, 46.4 mg, 0.13 mmol, 45%); R_f = 0.15 (CH_2Cl_2/hexane = 2/1); mp 158–160 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 3.32 (s, 3H), 3.89 (s, 3H), 4.97 (s, H), 8.47 (d, *J* = 2.4 Hz, 1H), 8.68 (d, *J* = 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 36.0 (CH_3), 62.4 (CH_3), 81.6 (CH), 97.9 (C), 122.5 (CH), 124.6 (CH), 128.4 (C), 137.2 (C), 139.6 (C), 143.3 (C), 158.3 (C); IR: ν (cm^{-1}) 1682, 1573, 1537, 1344; HRMS (ESI) Calcd for $C_{11}H_{10}ClN_4O_8$ [$(M+H)^+$]: 361.0182, found 361.0186.

Synthesis of 2,5-dioxopyrrolidino substituted MeQone 2

To a solution of **TNQ** (70 mg, 0.24 mmol) in MeCN (0.5 ml), was added NCS (38 mg, 0.29 mmol) and Na-SI (29 mg, 0.24 mmol), and the resultant mixture was stirred at room temperature for 6 h. Then, the solvent was evaporated to afford a reaction mixture as a

yellow residue, from which **2** was isolated through SiO_2 column chromatography (eluted with CH_2Cl_2) as a yellow solid (59 mg, 0.15 mmol, 65%). R_f = 0.10 (CH_2Cl_2); mp 294–297 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ = 3.05–3.23 (m, 4H), 3.52 (s, 3H), 8.98 (d, *J* = 2.4 Hz, 1H), 9.04 (d, *J* = 2.4 Hz, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ = 29.6 (CH_2), 36.4 (CH_3), 120.2 (C), 123.4 (CH), 124.1 (CH), 128.9 (C), 135.5 (C), 137.3 (C), 139.0 (C), 141.3 (C), 157.8 (C), 175.3 (C); IR: ν (cm^{-1}) 1682, 1537, 1531, 1385, 1336; HRMS (ESI) Calcd for $C_{14}H_{10}ClN_4O_7$ [$(M+H)^+$]: 381.0233, found 381.0238.

Hydrazinolysis of 2

To a solution of **2** (50 mg, 0.13 mmol) in MeOH (2.0 mL), NH_2NH_2•H_2O (18 mg, 0.36 mmol) was added, and the resultant mixture was heated at 70 °C for 3 h. Then, the solvent was evaporated to afford a reaction mixture as a yellow solid. After the solid was washed by water (5 mL × 1), **NH_2-Cl-DNQ** was isolated through filtration as a yellow solid (20 mg, 0.07 mmol, 51%); R_f = 0.36 (CH_2Cl_2/MeOH = 10/1); mp > 300 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ = 3.29 (s, 3H), 7.54 (br s, 2H), 8.89 (d, *J* = 2.0 Hz, 1H), 9.35 (d, *J* = 2.0 Hz, 1H); ^{13}C NMR (DMSO-d_6, 400 MHz) δ = 35.1 (CH_3), 99.8 (C), 117.2 (C), 122.5 (CH), 123.2 (CH), 136.5 (C), 138.5 (C), 139.7 (C), 147.1 (C), 158.2 (C); IR: ν (cm^{-1}) 1651, 1537, 1531, 1331, 1300; HRMS (ESI) Calcd for $C_{10}H_8ClN_4O_5$ [$(M+H)^+$]: m/z=299.0178, found m/z= 299.0172.

Suzuki-Miyaura coupling reaction of MeO-Cl-DNQ

To a solution of **MeO-Cl-DNQ** (60 mg, 0.19 mmol) in 1,4-dioxane (1.0 mL), were added *p*-$MeC_6H_4B(OH)_2$ (39 mg, 0.29 mmol), $Pd(PPh_3)_2Cl_2$ (14 mg, 0.02 mmol) and Cs_2CO_3 (94 mg, 0.29 mmol), and the resultant mixture was heated at 100 °C for 1 d. Then, the solvent was evaporated to afford a reaction mixture as a yellow residue, from which arylated product **16** was isolated by SiO_2 column chromatography (eluted with CH_2Cl_2/hexane = 4/1) as a yellow solid (38 mg, 0.10 mmol, 54%); R_f = 0.22 (CH_2Cl_2/hexane = 4/1); mp 172–175 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.42 (s, 3H), 3.49 (s, 3H), 3.59 (s, 3H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 8.71 (d, *J* = 2.4 Hz, 1H), 9.05 (d, *J* = 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 21.4 (CH_3), 35.0 (CH_3), 61.5 (CH_3), 119.9 (C), 121.9 (CH), 122.0 (C), 123.2 (CH), 128.4 (C), 129.2 (CH), 130.4 (CH), 136.5 (C), 138.5 (C), 139.0 (C), 140.3 (C), 158.2 (C), 163.8 (C); IR: ν (cm^{-1}) 1667, 1537, 1531, 1360, 1332; HRMS (ESI) Calcd for $C_{18}H_{16}N_3O_6$ [$(M+H)^+$]: 370.1034, found 370.1037.

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