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Novel functionalization of 1-methyl-2-quinolone; dimerization and denitration of trinitroquinolone

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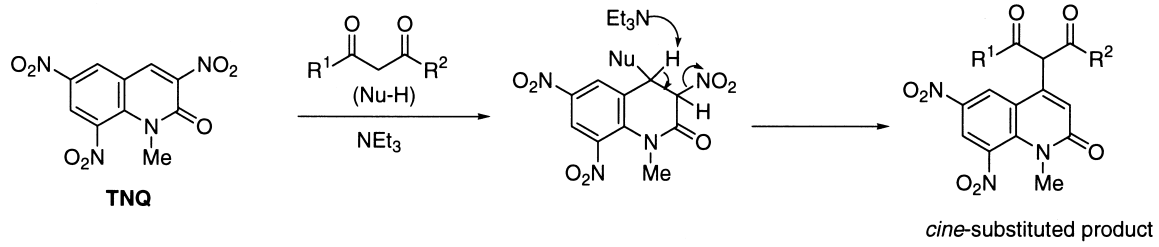
Abstract—New methods for functionalization of 1-methyl-2-quinolone (MeQone) skeleton are provided. The reaction of 1-methyl-3,6,8-trinitro-2-quinolone (TNQ) with amines affords quinolone dimer **1** and 6,8-dinitroquinolone (6,8-DNQ). Dimerization predominantly proceeds at room temperature, and denitration takes place under heated and diluted conditions. We also provide a plausible mechanism for these reactions on the basis of structure–reactivity relationship of amines.

1. Introduction

The 1-methyl-2-quinolone (MeQone) skeleton is seen in more than 300 quinoline alkaloids isolated from the Rutaceae family,[1–3] and the isolation, the structural determination and total syntheses of new quinoline alkaloids containing MeQone are still active area.[4–10] 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.[11–17] Thus, it is highly demanded to develop new methods for both functionalization[18,19] and construction[20] of MeQone derivatives.

The cycloaddition of the α,β-unsaturated carbonyl moiety in the MeQone skeleton has been employed for this purpose.[21–24] It is possible to prepare various kinds of ring-fused systems, which are converted to MeQone derivatives functionalized at the 3- and 4-positions. In our course of study on another strategy, we have shown that 1-methyl-3,6,8-trinitro-2-quinolone (TNQ) is an excellent synthetic intermediate for direct functionalization of MeQone. TNQ attains high reactivity with steric strain resulting from repulsion between 8-nitro and 1-methyl groups besides electron-deficiency.[25] The C–C bond is regioselectively formed at the 4-position with loss of an adjacent nitro group (*cine*-substitution) when TNQ is treated with 1,3-dicarbonyl compounds in the presence of triethylamine.[26] This reaction proceeds in the addition–elimination mechanism, in which nitrous acid is eliminated from the adduct intermediate, 3,4-dihydroquinolone, as illustrated in Scheme 1.

On the other hand, quite different reactivity is observed in the reaction of TNQ with amine in the absence of nucleophile, namely, dimerization and denitration proceed. Since these transformations will be novel procedures for functionalization of the MeQone skeleton, we have screened



Scheme 1.

Keywords: trinitroquinolone; nitration; denitration; dimerization; *cine*-substitution.
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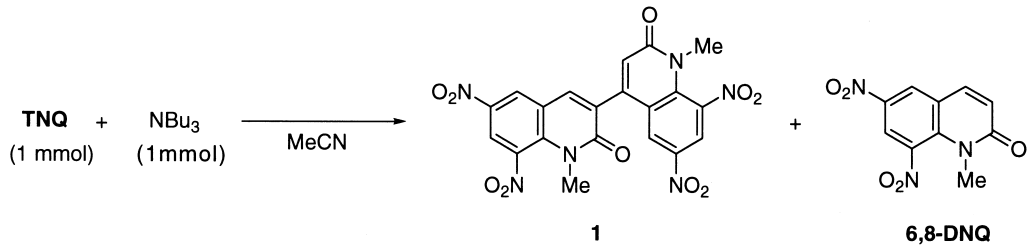
Table 1. Reactions of TNQ with NBu_3 under various conditions



1 **6,8-DNQ**

Run	Temperature (°C)	Solvent (cm^3)	Time (d)	1/6,8-DNQ[a,b]	Yield (%)[c]	
					1[b]	6,8-DNQ
1	rt[d]	10	7	88/12	81	6
2	60	10	1	63/37		
3	80	10	1	40/60[e]		
4	rt[d]	50	7	82/18		
5	60	30	1	25/75		
6	60	50	1	25/75	20	58

[a] Determined by ^{1}H NMR.
[b] Based on TNQ.
[c] Isolated yield.
[d] Room temperature.
[e] Reaction mixture was somewhat complicated.

reaction conditions using several kinds of amines. A plausible mechanism for these reactions is also presented here on the basis of structure–reactivity relationship of amines.

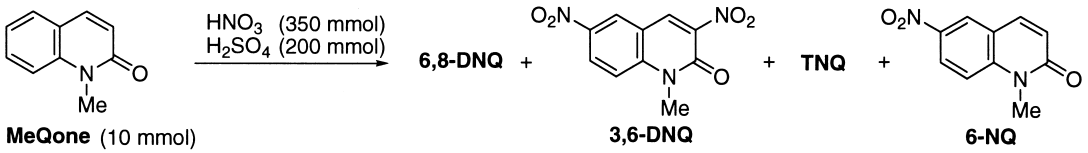
2. Results and discussions

The reaction of TNQ with tributylamine at room temperature afforded 3,4′-bis(1-methyl-6,8-dinitro-2-quinolone) (**1**) and 6,8-dinitro-1-methyl-2-quinolone (6,8-DNQ)[25] in 81 and 6% yields, respectively (Table 1, run 1). In the ^{1}H NMR of dimer **1**, two singlet signals were observed at 7.06 and 8.56 ppm in addition to two pairs of doublets (H5, H7, H5′ and H7′ protons) and two singlets (*N*-methyl groups). This observation revealed that a couple of 1,2-dihydro-6,8-dinitro-1-methyl-2-oxoquinolyl groups connected at the 3- and the 4′-positions. Analytical and other spectral data (IR, MS, ^{13}C NMR) also supported this dimeric structure. The structure of 6,8-DNQ was confirmed by comparison of spectral data with those of authentic sample.

The ratio of products (1/6,8-DNQ) varies with reaction conditions as summarized in Table 1. In each case, TNQ is quantitatively consumed without detection of by-product except for run 3. 6,8-DNQ is predominantly formed under heated conditions (runs 2 and 3). Dilution is considerably effective to prevent the dimerization affording 6,8-DNQ in a good yield (runs 5 and 6).

When MeQone is directly nitrated, the nitro groups are introduced in the order of 6-$>$3-$\cong$8-positions. Since the 3-position is somewhat rapidly nitrated than the 8-position, the preparation of 6,8-DNQ is more difficult than that of 3,6-DNQ. Only mononitration proceeds without formation of DNQs at low temperature (Table 2, run 1). At a little higher temperature, 6,8-DNQ and 3,6-DNQ are produced, but separation of four nitroquinolones is very troublesome because of similar property (runs 2 and 3). As MeQone is

Table 2. Nitration of MeQone leading to four nitroquinolones



MeQone (10 mmol) **3,6-DNQ** **6-NQ**

Run	Temperature (°C)	Time (d)	Yield (%)[a]			
			6,8-DNQ	3,6-DNQ	TNQ	6-NQ
1	50	5	0	0	0	72
2	70	5	10	26	4	19
3	80	5	29	41	8	18
4	120	7	0	0	63	0
5	120[b]	7	0	0	90	0

[a] Run 1,2,5: isolated yield, run 3,4: determined by ^{1}H NMR.
[b] MeQone was heated in fuming HNO_3 (d=1.52).

effectively converted to TNQ under severe conditions (run 5), the present denitration reaction affords 6,8-DNQ more easily in an improved yield than the direct nitration of MeQone.

Isolated dimer **1** is stable not leading to 6,8-DNQ under heated conditions (at 60°C, in the presence of tributylamine). In addition, 6,8-DNQ and tributylamine furnish no dimer **1** at room temperature. Since interconversion between **1** and 6,8-DNQ does not proceed, one product is found not to be an intermediate of the other product.

Trialkylamine often behaves as the single electron donor in the photochemistry, but this reaction is unrelated to the light. Dimer **1** and 6,8-DNQ are similarly obtained in both cases in the dark and under UV irradiation. The presence of the electron acceptor, anthracene or benzophenone, also has no influence on the reaction, and they remain unchanged. When metal (sodium, magnesium) and copper(I) salts are used instead of amine, TNQ is intact to be recovered. We obtained no evidence that single electron transfer from amine to TNQ initiates the reaction.

Several tertiary amines are employed, and the reaction mixture is monitored with ^{1}H NMR. In each case, only signals of TNQ and dimer **1** are observed in the aromatic region. There are large differences of reactivity among amines (Fig. 1). When trimethylamine and tribenzylamine are used, TNQ was quantitatively recovered without changing. Amines substituted with longer alkyl chains caused the dimerization, and the reaction using tributylamine proceeds much faster than the cases of tripropyl- and triethylamines. However, tertiary amines having one long chain is unexpectedly less reactive. Butyldimethylamine and other alkyldimethylamines afford dimer **1** in only poor yields (Table 3). On the contrary, dibutylmethylamine undergoes as effectively as tributylamine. Hence, more than two long alkyl chains are found to be necessary in the present reaction.

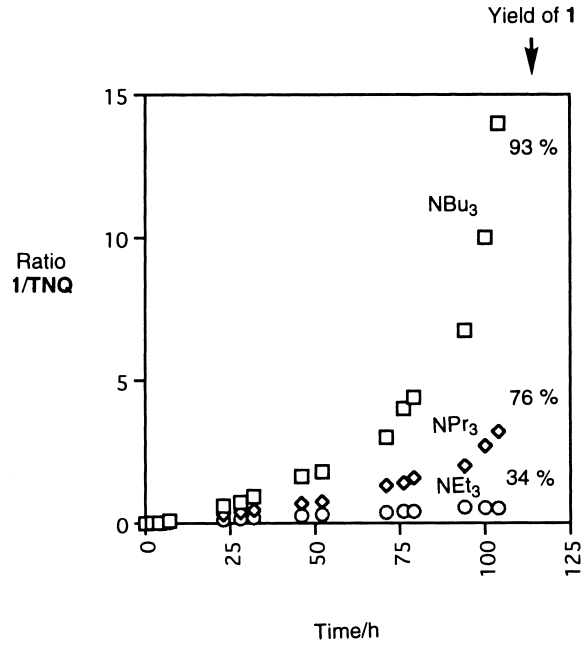


Figure 1. Comparison of reaction rates using three amine homologs.

Table 3. Reaction of TNQ with dimethylamines having a long alkyl chain

TNQ + $RNMe_2$ —MeCN, rt, 7 d→ **1**

R	Yield **1** (%)[a]	Recovery TNQ (%)[a]
Butyl	18	82
Pentyl	22	78
i-Pentyl	19	81
Hexyl	31	69

[a] Determined by ^{1}H NMR.

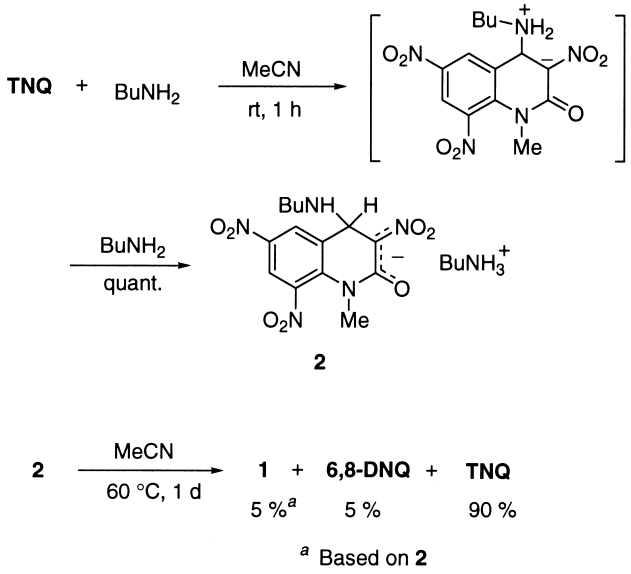
The above results encouraged us to employ secondary and primary amines instead of tertiary ones. In the case of dibutylamine, conversion from TNQ to dimer **1** is smoothly performed. Importantly, this reaction is also caused by secondary amine, which has two long alkyl chains. Even diethylamine affords dimer **1** more effectively than tertiary amines shown in Table 3 (Scheme 2).

TNQ (1 mmol) + $R^1NR^2_2$ (1 mmol) —MeCN (10 cm^3)→ **1** + **6,8-DNQ** + **TNQ**

R^1 = Me, R^2 = Bu	rt, 7 d	79 %	14 %	7 %
R^1 = H, R^2 = Bu	60 °C, 1 d	90 %	10 %	0 %
R^1 = H, R^2 = Et	60 °C, 1 d	49 %	trace	47 %

Scheme 2.

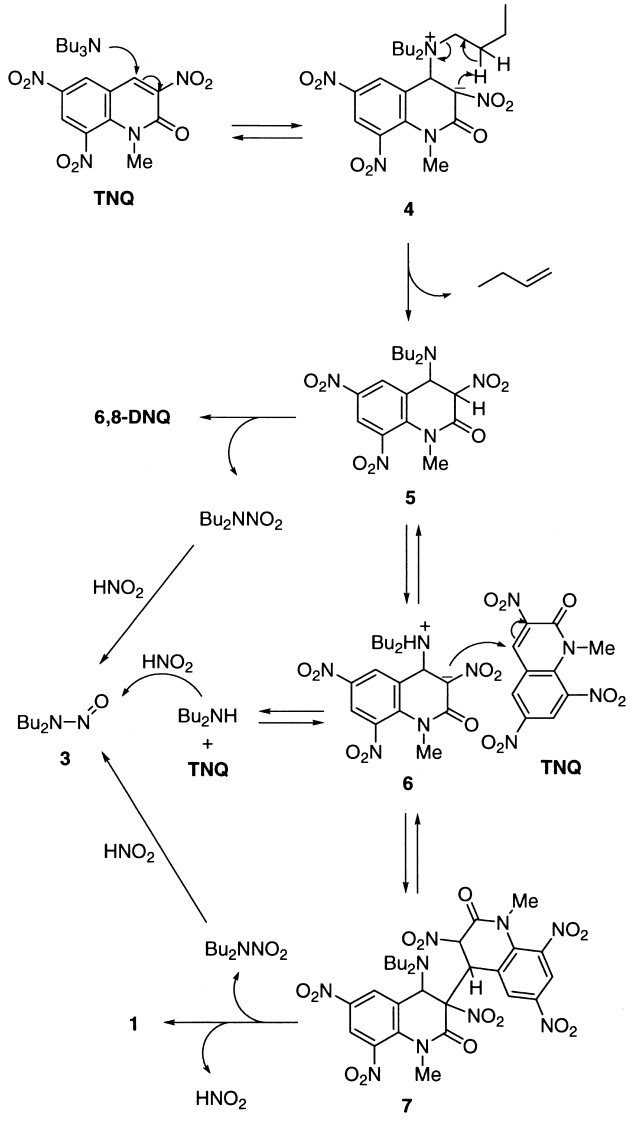
On the other hand, butylamine shows interesting reactivity. Ammonium salt of Meisenheimer complex **2** is immediately precipitated as yellowish solid just after addition of butylamine. When a suspension of isolated salt in acetonitrile is heated at 60°C for 1 day, small amount of dimer **1** and 6,8-DNQ are furnished while the greater part of the salt is reversed to TNQ (Scheme 3). These facts suggest that



Scheme 3.

Meisenheimer complex, the adduct of TNQ with amine, is a key intermediate in both dimerization and denitration.

As a result of various trials, *N*-nitrosodibutylamine **3** could be isolated with column chromatography on silica gel. The spectral data of **3** conform to those of the authentic sample prepared by nitrosoation of dibutylamine with nitrous acid.[27] Taking this result into consideration, a plausible mechanism for these two kinds of reactions is illustrated in Scheme 4. Tributylamine attacks at the electron deficient 4-position of TNQ leading to Meisenheimer complex **4**, from which β-elimination proceeds with release of 1-butene to afford dihydroquinolone **5**. Under heated conditions, 6,8-DNQ is formed with elimination of dibutylamino and nitro groups as nitroamine. When dihydroquinolone **5** is converted to zwitter ion **6** with proton transfer from 3-position to adjacent dibutylamino group, *cine*-substitution of salt **6** and unreacted TNQ proceeds to give dimer **1** via **7**. Steric hindrance of dimeric adduct **7** assists elimination of nitrous acid and prevents further oligomerization. Nitrosoamine **3** is considered to be a nitrosoated product of



Scheme 4.

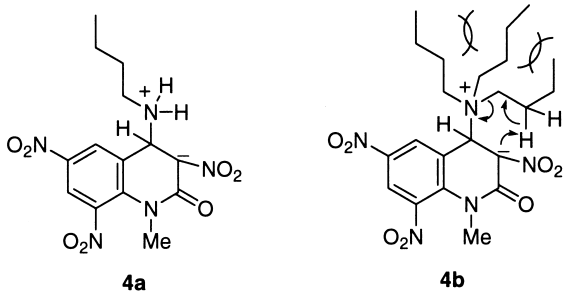


Figure 2.

dibutylamine with nitrous acid or a reduced product of nitroamine by nitrous acid. In the case of diethylamine, it cannot be ignored competitive nitrosoation proceeds before the addition of amine to TNQ and successive dimerization.

The structure–reactivity relationship of amines is rationalized as follows. The key step of the present reaction is the intramolecular prototropy of Meisenheimer complex **4** accompanied with elimination of an alkyl chain on the amino group as the alkene. Since trimethylamine and tribenzylamine have no β-hydrogen, only elimination of tertiary amine from the adduct proceeds to give TNQ. In the cases of alkyldimethylamines and primary amine, the alkyl chain avoids steric repulsion with adjacent nitro group (Fig. 2, structure **4a**), and the suitable conformation for β-elimination is hardly present. On the other hand, one of alkyl chains surely locates nearby the 3-nitro group when the amino group has more than two alkyl groups (Fig. 2, structure **4b**). Hence, amine should have proper steric bulk for the smooth reaction. The different reactivity between triethyl-, tripropyl- and tributylamines supports this speculation.

3. Conclusion

In this paper, two novel methods for functionalization of the MeQone skeleton are provided. The choice of reaction path whether dimerization or denitration is easily performed by varying reaction temperature and concentration of substrates. Denitration is more competent method for preparation of 6,8-DNQ than the direct nitration of MeQone. The present reactions are caused by tertiary and secondary amines having more than two long alkyl chains. On the basis of the structure–reactivity relationship of amines, we suggest the β-elimination of **4** with release of alkene affording **5** is a key step.

4. Experimental

4.1. General

The melting points were determined on a Yanaco micro-melting-points apparatus, and were uncorrected. All the reagents and solvents were commercially available and used as received. ^{1}H and ^{13}C NMR spectra were measured on a Bruker DPX-400 at 400 and at 100 MHz with TMS as an internal standard. IR spectra were recorded on a Horiba FT-200 IR spectrometer. Mass spectrum was recorded on a

JEOL JMS-AX505HA. Elemental microanalyses were performed using a Yanaco MT-3 CHN corder.

4.2. 1-Methyl-3,6,8-trinitro-2-quinolone (TNQ)

MeQone was prepared by oxidation of 1-methylquinolinium ion using $K_3[Fe(CN)_6]$ under alkaline conditions after methylation of quinoline with dimethyl sulfate. Nitration of MeQone with fuming nitric acid (d=1.52) afforded TNQ in 90% yield.[26]

4.3. Amines

Amines were commercially available and used as received. Methylamines and dimethylamines were prepared from corresponding amines by methylation with formaldehyde in the presence of formic acid.[28]

4.4. Reaction of TNQ with tributylamine

To a solution of TNQ (294 mg, 1 mmol) in acetonitrile (10 cm^3), tributylamine (0.24 cm^3, 1 mmol) was added. After stirring at room temperature for 7 days, the mixture was concentrated under reduced pressure. The residue was treated with column chromatography on silica gel (eluent: $CHCl_3$/ethyl acetate=9/1) to afford dimer **1** (193 mg, 0.41 mmol) and 6,8-DNQ (14 mg, 0.06 mmol). In other reactions under different conditions or reactions using other amines, experiments were conducted similarly.

4.4.1. 3,4′-Bis(1-methyl-6,8-dinitro-2-quinolone) (1). Pale yellow powder; mp 288–291°C (dec.); IR (Nujol) 1662, 1554, 1346 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 3.41 (s, 3H), 3.43 (s, 3H), 7.06 (s, 1H), 8.56 (s, 1H), 8.57 (d, J=2.5 Hz, 1H), 8.95 (d, J=2.5 Hz, 1H), 9.02 (d, J=2.6 Hz, 1H), 9.10 (d, J=2.6 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 34.7 (q), 34.7 (q), 122.0 (s), 122.6 (d), 122.7 (d), 122.7 (d), 124.6 (s), 126.1 (s), 128.4 (d), 129.4 (s), 137.3 (s), 137.5 (s), 137.7 (s), 138.2 (s), 140.1 (d), 140.2 (d), 140.3 (s), 145.0 (s), 160.8 (s), 161.1 (s); MS (FAB) 497 (M^++1). Anal. calcd for $C_{20}H_{12}N_6O_{10}$: C, 48.40; H, 2.44; N, 16.93. Found: C, 48.50; H, 2.42; N, 17.22.

4.5. Nitration of MeQone

To cold 18 M H_2SO_4 (11.1 cm^3, 200 mmol), MeQone (1.6 g, 10 mmol) was gradually added. After gradual addition of 15 M HNO_3 (23.3 cm^3, 350 mmol), the mixture was heated at 80°C for 5 h. The solution was cooled down to room temperature, and H_2O (100 cm^3) was poured into the reaction mixture. The generated yellow precipitate (2.4 g) was collected. ^{1}H NMR (DMSO-d_6) showed this product was a mixture of four nitrated quinolones. Each product was assigned as follows.

4.5.1. 1-Methyl-6,8-dinitro-2-quinolone (6,8-DNQ).[25] δ 3.34 (s, 3H), 6.95 (d, J=9.6 Hz, 1H), 8.28 (d, J=9.6 Hz, 1H), 8.87 (d, J=2.2 Hz, 1H), 9.02 (d, J=2.2 Hz, 1H).

4.5.2. 1-Methyl-3,6-dinitro-2-quinolone (3,6-DNQ).[25] δ 3.74 (s, 3H), 7.83 (d, J=9.5 Hz, 1H), 8.53 (dd, J=9.5, 2.0 Hz, 1H), 8.93 (d, J=2.0 Hz, 1H), 9.09 (1H, s).

4.5.3. 1-Methyl-6-nitro-2-quinolone (6-NQ).[25] δ 3.65 (s, 3H), 6.75 (d, J=9.6 Hz, 1H), 7.68 (d, J=9.3 Hz, 1H), 8.09 (d, J=9.6 Hz, 1H), 8.53 (dd, J=9.3, 2.3 Hz, 1H), 8.68 (d, J=2.3 Hz, 1H).

4.5.4. TNQ.[26] δ 3.42 (s, 3H), 9.04 (d, J=2.7 Hz, 1H), 9.24 (d, J=2.7 Hz, 1H), 9.26 (s, 1H).

4.6. Dimerization with monitoring by ^{1}H NMR

To a solution of TNQ (29.4 mg, 0.1 mmol) in CD_3CN (0.3 cm^3), trialkylamine (0.1 mmol) was added, and the solution was stood at 25°C. The monitoring was performed with ^{1}H NMR at interval of a few or several hours. Since no other signal than TNQ and dimer **1** was observed in the aromatic region, the integral ratio of 1/(TNQ+1) could be regarded as the conversion and yield of **1**. Reactions of TNQ with alkyldimethylamines were also conducted in a similar way.

4.7. Reaction of TNQ with butylamine

To a solution of TNQ (294 mg, 1 mmol) in acetonitrile (10 cm^3), butylamine (0.10 cm^3, 1 mmol) was added at room temperature. When amine was added, yellowish solid was immediately precipitated. After stirring for 3 h, the solid was collected by filtration (220 mg, 0.5 mmol, quantitatively obtained based on amine).

4.7.1. Butylammonium salt of 4-butylamino-3,4-dihydro-1-methyl-3,6,8-trinitro-2-quinolone 2. Since this salt was not stable under ambient conditions to give TNQ and it was too hygroscopic, only ^{1}H NMR could be measured. ^{1}H NMR (DMSO-d_6) δ 0.7–1.0 (br, 6H), 1.2–1.7 (br, 8H), 2.8–3.6 (br, 10H), 5.2–5.6 (br, 1H), 8.3–8.7 (br, 2H).

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