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Direct Functionalization of 1-Methyl-2-quinolones and Nitroalkenes

by

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in partial fulfillment of the requirements for the degree of
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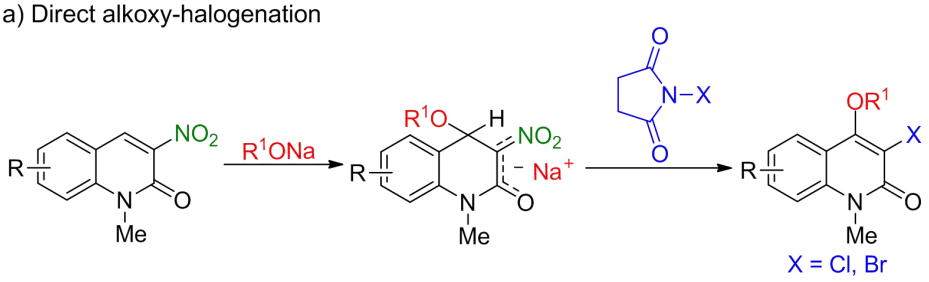
Abstract

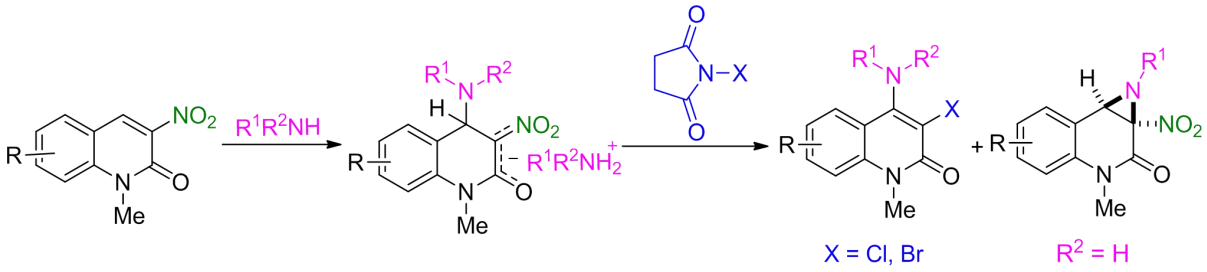
Natural as well as unnatural 1-methyl-2-quinolones (**MeQone**s) are heterocyclic compounds with a wide range of pharmacologically important activities. In addition, they also serve as important building blocks and intermediates in organic synthesis. Therefore, a number of methods have been studied in great detail for the preparation of **MeQone**s. However, among these methods, only a few methods for direct functionalization of the **MeQone** framework are currently available because of the inertness caused by the aromaticity. Accordingly, development of a facile method for direct modification of the **MeQone** framework is one of the highly demanded projects.

A nitro group is one of the most important functional groups in organic syntheses because of its strongly electron-withdrawing ability to activate the scaffold, facilitating the reaction with nucleophilic reagents. Moreover, a nitro group serves not only as a precursor of versatile functionalities but also as a good leaving group. Inspired by these properties of the nitro group, I successfully achieved the direct 4-alkoxylation and 3-halogenation of the **MeQone** framework by a sequential treatment of 3-nitrated **MeQone**s with sodium alkoxides and *N*-halosuccinimide under mild conditions (Scheme 1, a). In addition, direct amino-halogenation and aziridination of the **MeQone** framework was also developed by replacing sodium alkoxides with amines as nucleophiles (Scheme 1, b).

a) Direct alkoxy-halogenation



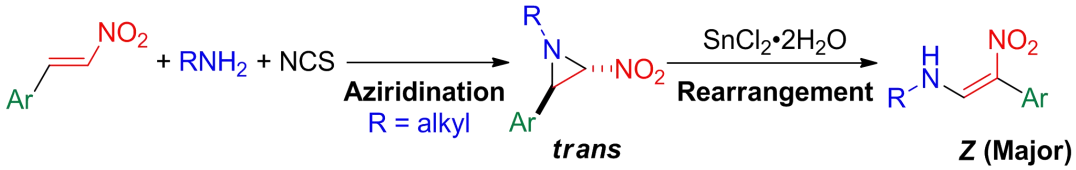
b) Direct amino-halogenation and aziridination



Scheme 1. Direct functionalization of the **MeQone** framework

C-Nitroaziridines serve as useful building blocks in organic synthesis because of the high reactivity caused by strongly electron-withdrawing nitro group and ring strain. Although direct aziridination of nitroalkenes is the most efficient approach to *C*-nitroaziridines, there is no report with regard to preparing *N*-alkyl derivatives.

I demonstrate here an efficient and highly diastereoselective one-pot synthesis of *trans*-*N*-alkyl-*C*-nitroaziridines upon treatment of nitroalkenes with aliphatic amines and *N*-chlorosuccinimide. The resultant aziridines are found to isomerize into (*Z*)-β-aryl-β-nitroenamines with high diastereoselectivity through Lewis acid-mediated ring opening and rearrangement of the aryl group (Scheme 2).



Scheme 2. Direct aziridination of nitroalkenes and the subsequent isomerization

Overall, several facile and efficients methods for direct functionalization of the **MeQone** framework and nitroalkenes were successfully developed. The tolerance of a wide range of functional groups and operational simplicity are the notable advantages of these protocol. The resultant products can be easily transformed into other useful building blocks. Therefore, these methods will be surely useful as powerful tools for preparation of novel compounds with structural diversity and complexity. The results of these investigations are disclosed in this thesis.

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Chapter 1. General Introduction
Part I

1. Significance of 1-methyl-2-quinolones (MeQones)

The 1-methyl-2-quinolone (**MeQone**) framework can be found in more than 300 quinoline alkaloids exhibiting a wide range of biological activities such as melanogenesis inhibitory activity,[1] nicotinic agonistic activity,[2] SRS-A antagonistic activity,[3] cytotoxic activity,[4] and antitumor activity (Figure 1).[5] Due to the important role of these alkaloids in medicinal chemistry, numerous efforts have been dedicated to the the isolation, structural determination, total synthesis and structral modification of quinoline alkaloids containing the **MeQone** skeleton.

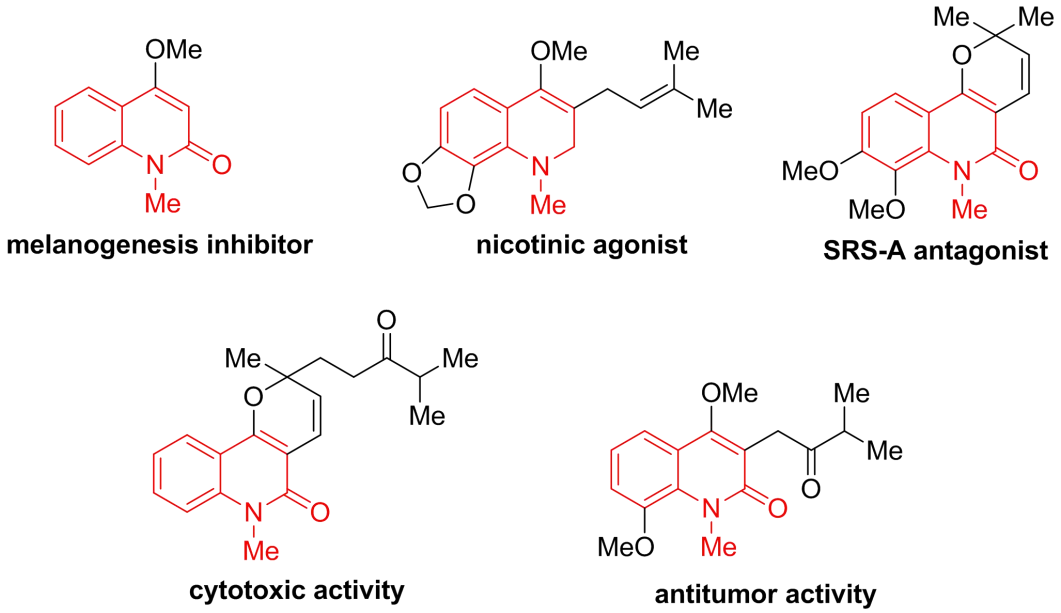


Figure 1. Biological activities of naturally occurring **MeQone** derivatives

Besides naturally occurring **MeQone**s, a large number of unnatural **MeQone** derivatives with structural diversity and complexity have also been synthesized with the aim of finding more useful biological compounds. Indeed, various medicinal properties of **MeQone** derivatives have been disclosed, such as antitumor activity,[6] antianemia activity,[7] antimicrobial activity,[8] anti-HIV activity,[9] and so on (Figure 2).[10]

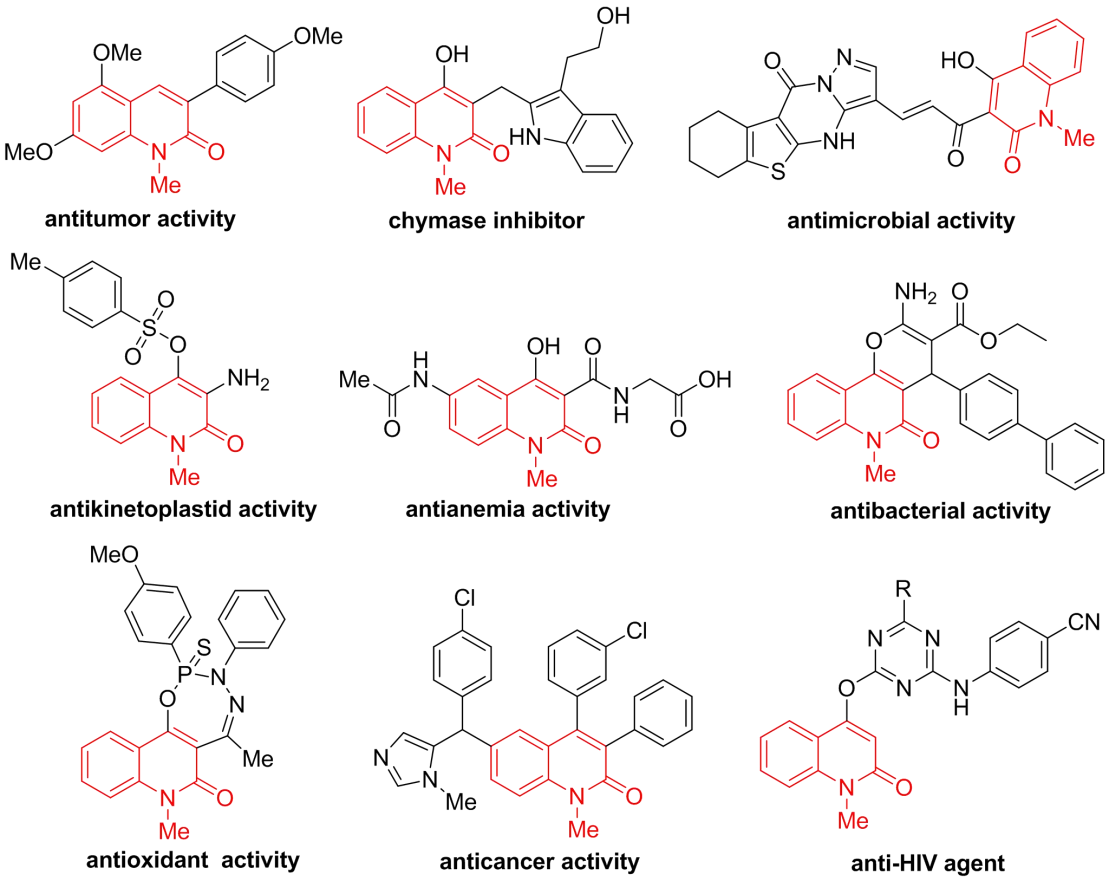


Figure 2. Biological activities of unnatural **MeQone** derivatives

Except for the widespread use in medicinal field, the functionalized **MeQone**s also serve as an important building block in functional materials such as photosensitizers[11] and cyanine dyes (Figure 3).[12]

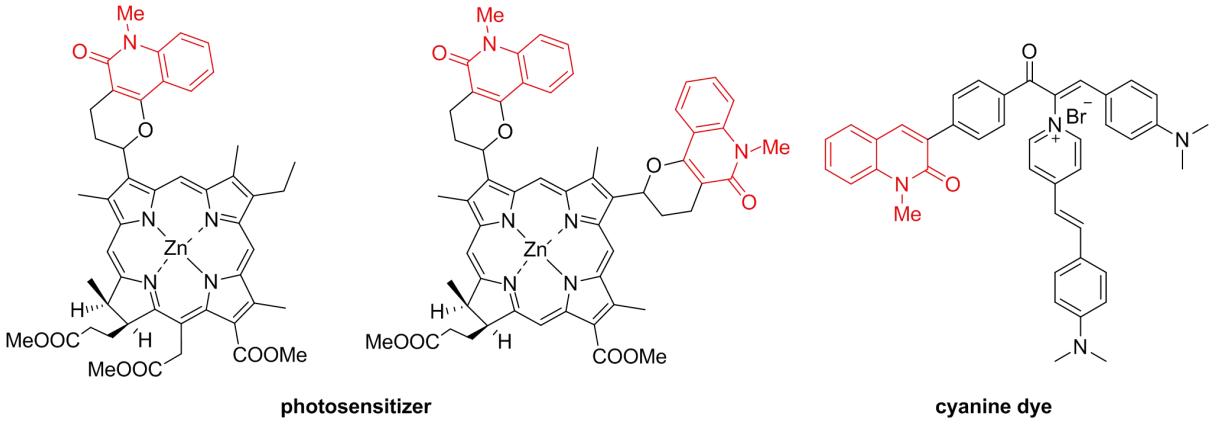


Figure 3. MeQone framework in functional materials

Due to these significant applications, highly efficient methods for synthesis and functionalization of the **MeQone**s are highly demanded over the past decades. In particular, it is very important to find a useful scaffold leading to various kinds of **MeQone**s, which enables the construction of a new compound libraries for biological evaluation.

2. Synthesis of functionalized MeQones

Conventional strategies for the synthesis of functionalized **MeQone**s involve (1) construction of **MeQone** frameworks from pre-functionalized starting materials, (2) ring transformation leading to **MeQone** frameworks, and (3) direct functionalization of the **MeQone** framework, which are supplementary to each other (Figure 4).[13]

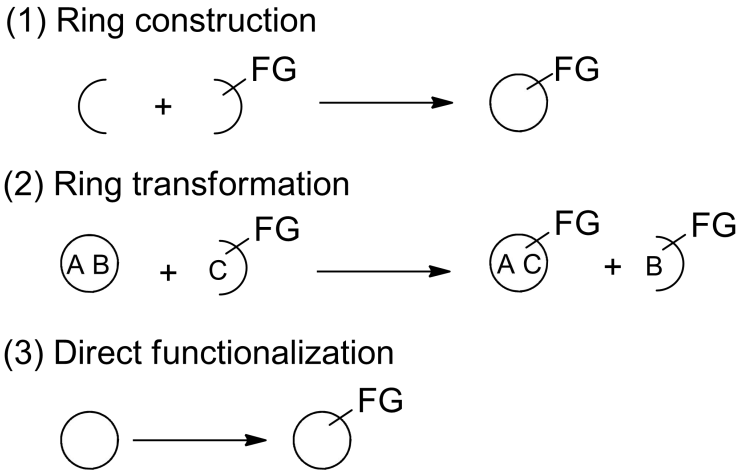


Figure 4. Strategies for synthesizing **MeQone**s

Among these three protocols, direct functionalization of the **MeQone** framework for preparing newly and diversely functionalized **MeQone**s is the most efficient approach from a practical viewpoint, as it requires only simple experimental manipulations. However, only a few methods for direct functionalization of the **MeQone** framework are currently available because of the inertness caused by the aromaticity from the betaine resonance structure (**Figure 5**).[13]

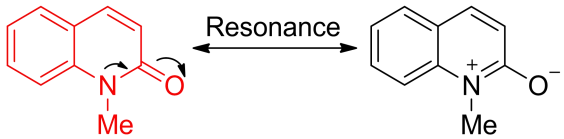
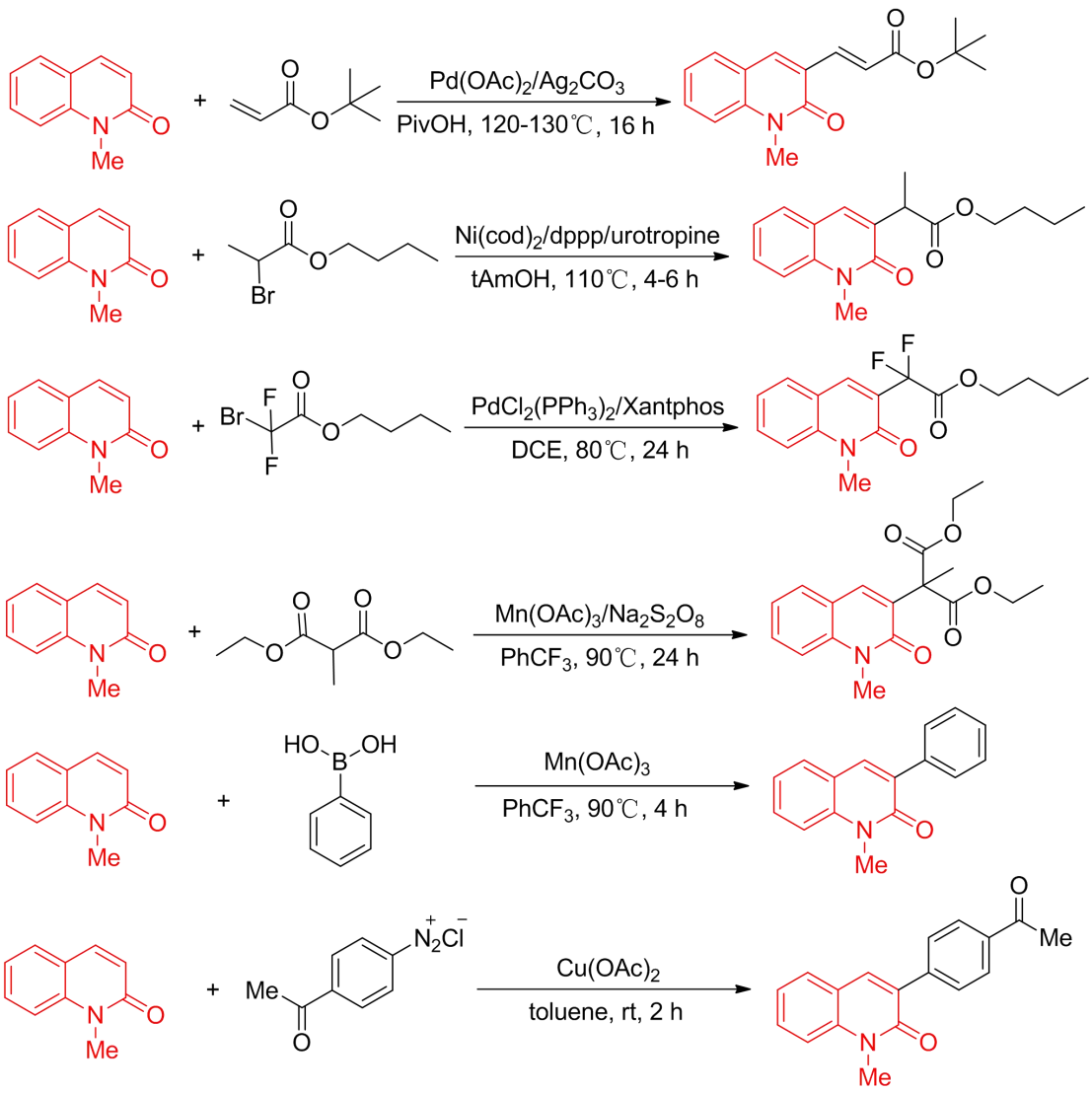


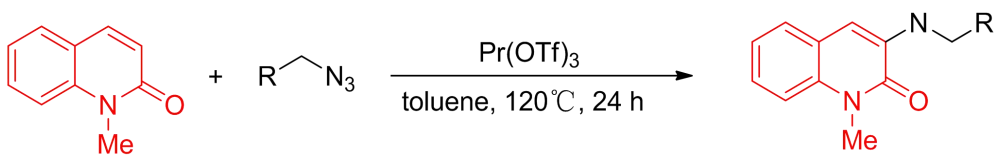
Figure 5. Resonance structure of **MeQone**

To the best of our knowledge, the current methods for direct functionalization of the **MeQone** framework are mainly limited to the C-C or C-N bond formation through

transition-metal-catalyzed cross-coupling reaction or C-H activation (Scheme 1 and 2).[14-19] However, most of these methods suffer from some limitations such as the use of potentially poisonous and expensive noble metal together with harsh reaction conditions.

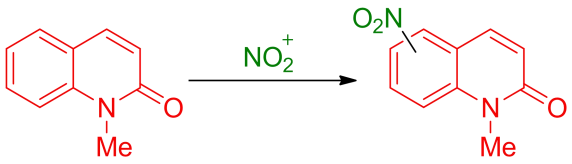


Scheme 1. Transition-metal-catalyzed C-C bond formation



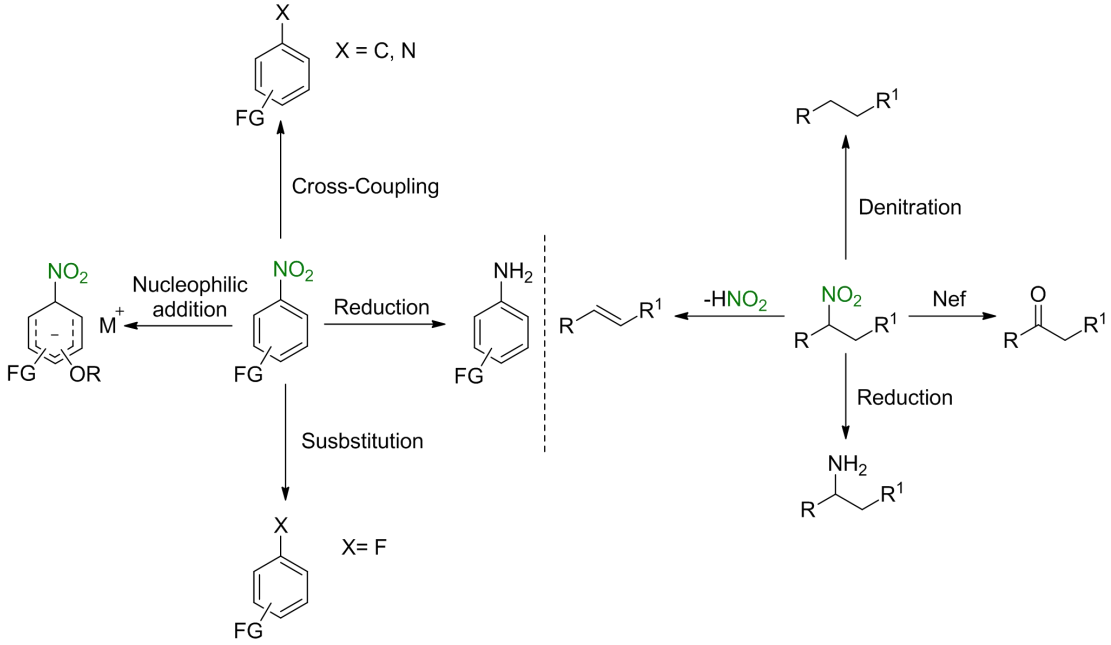
Scheme 2. Transition-metal-catalyzed C-N bond formation

As an alternative, the electrophilic nitration has been proved as a highly efficient manner for directly introducing nitro groups into the **MeQone** framework (Scheme 3).[13]



Scheme 3. Electrophilic nitration of the **MeQone** framework

It is well known that a nitro group is one of the most important functional groups in organic synthesis because of its strongly electron-withdrawing ability to activate the scaffold, facilitating the reaction with nucleophilic reagents.[20] Moreover, a nitro group serves not only as a precursor of versatile functionalities but also as a good leaving group (Scheme 4).[21]



Scheme 4. Properties of a nitro group

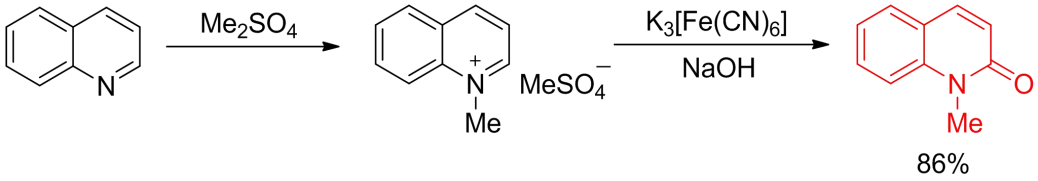
Inspired by these significant properties of the nitro group, the synthetic utility of nitrated **MeQone**s in preparation of unnatural **MeQone** derivatives have been widely investigated. Indeed, the introduction of the nitro groups has been proved to facilitate the straightforward introduction of other functional groups to afford diversely functionalized **MeQone**s.

3. Chemsitry of nitroquinolones

3.1 Preparation of MeQone from quinoline

The most facile and efficient method for the preparation of **MeQone** is methylation of

quinoline, followed by oxidation. As indicated, a *N*-methylquinolinum salt is prepared by methylation of quinoline with dimethyl sulfate, and then is oxidized by potassium ferricyanide under alkaline conditions to form the **MeQone** framework (Scheme 5).[22]



Scheme 5. Preparation of **MeQone** from quinoline

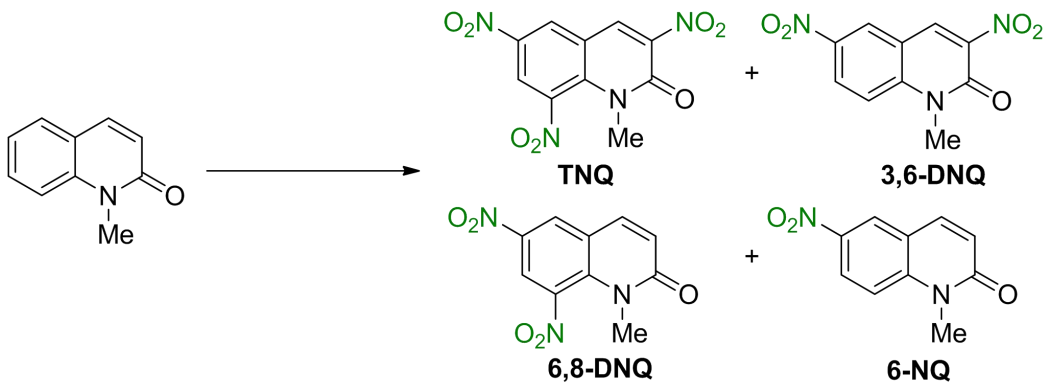
3.2 Nitration of the MeQone framework

3.2.1 Nitration of unsubstituted MeQone

The electrophilic nitration using fuming HNO_3 or a combination of HNO_3 and H_2SO_4 as nitrating agent is the most common and straightforward way to introduce a nitro group into the scaffold.[23]

Treatment of **MeQone** with 15 M nitric acid in sulfuric acid at 50 ℃ for 5 h exclusively introduces the nitro group at the 6-position, affording **6-NQ** in 72% yield (Table 1, entry 1).[24] After increasing the reaction temperature to 70 ℃ and 80 ℃, di-nitrated **MeQone**s, **3,6-DNQ** and **6,8-DNQ**, are main products (entries 2–3). On the other hand, when **MeQone** is nitrated with 15 M nitric acid under higher temperature, 1-methyl-3,6,8-trinitro-2-quinolone (abbreviated as **TNQ**) is the only product (entry 4). The yield of **TNQ** is further increased by replacing 15 M nitric acid with fuming nitric acid (entry 5). On the basis of these results, the nitro group is introduced following the order of 6- > 3- ≈ 8-positions, in which nitration at the 3-position is somewhat easier than at the 8-position.

Table 1. Nitration of **MeQone**



Entry	Nitrating Reagent	Temp./°C	Time/h	Yield/%			
				TNQ	**3,6-DNQ**	**6,8-DNQ**	**6-NQ**
1	HNO_3/H_2SO_4	50	5	0	0	0	72
2	HNO_3/H_2SO_4	70	5	4	26	10	19
3	HNO_3/H_2SO_4	80	5	8	41	29	18
4	HNO_3/H_2SO_4	120	7	63	0	0	0
5	fuming HNO_3	120	7	90	0	0	0

3.2.2 Nitration of substituted MeQones

In addition to the unsubstituted **MeQone**, the nitration of other **MeQone**s with diffrent substitutents on the benzene ring was also investigated by organic chemists.

3.2.2.1 Nitration of 1,6-dimethyl-2-quinolone

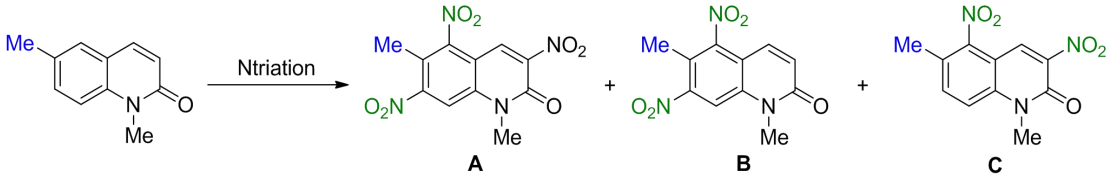
1,6-Dimethyl-2-quinolone (abbreviated as **MeQone-Me^6**) is easily prepared from commercially available 6-methylquinoline through methylation with dimethyl sulfate and oxidation with potassium ferricyanide under alkaline conditions.[25]

In the nitration of **MeQone-Me^6**, the nitro groups are mainly introduced at the 5- and the 7-positions as well as at the 3-position, in which the electron-donating 6-methyl group serves as an *ortho*-directing group (Table 2).[25] Moreover, the steric hindrance of 1-methyl group prevented the nitration at the 8-position.

When the nitration of **MeQone-Me^6** is conducted at 50 ℃, dinitroquinolones **B** and **C** are obtained as main products (Table 2, entry 1). The reaction at higher temperature and for longer time leads to the formation of products **A** and **B** (entries 2 and 3). On the other hand, harsh reaction conditions using fuming HNO_3 at 120 ℃ induce the decomposition of substrate and product, leading to nitrated quinolones with low yields (entry 4). On the basis of these experimental results, the nitro groups are found to be introduced in the order of 5- > 3- ≈

7-positions.

Table 2. Nitration of **MeQone-Me**[6]



Entry	Nitrating Reagent	Temp./°C	Time/h	Yield/%		
				A	**B**	**C**
1	HNO_3/H_2SO_4	50	24	16	21	45
2	HNO_3/H_2SO_4	80	5	11	11	5
3	HNO_3/H_2SO_4	80	24	33	49	0
4	fuming HNO_3	120	7	10	0	0

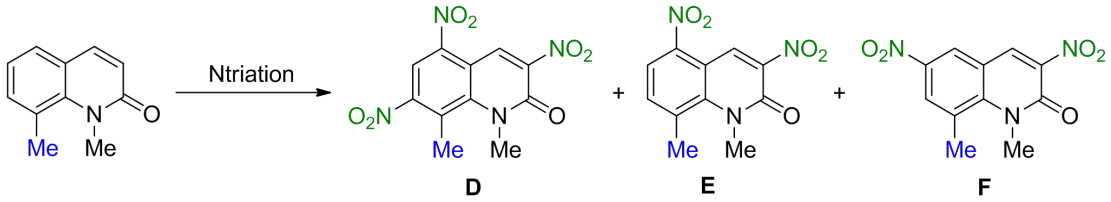
3.2.2.2 Nitration of 1,8-dimethyl-2-quinolone

1,8-Dimethyl-2-quinolone (abbreviated as **MeQone-Me**[8]) is prepared from commercially available 8-methylquinoline through methylation with dimethyl sulfate and oxidation with potassium ferricyanide under alkaline conditions.[25]

Due to the stronger *ortho*, *para*-direction ability of the methyl group than the acylamino group (the ring nitrogen), the nitro groups are mainly introduced at the 5- and 7-positions when **MeQone-Me**[8] is subjected to the nitration conditions (Table 3).[25] Therefore, 1,8-dimethyl-3,5,7-trinitro-2-quinolone **D** and 1,8-dimethyl-3,5-dinitro-2-quinolone **E** are formed as the products (entry 1). 1,8-Dimethyl-3,6-dinitro-2-quinolone **F** is also formed owing to the *para*-directing ability of the acylamino group (entry 1).

While relatively mild conditions afford the 3,5-dinitrated quinolone as the major product, harsh reaction conditions with higher temperature and longer time lead to the formation of 3,5,7-trinitrated quinolone **D** (entries 2–5). On the basis of these experimental results, the nitro groups are found to be introduced in the order of 5- ≈ 3- > 7- > 6-positions.

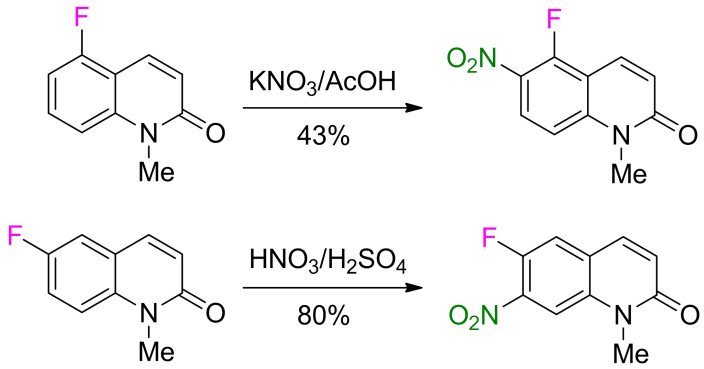
Table 3. Nitration of **MeQone-Me**[8]



Entry	Nitrating Reagent	Temp./°C	Time/h	Yield/%		
				D	**E**	**F**
1	HNO_3/H_2SO_4	50	12	12	47	28
2	HNO_3/H_2SO_4	50	24	27	40	28
3	HNO_3/H_2SO_4	80	5	trace	39	0
4	HNO_3/H_2SO_4	80	24	45	17	0
5	fuming HNO_3	120	24	31	0	0

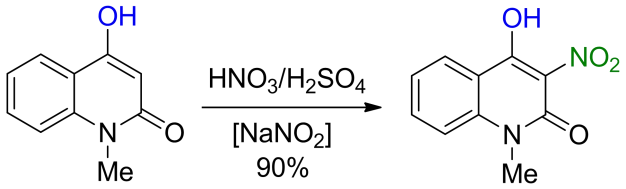
3.2.2.3 Nitration of other substituted MeQones

When 5-fluoro or 6-fluoro-1-methyl-2-quinolone is used as the substrate, nitration takes place at the vicinal position of the fluoro group predominately (Scheme 6).[26-27]



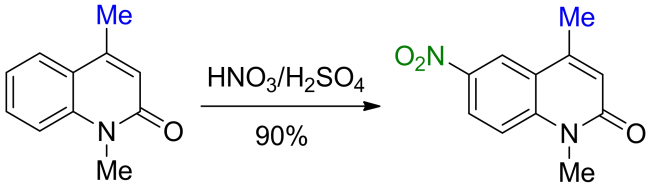
Scheme 6. Nitration of **MeQone-F**[5 or 6]

On the other hand, an electron-donating hydroxy group at the 4-position activates the pyridone moiety, facilitating the nitration at the 3-position (Scheme 7). The resultant vicinal functionalities are useful for the successive construction of a new condensed ring on the pyridone ring, leading to polycyclic compounds.[28-29]



Scheme 7. Nitration of **MeQone-OH**[4]

However, the replacement of a hydroxy group at the 4-position with a methyl group leads to the nitration at the 6-position rather than 3-position.[30] This might be caused by the steric hindrance of the methyl group, preventing the nitration at the adjacent position and facilitating the nitration at the *para*-direction of the electron-donating acylamino group (Scheme 8).



Scheme 8. Nitration of **MeQone-Me**[4]

3.3 Nitro-induced direct functionalization of the MeQone framework

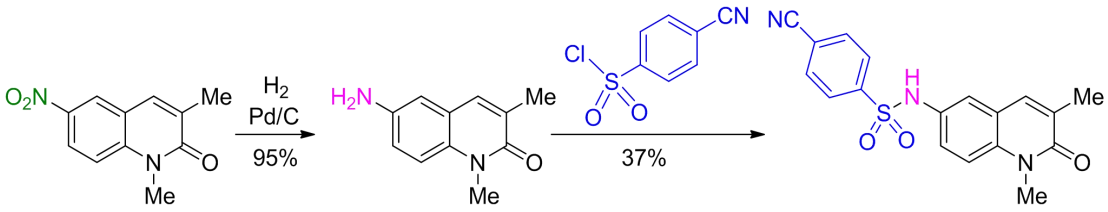
Nitro compounds play an important role in organic synthesis because the facile transformation of the nitro group into other functionalities. Additionally, the strong electron-withdrawing ability of the nitro group can efficiently activate the scaffold, facilitating the reaction with nucleophiles. Furthermore, the nitro group having a good leaving ability can be easily eliminated after nucleophilic additions. According to these properties of nitro group, direct functionalization of the **MeQone** framework using nitroquinolones as useful precursors have been developed.

3.3.1 Chemical transformation of a nitro Group

Nitro compounds are versatile precursors for diverse functionalities.[31] Their conversion into carbonyl compounds by the Nef reaction, conversion into amines by reduction, and conversion into nitrile oxides by dehydration are the most widely used processes in organic synthesis. Nitro compounds are also good precursors for various nitrogen derivatives such as nitriles, oximes, hydroxylamines, and imines. Moreover, nitroarenes can replace haloarenes to undergo the transition-metal-catalyzed cross-coupling reactions to construct C-C and C-N bonds.[32,33] Furthermore, S_NAr fluorination of nitroarenes proceeds to afford fluoroarenes which appear in a variety of pharmaceuticals and agrochemicals.[34] All of these

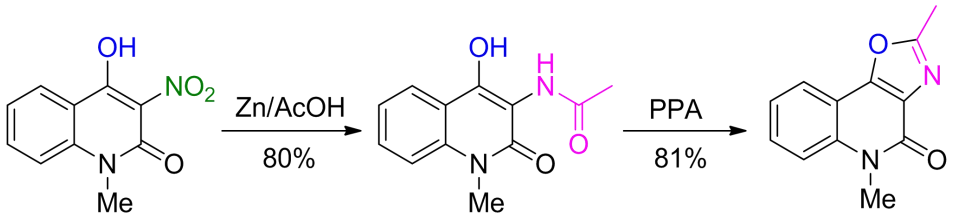
transformations of nitro compounds are well established and are used routinely in organic synthesis.

1,3-Dimethyl-6-nitro-2-quinolone is reduced by palladium-catalyzed hydrogenation followed by sulfoamidation with benzenesulfonyl chloride to prepare functionalized aminoquinolones as anticancer agents (Scheme 9).[35]



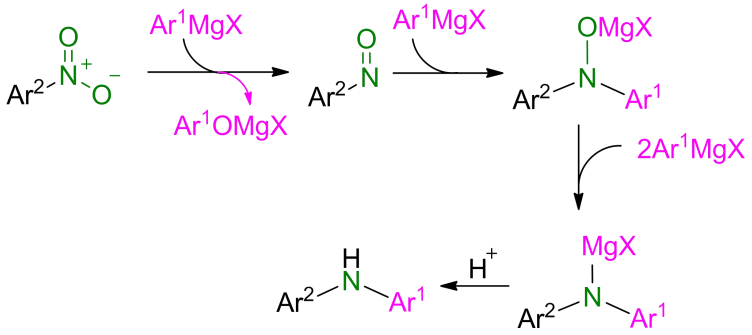
Scheme 9. Transformation of a nitro group

The vicinal functions of 4-hydroxy-3-nitro-2-quinolone are used for construction of a fused ring on the [*c*]-face. The reduction of the nitro group with zinc in acetic acid followed by acylation with acetic anhydride, and the succeeding cyclization successfully affords an isoxazoloquinoline (Scheme 10).[36]



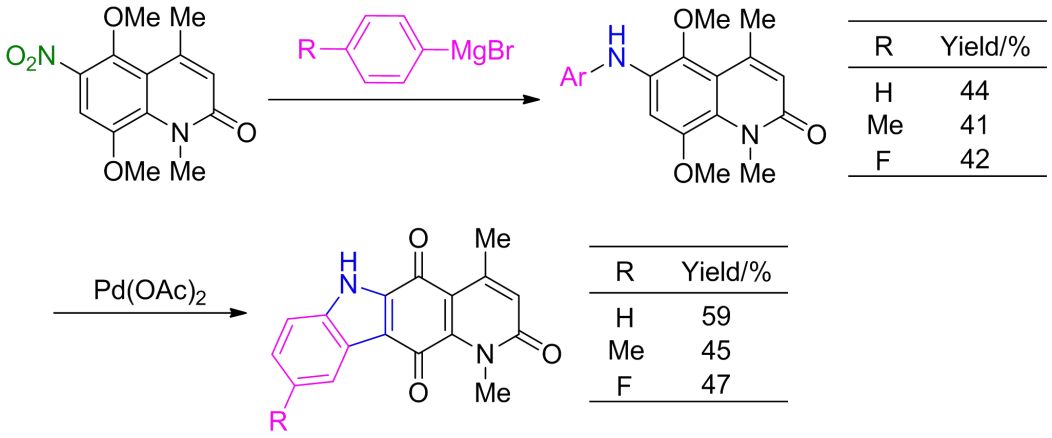
Scheme 10. Construction of the [*c*]-fused isoxazole ring

An efficient method for preparing diarylamines is developed by treating nitroarenes with aryl Grignard reagents (Scheme 11).[13]



Scheme 11. Reaction of nitroarene and aryl Grignard reagent

5,8-Dimethoxy-6-nitroquinolone reacts with aryl Grignard reagents to furnish 6-arylamino derivatives (Scheme 12). The subsequent palladium-catalyzed successive oxidative coupling and demethylation yield pyrido[3,2-*b*]carbazolequinones with potential anti-tumor activity.[37]



R	Yield/%
H	44
Me	41
F	42

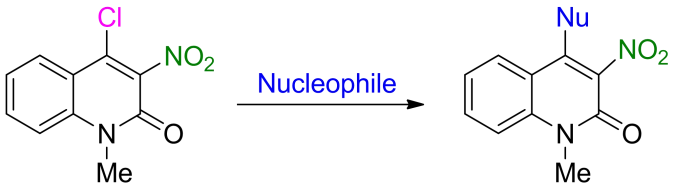
R	Yield/%
H	59
Me	45
F	47

Scheme 12. Arylamination of nitroquinolone followed by cyclization

3.3.2 Activation of the vicinal position by a nitro group

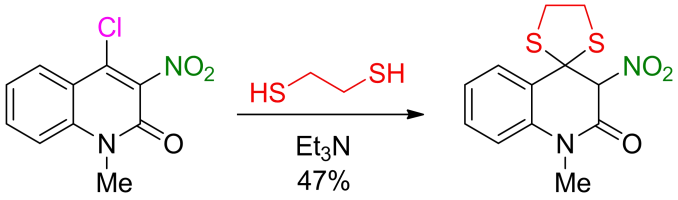
The vicinal position of the nitro group is especially electron-deficient because of its both electron-withdrawing inductive and resonance effects. The nitro group at the 3-position of **MeQone** markedly activates a chloro group at the 4-position, promoting the nucleophilic substitution of the chloro group to give 4-functionalized 3-nitroquinolones (Table 4). By this method, functional groups such as fluoro, alkoxy, amino, azide, alkylthio groups, and malonates are introduced at the 4-position.[38-40]

Table 4. Nucleophilic substitution of 4-chloro-3-nitroquinolone.



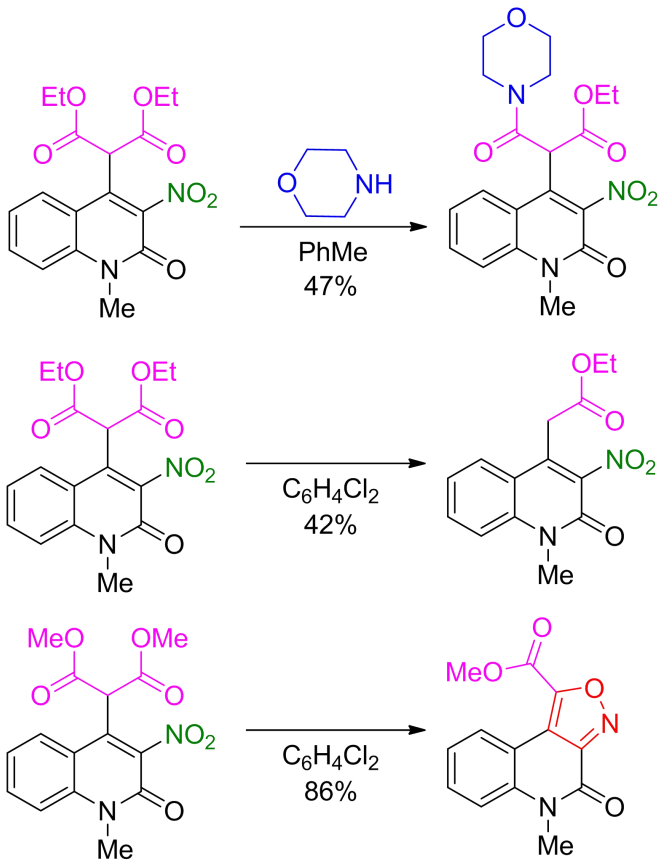
Nucleophile	Nu	Yield/%	Nucleophile	Nu	Yield/%
KF / 18-Crown-6	F	95	$PhNH_2$	PhNH	98
MeONa	MeO	85	$PhCH_2NH_2$	$PhCH_2NH$	94
PhOH / K_2CO_3	PhO	93	piperidine	piperidino	96
EtSH / NEt_3	EtS	95	$CH_2(COOMe)_2$/ K_2CO_3	$CH(COOMe)_2$	95
PhSH + pyridine	PhS	96	$CH_2(COOEt)_2$ / K_2CO_3	$CH(COOEt)_2$	94
NaN_3	N_3	95	$AcCH_2COOEt$ / K_2CO_3	AcCHCOOEt	90
NH_3	NH_2	91	$NCCH_2COOEt$/ K_2CO_3	NCCHCOOEt	95

On the other hand, when 1,2-ethanedithiol is used as the nucleophile in this transformation, substitution followed by intramolecular conjugate addition proceeds to afford spiro thioacetal (Scheme 13).[41]



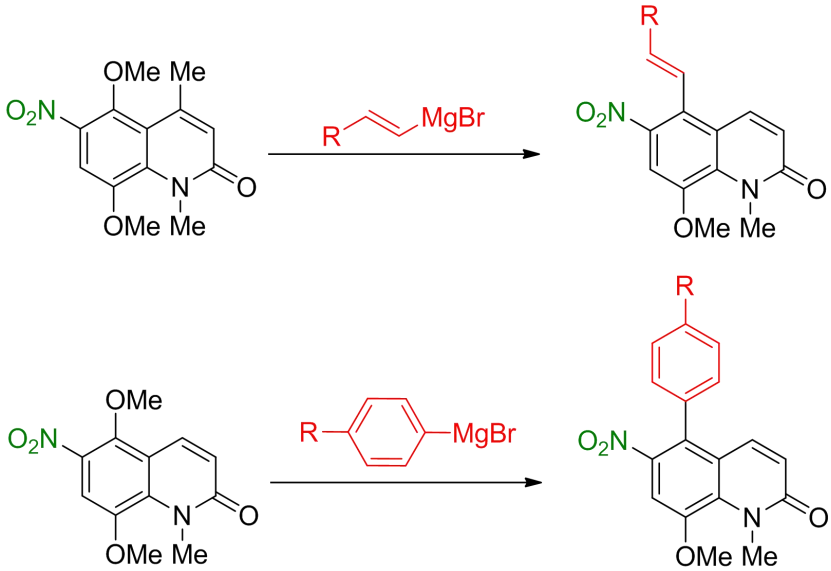
Scheme 13. Tandem addition of ethanedithiol leading to a spiro compound

The malonate moieties at the 4-position of on the **MeQone** ring are activated by the adjacent nitro group, and then an unsymmetrical amide ester is readily formed in the presence of morpholine (Scheme 14).[39] Interestingly, the reactivity of quinolylmalonate varies with the alkoxy group of the ester function. While dealkoxycarbonylation proceeds in the case of diethyl ester, an isoxazole ring is constructed on the [*c*]-face in the case of the dimethyl ester.[40]



Scheme 14. Chemical transformation of malonylquinolones

Furthermore, when 5,8-dimethoxy-6-nitroquinolone is subjected to reaction with vinyl/aryl Grignard reagents, the substitution of the methoxy group with vinyl or aryl group at the 5-position is also facilitated by the vicinal nitro group (Scheme 15).[37,42]



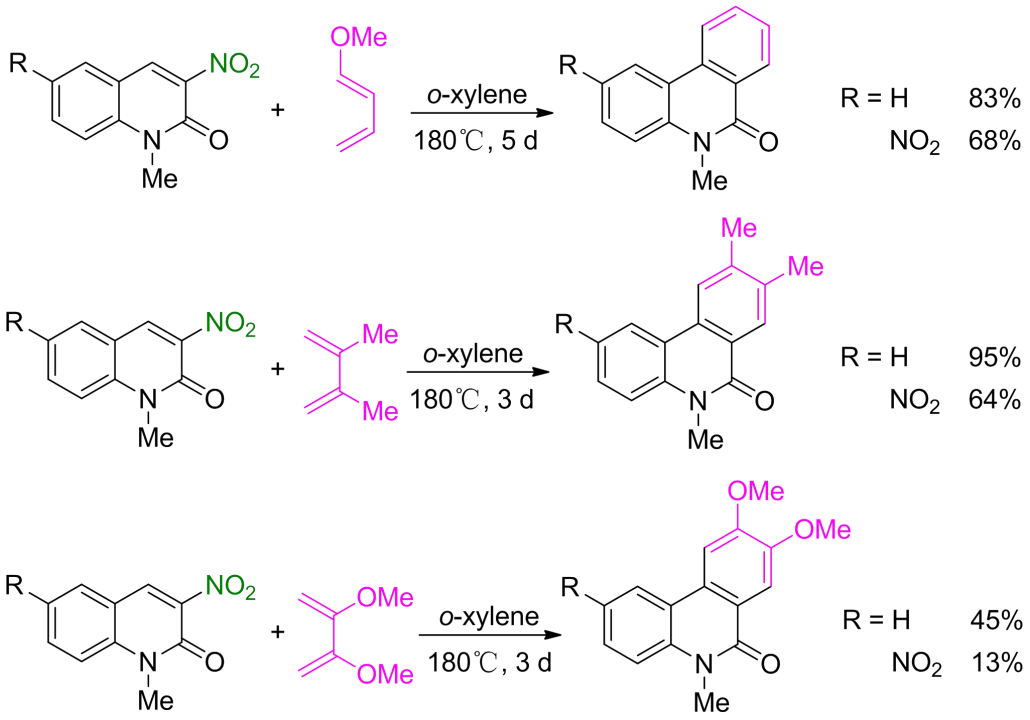
R	Yield/%
H	94
Me	92
Ph	75

R	Yield/%
H	18
Me	13
F	29

Scheme 15. Substitution with Grignard reagents

3.3.3 Cycloaddition of nitroalkene moiety

Diels-Alder reactions at the nitroalkene moiety of 3-nitrated **MeQone**s with electron-rich dienes lead to benzoquinoline derivatives, which undergo aromatization accompanied by elimination of a nitrous acid (Scheme 16). Although this method enables simultaneous C-C bond formation at the 3- and 4-positions of the **MeQone** framework, severe reaction conditions must be employed.[43,44] To the contrary, trinitroquinolone (**TNQ**) quite easily undergoes cycloaddition under mild conditions as detailed in the next section.



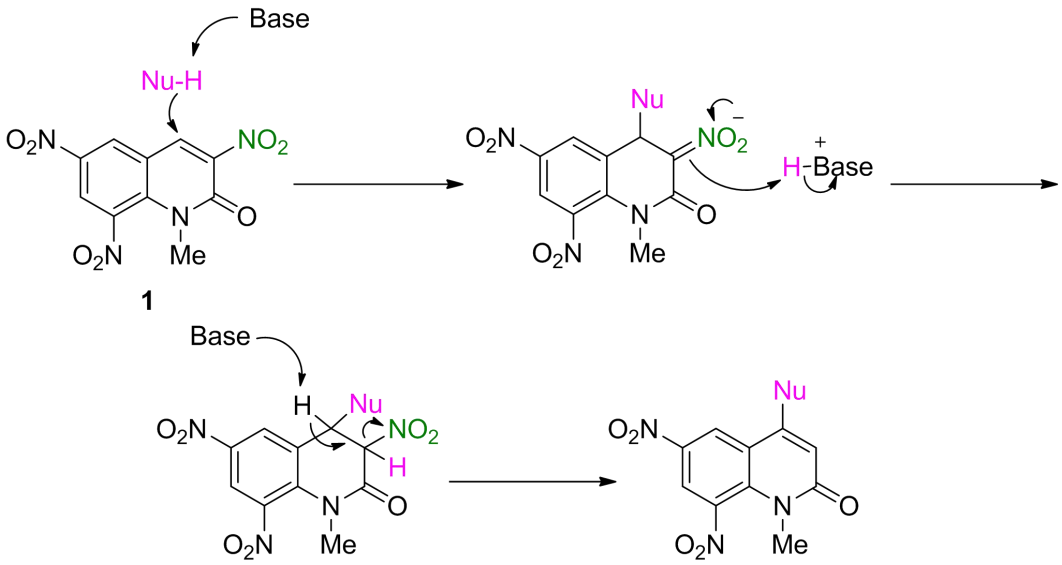
Scheme 16. Diels-Alder reactions of 3-nitroquinolones

3.4 High reactivity of 1-methyl-3,6,8-trinitro-2-quinolone

Interested in the abovementioned results and with the aim of achieving versatile functionalization of the **MeQone** framework, our group have always been focusing on the chemistry of nitrated **MeQone**s, especially highly electron-deficient 1-methyl-3,6,8-trinitro-2-quinolone (abbreviated as **TNQ**). **TNQ** exhibits significantly high reactivity, and is used as a key precursor for versatile functionalized **MeQone** derivatives.[13]

Indeed, **TNQ** reacts with versatile nucleophiles to undergo *cine*-substitution to prepare 4-functionalized 6,8-dinitro-1-methyl-2-quinolones (**4FDNQ**). Initially, the nucleophilic substitution proceeds at the 4-position of **TNQ** to form adduct intermediate, then the proton is transferred from basic group to the 3-position of adduct intermediate affording 3,4-dihydroquinolone. As a result of elimination of the vicinal nitro group, **4FDNQ** is formed

(Scheme 17). This reaction enables the functionalization at the 4-position of **TNQ** with forming a C-C or a C-N bond regioselectively.



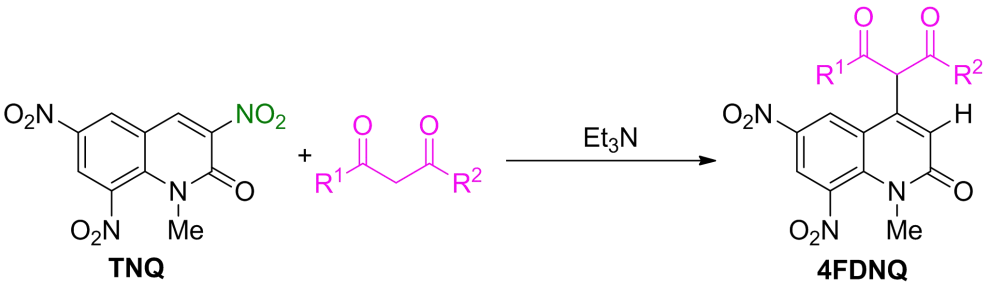
Scheme 17. *cine*-substitution of **TNQ**

3.4.1 *cine*-Substitution of TNQ with carbon nucleophiles

Direct C-C bond formation at the 4-position of the **MeQone** framework is achieved upon treatment of **TNQ** with carbon nucleophiles, including 1,3-dicarbonyl compounds, nitroalkanes, aldehydes/ketones, enamines and phenoxides, leading to versatile skeletons.

When 1,3-dicarbonyl compounds such as β-diketones, β-keto esters and β-diesters easily react with **TNQ** in the presence of triethylamine at room temperature, dicarbonyl methyl groups are smoothly introduced at the 4-position (Table 5).[22]

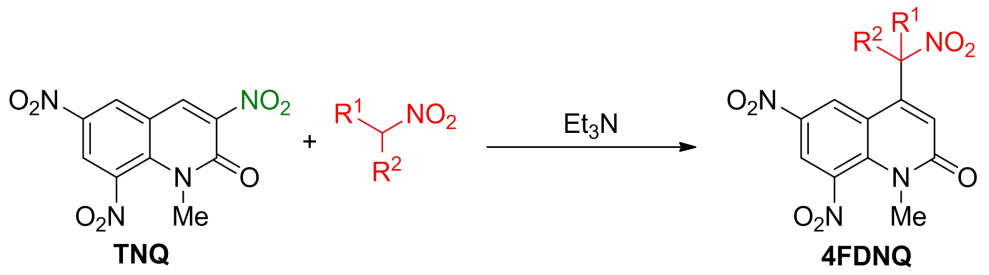
Table 5. Reactions of **TNQ** with 1,3-dicarbonyl compounds



R^1	R^2	Yield/%
CH_2COOEt	OEt	26
	$-(CH_2)_3-$	60
Me	Me	88
Me	OEt	93
OEt	OEt	93

Nitroalkylation of **TNQ** with a nitroalkane as a C-H acid proceeds in the presence of triethylamine. While primary nitroalkanes undergo the *cine*-substitution efficiently, secondary nitroalkanes with steric hindrance are less reactive, requiring longer reaction time (Table 6).[45]

Table 6. Reactions of **TNQ** with nitroalkanes

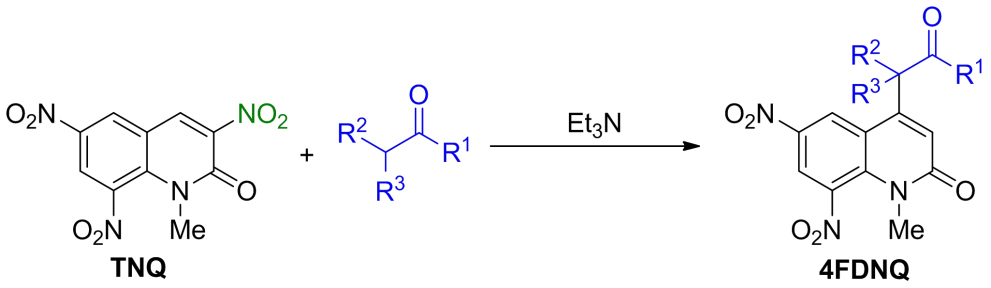


R^1	R^2	Yield/%
Me	H	80
Et	H	98
Me	Me	77

Functionalized ketones such as aliphatic, alicyclic, aromatic, and heteroaromatic ketones also work well as carbon nucleophiles in the *cine*-substitution of **TNQ**, giving acylmethylated product (Table 7).[46] Since the acylmethyl group is expected to serve as a scaffold for further chemical transformations, this method would be useful for construction of a new libraries of

compounds having a **MeQone** framework.

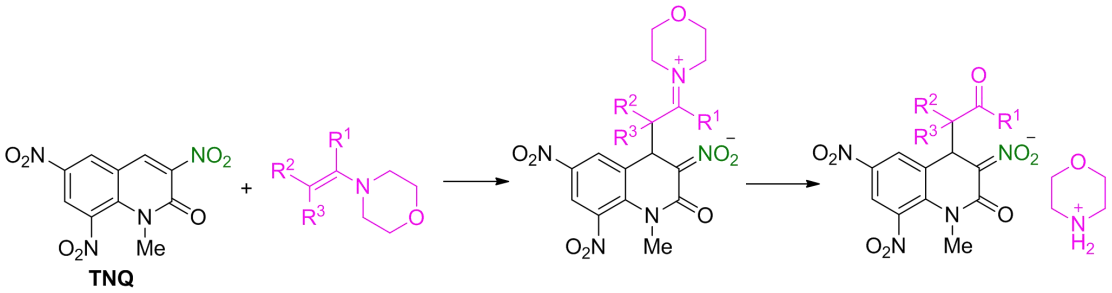
Table 7. Reactions of **TNQ** with aldehydes/ketones



R^1	R^2	R^3	Yield/%
H	Me	Me	41
2-furyl	H	H	45
2-pyridyl	H	H	74
Me	H	H	83
Ph	H	H	83
Et	Me	H	18
Ph	Ph	H	69
Ph	Me	H	77
	$-(CH_2)_4-$	H	82

Treatment of **TNQ** with enamines lead to the formation of morpholinium salts, in which intermediate iminium ions are hydrolyzed and deprotonation at the 3-position by the liberated morpholine (Table 8).[46]

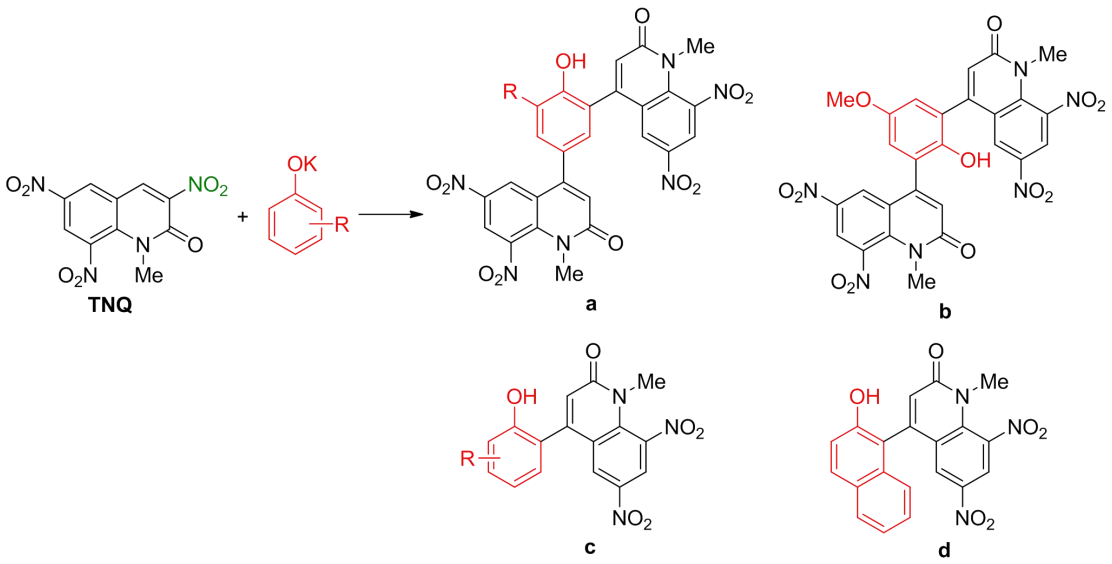
Table 8. Reactions of **TNQ** with enamines



R^1	R^2	R^3	Yield/%
	-$(CH_2)_3$-	H	40
Ph	Me	H	43
Ph	Ph	H	98
H	Me	H	98

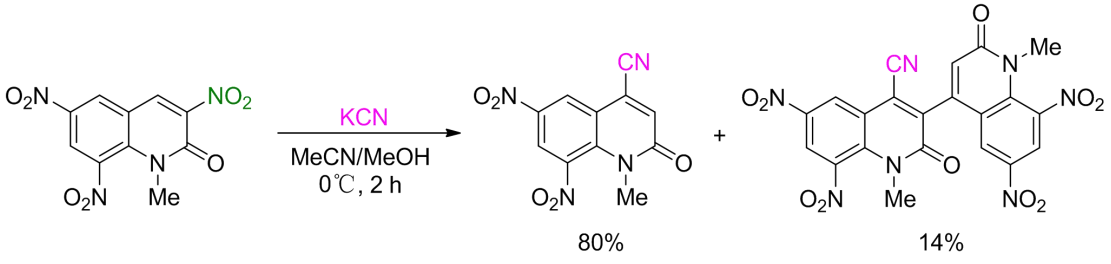
A combination of electrophilic **TNQ** and nucleophilic phenoxide ions results in the direct arylation of the **MeQone** framework (Table 9).[47] While phenol, 2-methylphenol, and 4-methoxyphenol undergo double substitution to afford bis(quinolyl)phenols, bulky or electron-poor phenoxides give monoquinolylphenols as a sole product. As it is quite difficult to straightforwardly introduce an aryl group into the **MeQone** framework, this method is surely regarded as one of the more useful modifications.

Table 9. Reactions of **TNQ** with phenoxides



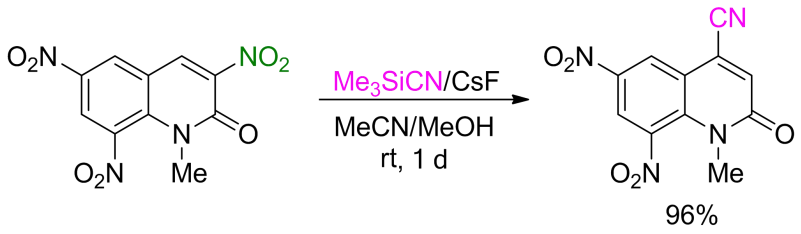
R	Product	Yield/%
H	**a**	51
2-Me	**a**	91
4-MeO	**b**	67
3-Me	**c**	35
4-Me	**c**	82
4-NO_2	**c**	36
O-Phenylene	**d**	75

Nitriles represent an important structural motif in medicinal chemistry due to their versatile biological activities.[48] Besides, nitriles have also been recognized as extremely useful intermediates for the preparation of other useful building blocks.[49] Therefore, numerous efforts have been dedicated to the development of methods for introducing cyano groups into organic molecules.[50] Inspired by the above methods for direct C-C bond formation on the **MeQone** framework, potassium cyanide was used as a carbon nucleophile to react with **TNQ** to prepare 4-cyano-2-quinolone derivative together with a dimeric product (Scheme 17).[25]



Scheme 17. Reaction of **TNQ** with KCN

When trimethylsilyl cyanide/cesium fluoride was employed to replace potassium cyanide, cyanoquinolone was formed as the sole product without any detectable dimer (Scheme 18).[25] While conventional strategies for cyanation of the **MeQone** framework often involve multi-step reactions or severe conditions, the present method enables the cyanation through facile schemes.[51] Thus, this protocol will be used as a powerful tool for constructing a library of versatile **MeQone** derivatives by the further chemical conversion of the cyano and nitro functionalities.[31,49]

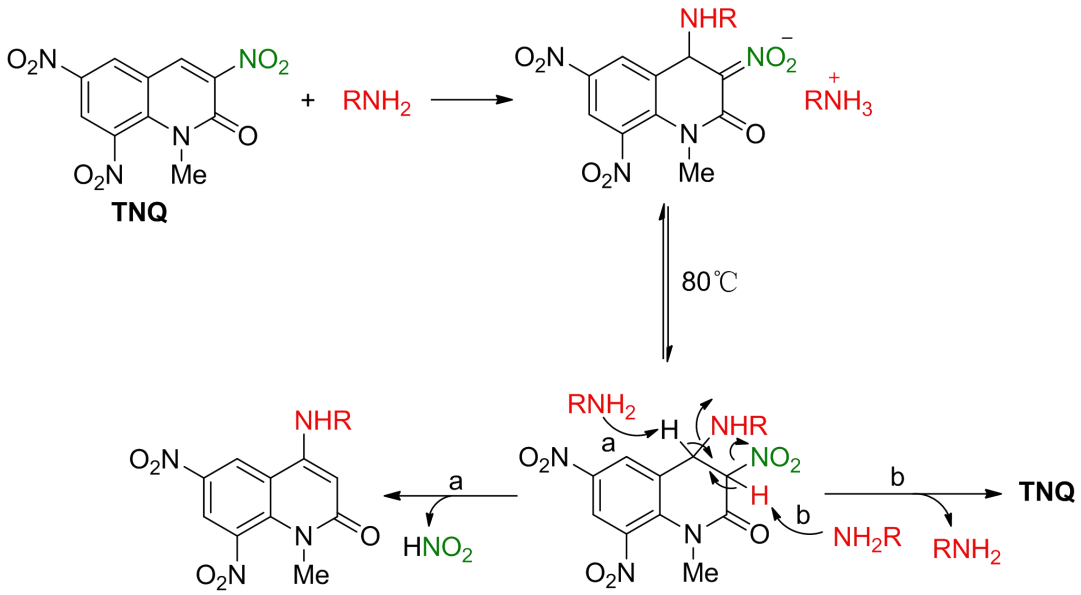


Scheme 18. Reaction of **TNQ** with Me_3SiCN

3.4.2 *cine*-Substitution of TNQ with amines

When amines as the nucleophiles are reacted with **TNQ**, a C-N bond is formed at the 4-position (Table 10).[52] Initially, a Meisenheimer complex is formed by the conjugate addition of primary amines at the 4-position of **TNQ** and the subsequent deprotonation of another molecule of amine. When Meisenheimer complex is heated, a small amount of *cine*-substituted product is formed, together with recovery of a large amount of **TNQ**. In this reaction, 3,4-dihydroquinolone is formed under equilibrium at reflux temperature, from which the former product is afforded by deprotonation at the 4-position via route **a**, and the latter product is a result of deprotonation at the 3-position via route **b**.

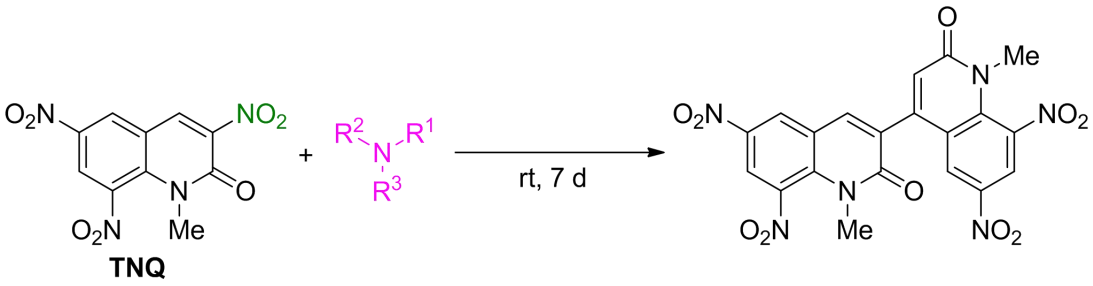
Table 10. Reactions of **TNQ** with primary amines



R	Yield/%	
	ammonium	*cine*-substituted product
Pr	71	36
i-Bu	74	29
s-Bu	56	0
t-Bu	74	0

On the other hand, when **TNQ** is treated with less nucleophilic tertiary amines, dimerization proceeds to afford a dimer connected between the 3- and the 4'-positions (Table 12).[53] The length and the number of alkyl chains of the amine have a significant impact on the reaction rate. While tributylamine causes the reaction faster than tripropylamine and triethylamine, no reaction proceeds in the cases of trimethylamine and tribenzylamine. Therefore, more than two long alkyl chains are necessary for the reaction to occur efficiently.

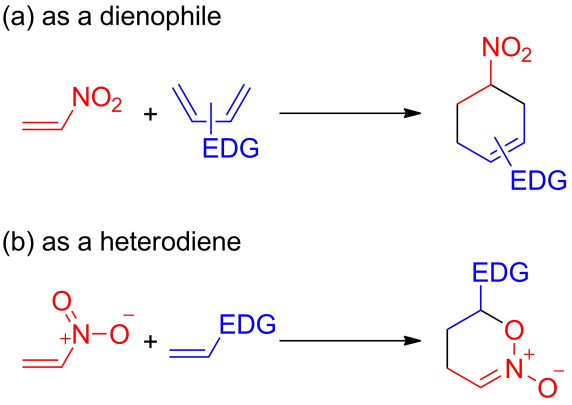
Table 12. Reactions of **TNQ** with tertiary amines



R^1	R^2	R^3	Yield/%
Me	Me	Bu	18
Et	Et	Et	34
Pr	Pr	Pr	76
Bu	Bu	Me	79
Bu	Bu	Bu	93

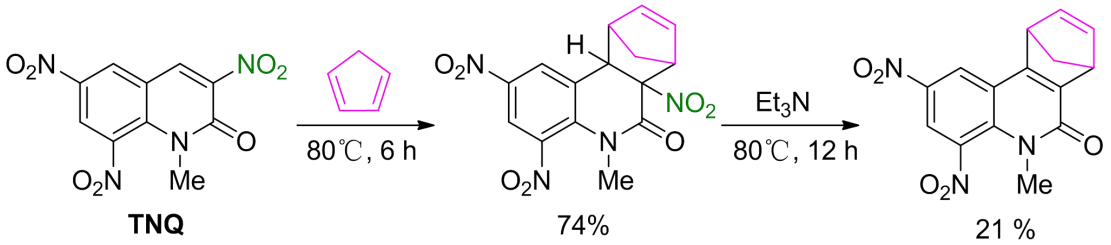
3.4.3 Cycloaddition of TNQ

Nitro compounds have been converted into various cyclic compounds via cycloaddition reactions. In particular, nitroalkenes have proved to be useful in Diels-Alder reactions. Under thermal conditions, they behave as electron-deficient dienophiles and react with dienes to afford 3-nitrocyclohexenes (Scheme 19, a).[54] Nitroalkenes can also act as heterodienes and react with olefins in the presence of Lewis acid to yield alkyl nitronates, which undergo the [3+2] cycloaddition (Scheme 19, b).[55] Thus, nitro compounds play important roles in the chemistry of cycloaddition reactions.



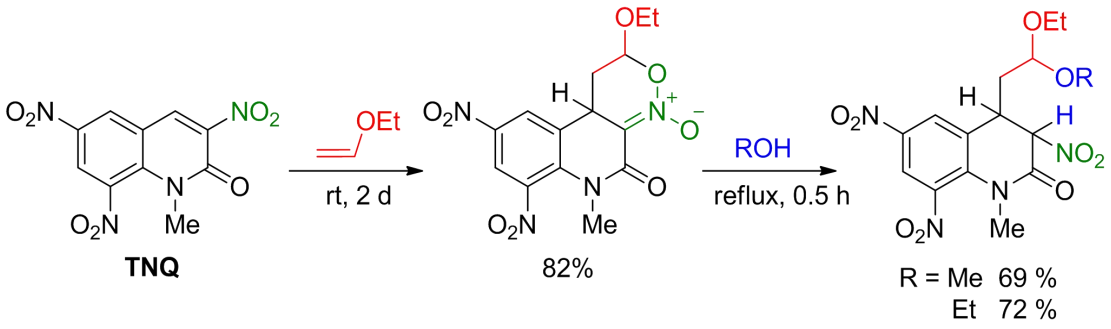
Scheme 19. Dual reactivity of nitroalkene in the cycloaddition

The pyridone moiety of **TNQ** exhibits nitroalkene property rather than aromaticity, which means that the C^3-C^4 moiety could undergo cycloaddition with electron-rich dienes under mild conditions, compared with Diels-Alder reactions of 3-nitroquinlone and 3,6-dinitroquinolone with electron-rich dienes require quite severe conditions.[43,44] Indeed, cycloaddition of **TNQ** with cyclopentadiene proceeds to furnish tetracyclic compounds (Scheme 20).[56] The cycloadduct aromatizes with elimination of nitrous acid in the presence triethylamine.



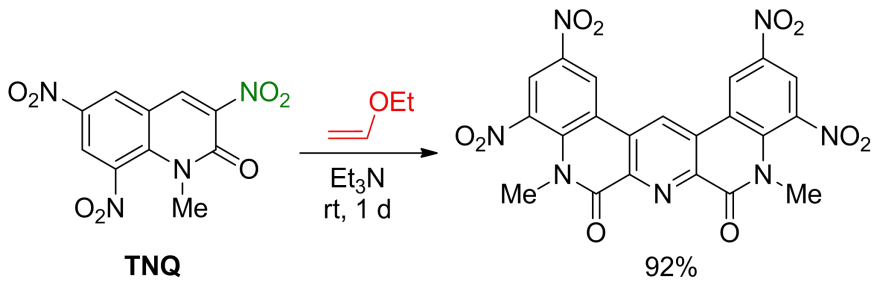
Scheme 20. Diels-Alder reaction of **TNQ** with cyclopentadiene

On the other hand, the nitroalkene moiety of **TNQ** also serves as a heterodiene in the reaction with ethoxyethene to construct a fused oxazine ring. The subsequent treatment of the cycloadduct with alcohol under heating conditions yields an acetal through a ring opening reaction (Scheme 21).[57]



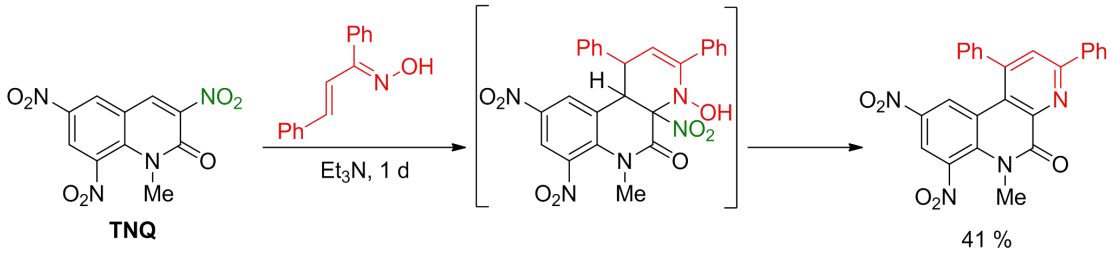
Scheme 21. Cycloaddition of **TNQ** with ethoxyethene in the absence of Et_3N

Interestingly, a quinolino[3,4-*b*][1,9]diazaphenanthrene derivative is formed when the same substrates are treated in the presence of triethylamine (Scheme 22).[57]



Scheme 22. Cycloaddition of **TNQ** with ethoxyethene in the presence of Et_3N

In the present process, the former intermediate oxime behaves as an electron-rich heterodiene and the latter **TNQ** behaves as an electron-poor dienophile. This mechanism is supported by the experimental fact that polycyclic diazaphenanthrene is isolated in a moderate yield as a result of cycloaddition of **TNQ** with α,β-unsaturated oxime as the electron-rich heterodiene (Scheme 23).[57]



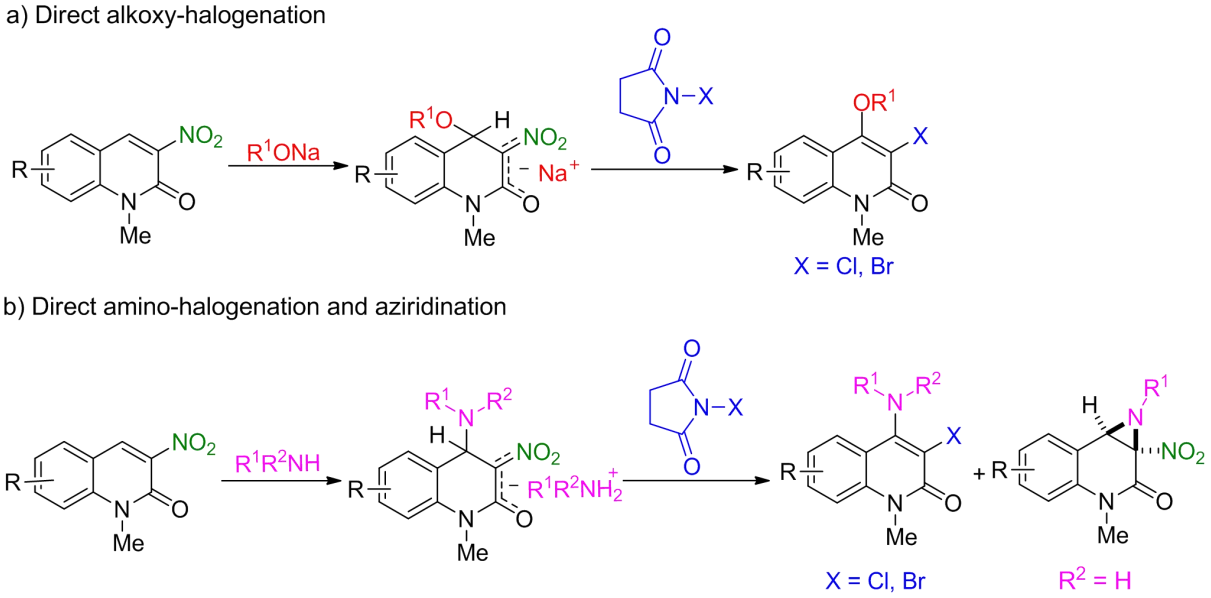
Scheme 23. Cycloaddition of **TNQ** with ethoxyethene in the presence of Et_3N

4. Research purpose

Although **MeQone** derivatives play an important role in both medicinal chemistry and organic synthesis, only few methods for direct functionalization of the **MeQone** framework are currently available because of the inertness caused by the aromaticity. Accordingly, development of a facile method for directly modifying the **MeQone** framework is one of the highly demanded projects.

On the other hand, a variety of unnatural **MeQone** derivatives are easily prepared from nitroquinolones. Especially, **TNQ** is highly reactive in direct C-C or C-N bond formation at the 4- and 3-positions through *cine*-substitution or cycloaddition. However, in these protocols, the substrate is only restricted to the highly electron-deficient quinolone **TNQ**. In order to improve the synthetic utility of this method for directly modifying the **MeQone** framework, novel functionalization protocols using diversely functionalized nitroquinolones are necessary to be explored.

In this thesis, direct 4-alkoxylation and 3-halogenation of the **MeQone** framework is achieved by a sequential treatment of 3-nitrated **MeQone** with sodium alkoxide and *N*-halosuccinimide (Scheme 24, a). Moreover, direct amino-halogenation and aziridination of the **MeQone** framework was also achieved by replacing sodium alkoxides with amines as nucleophiles (Scheme 24, b). In these two methods, based on the employment of alkoxide anions or amines as nucleophiles, the scope of nitroquinolones has been successfully expanded to 3-nitrated **MeQone**s with different substituents on the benzene ring. Therefore, these protocols will be surely useful as powerful tools for constructing a compound library of **MeQone**s with the purpose of finding bioactive compounds.



Scheme 24. Direct and vicinal functionalization of 3-nitrated **MeQone**s

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Part II

1. Property of aziridines

Three-membered aza-heterocyclic compounds, aziridines, represent an important structural motif in a large variety of natural products such as ficellomycin, porfiromycin, mitomycin, maduropeptin, azinomycin, and miraziridine, and they reveal a series of biological activities, such as antitumor, antimicrobial, and antibiotic activity (Figure 1).[1-4] Therefore, isolation, structural characterization, and total synthesis of aziridine-containing natural products have received considerable attention from organic chemists in recent years.[1]

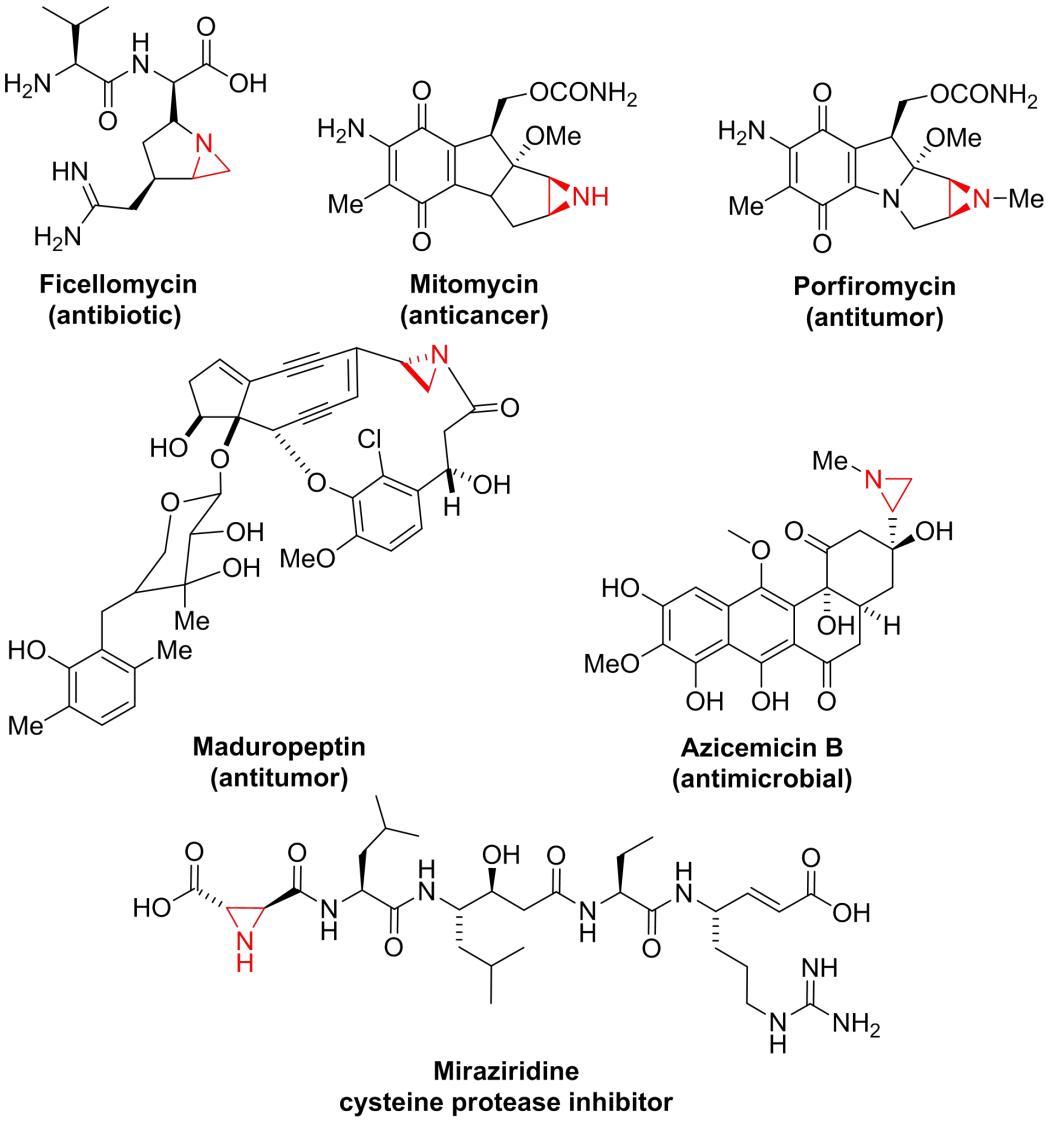


Figure 1. Aziridine rings in bioactive natural products

Additionally, a multitude of unnatural compounds containing aziridine rings have also been synthesized and reported to exhibit varied and extensive biological activities such as

antileishmanial activity,[5] antibacterial activity,[6] estrogenic activity,[7] insecticidal activity,[8] and antitumor activity.[9]

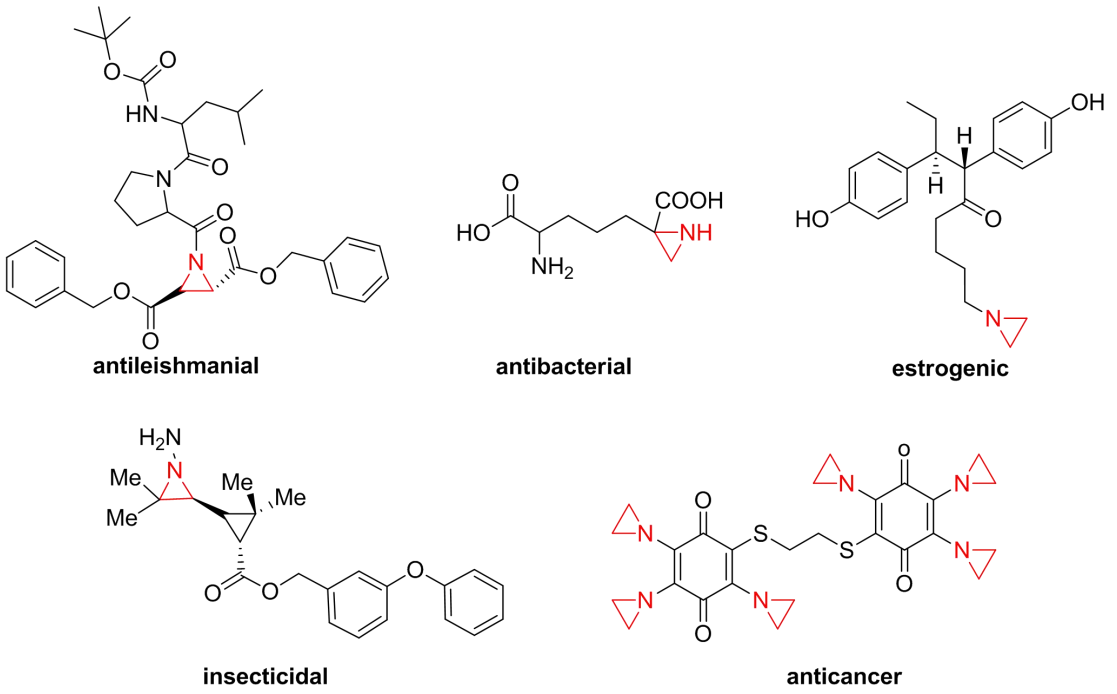
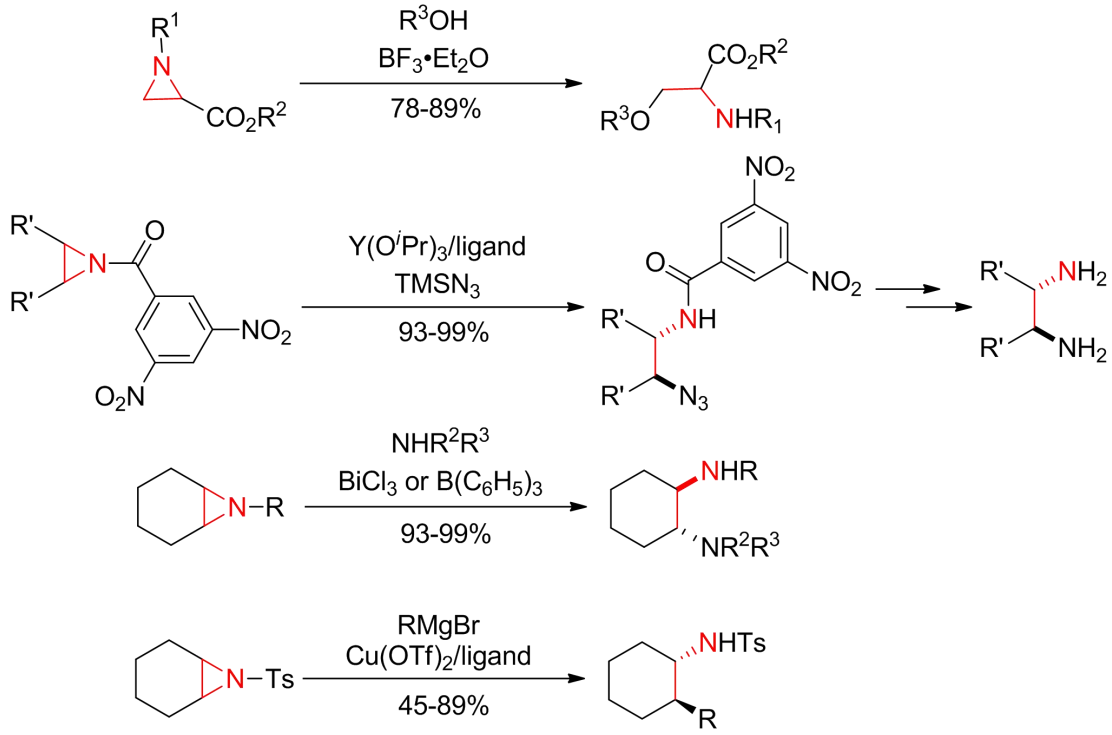


Figure 2. Examples of synthetic bioactive aziridines

Functionalized aziridines are not only biologically interesting components but also serve as versatile building blocks for the synthesis of other nitrogen-containing compounds.[1,10] The instability of aziridines is attributable to the combined effects of bond shortening and angle compression, and the reactivity is associated with the presence of the highly electronegative nitrogen atom possessing basicity and nucleophilicity.[11] Moreover, the exocyclic *N*-substituents also have an important impact on the property and reactivity of the aziridine ring.[11]

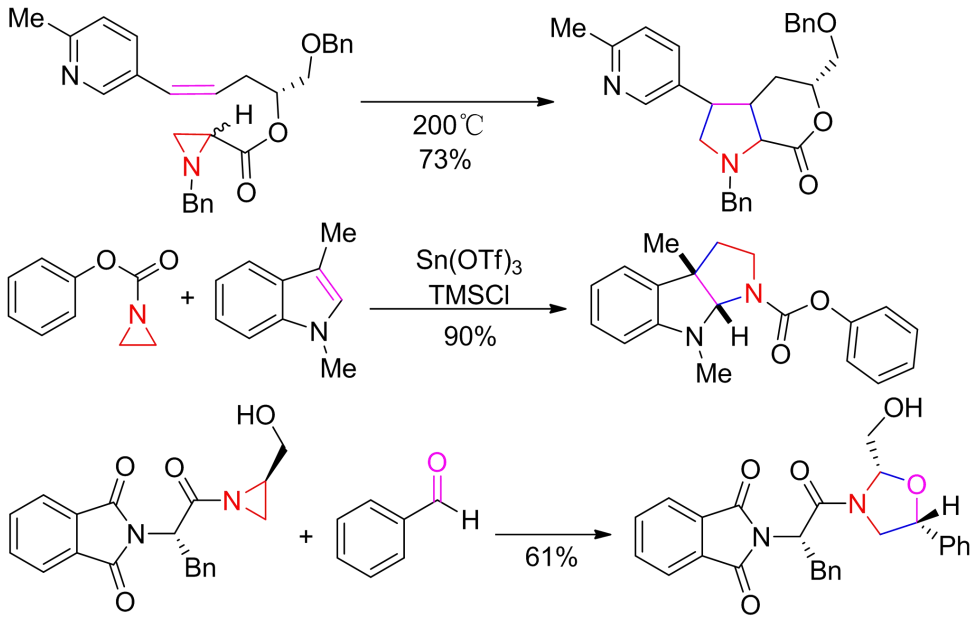
Since aziridines are the nitrogen analogues of epoxides, they also display similar electrophilic reactivity.[11] As a result of ring strain, aziridines undergo various nucleophilic ring opening reactions with various nucleophiles to yield nitrogen-containing compounds such as substituted amines, diamines, amino alcohols and amino acids (Scheme 1).[12-15]



Scheme 1. Ring opening of aziridines with nucleophiles

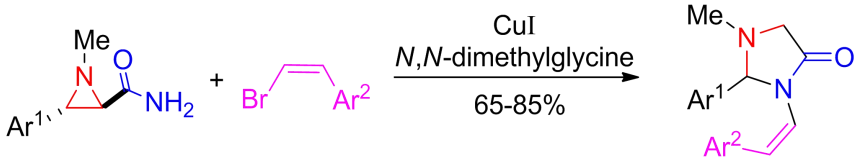
Nitrogen-containing heterocycles present as an important motif in both medicinal chemistry and organic synthesis.[16-17] During the last decades, a number of studies have been devoted to the synthesis of a large variety of aza-heterocycles with highly structural diversity and complexity.[18] Among the several strategies available, cycloaddition is one of the most efficient approaches since multiple bonds can be created in one step with high efficiency, site- or stereoselectivity, and atom economy.[19] 1,3-Dipolar cycloaddition has been disclosed as a prevalent method for the construction of heterocyclic five-membered rings in organic synthesis.[19c,20]

Aziridines are the one of the most widely used synthetic precursors for 1,3-dipoles through C-C or C-N bond-breaking.[21] Therefore, functionalized aziridines undergo [3+2] cycloaddition with various dipolarophiles, such as alkenes, alkynes, and aldehydes to afford five-membered aza-heterocycles (Scheme 2).[21]

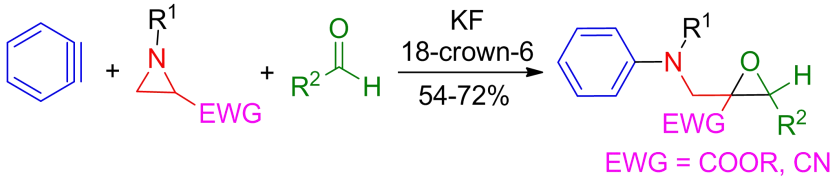


Scheme 2. Aziridines in 1,3-dipolar cycloaddition

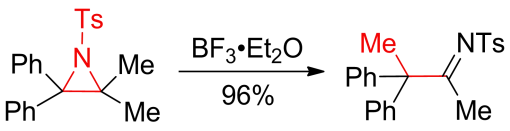
Furthermore, a substantial number of functionalized aziridines can be also transformed into valuable compounds through ring expansion reactions (Scheme 3),[22] multi-component coupling reactions (Scheme 4),[23] and rearrangement (Scheme 5).[24]



Scheme 3. Ring expansion reaction of aziridines

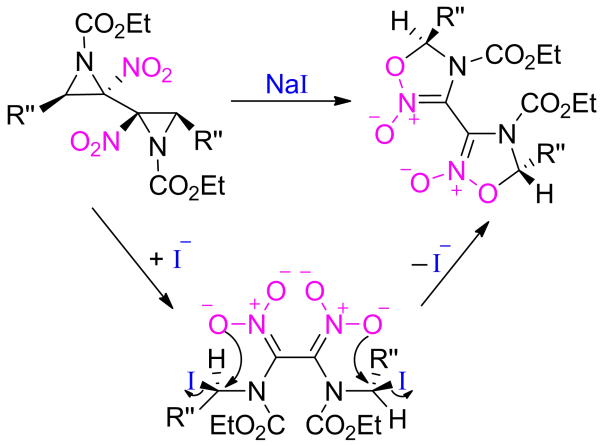


Scheme 4. Three-component coupling involving aziridines



Scheme 5. Rearrangement of aziridines

Among the functionalized aziridines, *C*-nitroaziridines play an important role in chemical transformations because of the strongly electron-withdrawing ability of the nitro group. Treatment of 2,2'-dinitro-2,2'-diaziridines with sodium iodide affords 3,3'-bi(1,2,4-oxadiazole) through C-C bond cleavage (Scheme 6).[25] This kind of ring opening can occur because of the driving effect of the nitro group which is able to delocalize the nagative charge in the intermediate anion.



Scheme 6. Nitro group driven ring enlargement of aziridine ring

In addition, a nitro group is a versatile precursor for diverse functionalities, providing possiblity of *C*-nitroaziridines for further transfomation.[26] Hence, the development of facile methods for the preparation of *C*-nitroaziridines and efficient transformations of *C*-nitroaziridines into other useful compounds is of great interest.

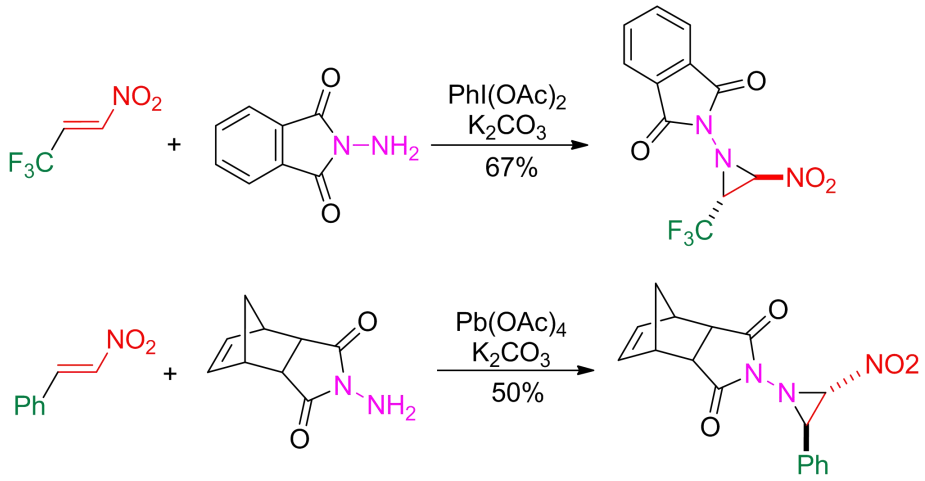
2. Synthesis of *C*-nitroaziridines

Direct aziridination of nitroalkenes is a powerful tool to introduce a nitrogen functionality onto hydrocarbon scaffolds, leading to the formation of *C*-nitroaziridine rings. Thus, direct aziridination of nitroalkenes for synthesizing diversely structural *C*-nitroaziridines has captured considerable attention in modern organic synthesis.

2.1 Synthesis of *N*-Imido-*C*-nitroaziridines

N-Amino aziridines can be found in a variety of biologically active compounds.[8] Moreover, *N*-aminoaziridines serve as synthetic precursors of α- and β-hydrazino acids.[27,28] They also can be regarded as constrained analogues of those hydrazino acids, providing a growing interest in the preparation of peptidomimetics with particular structural and biological properties such as antibiotic activity[29] and inhibition of the human leukocyte elastate.[30]

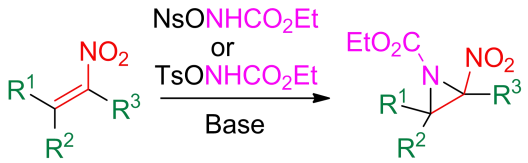
Treatment of nitroalkenes with *N*-aminoimides in the presence of an oxidant affords *N*-imido-*C*-nitroaziridines through the oxidative addition (Scheme 7).[31,32]



Scheme 7. Synthesis of *N*-imido-*C*-nitroaziridines through oxidative addition

2.2 Synthesis of *N*-alkoxycarbonyl-*C*-nitroaziridines

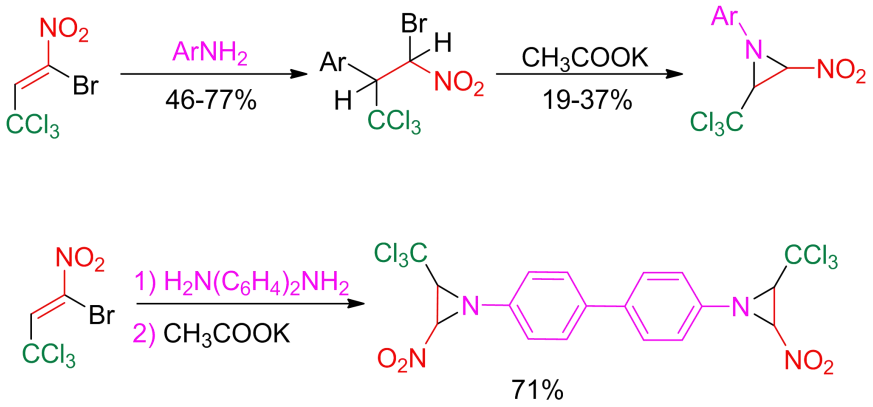
Electron-deficient nitroalkenes undergo aza-MIRC (Michael Initiated Ring Closure) reactions with $NsONHCO_2Et$ or $TsONHCO_2Et$ in the presence of a base, giving an access to *N*-alkoxycarbonyl-*C*-nitroaziridines (Scheme 8).[33]



Scheme 8. Aziridination of nitroalkenes with $NsONHCO_2Et$ or $TsONHCO_2Et$

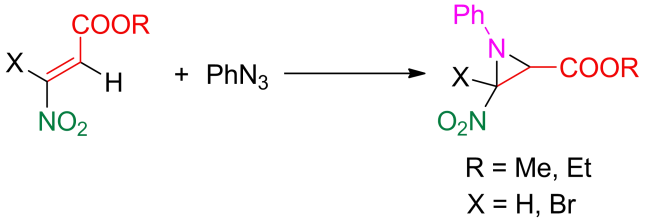
2.3 Synthesis of *N*-aryl-*C*-nitroaziridines

Halonitroalkenes containing highly electrophilic C=C bond are widely used as reactive synthons for furnishing various types of heterocycles.[34] A two-step method was developed for the synthesis of *N*-arylated aziridines invovling the nucleophilic addition of anilines to highly electron-deficient 1-bromo-3,3,3-trichloro-1-nitropropene and base-promoted dehydrobromination of the resulting adducts (Scheme 9).[35] Moreover, the use of aromatic diamines in this transformation successfully affords bis-aziridines.[36]



Scheme 9. Aziridination of nitroalkenes with aromatic amines

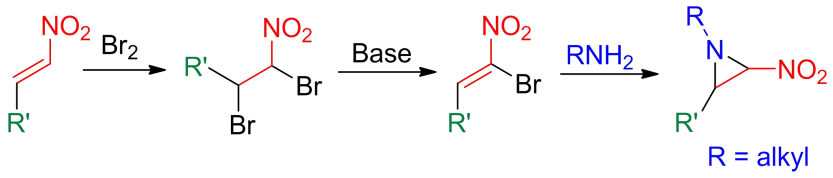
As an alternative, *N*-aryl-*C*-nitroaziridines can also be obtained upon treatment of 3-nitroacrylate or 3-bromo-3-nitroacrylate with phenyl azide which affords a nitrene through the loss of a molecular nitrogen (Scheme 10).[35]



Scheme 10. Aziridination of nitroalkenes with phenyl azide

3. Research purpose

Although many methods for the synthesis of *N*-functionalized *C*-nitroaziridines have been disclosed, there is no report on the synthesis of *N*-alkyl-*C*-nitroaziridines from nitroalkenes through direct aziridination, except for the multistep synthesis via β-bromonitroalkenes; however, the substrate scope is not investigated further (Scheme 11).[38]

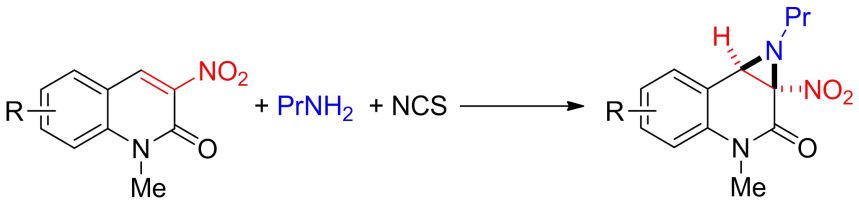


Scheme 11. Synthesis of *N*-alkyl-*C*-nitroaziridines through multistep schemes

Thus, a facile and efficient aziridination of nitroalkenes for the synthesis of *N*-alkylated nitroaziridines is of great interest.

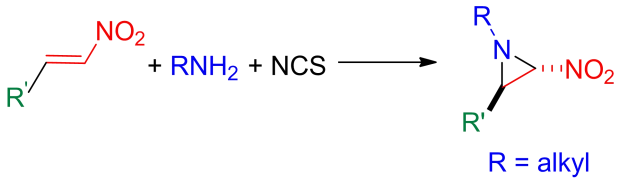
As part of my continuing interest in methods for the direct functionalization of the

2-quinolone framework, we achieved the direct aziridination by sequential treatment of 3-nitro-1-methyl-2-quinolones with an amine and *N*-chlorosuccinimide (NCS), which is described in detail in **Chapter 3** (Scheme 12).



Scheme 12. Direct aziridination of 3-nitro-1-methyl-2-quinolones

Inspired by this protocol, direct aziridination of nitroalkenes for preparing *N*-alkyl-*C*-nitroaziridines is developed by sequential treatment with aliphatic amine and NCS (Scheme 13).



Scheme 13. Synthesis of *N*-alkyl-*C*-nitroaziridines

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Chapter 2. Direct 4-Alkoxylation and 3-Halogenation of the 1-Methyl-2-quinolone Framework

Direct 4-alkoxylation and 3-chlorination of the **MeQone** framework was achieved under mild conditions by a sequential treatment of 3-nitrated **MeQone**s with sodium alkoxide and *N*-chlorosuccinimide. Moreover, a succinimide group could be introduced instead of an alkoxy group at the 4-position, affording a masked form of the 4-amino-3-chloro-2-quinolone derivative.

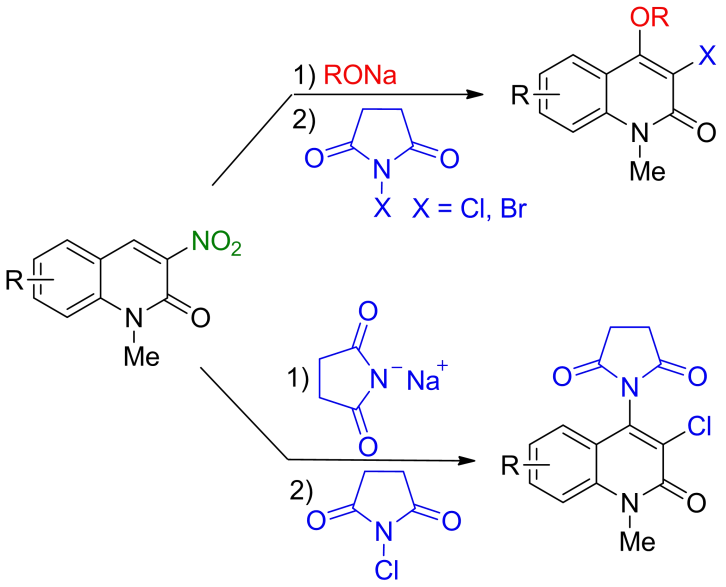


Figure 1. Direct functionalization of the **MeQone** framework

1. 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 because 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 a C–N bond at the 4-position regioselectively or to undergo a cycloaddition reaction readily.[8-11] Inspired by these results, we envisioned that a 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]

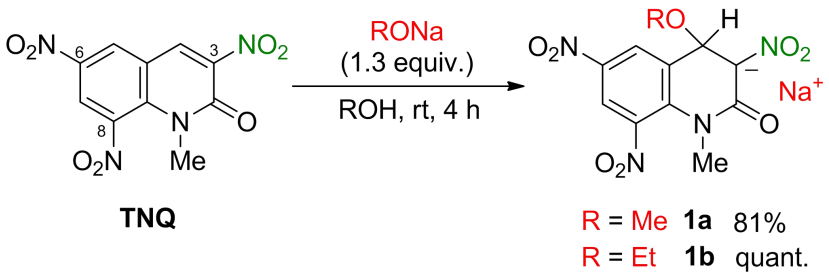
Halogenation at the 3-position of the **MeQone** framework is usually achieved by the treatment of 4-hydroxylated **MeQone**s with halogenating agents such as thionyl chloride,[14] *N*-bromosuccinimide (NBS),[15] bromine,[16] *N*-iodosuccinimide (NIS)[13] and iodine.[17] However, only a few examples 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.

2. Results and Discussion

2.1 Micheal addition of TNQ with sodium alkoxide

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 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 similar formation of the corresponding adducts **1** was confirmed by the ^{1}H NMR

spectrum of the residue after the removal of the solvent.



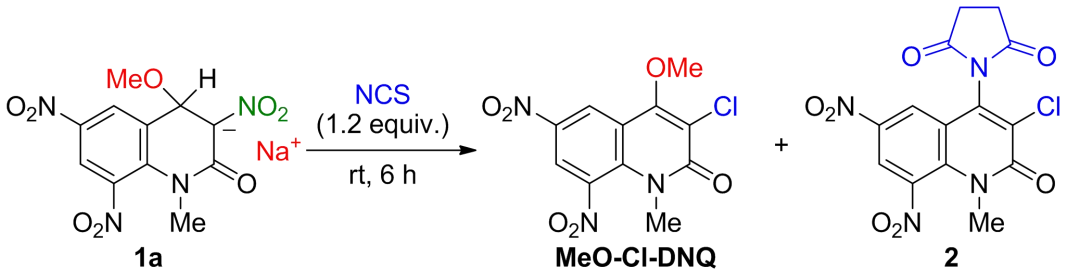
Scheme 1. 4-Alkoxylation of **TNQ**

2.2 Optimization of the chlorination conditions

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).

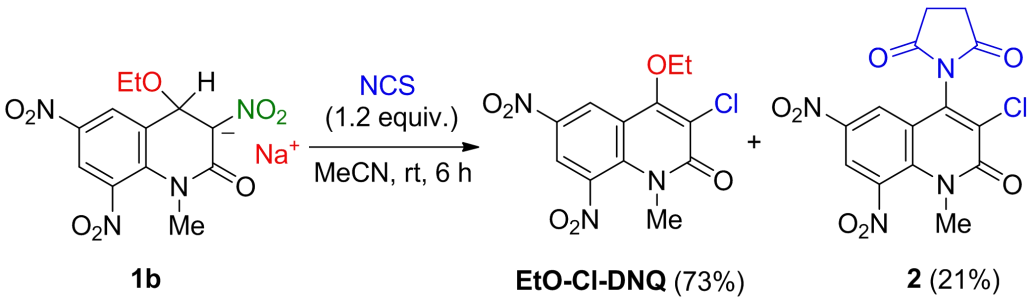
Table 1. Solvent effect on the chlorination and imidation



Entry	Solvent	Yield/%	
		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

2.3 Study on alkoxide scope

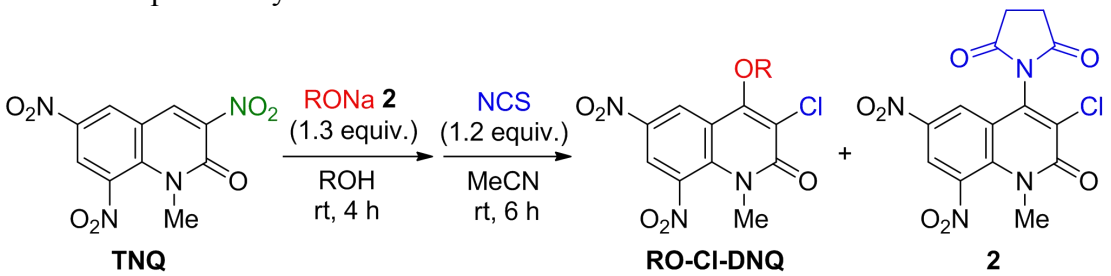
Under these optimized reaction conditions, **EtO-Cl-DNQ** was obtained similarly as a yellow solid in 73% yield along with **2** in 21% yield (Scheme 2).



Scheme 2. 4-Ethoxylation and 3-chlorination of the **MeQone** framework

In the cases of other chloroalkoxylations, 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, facilitating further chemical transformations (entries 5 and 6).

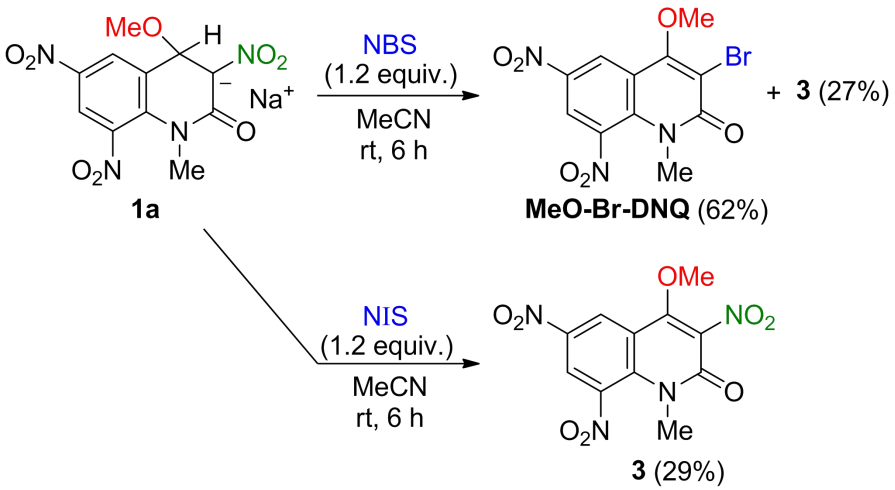
Table 2. One-pot alkoxy-chlorination



Entry	R	Yield/%	
		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

2.4 Scanning of halogenating agents

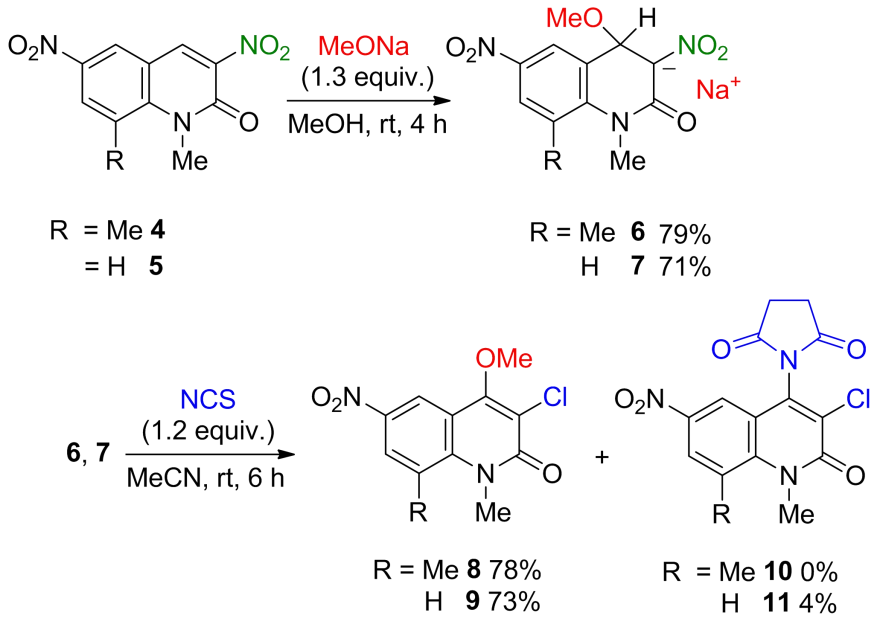
To expand the substrate scope of this protocol, sodium salt **1a** was reacted with other *N*-halosuccinimides. Bromination using NBS afforded the corresponding **MeO-Br-DNQ** in 62% yield (Scheme 3). In this reaction, 4-methoxylated trinitroquinolone **3** was also obtained in 27% yield, probably because 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 3. Reactions of **1a** with other *N*-halosuccinimides

2.5 Scanning of 3-nitrated MeQones

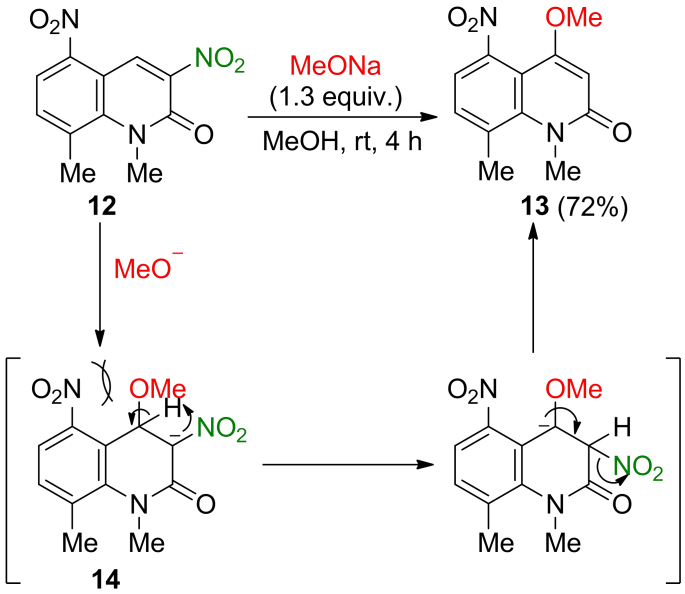
In our previous work, we had clarified the high reactivity of **TNQ** was caused by the steric repulsion between the 1-methyl and 8-nitro groups, distorting the **MeQone** framework to reduce the aromaticity.[9] To the contrary, such steric repulsion was not crucial for this reaction because of the high nucleophilicity of the alkoxide anion. 1,8-Dimethyl-3,6-dinitro-2-quinolone (**4**), 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 a considerable decrease of the yield, respectively (Scheme 4). Subsequent chlorination of **6** and **7** also proceeded upon treatment with NCS leading to **8** and **9** in high yields, respectively.



Scheme 4. Study on scope of 3-nitrated **MeQone**s

2.6 *cine*-Substitution of 1,8-dimethyl-3,5-dinitro-2-quinolone 12

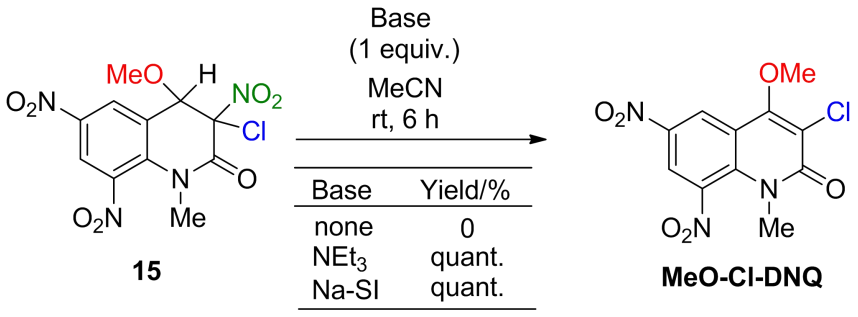
On the other hand, when 1,8-dimethyl-3,5-dinitro-2-quinolone **12** was employed as the substrate, *cine*-substituted product **13** was obtained without any detectable adduct intermediate **14**. In this reaction, addition of a methoxide surely occurred to afford **14**, however, it is not stable because 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 5).



Scheme 5. Reaction of 3,5-dinitroquinolone **12** with sodium methoxide

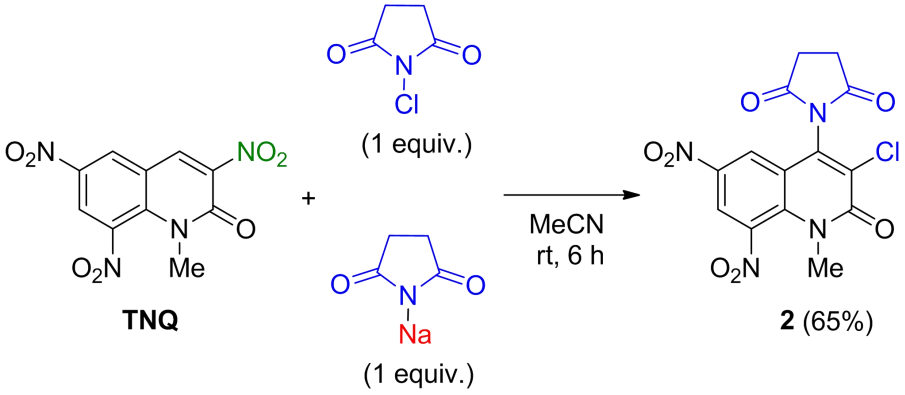
2.7 Control experiments

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 6). 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 6).



Scheme 6. 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 7). Hence, imidation proceeds competitively with the alkoxylation of **TNQ.**



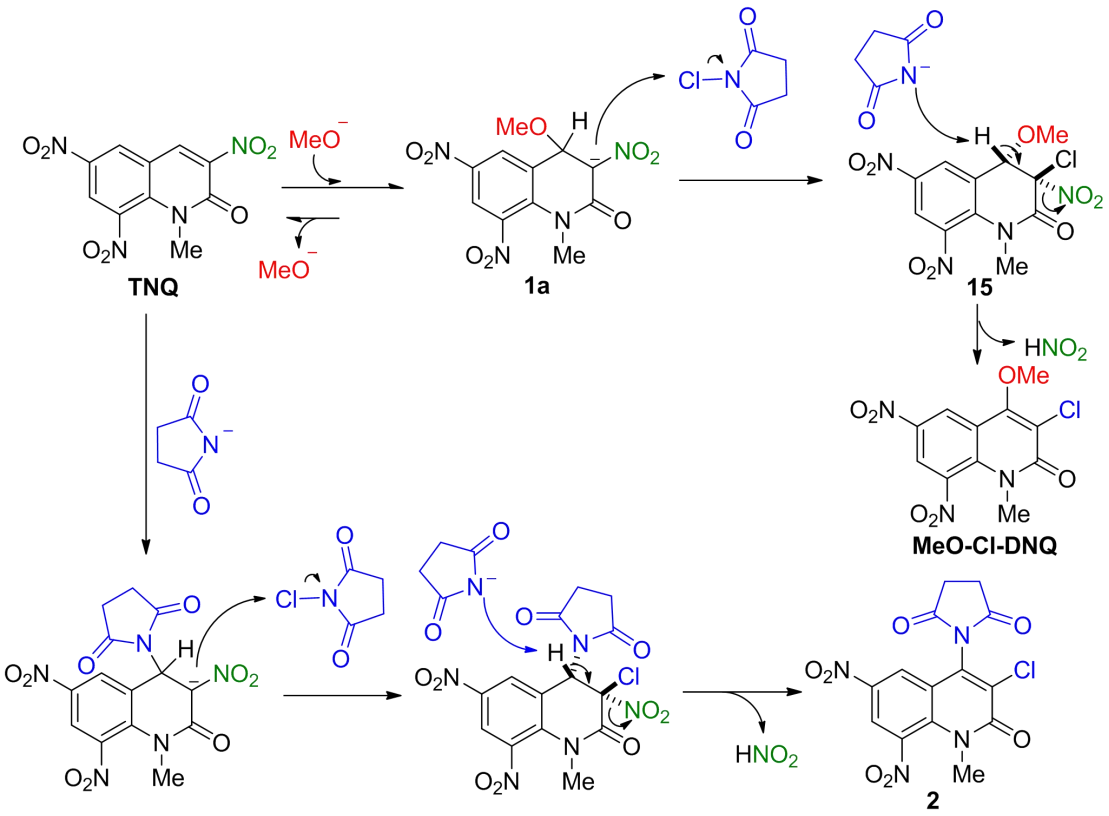
Scheme 7. Chloro-imidation of **TNQ**

2.8 A plausible mechanism for the formation of MeO-Cl-DNQ and 2

Based on the abovementioned results, a plausible mechanism of this transformation is illustrated in Scheme 8. 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**.

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

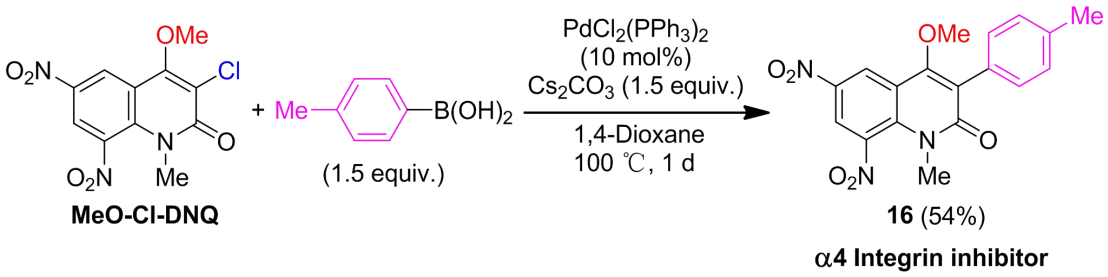
hydrogen chloride in the next rearomatization step because a hydrogen atom and a nitro group are antiperiplanar.[18]



Scheme 8. A plausible mechanism for the formation of **MeO-Cl-DNQ** and **2**

2.9 Transformations of MeO-Cl-DNQ and 2

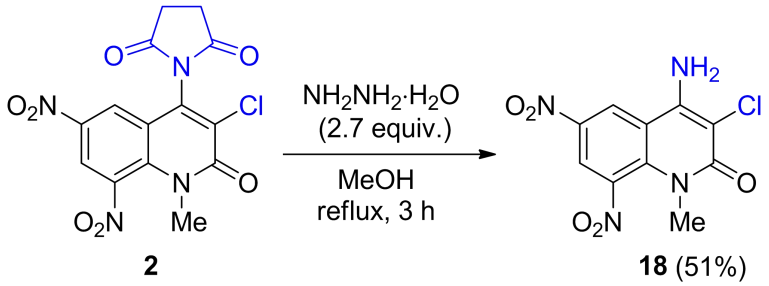
Finally, to illustrate the synthetic potential of this protocol, compound **MeO-Cl-DNQ** was subjected to Suzuki−Miyaura coupling reaction[19] because **MeQone**s possessing an alkoxy group and an aryl group at the vicinal positions serve as α4 integrin inhibitors.[20] When **MeO-Cl-DNQ** was reacted with 4-methylphenylboronic acid in the presence of a palladium catalyst, arylated product **16** was successfully obtained in a moderate yield (Scheme 9).



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

Moreover, the imido-chlorinated product **2** 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 10). Aminated **MeQone**s are usually synthesized by chemical conversion from hydroxy derivatives *via* chloro derivatives.[21] As an alternative approach, a ring is also constructed on an aniline derivative. However, no direct amination method for the **MeQone** framework has been reported, except for our report.[22] Hence, this imidation is a useful method for the direct aminochlorination of the **MeQone** framework.



2 **18** (51%)

Scheme 10. Hydrazinolysis of imidated product **2**

3. Conclusion

I have developed a direct and vicinal functionalization of the **MeQone** framework under mild conditions by the treatment of 3-nitrated **MeQone**s with sodium alkoxides followed by treatment with NCS. This procedure facilitates the regioselective halo-alkoxylation readily with simple experimental manipulations. Moreover, chloro-imidation 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.

4. Experimental section

4.1 General information

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 4600. The gas chromatography mass spectrum was measured on a JEOL JMS-Q1050GC Ultra Quad

GC/MS.

4.2 General procedure for the 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]

4.3 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; 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; HRMS (ESI) Calcd for $C_{12}H_{12}N_4NaO_8$ [$(M+H)^+$]: 363.0547, found 363.0541.

4.4 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; MS (EI): 315 (M+2), 313 (M), 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; HRMS (ESI) Calcd for $C_{12}H_9ClN_3O_6$ [$(M-H)^-$]: 326.0185, found 326.0201.

4.5 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; 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; 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; 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; 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; 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; 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 powder (43 mg, 0.12 mmol, 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; 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 powder (17 mg, 0.05 mmol, 27%); R_f = 0.21 (CH_2Cl_2/hexane = 4/1); mp 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; 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); 13C NMR (DMSO-d_6, 100 MHz) δ = 21.3 (CH3), 35.9 (CH3), 53.8 (CH3), 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. 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. Satisfactory analytical data were not given despite several attempts.

3-Chloro-1,8-dimethyl-4-methoxy-6-nitroquinolin-2(1*H*)-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; 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(1*H*)-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; HRMS (ESI) Calcd for $C_{11}H_{10}ClN_2O_4$ [$(M+H)^+$]: 269.0324, found 269.0322.

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; HRMS (ESI) Calcd for $C_{14}H_{11}ClN_3O_5$ [$(M+H)^+$]: 336.0382, found 336.0387.

4.6 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 = (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; 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; HRMS (ESI) Calcd for $C_{11}H_{10}ClN_4O_8$ [$(M+H)^+$]: 361.0182, found 361.0186.

4.7 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; HRMS (ESI) Calcd for $C_{14}H_{10}ClN_4O_7$ [$(M+H)^+$]: 381.0233, found 381.0238.

4.8 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; HRMS (ESI) Calcd for $C_{10}H_8ClN_4O_5$ [$(M+H)^+$]: 299.0178, found 299.0172.

4.9 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; HRMS (ESI) Calcd for $C_{18}H_{16}N_3O_6$ [$(M+H)^+$]: 370.1034, found 370.1037.

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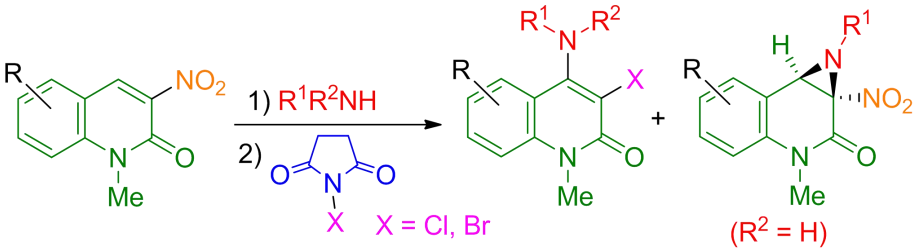
Chapter 3. Direct Amino-halogenation and Aziridination of the 1-Methyl-2-quinolone Framework

The sequential treatment of 3-nitro-2-quinolones with amines and *N*-halosuccinimides under mild conditions facilitated the direct amino-halogenation and aziridination at the 4- and 3-positions of the 2-quinolone framework. The selectivity of the functionalization was influenced by the electronic properties of the substituents on the benzene moiety of the nitroquinolone. The electron-withdrawing nitro group promoted the amino-halogenation, and replacement of the nitro group with a halogen or hydrogen markedly increased the selectivity of the aziridination. Moreover, a succinimide group instead of an alkylamino group was introduced at the 4-position, affording the masked form of the 4-amino-3-chloro-2-quinolone derivative. Furthermore, the prepared bis-functionalized quinolones were subjected to Suzuki-Miyaura coupling reaction, ring opening, and hydrazinolysis to afford differently functionalized quinolones.



1. Introduction

4-Aminated 2-quinolones have garnered considerable attention owing to their various applications in medicinal chemistry. For example, 4-aminated 6-thiazolyl-2-quinolones are potent CD38 inhibitors for the treatment of metabolic syndrome (Figure 1, a).[1] Recently, the design, synthesis, and evaluation of new acetylcholinesterase inhibitors combining 4-amino-2-quinolone rings and benzylpiperidino groups joined by a carboxamide fragment was described (Figure 1, b).[2] In addition, 4-amino-2-quinolones possessing benzimidazole rings at the 3-position have been found to serve as a novel class of receptor tyrosine kinase inhibitors for the treatment of cancer (Figure 1, c).[3] Furthermore, 4-aminated 3-phenyl-2-quinolones have been reported to be *N*-methyl-D-aspartate receptor antagonists with anticonvulsant activities (Figure 1, d).[4]

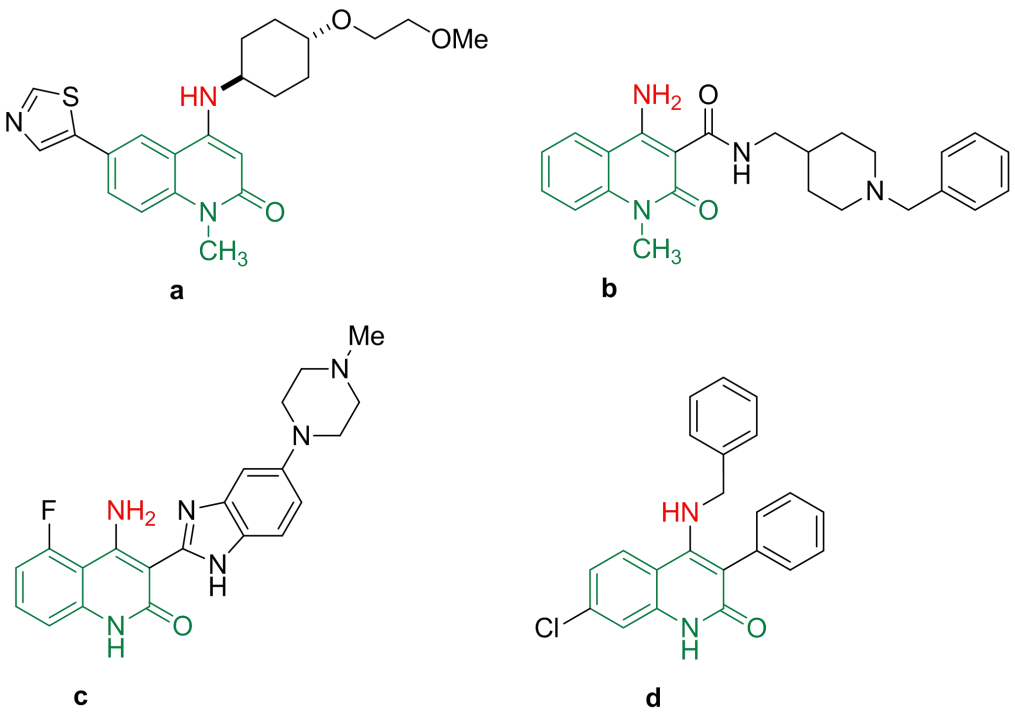


Figure 1. Examples of bioactive compounds based on the 4-aminated 2-quinolones

Despite these significant applications, 2-quinolones are inert because of their inherent aromaticity, which prevents their direct amination.[5] Hence, conventional strategies for the preparation of such scaffolds involve the construction of heterocyclic rings through cumbersome multistep reaction sequences, some of which involve expensive reagents, harsh reaction conditions and low yields.[4,6] As an alternative approach, 4-aminated 2-quinolones can be also synthesized by chemical conversion from the 4-hydroxy[4,7] or 4-chloro[1,2,8] derivatives. Therefore, the direct and practical amination of the 2-quinolone framework is strongly demanded.

A nitro group is one of the most important functional groups in organic syntheses because of its strong electron-withdrawing ability to activate the scaffold, facilitating the reaction with nucleophilic reagents.[9] Moreover, a nitro group serves not only as a precursor of versatile functionalities but also as a good leaving group.[10] Inspired by these properties of nitro group, we have found that 3-nitrated 1-methyl-2-quinolones (**MeQone**s) are highly reactive in direct C-C/C-O bond formation at the 4-position with carbon nucleophiles[11,12] and alkoxy anions,[13] respectively.

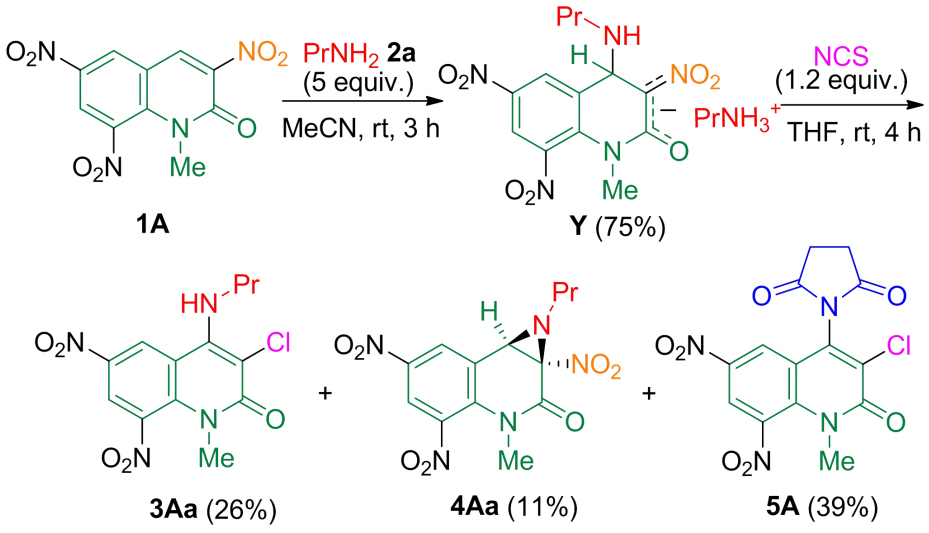
Interested in these results and with the aim of achieving versatile functionalization of the 2-quinolone framework, we decided to investigate direct C-N bond formation at the 4-position of the **MeQone** framework upon treatment of 3-nitrated **MeQone**s with amines, in which an electrophile is necessary to trap the anionic adduct intermediate

because a heteronucleophile is easily eliminated even though it adds to quinolone framework.[14] We focused on the halogenation because the hitherto unknown 4-aminated and 3-halogenated 2-quinolones compose a novel class of 2-quinolones with potentially interesting and valuable bioactivities, and will surely serve as key intermediates for constructing a library of versatile 2-quinolones.

2. Results and discussion

2.1 Amino-halogenation and aziridination of the MeQone Framework

To evaluate the potential for vicinal functionalization, trinitro-2-quinolone **1A** was chosen as a model substrate. Initially, a Meisenheimer complex **Y** was synthesized by treating **1A** with excess propylamine **2a**; subsequent reaction with *N*-chlorosuccinimide (NCS) gave the amino-chlorinated product **3Aa** in 26% yield, thus confirming the feasibility of the introduction of vicinal amino and halo groups onto the 2-quinolone framework (Scheme 1). The *N*-propylaziridine ring fused compound **4Aa** was obtained in 11% yield, of which the structure was definitely confirmed by X-ray diffraction of single crystal of **4Fa**,[15] an analogue of **4Aa** (Figure 2). To the best of our knowledge, there is very few report about the aziridination on the **MeQone** framework.[16] Therefore, our investigation will facilitate efficient access to functionalized quinolones. Moreover, the imido-chlorinated product **5A**, which was formed through the reaction of **1A** with NCS and a succinimide anion,[13] was obtained in 39% yield, indicating that regeneration of **1A** from **Y** proceeded under equlibrium.



Scheme 1. Reaction of Meisenheimer complex **Y** with NCS

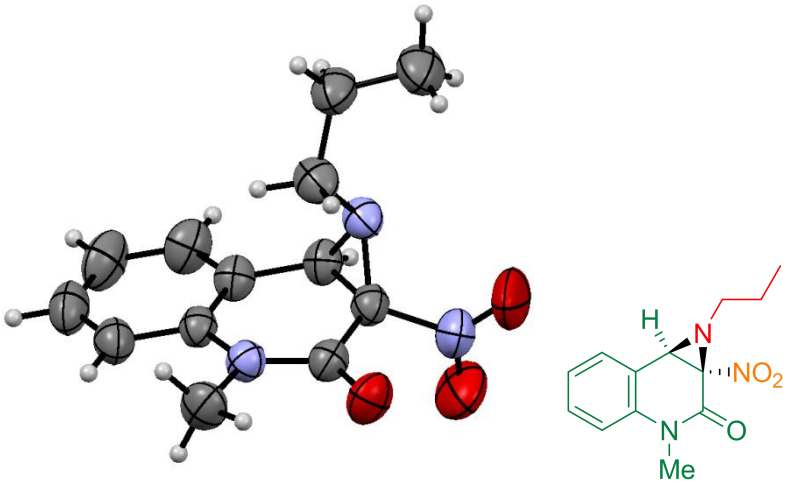
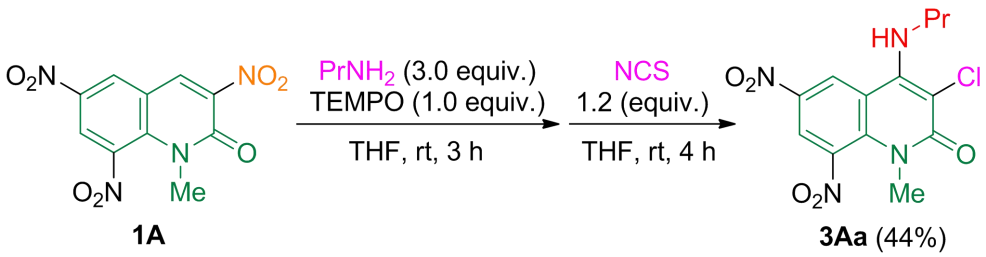


Figure 2. Structure of **4Fa** from X-ray diffraction analysis (the thermal ellipsoid plots are drawn at 50% probability level)

2.2 Control reaction involving radical scavenger

In order to gain insight into the mechanism of the reaction, a control experiment involving a radical scavenger was performed.[17] The addition of TEMPO had a slight influence on the reaction, but did not completely inhibit the reaction, thus suggesting that radical intermediates were not involved in the process (Scheme 2).

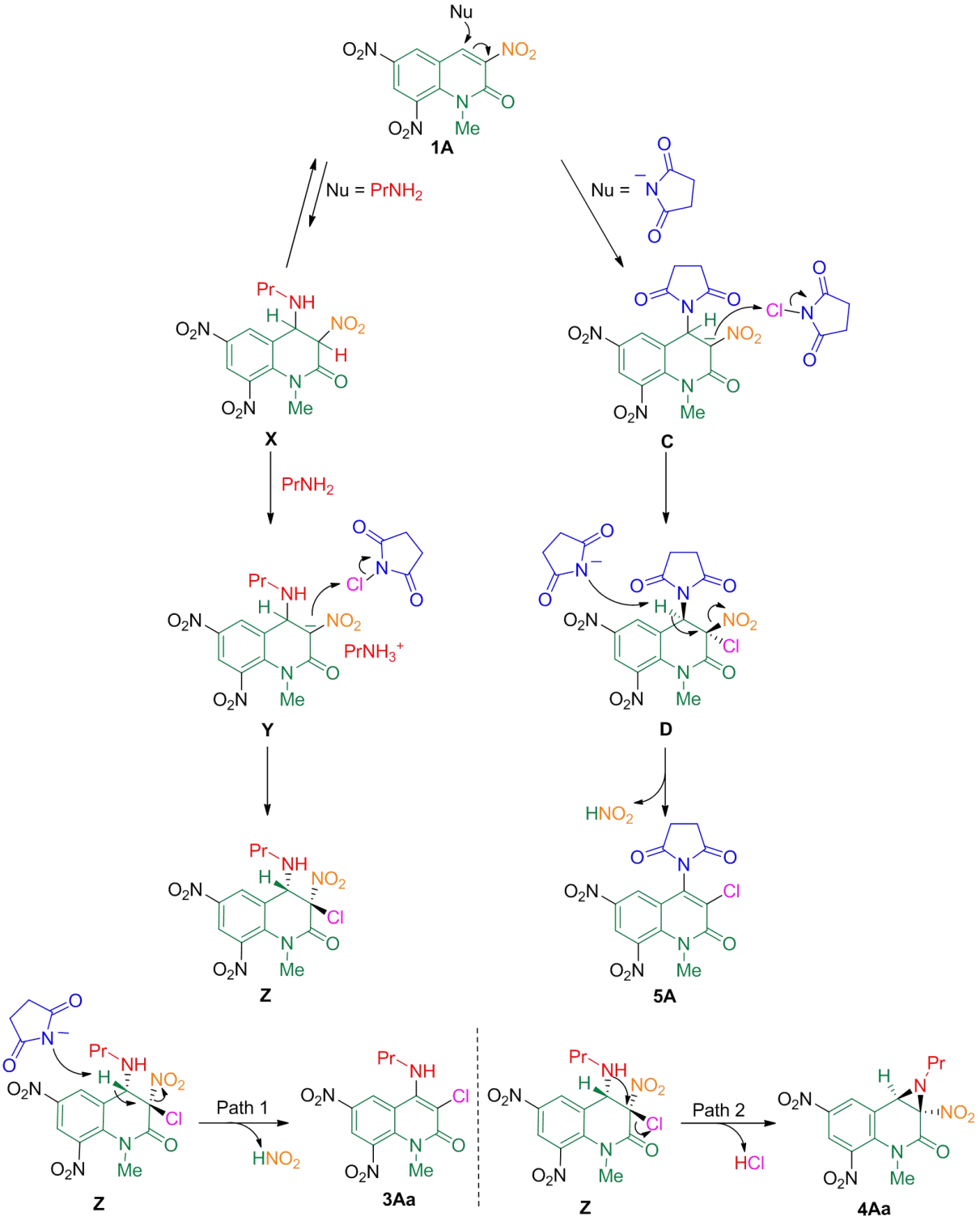


Scheme 2. Control reaction involving radical scavenger

2.3 A plausible mechanism for the formation of 3Aa and 4Aa

Based on the aforementioned results, it was postulated that the amine attacks the 4-position of **1A** to give dihydroquinolone **X** (Scheme 3). As a result of deprotonation at the 3-position by another amine, a Meisenheimer complex **Y** is formed. The reaction of **Y** with NCS facilitates chlorination at the 3-position by nucleophilic substitution, whereby NCS approaches from the *trans* direction to avoid the steric hindrance of the propylamino group, thus affording intermediate **Z**.[18] Hence, the base-promoted rearomatization takes place via the preferred bimolecular antiperiplanar elimination, which leads to the formation of amino-halogenated product **3Aa**. Meanwhile, the intramolecular substitution of the chloro

group by the adjacent amino group can occur to form the *N*-propylaziridine ring at the 3- and 4-positions, affording product **4Aa**.[16,19] Additionally, **1A** was regenerated under equilibrium from **X** and then underwent a nucleophilic addition with the succinimide anion followed by chlorination and rearomatization, delivering imido-chlorinated product **5A**.[13]

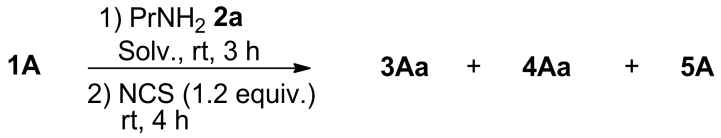


Scheme 3. A plausible mechanism for formation of **3Aa**, **4Aa** and **5A**

2.4 Conditions screening for one-pot amino-chlorination

In order to enhance the practicality of the method, we attempted to carry out the reaction in a one-pot, two-step fashion using trinitroquinolone **1A**, propylamine **2a**, and NCS as model substrates (Table 1). After a solution of **1A** and **2a** was stirred at room temperature for 3 h, NCS was added, and the resulting mixture was stirred at room temperature for 4 h. We tested a variety of solvents in the presence of 2.5 equiv. of **2a** in order to find the optimal conditions (Table 1). The conversion of **1A** into amino-chlorinated product **3Aa** did not work well in ethanol or dichloromethane, because imido-chlorinated product **5A** was the major product in these two solvents (entries 1 and 2). The Meisenheimer complex **Y** is considered to be more solvated with ethanol than **C** by forming hydrogen bonds, which might prevent the approach of NCS. Thus, polar aprotic solvents (MeCN, DMF and THF) were more suitable for the amino-chlorination, and the yield was improved to 45% when THF was used (entries 3–5). In these cases, **4Aa** was obtained as well. Next, a larger amount of **2a** was added to promote the conversion of **1A**, giving **3Aa** in 62% yield without concomitant formation of **5A**. **4Aa** decomposed into other compounds in this process (entry 6), as confirmed by the reaction of **4Aa** with propylamine **2a**. However, low temperature did not further improve the yield (entry 7). This is presumably due to the incomplete conversion of **1A** to **X**, which also underwent the competitive reaction of **1A** with the succinimide anion. Meanwhile, the decomposition of **4Aa** was suppressed at low temperature. Thus, the reaction conditions utilized in entry 6 were determined to be optimal.

Table 1. Conditions screening for aminochlorination



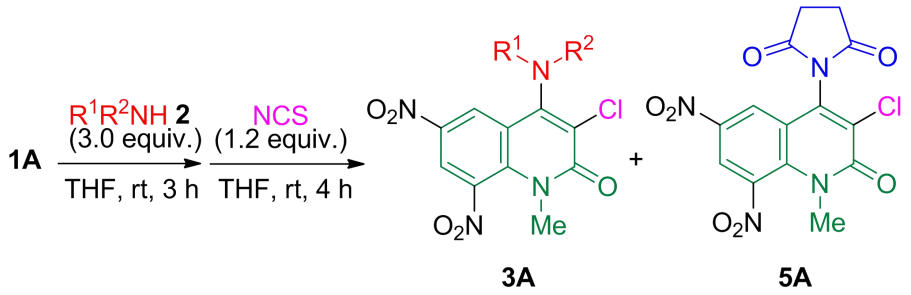
Entry	Solvent	$PrNH_2$ (Equiv.)	Yield (%)		
			3Aa	**4Aa**	**5A**
1	EtOH	2.5	11	5	48
2	CH_2Cl_2	2.5	14	12	34
3	MeCN	2.5	31	11	16
4	DMF	2.5	39	15	3
5	THF	2.5	45	10	19
6	THF	3.0	62	trace	0
7[a]	THF	3.0	37	13	21

[a]The reaction was conducted at -20 ℃.

2.5 Study on amine scope

With the optimized reaction conditions in hand, we surveyed the scope of amines **2** (Table 2). Reactions of **1A** with various aliphatic primary amines **2b–f** afforded the corresponding vicinally amino-chlorinated compounds **3Ab–f** in moderate to good yields (entries 1–5); however, **4** was not observed. Alicyclic amines such as piperidine **2g** and morpholine **2h** worked well (entries 6 and 7). Moreover, anilines **2i-m** were also examined. Several functional groups, such as butyl, methoxy and iodo groups on the benzene ring were tolerated, and a larger amount of aniline **2i** promoted the conversion of **1A** (entry 8). However, only a trace amount of **3Am** was detected in the case of 4-nitroaniline **2m** owing to the strong electron-withdrawing effect of the nitro group (entry 12). Due to the steric hindrance preventing the approach of NCS, the target product was not formed in the presence of diethylamine **2n**, and only a trace amount of the desired product was observed in the reaction with *N*-methylaniline **2o** (entries 13 and 14). In some cases, the succinimide anion was produced under basic conditions, and underwent imido-chlorination to furnish **5A** (entries 2, 7 and 13).

Table 2. Study on amine scope

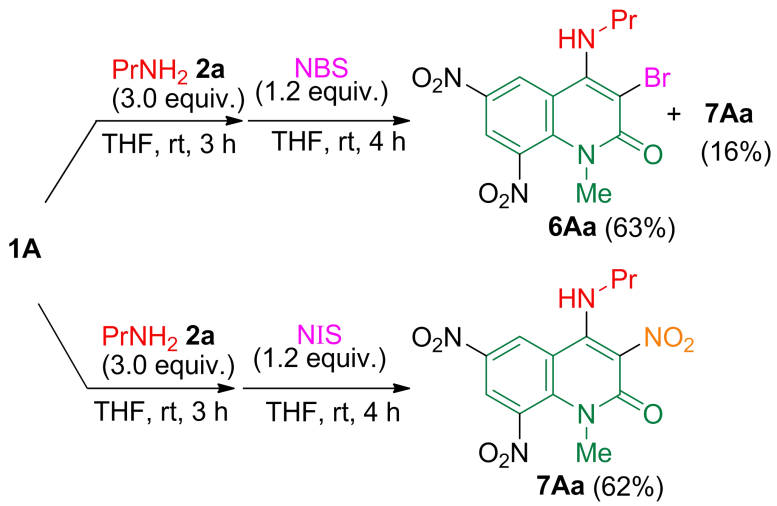


Entry	R^1	R^2		Yield (%)	
				3A	**5A**
1	*i*-Bu	H	**b**	70	0
2	*sec*-Bu	H	**c**	49	26
3	$HOCH_2CH_2$	H	**d**	56	0
4	Allyl	H	**e**	35	0
5	Benzyl	H	**f**	54	0
6	$-(CH_2)_5-$		**g**	48	0
7	$-CH_2CH_2OCH_2CH_2-$		**h**	62	3
8	Ph	H	**i**	41 (54[a])	0
9	4-BuC_6H_4	H	**j**	41	0
10	4-$MeOC_6H_4$	H	**k**	37	0
11	4-IC_6H_4	H	**l**	62[a]	0
12	4-$NO_2C_6H_4$	H	**m**	trace	0
13	Et	Et	**n**	0	27
14	Ph	Me	**o**	trace	0

[a]5 equiv. of amine was used.

2.6 Scanning of halogenating agents

In order to expand the scope of the protocol, two other *N*-halosuccinimides, NBS and NIS, were also employed (Scheme 4). The bromo-amination proceeded smoothly to give **6Aa** in 63% yield. Notably, 4-aminated trinitroquinolone **7Aa** was also obtained in 16% yield, which was presumably due to the higher leaving ability of bromide than chloride. **7Aa** was obtained in 62% yield without detectable iodo-aminated product in the reaction using NIS.

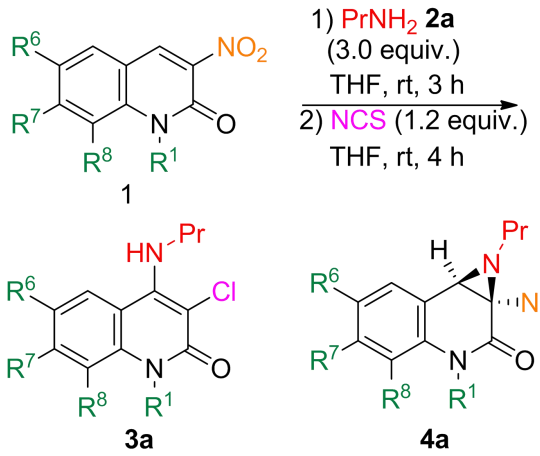


Scheme 4. The reaction invoving NBS and NIS

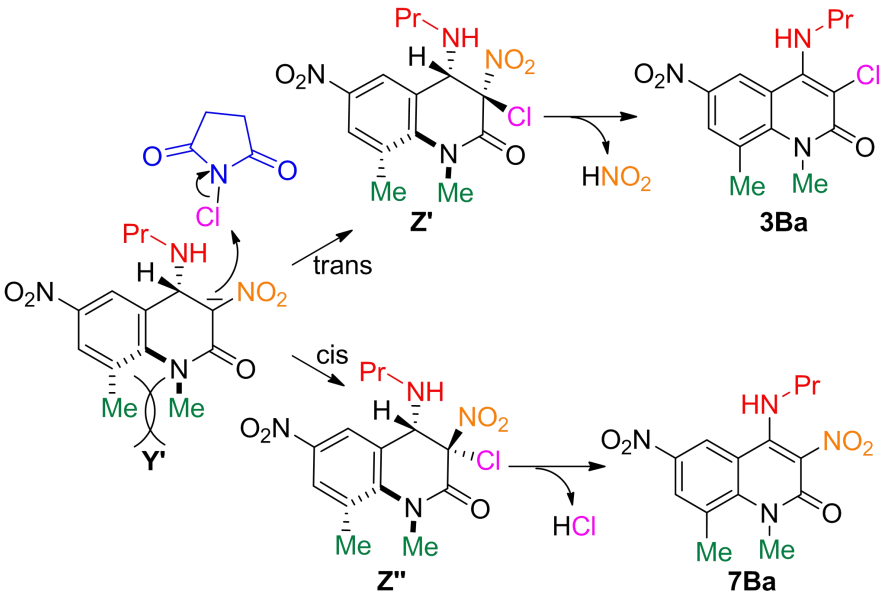
2.7 Scanning of 3-nitrated MeQones

Next, 3-nitrated **MeQone**s with different substituents on the benzene ring were further investigated. As indicated in Table 3, a reduction in the number of nitro groups on the benzene ring had a negative impact on the formation of amino-chlorinated product **3**. When the 8-nitro group was replaced with a methyl group or hydrogen atom, **3Ba** and **3Ca** were furnished in 13% yield (entries 1 and 2). Interestingly, the reaction involving **1B** afforded 3-nitro-4-propylamino substituted product **7Ba**, an analogue of **7Aa**, in 21% yield. This might be due to the steric repulsion between the 1-methyl and the 8-methyl groups, leading to the torsional strain in the 2-quinolone ring;[12] accordingly, NCS could approach the carbanion **Y'** from the *cis* direction (Scheme 5). Consequently, the elimination of nitrous acid together with hydrogen chloride resulted in the formation of 3-chlorinated and 3-nitrated products (**3Ba** and **7Ba**) simultaneously (Scheme 5). Moreover, a nitro group with a bromo atom or hydrogen atom on the benzene ring markedly decreased the selectivity of the formation of **3** (entries 3–5). On the other hand, in these reactions, the *N*-propylaziridine ring fused compounds **4Ba**–**4Fa** were obtained as the major products in moderate to good yields. These aziridines were stable while **4Aa** easily decomposed because the benzylic position of **4Aa**, which is activated by the electron-withdrawing effect of the nitro group at the 8-position, is easily attacked by nucleophiles. Indeed, **4Fa** caused no change even though it was heated with propylamine at 60 °C for 12 hours. The reaction did not proceed in the case of 3-nitrated **MeQone** with two electron-donating groups on the benzene ring (entry 6). Additionally, the methyl group was not crucial for the aziridine formation, and **4Ha** was obtained in 61% yield in the reaction using **1H** (entry 7).

Table 3. Reactions of 3-nitrated **MeQone**s with **2a** and NCS



Entry	1					Yield (%)		
	R^1	R^6	R^7	R^8		**3a**	**4a**	**5**
1	Me	NO^2	H	Me	**B**	13	21	trace
2	Me	NO^2	H	H	**C**	13	49	7
3	Me	Br	H	H	**D**	trace	68	0
4	Me	H	Br	H	**E**	0	65	0
5	Me	H	H	H	**F**	0	71	0
6	Me	MeO	MeO	H	**G**	0	0	0
7	H	H	H	H	**H**	0	61	0



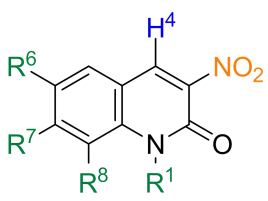
Scheme 5. Steric repulsion between *peri*-substituents affording **7**

2.8 Selectivity in amino-chlorination and aziridination

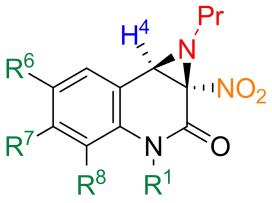
Based on the aforementioned results, the selective formation of **3** and **4** was attributed to the electronic effects of the substituents on the benzene ring. As depicted in Scheme 3, the intermediate ***Z*** likely played a very important role in this reaction, and the benzylic hydrogen atom in the 4-position determined the direct halo-amination or aziridination of the **MeQone** framework. Although ***Z*** was not detected during the reaction, we could indirectly characterize the electronic properties of the 4-H on nitroquinolone **1** and the resultant aziridine **4** by ^{1}H NMR analysis (Table 4).

As described previously, more nitro groups led to lower field, indicating that the electron density at the 4-position decreased owing to the nitro group on the benzene ring through the electron-withdrawing effect, thus increasing the acidity of the benzylic proton (Table 4).[20] As a result, a nitrous acid is easily eliminated via an antiperiplanar elimination, leading to the formation of amino-halogenated product **3** (Scheme 3, Path 1). In contrast, the hydrogen atom becomes less acidic in the presence of weaker electron-withdrawing groups such as bromo atoms or in the absence of electron-withdrawing groups, thus resulting in an intramolecular substitution to form an aziridine ring (Scheme 3, Path 2). On the other hand, when electron-donating groups such as methoxy were introduced on the aromatic ring, the electron density was significantly increased, thus preventing the nucleophilic addition at the 4-position of the **MeQone** system.

Table 4. Chemical shift of H^4 of **1** and **4a** in ^{1}H NMR spectra



1

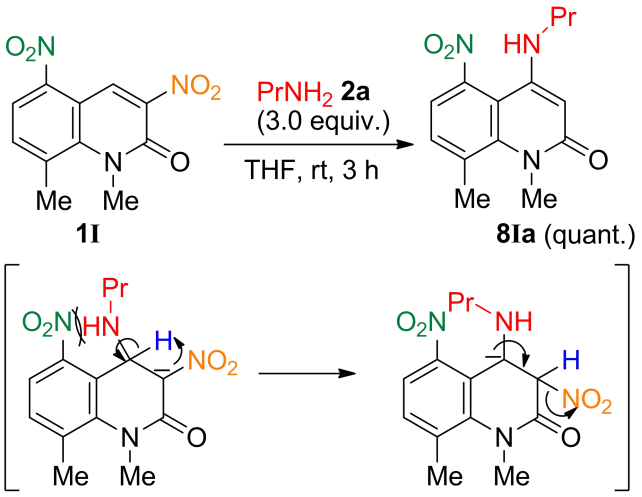


4a

R^1	R^6	R^7	R^8		Chemical shift of H^4 (ppm)	
					1	**4a**
Me	NO_2	H	NO_2	**A**	9.26	4.32
Me	NO_2	H	H	**C**	9.13	4.22
Me	H	H	H	**F**	8.90	4.12
Me	MeO	MeO	H	**G**	8.82	——
H	H	H	H	**H**	8.93	4.16

2.9 *cine*-Substitution of 1,8-dimethyl-3,5-dinitro-2-quinolone 12

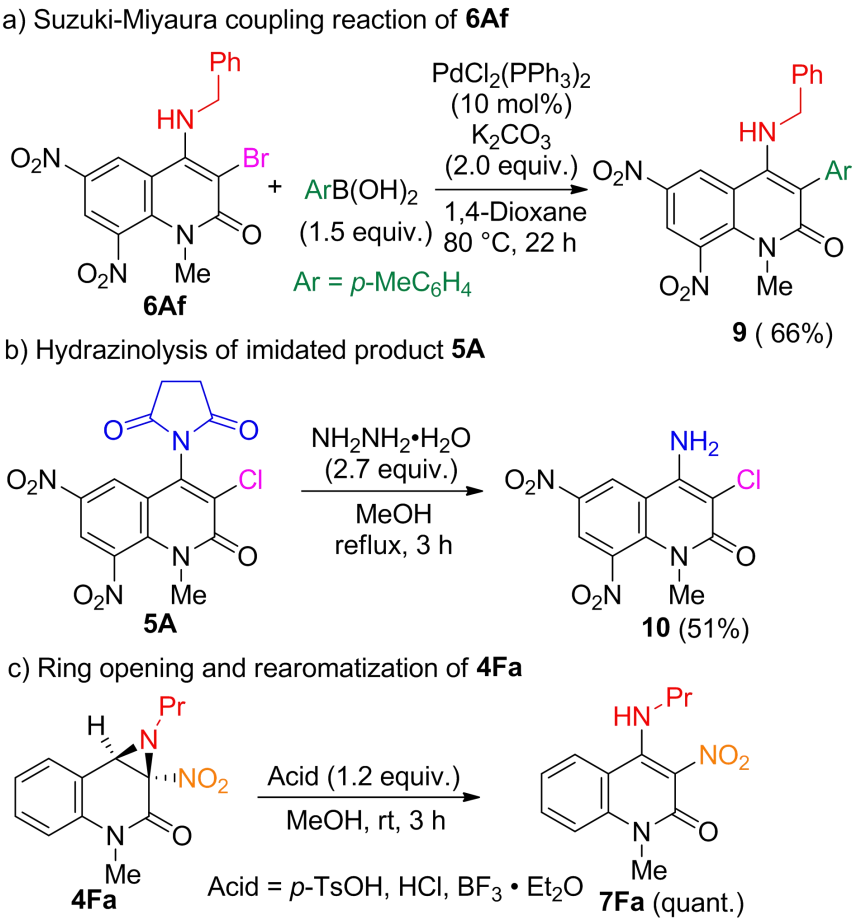
Interestingly, when 1,8-dimethyl-3,5-dinitro-2-quinolone (**1I**) was employed under the same conditions, *cine*-substituted product **8Ia** was obtained without **3Ia** or **4Ia**. In this reaction, addition of a propylamine **2a** afforded the Meisenheimer complex; however, it was not stable due to the steric repulsion of the *peri*-substituent (Scheme 6). Therefore, proton transfer to the 3-position likely releasing this repulsion and facilitating the elimination of the nitrite ion accompanied by aromatization to afford *cine*-substituted product **8Ia**.



Scheme 6. Reaction of 3,5-dinitroquinolone **1I** with propylamine **2a**

2.10 Conversion of the obtained products 6Af, 5A and 4Fa

Finally, to illustrate the synthetic utility of the developed protocol, the conversion of the resulting products into other useful synthetic building blocks was investigated. Using the present method, benzylamino-brominated compound **6Af** was synthesized in 55% yield, and was subjected to Suzuki-Miyaura coupling,[21] as **MeQone**s with an benzylamino group and an aryl group in the vicinal positions are known *N*-methyl-D-aspartate receptor antagonists.[4] When **3Af** and **6Af** were reacted with 4-methylphenylboronic acid in the presence of a palladium catalyst, 3-arylated product **9** was successfully obtained in 27% and 66% yields, respectively, indicating that the higher reactivity of C-Br than C-Cl bond facilitated the transformation (Scheme 7, a). Furthermore, imido-chlorinated product **5A** is a masked form of an aminated quinolone, and the hydrazinolysis of the imidated ring introduced an unsubstituted amino group at the 4-position (Scheme 7, b). Compound **4Fa** underwent a ring-opening reaction followed by rearomatization in the presence of an acid, leading to vicinally amino-nitrated MeQone **7Fa** in quantitative yield (Scheme 7, c).



Scheme 7. Conversion of **6Af**, **5A** and **4Fa** into other useful building blocks

3. Conclusion

In conclusion, an operationally simple protocol for the direct 4-amination and 3-halogenation of **MeQone** was developed by treatment of 3-nitrated **MeQone**s with amines followed by addition of *N*-halosuccinimides under mild conditions. The vicinally functionalized **MeQone**s will serve as key synthetic intermediates for a versatile library of **MeQone**s, as demonstrated through the palladium-catalyzed arylation at the 3-position. Meanwhile, we found that aziridination occurred at the 3- and 4-positions of the **MeQone** framework through intramolecular substitution. The selectivity between vicinal amino-halogenation and aziridination was associated with the electronic properties of the substituents on the benzene ring. Moreover, imido-chlorination proceeded in some cases, leading to 4-imidated product, a masked form of the 4-aminoquinolone. Further investigations focused on the ring opening of the aziridine ring are currently in progress, and may facilitate the efficient and practical functionalization of **MeQone**s.

4. Experimental section

4.1 General information

The melting points were determined on SRS-Optimelt Automated Melting Point System, 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 high-resolution mass spectra were measured on an AB SCIEX Triple TOF 4600. X-ray diffraction was conducted on a Rigaku AFC7R diffractometer with graphite monochromatized Mo-K radiation. The IR spectra were recorded on a JASCO FT/IR-4200 spectrometer.

4.2 General procedure for the 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 trinitroquinolone **1A** in 86% total yield.[22] Other dinitroquinolones **1B**, **1C** and **1I** were also prepared in a similar way except for using milder reaction conditions in the nitration step.[12a]

Mononitrated quinolones **1D**–**H** were successfully synthesized using 2-nitrobenzaldehyde as the starting material via sequential reduction using Fe/HCl,[23] condensation with ethyl nitroacetate,[24] intramolecular cyclization,[24] and methylation with iodomethane.[25]

4.3 Reaction of trinitroquinolone 1A with propylamine 2a

To a solution of trinitroquinolone **1A** (100.0 mg, 0.34 mmol) in acetonitrile (2.5 mL), propylamine **2a** (102.5 mg, 1.70 mmol) was added at room temperature. When amine was added, yellowish solid immediately precipitated. After stirring for 3 h, the Meisenheimer complex **Y** was collected by filtration as a yellow solid (105.1 mg, 0.26 mmol, 75%);[26] Since this salt was not stable under ambient conditions to give **TNQ** and it was too hydroscopic, only ^{1}H NMR could be measured, and satisfactory analytical data were not obtained despite several attempts. In the ^{1}H NMR of **Y** using DMSO-d_6 as the solvent, the signals were considerably broadened, and the decomposition of **Y** into **TNQ** and propylamine **2a** was observed in $CDCl_3$.

4.4 General procedure for amino-halogenation and aziridination of the 2-quinolone framework

To a solution of 3-nitrated quinolones **1** (100.0 mg) in THF (1.0 mL), amine **2** (3.0 equiv.) was added, and the resultant mixture was stirred at room temperature for 3 h. Then, a solution of *N*-halosuccinimide (1.2 equiv.) in THF (0.5 mL) was added, and the resultant mixture was stirred at room temperature for further 4 h. The solvent was evaporated to afford a reaction mixture as a yellow residue, from which amino-halogenated and aziridine fused quinolone, **3** and **4**, were isolated through SiO_2 column chromatography (eluted with CH_2Cl_2).

3-Chloro-1-methyl-6,8-dinitro-4-(propylamino)-2-quinolone (3Aa)

Yellow solid (71.2 mg, 0.21 mmol, 62%); R_f = 0.44 (CH_2Cl_2); mp 131−133 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.07 (t, *J* = 7.2 Hz, 3H), 1.79 (tq, *J* = 7.2, 7.2 Hz, 2H), 3.50 (s, 3H), 3.55 (dt, *J* = 6.8, 7.2 Hz, 2H), 4.86 (br s, 1H), 8.73 (d, *J* = 2.4 Hz, 1H), 8.96 (d, *J* = 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 11.2 (CH_3), 24.8 (CH_2), 35.4 (CH_3), 51.0 (CH_2), 110.2 (C), 118.9 (C), 121.8 (CH), 124.0 (CH), 136.7 (C), 139.1 (C), 139.5 (C), 149.0 (C), 158.4 (C); IR: ν (cm^{-1}) 3372, 1645, 1537, 1531; HRMS (ESI-TOF) Calcd for $C_{13}H_{14}ClN_4O_5$ [$(M+H)^+$]: 341.0647, found 341.0647.

3-Chloro-1-methyl-4-(2-methylpropylamino)-6,8-dinitro-2-quinolone (3Ab)

Yellow solid (83.5 mg, 0.24 mmol, 70%); R_f = 0.44 (CH_2Cl_2); mp 122−123 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.07 (d, *J* = 6.8 Hz, 6H), 1.97 (triple septet, *J* = 6.8, 6.8 Hz, 1H), 3.38 (dd, *J* = 6.8, 6.8 Hz, 2H), 3.50 (s, 3H), 4.89 (br s, 1H), 8.73 (d, *J* = 2.4 Hz, 1H), 8.95 (d, *J* = 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 20.0 (CH_3), 30.5 (CH), 35.4 (CH_3), 56.9 (CH_2), 110.1 (C), 118.8 (C), 121.8 (CH), 124.1 (CH), 136.7 (C), 139.1 (C), 139.4 (C), 149.2 (C), 158.3 (C); IR: ν (cm^{-1}) 3343, 1645, 1537, 1531; HRMS (ESI-TOF) Calcd for $C_{14}H_{16}ClN_4O_5$ [$(M+H)^+$]: 355.0804, found 355.0802.

4-(2-Butylamino)-3-chloro-1-methyl-6,8-dinitro-2-quinolone (3Ac)

Yellow solid (58.2 mg, 0.16 mmol, 49%); R_f = 0.51 (CH_2Cl_2); mp 153−155 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.08 (t, *J* = 7.2 Hz, 3H), 1.34 (d, *J* = 6.4 Hz, 3H), 1.65-1.78 (m, 2H), 3.51 (s, 3H), 3.67−3.74 (m, 1H), 4.46 (d, *J* = 10.0 Hz, 1H), 8.72 (d, *J* = 2.4 Hz, 1H), 8.93 (d, *J* = 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 10.5 (CH_3), 21.9 (CH_3), 31.6 (CH_2), 35.4 (CH_3), 57.1 (CH), 112.7 (C), 119.4 (C), 121.8 (CH), 124.0 (CH), 136.5 (C), 139.2 (C), 139.7 (C), 148.9 (C), 158.4 (C); IR: ν (cm^{-1}) 3345, 1667, 1537, 1531; HRMS (ESI-TOF) Calcd for $C_{14}H_{16}ClN_4O_5$ [$(M+H)^+$]: 355.0804, found 355.0814.

3-Chloro-4-(2-hydroxyethylamino)-1-methyl-6,8-dinitro-2-quinolone (3Ad)

Yellow solid (64.4 mg, 0.19 mmol, 56%); R_f = 0.35 (CH_2Cl_2/MeOH = 20:1); mp

125−128 °C; ^{1}H NMR (CD_3CN, 400 MHz) δ = 3.40 (s, 3H), 3.71−3.74 (m, 4H), 5.59 (br s, 1H), 8.76 (d, *J* = 2.4 Hz, 1H), 9.06 (d, *J* = 2.4 Hz, 1H); ^{13}C NMR (CD_3CN, 100 MHz) δ = 34.8 (CH_3), 49.5 (CH_2), 60.8 (CH_2), 107.9 (C), 119.3 (C), 121.8 (CH), 123.5 (CH), 136.7 (C), 138.6 (C), 139.5 (C), 148.6 (C), 158.6 (C); IR: ν (cm^{-1}) 3352, 1651, 1537, 1531; HRMS (ESI-TOF) Calcd for $C_{12}H_{12}ClN_4O_6$ [$(M+H)^+$]: 343.0440, found 343.0427.

3-Chloro-1-methyl-6,8-dinitro-4-(2-propenylamino)-2-quinolone (3Ae)

Yellow solid (39.9 mg, 0.12 mmol, 35%); R_f = 0.14 (CH_2Cl_2); mp 148−149 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 3.51 (s, 3H), 4.16 (dd, *J* = 5.3, 5.3 Hz, 2H), 4.96 (br s, 1H), 5.38 (dd, *J* = 0.8, 10.2 Hz, 1H), 5.49 (dd, *J* = 0.8, 17.0 Hz, 1H), 6.03 (ddt, *J* = 5.3, 10.2, 17.0 Hz, 1H), 8.73 (d, *J* = 2.4 Hz, 1H), 8.95 (d, *J* = 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 35.5 (CH_3), 51.0 (CH_2), 111.1 (C), 118.5 (CH_2), 118.7 (C), 121.9 (CH), 123.9 (CH), 133.7 (CH), 136.6 (C), 139.2 (C), 139.7 (C), 148.8 (C), 158.4 (C); IR: ν (cm^{-1}) 3360, 1651, 1537, 1531; HRMS (ESI-TOF) Calcd for $C_{13}H_{12}ClN_4O_5$ [$(M+H)^+$]: 339.0491, found 339.0500.

4-(Benzylamino)-3-chloro-1-methyl-6,8-dinitro-2-quinolone (3Af)

Yellow solid (70.0 mg, 0.18 mmol, 54%); R_f = 0.40 (CH_2Cl_2); mp 178−179 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 3.50 (s, 3H), 4.73 (d, *J* = 6.0 Hz, 2H), 5.21 (t, *J* = 6.0 Hz, 1H), 7.36−7.43 (m, 5H), 8.72 (d, *J* = 2.4 Hz, 1H), 8.99 (d, *J* = 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 35.5 (CH_3), 52.9 (CH_2), 111.1 (C), 118.8 (C), 121.9 (CH), 123.9 (CH), 127.4 (CH), 128.6 (CH), 129.3 (CH), 136.6 (C), 137.3 (C), 139.2 (C), 139.6 (C), 148.6 (C), 158.4 (C); IR: ν (cm^{-1}) 3360, 1651, 1537, 1531; HRMS (ESI-TOF) Calcd for $C_{17}H_{14}ClN_4O_5$ [$(M+H)^+$]: 389.0647, found 389.0643.

3-Chloro-1-methyl-6,8-dinitro-4-piperidino-2-quinolone (3Ag)

Yellow solid (59.8 mg, 0.16 mmol, 48%); R_f = 0.40 (CH_2Cl_2); mp 181−183 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.78−1.85 (m, 6H), 3.2−3.4 (m, 4H), 3.50 (s, 3H), 8.71 (d, *J* = 2.4 Hz, 1H), 9.07 (d, *J* = 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 23.9 (CH_2), 26.5 (CH_2), 35.8 (CH_3), 52.1 (CH_2), 121.5 (C), 121.8 (CH), 124.0 (C), 124.4 (CH), 136.4 (C), 139.1 (C), 140.4 (C), 152.1 (C), 160.0 (C); IR: ν (cm^{-1}) 1651, 1537, 1531; HRMS (ESI-TOF) Calcd for $C_{15}H_{15}ClN_4NaO_5$ [$(M+Na)^+$]: 389.0623, found 389.0609.

3-Chloro-1-methyl-4-morpholino-6,8-dinitro-2-quinolone (3Ah)

Yellow solid (76.9 mg, 0.21 mmol, 62%); R_f = 0.09 (CH_2Cl_2); mp 248−250 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ = 3.35−3.37 (m, 7H), 3.85 (t, *J* = 4.4 Hz, 4H), 8.94 (d, *J* = 2.4 Hz, 1H), 8.98 (d, *J* = 2.4 Hz, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ = 35.7 (CH_3), 50.1 (CH_2), 66.7 (CH_2), 120.7 (C), 122.4 (CH), 122.8 (C), 124.2 (CH), 136.2 (C), 138.7 (C), 140.2 (C), 150.7 (C), 159.4 (C); IR: ν (cm^{-1}) 1651, 1537, 1531; HRMS (ESI-TOF) Calcd for

$C_{14}H_{13}ClN_4NaO_6$ [$(M+Na)^+$]: 391.0416, found 391.0422.

3-Chloro-1-methyl-6,8-dinitro-4-phenylamino-2-quinolone (3Ai)

Yellow solid (68.5 mg, 0.18 mmol, 54%); R_f = 0.24 (CH_2Cl_2); mp 199−201 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 3.56 (s, 3H), 6.72 (br s, 1H), 6.99 (d, *J* = 7.6 Hz, 2H), 7.20 (t, *J* = 7.6 Hz, 1H), 7.35 (dd, *J* = 7.6, 7.6 Hz, 2H), 8.58 (d, *J* = 2.4 Hz, 1H), 8.63 (d, *J* = 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 35.7 (CH_3), 114.9 (C), 118.6 (C), 121.6 (CH), 121.7 (CH), 125.1 (CH), 125.5 (CH), 130.1 (CH), 136.5 (C), 139.3 (C), 139.6 (C), 141.1 (C), 144.1 (C), 158.6 (C); IR: ν (cm^{-1}) 3341, 1651, 1537, 1531; HRMS (ESI-TOF) Calcd for $C_{16}H_{11}ClN_4NaO_5$ [$(M+Na)^+$]: 397.0310, found 397.0314.

4-(4-Butylphenylamino)-3-chloro-1-methyl-6,8-dinitro-2-quinolone (3Aj)

Yellow solid (58.9 mg, 0.14 mmol, 41%); R_f = 0.50 (CH_2Cl_2); mp 109−110 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 0.92 (t, *J* = 7.6 Hz, 3H), 1.33 (tq, *J* = 7.6, 7.6 Hz, 2H), 1.58 (tt, *J* = 7.6, 7.6 Hz, 2H), 2.60 (t, *J* = 7.6 Hz, 3H), 3.55 (s, 3H), 6.72 (s, 1H), 6.93 (d, *J* = 8.0 Hz, 2H), 7.15 (d, *J* = 8.0 Hz, 2H), 8.57 (d, *J* = 2.8 Hz, 1H), 8.61 (d, *J* = 2.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 13.9 (CH_3), 22.1 (CH_2), 33.4 (CH_2), 35.0 (CH_2), 35.7 (CH_3), 113.6 (C), 118.4 (C), 121.6 (CH), 122.3 (CH), 125.3 (CH), 130.1 (CH), 136.6 (C), 138.6 (C), 139.2 (C), 139.4 (C), 140.9 (C), 144.5 (C), 158.6 (C); IR: ν (cm^{-1}) 3352, 1667, 1537, 1531; HRMS (ESI-TOF) Calcd for $C_{20}H_{20}ClN_4O_5$ [$(M+H)^+$]: 431.1117, found 431.1115.

3-Chloro-4-(4-methoxyphenylamino)-1-methyl-6,8-dinitro-2-quinolone (3Ak)

Yellow solid (50.7 mg, 0.13 mmol, 37%); R_f = 0.36 (CH_2Cl_2); mp 100−102 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 3.54 (s, 3H), 3.81 (s, 3H), 6.69 (s, 1H), 6.88 (d, *J* = 8.8 Hz, 2H), 7.00 (d, *J* = 8.8 Hz, 2H), 8.59 (d, *J* = 2.8 Hz, 1H), 8.61 (d, *J* = 2.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 35.7 (CH_3), 55.6 (CH_3), 112.7 (C), 115.4 (CH), 118.3 (C), 121.6 (CH), 124.5 (CH), 125.2 (CH), 133.8 (C), 136.7 (C), 139.2 (C), 139.3 (C), 144.8 (C), 158.0 (C), 158.5 (C); IR: ν (cm^{-1}) 3354, 1651, 1537, 1531; HRMS (ESI-TOF) Calcd for $C_{17}H_{14}ClN_4O_6$ [$(M+H)^+$]: 405.0596, found 405.0604.

3-Chloro-4-(4-iodophenylamino)-1-methyl-6,8-dinitro-2-quinolone (3Al)

Yellow solid (104.7 mg, 0.21 mmol, 62%); R_f = 0.39 (CH_2Cl_2); mp 135−137°C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 3.57 (s, 3H), 6.56 (s, 1H), 6.71 (d, *J* = 8.4 Hz, 2H), 7.63 (d, *J* = 8.4 Hz, 2H), 8.59 (d, *J* = 2.4 Hz, 1H), 8.66 (d, *J* = 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 35.8 (CH_3), 88.4 (C), 116.7 (C), 118.8 (C), 121.9 (CH), 122.6 (CH), 124.7 (CH), 136.3 (C), 139.0 (CH), 139.4 (C), 139.9 (C), 141.1 (C), 143.4 (C), 158.5 (C); IR: ν (cm^{-1}) 3306, 1651, 1537, 1531; HRMS (ESI-TOF) Calcd for $C_{16}H_{10}ClIN_4NaO_5$ [$(M+Na)^+$]: 522.9277, found 522.9259.

3-Chloro-1,8-dimethyl-6-nitro-4-(propylamino)-2-quinolone (3Ba)

Yellow solid (15.1 mg, 0.05 mmol, 13%); R_f = 0.27 (CH_2Cl_2); mp 156−158 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.04 (t, *J* = 7.2 Hz, 3H), 1.74 (tq, *J* = 7.2, 7.2 Hz, 2H), 2.76 (s, 3H), 3.41 (t, *J* = 7.2 Hz, 2H), 3.81 (s, 3H), 4.67 (br s, 1H), 8.18 (d, *J* = 2.4 Hz, 1H), 8.62 (d, *J* = 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 11.2 (CH_3), 24.1 (CH_3), 24.8 (CH_2), 38.0 (CH_3), 50.9 (CH_2), 109.3 (C), 117.5 (C), 119.4 (CH), 127.2 (C), 128.5 (CH), 141.4 (C), 144.4 (C), 150.1 (C), 160.5 (C); IR: ν (cm^{-1}) 3372, 1651, 1599, 1574; HRMS (ESI-TOF) Calcd for $C_{14}H_{16}ClN_3NaO_3$ [$(M+Na)^+$]: 332.0772, found 332.0768.

3-Chloro-1-methyl-6-nitro-4-(propylamino)-2-quinolone (3Ca)

Yellow solid (15.3 mg, 0.05 mmol, 13%); R_f = 0.18 (CH_2Cl_2); mp 217−219 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.06 (t, *J* = 7.2 Hz, 3H), 1.76 (tq, *J* = 7.2, 7.2 Hz, 2H), 3.58 (dt, *J* = 6.0, 7.2 Hz, 2H), 3.79 (s, 3H), 4.76 (br s, 1H), 7.46 (d, *J* = 9.6 Hz, 1H), 8.39 (dd, *J* = 2.4, 9.6 Hz, 1H), 8.84 (d, *J* = 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 11.2 (CH_3), 24.8 (CH_2), 31.0 (CH_3), 50.8 (CH_2), 109.3 (C), 115.3 (C), 115.4 (CH), 121.6 (CH), 125.0 (CH), 141.5 (C), 142.5 (C), 149.4 (C), 158.3 (C); IR: ν (cm^{-1}) 3337, 1643, 1557, 1550; HRMS (ESI-TOF) Calcd for $C_{13}H_{15}ClN_3O_3$ [$(M+H)^+$]: 296.0797 found 296.0806.

1a,2,3,7b-Tetrahydro-3-methyl-1a,4,6-trinitro-2-oxo-1-propyl-*1H*-azirino[2,3-c]quinolin e (4Aa)

Yellow oil (17.6 mg, 0.05 mmol, 15%); R_f = 0.67 (CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 0.93 (t, *J* = 7.2 Hz, 3H), 1.56 (ddq, *J* = 7.2, 7.2, 7.2 Hz, 2H), 2.11 (dt, *J* = 6.8, 7.2 Hz, 1H), 2.33 (dt, *J* = 6.8, 7.2 Hz, 1H), 3.39 (s, 3H), 4.32 (s, 1H), 8.58 (d, *J* = 2.8 Hz, 1H), 8.68 (d, *J* = 2.8 Hz, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ = 11.2 (CH_3), 21.9 (CH_2), 35.4 (CH_3), 46.8 (CH), 47.4 (CH_2), 77.7 (C), 119.8 (C), 122.7 (CH), 129.1 (CH), 136.9 (C), 139.2 (C), 141.8 (C), 160.1 (C); IR: ν (cm^{-1}) 1694, 1543, 1537; HRMS (ESI-TOF) Calcd for $C_{13}H_{12}N_5O_7$ [$(M-H)^-$]: 350.0742, found 350.0759.

1a,2,3,7b-Tetrahydro-3,4-dimethyl-1a,6-dinitro-2-oxo-1-propyl-*1H*-azirino[2,3-c]quinoli ne (4Ba)

Pale yellow solid (24.4 mg, 0.08 mmol, 21%); R_f = 0.61 (CH_2Cl_2); mp 159−160 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ = 0.84 (t, *J* = 7.2 Hz, 3H), 1.43 (ddq, *J* = 7.2, 7.2, 7.2 Hz, 2H), 1.95 (dt, *J* = 5.6, 7.2 Hz, 1H), 2.31 (dt, *J* = 5.6, 7.2 Hz, 1H), 2.67 (s, 3H), 3.58 (s, 3H), 4.77 (s, 1H), 8.26 (d, *J* = 2.8 Hz, 1H), 8.42 (d, *J* = 2.8 Hz, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ = 11.3 (CH_3), 22.0 (CH_2), 22.7 (CH_3), 37.3 (CH_3), 47.2 (CH_2), 47.3 (CH), 77.9 (C), 117.4 (C), 124.0 (CH), 129.1 (C), 129.5 (CH), 142.8 (C), 144.2 (C), 161.1 (C); IR: ν (cm^{-1}) 1682, 1562, 1524; HRMS (ESI-TOF) Calcd for $C_{14}H_{16}N_4NaO_5$ [$(M+Na)^+$]: 343.1013, found 343.1014.

1a,2,3,7b-Tetrahydro-3-methyl-1a,6-dinitro-2-oxo-1-propyl-*1H*-azirino[2,3-c]quinoline (4Ca)

Pale yellow solid (60.2 mg, 0.20 mmol, 49%); R_f = 0.60 (CH_2Cl_2); mp 144−145 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 0.90 (t, *J* = 7.2 Hz, 3H), 1.55 (ddq, *J* = 6.8, 6.8, 7.2 Hz, 2H), 2.02 (dt, *J* = 5.2, 6.8 Hz, 1H), 2.30 (dt, *J* = 5.2, 6.8 Hz, 1H), 3.62 (s, 3H), 4.22 (s, 1H), 7.33 (d, *J* = 9.2 Hz, 1H), 8.39 (dd, *J* = 2.4, 9.2 Hz, 1H), 8.43 (d, *J* = 2.4 Hz, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ = 11.3 (CH_3), 21.9 (CH_2), 30.4 (CH_3), 46.5 (CH), 46.9 (CH_2), 78.2 (C), 115.4 (C), 117.0 (CH), 125.8 (CH), 126.3 (CH), 142.7 (C), 142.8 (C), 158.7 (C); IR: ν (cm^{-1}) 1682, 1562, 1526; HRMS (ESI-TOF) Calcd for $C_{13}H_{14}N_4NaO_5$ [$(M+Na)^+$]: 329.0856, found 329.0855.

6-Bromo-1a,2,3,7b-tetrahydro-3-methyl-1a-nitro-2-oxo-1-propyl-*1H*-azirino[2,3-c]quinoline (4Da)

White solid (81.2 mg, 0.24 mmol, 68%); R_f = 0.69 (CH_2Cl_2); mp 171−172 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 0.89 (t, *J* = 7.2 Hz, 3H), 1.54 (ddq, *J* = 7.2, 7.2, 7.2 Hz, 2H), 2.00 (dt, *J* = 5.2, 7.2 Hz, 1H), 2.28 (dt, *J* = 5.2, 7.2 Hz, 1H), 3.53 (s, 3H), 4.05 (s, 1H), 7.05 (d, *J* = 8.8 Hz, 1H), 7.60−7.63 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 11.5 (CH_3), 22.4 (CH_2), 29.9 (CH_3), 47.4 (CH), 47.7 (CH_2), 77.8 (C), 116.5 (CH), 116.6 (C), 116.9 (C), 133.3 (CH), 133.6 (CH), 137.3 (C), 158.4 (C); IR: ν (cm^{-1}) 1667, 1562, 1557; HRMS (ESI-TOF) Calcd for $C_{13}H_{13}BrN_3O_3$ [$(M-H)^-$]: 338.0146, found 338.0160.

5-Bromo-1a,2,3,7b-tetrahydro-3-methyl-1a-nitro-2-oxo-1-propyl-*1H*-azirino[2,3-c]quinoline (4Ea)

Pale yellow solid (77.6 mg, 0.23 mmol, 65%); R_f = 0.73 (CH_2Cl_2); mp 120−122 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 0.88 (t, *J* = 7.2 Hz, 3H), 1.52 (ddq, *J* = 7.2, 7.2, 7.2 Hz, 2H), 1.96 (dt, *J* = 5.2, 7.2 Hz, 1H), 2.30 (dt, *J* = 5.2, 7.2 Hz, 1H), 3.53 (s, 3H), 4.08 (s, 1H), 7.32−7.37 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 11.5 (CH_3), 22.4 (CH_2), 29.9 (CH_3), 47.6 (CH_2), 47.7 (CH), 77.8 (C), 113.5 (C), 118.1 (CH), 124.6 (C), 127.0 (CH), 132.0 (CH), 139.3 (C), 158.6 (C); IR: ν (cm^{-1}) 1678, 1597, 1562; HRMS (ESI-TOF) Calcd for $C_{13}H_{13}BrN_3O_3$ [$(M-H)^-$]: 338.0146, found 338.0159.

1a,2,3,7b-Tetrahydro-3-methyl-1a-nitro-2-oxo-1-propyl-*1H*-azirino[2,3-c]quinoline (4Fa)

Pale yellow solid (89.8 mg, 0.34 mmol, 71%); R_f = 0.55 (CH_2Cl_2); mp 98−100 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 0.86 (t, *J* = 7.2 Hz, 3H), 1.52 (ddq, *J* = 7.2, 7.2, 7.2 Hz, 2H), 1.95 (dt, *J* = 5.2, 7.2 Hz, 1H), 2.31 (dt, *J* = 5.2, 7.2 Hz, 1H), 3.55 (s, 3H), 4.12 (s, 1H), 7.18 (d,

J = 8.4 Hz, 1H), 7.26 (d, J = 8.4 Hz, 1H), 7.50-7.54 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 11.5 (CH_3), 22.4 (CH_2), 29.8 (CH_3), 47.5 (CH_2), 48.2 (CH), 78.2 (C), 114.5 (C), 114.8 (CH), 124.1 (CH), 130.7 (CH), 130.8 (CH), 138.1 (C), 158.7 (C); IR: ν (cm^{-1}) 1668, 1562, 1557; HRMS (ESI-TOF) Calcd for $C_{13}H_{15}N_3NaO_3$ [$(M+Na)^+$]: 284.1006, found 284.1012.

1a,2,3,7b-Tetrahydro-1a-nitro-2-oxo-1-propyl-*1H*-azirino[2,3-c]quinoline (4Ha)

Yellow solid (78.1 mg, 0.32 mmol, 61%); R_f = 0.18 (CH_2Cl_2); mp 122−123 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 0.89 (t, J = 7.2 Hz, 3H), 1.56 (ddq, J = 7.2, 7.2, 7.2 Hz, 2H), 2.08 (dt, J = 5.2, 7.2 Hz, 1H), 2.44 (dt, J = 5.2, 7.2 Hz, 1H), 4.16 (s, 1H), 7.07 (d, J = 7.6 Hz, 1H), 7.22 (dd, J = 7.6, 7.6 Hz, 1H), 7.44 (dd, J = 7.6, 7.6 Hz, 1H), 7.49 (d, J = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 11.5 (CH_3), 22.4 (CH_2), 47.6 (CH_2), 49.1 (CH), 77.9 (C), 113.6 (C), 116.3 (CH), 124.7 (CH), 130.2 (CH), 130.7 (CH), 135.4 (C), 160.3 (C); IR: ν (cm^{-1}) 1681, 1562, 1557; HRMS (ESI-TOF) Calcd for $C_{12}H_{13}N_3NaO_3$ [$(M+Na)^+$]: 270.0849, found 270.0843.

3-Chloro-1-methyl-6,8-dinitro-4-(2,5-dioxopyrrolidino)-2-quinolone (5A)

Yellow solid (61.2 mg, 0.16 mmol, 48%). 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; HRMS (ESI-TOF) Calcd for $C_{14}H_{10}ClN_4O_7$ [$(M+H)^+$]: 381.0233, found 381.0238.

3-Chloro-1-methyl-6-nitro-4-(2,5-dioxopyrrolidino)-2-quinolone (5C)

Yellow powder (8.9 mg, 0.03 mmol, 7%); 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; HRMS (ESI-TOF) Calcd for $C_{14}H_{11}ClN_3O_5$ [$(M+H)^+$]: 336.0382, found 336.0387.

3-Bromo-1-methyl-6,8-dinitro-4-(propylamino)-2-quinolone (6Aa)

Yellow solid (81.8 mg, 0.21 mmol, 63%); R_f = 0.35 (ethyl acetate/hexane = 1/2); mp 213-215 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.06 (t, J = 7.2 Hz, 3H), 1.66 (tq, J = 7.2, 7.2 Hz, 2H), 3.49−3.53 (m, 5H), 4.89 (br s, 1H), 8.73 (d, J = 2.4 Hz, 1H), 8.96 (d, J = 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ = 11.2 (CH_3), 24.8 (CH_2), 35.7 (CH_3), 51.5 (CH_2), 103.0 (C), 118.6 (C), 122.0 (CH), 124.3 (CH), 137.2 (C), 139.1 (C), 139.4 (C), 151.3 (C), 158.5 (C); IR: ν (cm^{-1}) 3374, 1651, 1537, 1531; HRMS (ESI-TOF) Calcd for $C_{13}H_{12}BrN_4O_5$ [$(M-H)^-$]:

382.9997, found 383.0007.

4-(Benzylamino)-3-bromo-1-methyl-6,8-dinitro-2-quinolone (6Af)

Yellow solid (79.8 mg, 0.19 mmol, 55%); R_f = 0.45 (CH_2Cl_2); mp 134−136 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 3.51 (s, 3H), 4.69 (d, *J* = 6.4 Hz, 2H), 5.26 (t, *J* = 6.4 Hz, 1H), 7.34−7.44 (m, 5H), 8.73 (d, *J* = 2.4 Hz, 1H), 8.99 (d, *J* = 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 35.8 (CH_3), 53.2 (CH_2), 104.1 (C), 118.6 (C), 122.0 (CH), 124.2 (CH), 127.4 (CH), 128.6 (CH), 129.3 (CH), 137.1 (C), 137.2 (C), 139.1 (C), 139.5 (C), 150.9 (C), 158.5 (C); IR: ν (cm^{-1}) 3352, 1651, 1537, 1531; HRMS (ESI-TOF) Calcd for $C_{17}H_{14}BrN_4O_5$ [$(M+H)^+$]: 433.0142, found 433.0160.

1-Methyl-3,6,8-trinitro-4-(propylamino)-2-quinolone (7Aa)

Yellow solid (73.0 mg, 0.21 mmol, 62%); R_f = 0.10 (CH_2Cl_2); mp 184−187 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.07 (t, *J* = 7.2 Hz, 3H), 1.85 (tq, *J* = 7.2, 7.2 Hz, 2H), 3.43 (s, 3H), 3.56 (dt, *J* = 6.8, 7.2 Hz, 2H), 7.69 (br s, 1H), 8.81 (d, *J* = 2.4 Hz, 1H), 9.04 (d, *J* = 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 11.1 (CH_3), 23.8 (CH_2), 35.0 (CH_3), 48.9 (CH_2), 117.9 (C), 122.7 (C), 124.0 (CH), 124.5 (CH), 138.4 (C), 139.3 (C), 139.6 (C), 146.2 (C), 156.2 (C); IR: ν (cm^{-1}) 3343, 1651, 1537, 1531; HRMS (ESI-TOF) Calcd for $C_{13}H_{14}N_5O_7$ [$(M+H)^+$]: 352.0888, found 352.0904.

1,8-Dimethyl-3,6-dinitro-4-(propylamino)-2-quinolone (7Ba)

Yellow solid (25.2 mg, 0.08 mmol, 21%); R_f = 0.17 (CH_2Cl_2); mp 208−210 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.07 (t, *J* = 7.2 Hz, 3H), 1.84 (tq, *J* = 7.2, 7.2 Hz, 2H), 2.72 (s, 3H), 3.61 (dt, *J* = 5.2, 7.2 Hz, 2H), 3.70 (s, 3H), 8.06 (br s, 1H), 8.27 (d, *J* = 2.4 Hz, 1H), 8.67 (d, *J* = 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 11.2 (CH_3), 23.7 (CH_3), 23.9 (CH_2), 37.6 (CH_3), 49.2 (CH_2), 116.3 (C), 119.8 (CH), 121.9 (C), 128.4 (C), 130.7 (CH), 141.6 (C), 145.9 (C), 149.0 (C), 158.1 (C); IR: ν (cm^{-1}) 3331, 1643, 1524, 1518; HRMS (ESI-TOF) Calcd for $C_{14}H_{16}N_4NaO_5$ [$(M+Na)^+$]: 343.1013, found 343.1022.

4.5 *cine*-Substitution of 1,8-dimethyl-3,5-dinitro-2-quinolone (1I)

To a solution of **1I** (70.0 mg, 0.27 mmol) in THF (1.0 mL) was added propylamine **2a** (47.2 mg, 0.80 mmol), and the resultant mixture was stirred at room temperature for 3 h. Then, the solvent was evaporated to afford a reaction mixture **8Ia** as a yellow solid (75.5 mg, 0.27 mmol, quant.); R_f = 0.27 (CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 0.97 (t, *J* = 7.2 Hz, 3H), 1.67 (tq, *J* = 7.2, 7.2 Hz, 2H), 2.59 (s, 3H), 3.41 (dt, *J* = 5.6, 7.2 Hz, 2H), 3.77 (s, 3H), 6.60 (d, *J* = 9.6 Hz, 1H), 7.82 (br s, 1H), 7.96 (d, *J* = 9.6 Hz, 1H), 8.04 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 11.3 (CH_3), 23.2 (CH_3), 24.9 (CH_2), 36.9 (CH_3), 54.0 (CH_2), 113.7 (C), 117.0 (C),

117.9 (CH), 131.0 (CH), 131.1 (C), 136.6 (CH), 146.0 (C), 149.0 (C), 163.9 (C); IR: ν (cm^{-1}) 3300, 1651, 1580, 1574; HRMS (ESI-TOF) Calcd for $C_{14}H_{18}N_3O_3$ [$(M+H)^+$]: 276.1343, found 276.1339.

4.6 Suzuki-Miyaura coupling reaction of benzylamino-brominated 6Af

To a solution of **6Af** (63.0 mg, 0.15 mmol) in 1,4-dioxane (2.0 mL), were added *p*-$MeC_6H_4B(OH)_2$ (29.7 mg, 0.22 mmol), $Pd(PPh_3)_2Cl_2$ (10.2 mg, 0.01 mmol) and K_2CO_3 (40.3 mg, 0.29 mmol). Then, the resultant mixture was heated at 80 °C for 22 h. After the mixture was filtrated, the solvent was evaporated to afford a reaction mixture as a yellow residue, from which arylated product **9** was isolated by SiO_2 column chromatography (eluted with ethyl acetate/hexane = 1/5) as a yellow solid (42.4 mg, 0.10 mmol, 66%); R_f = 0.29 (ethyl acetate/hexane = 1/5); mp 143−145 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.38 (s, 3H), 3.46 (s, 3H), 4.22 (d, *J* = 6.4 Hz, 2H), 4.57 (t, *J* = 6.4 Hz, 1H), 7.10−7.13 (m, 4H), 7.23 (d, *J* = 7.6 Hz, 2H), 7.31−7.32 (m, 3H), 8.72 (d, *J* = 2.4 Hz, 1H), 8.92 (d, *J* = 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 20.3 (CH_3), 33.8 (CH_3), 51.9 (CH_2), 116.8 (C), 119.4 (C), 120.7 (CH), 122.4 (CH), 126.5 (CH), 127.1 (CH), 128.0 (CH), 128.5 (C), 128.7 (CH), 129.1 (CH), 136.5 (C), 137.0 (C), 137.5 (C), 137.8 (C), 138.3 (C), 147.8 (C), 161.4 (C); IR: ν (cm^{-1}) 3352, 1651, 1537, 1531; HRMS (ESI-TOF) Calcd for $C_{24}H_{21}N_4O_5$ [$(M+H)^+$]: 445.1507, found 445.1505.

4.7 Hydrazinolysis of 5A

To a solution of **5A** (50.0 mg, 0.13 mmol) in MeOH (2.0 mL), NH_2NH_2•H_2O (17.8 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), 4-aminoquinolone **10** was isolated through filtration as a yellow solid (20.0 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; HRMS (ESI-TOF) Calcd for $C_{10}H_8ClN_4O_5$ [$(M+H)^+$]: 299.0178, found 299.0172.

4.8 Acid-catalyzed ring opening of aziridine ring

To a solution of **4Fa** (38.5 mg, 0.15 mmol) in MeOH (0.5 mL), acid (*p*-TsOH•H_2O or 1 N HCl aq. or BF_3•Et_2O, 0.18 mmol, 1.2 equiv.) was added, and the resultant mixture was

stirred at room temperature for 3 h. Then, the solvent was evaporated to afford a mixture as a yellow residue, from which vicinally amino-nitrated product **7Fa** was isolated by SiO_2 column chromatography (eluted with CH_2Cl_2) as a yellow solid (38.5 mg, 0.15 mmol, quant.); R_f = 0.60 (CH_2Cl_2); mp 121−122 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.00 (t, *J* = 7.2 Hz, 3H), 1.69 (tq, *J* = 7.2, 7.2 Hz, 2H), 3.11 (dt, *J* = 5.6, 7.2 Hz, 2H), 3.80 (s, 3H), 6.09 (br s, 1H), 7.27−7.30 (m, 1H), 7.33−7.40 (m, 2H), 7.48 (dd, *J* = 0.8, 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 11.3 (CH_3), 23.2 (CH_2), 31.1 (CH_3), 45.0 (CH_2), 114.3 (CH), 115.5 (C), 120.3 (CH), 124.1 (CH), 126.4 (CH), 128.2 (C), 129.6 (C), 131.2 (C), 158.9 (C); IR: ν (cm^{-1}) 3312, 1651, 1574, 1557; HRMS (ESI-TOF) Calcd for $C_{13}H_{16}N_3O_3$ [$(M+H)^+$]: 262.1186, found 262.1195.

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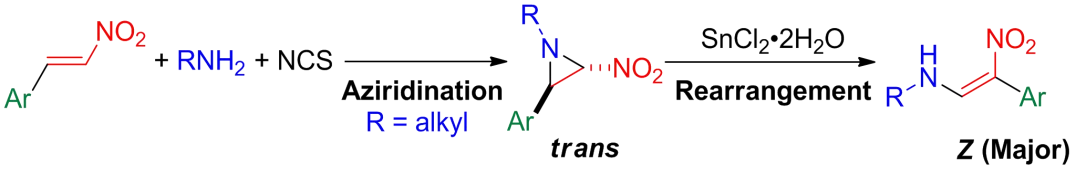
Chapter 4. Direct Aziridination of Nitroalkenes Affording *N*-Alkyl-*C*-nitroaziridines and the Subsequent Lewis Acid Mediated Isomerization to β-Nitroenamines

A mild and highly diastereoselective one-pot synthesis of *trans*-*N*-alkyl-*C*-nitroaziridines was achieved by the treatment of nitroalkenes with aliphatic amines and *N*-chlorosuccinimide. Treatment of the obtained aziridines with a Lewis acid resulted in a facile ring opening reaction, accompanied by rearrangement and isomerization into functionalized (*Z*)-β-nitroenamines.

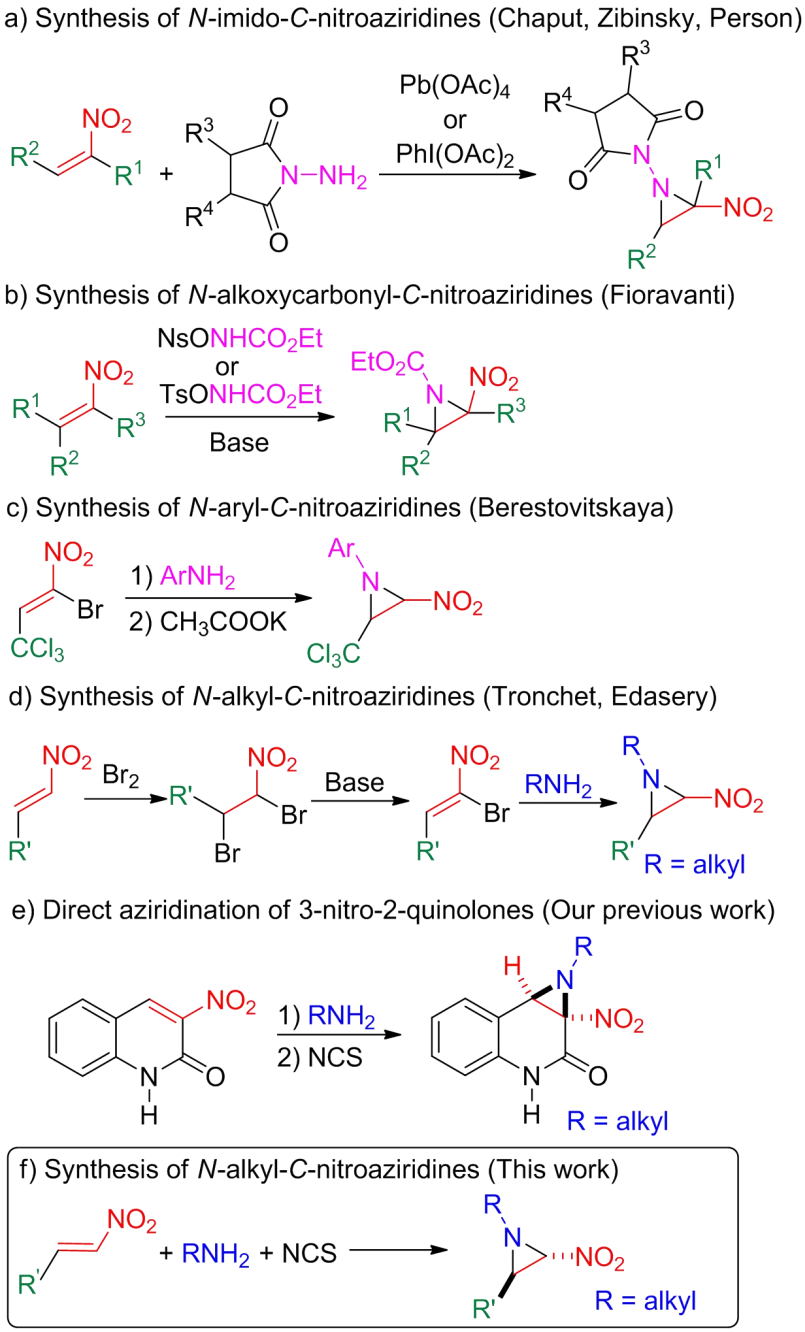


1. Introduction

The aziridines are an important class of nitrogen containing heterocycles and can be found in a number of biologically active compounds, such as mitomycin, porfiromycin, and azinomycin.[1] In addition, functionalized aziridines also serve as versatile building blocks in organic synthesis.[1,2] The ring opening reaction of aziridines with nucleophiles affords various 1,2-difunctionalized compounds.[1,2] A substantial number of functionalized aziridines can also be transformed into useful products such as HIV protease inhibitor,[3] communesin,[4] ceramide,[5] oseltamivir,[6] and isochroman[7] through rearrangement, cycloaddition, and ring expansion reactions.[2] Among the functionalized aziridines, *C*-nitroaziridines play an important role in chemical transformations because of the strong electron-withdrawing ability of the nitro group.[8] Hence, the development of efficient methods for the preparation of *C*-nitroaziridines has attracted much attention among organic chemists.

Among preparative methods for *C*-nitroaziridines, the direct aziridination of nitroalkenes is the most efficient approach from a practical viewpoint, as it requires only simple experimental manipulations. *N*-Imidoaziridines are obtained by the treatment of *N*-aminoimides with nitroalkenes in the presence of an oxidant (Scheme 1, a).[9] $NsONHCO_2Et$ and $TsONHCO_2Et$ serve as an N1 unit that can undergo direct aziridination of nitroalkenes under basic conditions to afford *N*-alkoxycarbonylaziridines (Scheme 1, b).[10] Additionally, *N*-arylaziridines are also available through the reaction of electron-deficient nitroalkenes with aromatic amines followed by ring closure (Scheme 1, c).[11] Unexpectedly, there are no reports on the synthesis of *N*-alkyl-*C*-nitroaziridines from nitroalkenes through direct aziridination,

except for the multistep synthesis via α-bromonitroalkenes; however, the substrate scope is not investigated further (Scheme 1, d).[12] Thus, a facile and efficient aziridination of nitroalkenes for the synthesis of *N*-alkylated nitroaziridines is of great interest.



Scheme 1. Direct aziridination of nitroalkenes

As part of my continuing interest in methods for the direct functionalization of the 2-quinolone framework, I achieved the direct aziridination by a sequential treatment of 3-nitro-2-quinolones with an amine and *N*-chlorosuccinimide (NCS) (Scheme 1, e).[13] Inspired

by this protocol, we envisaged that direct aziridination of nitroalkenes might proceed to afford *N*-alkyl-*C*-nitroaziridines by the sequential treatment with aliphatic amine and NCS (Scheme 1, f).

2. Results and Discussion

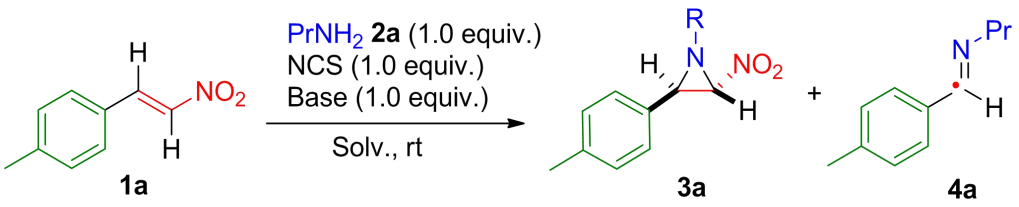
2.1 Optimization of reaction conditions for aziridination

To evaluate the potential for direct aziridination, nitrostyrene **1a** and propylamine **2a** were selected as model substrates. When β-nitrostyrene **1a** was reacted with propylamine **2a** and NCS at room temperature in THF in the presence of Et_3N, *N*-propyl-*C*-nitroaziridine **3a** was successfully obtained (Table 1, entry1). In the ^1H NMR, signals for the ring protons H^2 and H^3 were observed at 3.85 and 4.90 ppm, respectively, with a coupling constant of 1.6 Hz, located in the range (≤ 2 Hz) for the *trans* configuration.[14] Moreover, a correlation between protons H^3 and *ortho* proton (H^o) of the benzene ring in the NOESY spectrum revealed the resultant aziridine is a *trans* isomer.

As depicted in Table 1, the organic bases did not work enough, giving the aziridinated product **3a** in low yields even though the prolonged reaction time was used (entries 1–9). In some cases, the starting material **1a** was not consumed completely owing to the formation of ammonium nitronate of aza-Micheal adduct with another molecule of amine (entries 1–6). Although a complete conversion of **1a** was observed in the presence of more basic DBU, the imine **4a** was formed as a major product rather than the aziridine **3a** (entry 7). Compared to organic bases, inorganic bases such as carbonate and hydroxide were more suitable for this reaction, and the best result was obtained in the reaction using Cs_2CO_3 as the base (entries 10–14). Indeed, the use of Cs_2CO_3 as a base was proved to be crucial in a variety of aziridinations due to its proper solubility and basicity.[15]

Next, different solvents were screened in this transformation. However, replacing THF with other solvents did not improve the yield of **3a** (entries 15–19). In order to examine whether low temperature could suppress the formation of imine **4a** or not, the reaction was conducted at -10 °C, however, both reactions affording **3a** and **4a** were almost suppressed (entry 20). A better result was obtained in the presence of a slightly excess amount of propylamine **2a** and *N*-chlorosuccinimide (NCS), giving **3a** in 85% yield (entry 21). Although higher loadings of propylamine and NCS were employed to promote the conversion of nitroalkene, the transformation did not proceed thoroughly, which might be caused by the equilibrium process between propylamine and NCS (entry 22).[16]

Table 1. Optimization of reaction conditions for the aziridination of **1a**



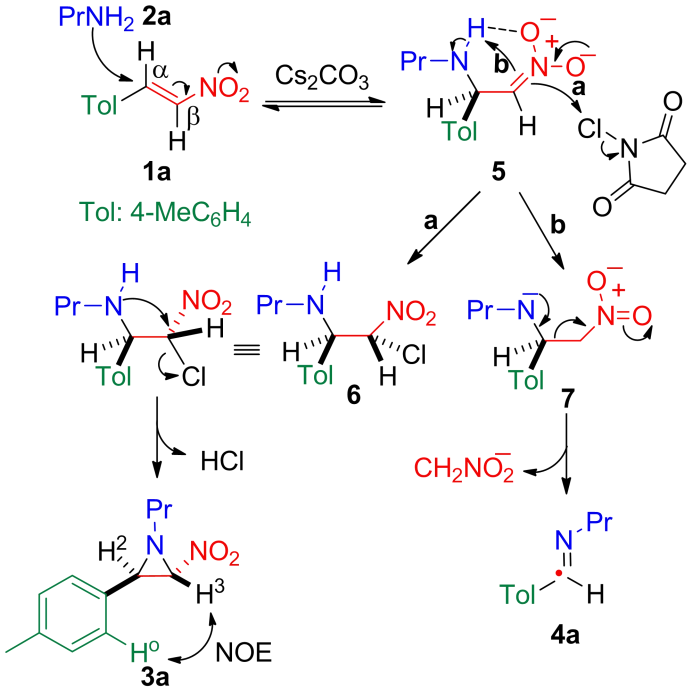
Entry	Base	Time (h)	Solvent	Yield[a] (%)		Recov.[a] (%)
				3a	**4a**	
1	Et_3N	5	THF	23	0	77
2	Et_3N	28	THF	21	39	38
3[b]	Et_3N	28	THF	17	32	51
4	$PrNH_2$	5	THF	17	19	64
5	$PrNH_2$	28	THF	39	20	38
6	Pyridine	28	THF	11	13	60
7	DBU	5	THF	0	74	0
8	*t*-BuOK	5	THF	52	48	0
9	AcONa	5	THF	29	3	37
10	K_2CO_3	5	THF	55	0	45
11	K_2CO_3	28	THF	73	18	5
12	NaOH	5	THF	47	9	33
13	NaOH	28	THF	71	22	0
14	Cs_2CO_3	5	THF	79	11	10
15	Cs_2CO_3	5	MeOH	14	86	0
16	Cs_2CO_3	5	MeCN	77	23	0
17	Cs_2CO_3	5	DMF	52	48	0
18	Cs_2CO_3	5	hexane	18	25	19
19	Cs_2CO_3	5	CH_2Cl_2	70	27	0
20[c]	Cs_2CO_3	5	THF	4	3	93
21[d]	**Cs_2CO_3**	**5**	**THF**	**85**	**6**	**9**
22[e]	Cs_2CO_3	5	THF	73	11	15

[a]Yield and recovery were determined by the integral of ^{1}H NMR of the reaction mixture. [b]2.0 Equiv. Of Et_3N was used. [c]The reaction was conducted at -10℃. [d]1.1 Equiv. of propylamine and NCS was used. [e]The reaction involved 1.3 equiv. of propylamine and NCS together with 1.1 equiv. of Cs_2CO_3.

Overall, the reaction conditions utilized in entry 21 were determined to be optimal. Instead of NCS, other halosuccinimides such as *N*-bromosuccinimide (NBS) and *N*-iodosuccinimide (NIS) were also examined, however, the aziridine was not formed owing to the higher steric hindrance of bromo and iodo groups than chloro group.

2.2 A plausible mechanism for aziridination

On the basis of the above results, a plausible mechanism for aziridination is proposed. The conjugate addition of amine to **1a** affords intermediate **5**, in which the conformation is fixed by intramolecular hydrogen bond (Scheme 2). Thus, NCS approaches to **5** from the *anti* direction of the aromatic group to avoid the steric hindrance, affording the adduct **6**. The subsequent backside attack of the amino group affords aziridine **3a** with the *trans* configuration (Path a). Meanwhile, the competitive proton transfer followed by elimination of anionic nitromethane leads to imine **4a** (Path b).[17] Indeed, **4a** was quantitatively obtained when the reaction was conducted in the absence of NCS.



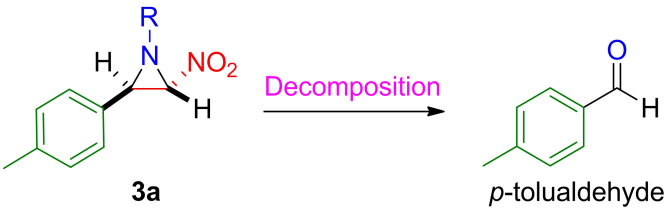
Scheme 2. A plausible mechanism for aziridination

2.3 Instability of *N*-alkyl-*C*-nitroaziridine 3a

Although the yield of the conversion of β-nitrostyrene **1a** into aziridine **3a** reached up to 85%, the isolated yield decreased to 31% after workup using water and purification by silica gel column chromatography. Control experiments revealed that aziridine **3a** in $CDCl_3$ gradually decomposed into *p*-tolualdehyde at room temperature (Table 2, entries 1–4). Furthermore, decomposition of **3a** readily occurs within shorter time under upon heating (entries 5 and 6).

The ^{1}H NMR spectra of the isolated aziridine **3a** were shown in Figure 1, by which formation of *p*-tolualdehyde was observed as a result of decomposition of **3a**.

Table 2. Decomposition of **3a**



Entry	Time (h)	Temp. (°C)	Ratio[a] of **3a**/*p*-tolualdehyde
1	—	rt	90/10
2	12	rt	70/30
3	24	rt	62/38
4	36	rt	50/50
5	1.5	45	75/25
6	2	60	43/57

[a]Ratio was determined by the integral values in the ^{1}H NMR.

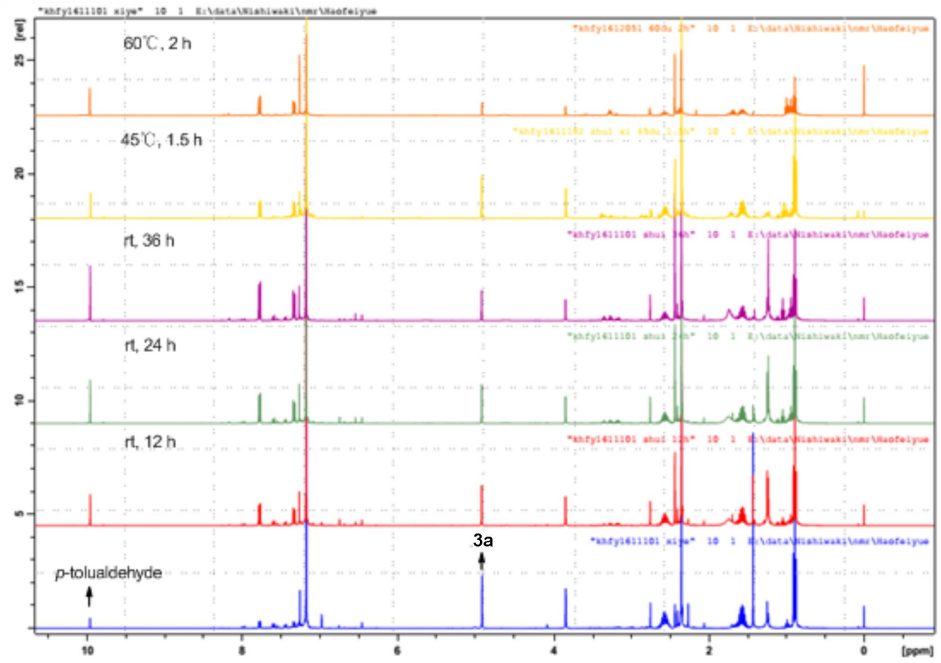


Figure 1. Confirmation of decomposition of **3a** through ^{1}H NMR

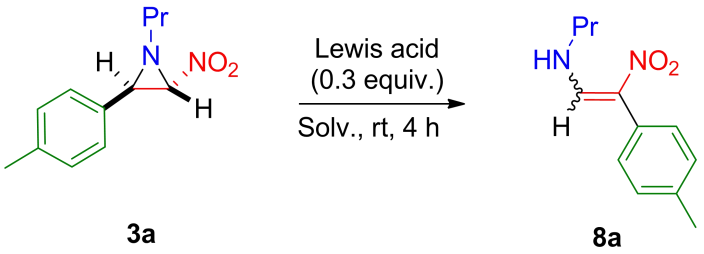
2.4 Lewis acid mediated ring opening and rearrangement of aziridine

Due to the instability at ambient conditions, we studied the conversion of aziridine **3a** into a useful and easily treatable reagent. *N*-propyl-*C*-nitroaziridine **3a** was found to isomerize into β-aryl-β-nitroenamine **8a** in the presence of a Lewis acid. Notably, the aryl group rearranged to the adjacent carbon. Due to their "push-pull" property, β-nitroenamines serve as key

synthetic intermediates for functional materials such as bioactive compounds and optical materials.[18] However, very few reports are focused on β-aryl-β-nitroenamines because of their poor availability.[19] Therefore, our method potentially yields a novel class of β-nitroenamines with structural diversity.

Among the several Lewis acids tested in MeCN, the isomerization of **3a** occurred most efficiently in the presence of $SnCl_2 \cdot 2H_2O$, giving **8a** with a 76% yield, as a mixture of *Z*/*E* isomers with a 93/7 ratio (Table 3, entry 9). The replacement of MeCN with other solvents did not afford better results (entries 11–14). Moreover, a low temperature had no impact on the reaction (entry 15). The correlation between protons H^{α} and *ortho* proton (H^{o}) of the benzene ring in the NOESY spectrum revealed the major isomer has a *Z*-configuration, which was finally confirmed by X-ray crystallography (Figure 2)。

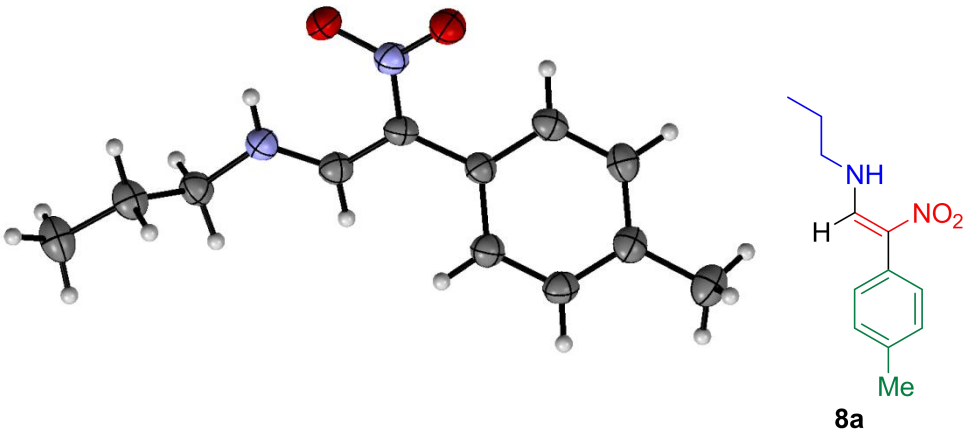
Table 3. Screening of the Lewis acids for the rearrangement of the aryl group



3a **8a**

Entry	Lewis acid	Solvent	Yield[a] (%)	*Z*:*E*[b]
1	CuI	MeCN	0	–
2	$Cu(OAc)_2$	MeCN	0	–
3	TsOH	MeCN	47	93:7
4	$BF_3{\cdot}Et_2O$	MeCN	63	93:7
5	$ZnCl_2$	MeCN	65	93:7
6	$FeCl_3$	MeCN	55	92:8
7	$FeCl_2{\cdot}4H_2O$	MeCN	66	93:7
8	$AlCl_3$	MeCN	32	91:9
9	**$SnCl_2{\cdot}2H_2O$**	**MeCN**	**81 (76[c])**	93:7
10	$SnCl_4{\cdot}5H_2O$	MeCN	69	93:7
11	$SnCl_2{\cdot}2H_2O$	THF	27	93:7
12	$SnCl_2{\cdot}2H_2O$	MeOH	15	93:7
13	$SnCl_2{\cdot}2H_2O$	hexane	0	93:7
14	$SnCl_2{\cdot}2H_2O$	CH_2Cl_2	62	93:7
15[b]	$SnCl_2{\cdot}2H_2O$	MeCN	78	93:7

[a]The yield and ratio were determined by ^{1}H NMR using dibromomethane as internal standard.
[b]The reaction was conducted at -10℃. [c]Isolated yield based on **3a**.

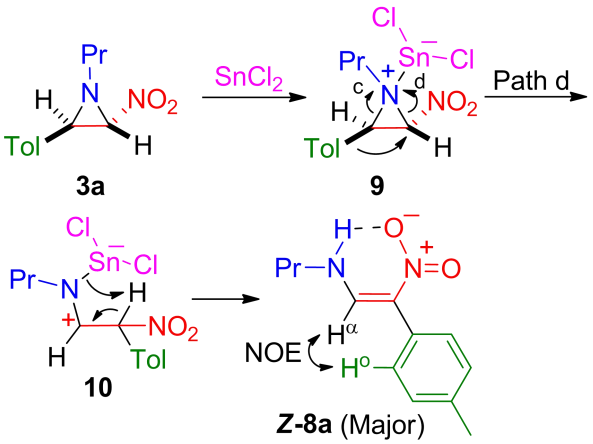


8a

Figure 2. X-ray single crystal structure of **8a** (50% probability factor for the thermal ellipsoids)

2.5 A plausible mechanism for isomerization of 3a into 8a

Lewis acid-catalyzed conversion of aziridines into enamines is hitherto unknown reaction to the best of our knowledge. Sugihara *et al*. reported a BF_3-catalyzed aza-pinacol rearrangement of *N*-tosylaziridines into *N*-tosylimines, tautomers of enamines, in which the hydrogen migration is preferable to the alkyl migration.[20] On the basis of our preliminary results and Sugihara's study, the plausible mechanism for this isomerization is illustrated (Scheme 3). Although a benzylic carbocation should be predominantly formed due to the resonance stabilization after ring opening of aziridine upon coordination of Lewis acid to the ring nitrogen (Path c),[21] the ring closure instead of the migration of the electron-deficient nitro group may easily proceed to regenerate aziridine ring. Thus, the ring opening is considered to proceed in Path d, in which the migration of the electron-rich tolyl group is preferable than the hydrogen migration due to the formation of lower-energy bridged phenonium ion; the subsequent deprotonation affords **8a**. In this step, the (*Z*)-isomer was mainly formed due to the stabilization by an intramolecular hydrogen bond between nitro and amino groups.[10a,19]



Scheme 3. A plausible mechanism for isomerization

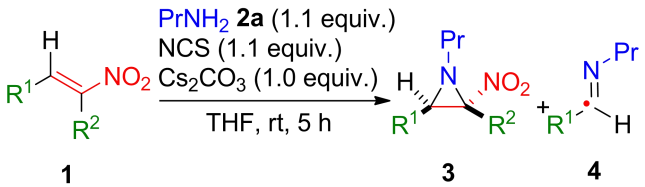
2.6 Study on nitroalkene scope

With the optimized reaction conditions in hand, the scope of these successive reactions was explored. We firstly screened a wide array of nitroalkenes (Table 4). After reactions of nitroalkenes **1** with amine **2a** and NCS, the mixtures were treated by a sequential workup; evaporation of the solvent, aqueous wash, extraction with CH_2Cl_2, and evaporation, which affords the crude aziridines **3** as an oil. Under the optimized reaction conditions, β-nitrostyrenes **1a**–**g** bearing electron-donating Me and MeO groups or weakly electron-withdrawing halo groups successfully gave the corresponding aziridines **3a**–**g** in moderate to good yields, respectively (entries 1–7). However, introduction of the strong

electron-withdrawing groups such as CN and NO_2 markedly decreased the formation of aziridines **3h** and **3i** (entries 8 and 9). In these cases, the low electron density at the benzylic position increases the acidity and decreases the nucleophilicity of the adjacent amino group in the intermediate **5** (Scheme 2). Consequently, the imidization is promoted.

While α-naphthylalkene **1j** afforded aziridine **3j** efficiently, neither electron-rich β-methylalkene **1k** nor electron-poor α-nitroacrylate **1l** underwent aziridination owing to the steric hindrance of the β-substituents, which suppressed the chlorination of carbanion (entries 10–12). Furthermore, the hetaryl-substituted nitroalkenes were also usable as the substrates to afford the corresponding aziridines **3m**–**o**, respectively (entries 13–15). Even though (*Z*)-nitroalkene **1e'** was instead of (*E*)-isomer **1e**, the *trans*-aziridine **3e** was obtained with similar reactivity and selectivity, indicating that both substrates **1e** and **1e'** afforded common intermediate **5** (entries 5 and 16). This protocol was also compatible with the aliphatic nitroalkene **1p**, affording *N*-alkyl-*C*-nitroaziridine **3p** in a moderate yield (entry 17).

Table 4. Scanning of nitroalkenes



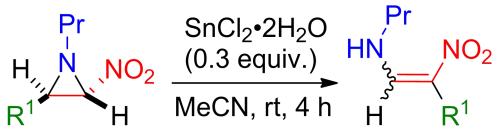
1 **3** **4**

Entry	R^1	R^2		Yield[a] (%)		ratio of **3**/**4**
				3	**4**	
1	4-MeC_6H_4	H	**a**	72	5	93:7
2	4-$MeOC_6H_4$	H	**b**	53[c]	8	87:13
3	2-$MeOC_6H_4$	H	**c**	54[c]	4	93:7
4	3,5-$(MeO)_2C_6H_3$	H	**d**	63	8	89:11
5	C_6H_5	H	**e**	63	9	88:12
6	4-BrC_6H_4	H	**f**	56	16	78:22
7	4-ClC_6H_4	H	**g**	51	20	72:28
8	4-NCC_6H_4	H	**h**	30	24	56:44
9	4-$O_2NC_6H_4$	H	**i**	6[c]	29	17:83
10	2-naphthyl	H	**j**	63	10	86:14
11	4-MeC_6H_4	Me	**k**	0	19	0:100
12	4-MeC_6H_4	COOEt	**l**	0	100	0:100
13	2-thienyl	H	**m**	34[c]	27	56:44
14	2-furyl	H	**n**	40[c]	11	78:22
15	3-pyridyl	H	**o**	46	13	78:22
16[b]	C_6H_5	H	**e'**	55	11	83:17
17	$PhCH_2CH_2$	H	**p**	65	0	100:0

[a]The yield was determined by ^{1}H NMR using 1,1,2,2-tetrachloroethane as internal standard. [b](*Z*)-β-nitrostyrene was used. [c]These compounds were characterized by ^{1}H NMR because they were unstable and rearranged to enamines **8** on silica gel.

The $SnCl_2$-mediated conversions of crude aziridines **3a**–**p** to β-nitroenamines **8a**–**p** were studied (Table 5). While electron-rich aromatic groups efficiently migrated (entries 1–3, 9–11), the efficiency of rearrangement of slightly electron-poor aromatic group decreased (entries 4–7). Furthermore, strongly electron-poor 4-cyanophenyl and 2-pyridyl groups did not migrate at all, which is due to the low migratory ability (entries 8 and 12). *N*-Alkylaziridine **3p** did not undergo the isomerization because of a similar reason (entry 13). In all these successful cases, β-nitroenamines **8** were diastereoselectively obtained in (*Z*)-configuration.

Table 5. Isomerization of aziridines into β-nitroenamines



3 **8**

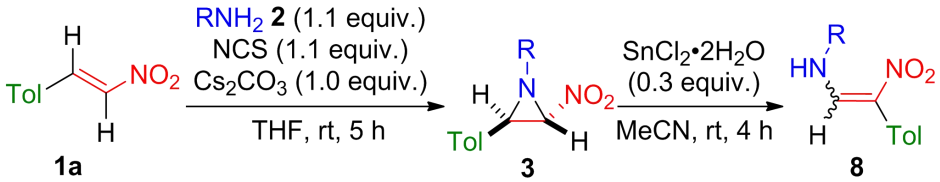
Entry	R^1		Yield (%) of **8**[c]/(***Z***:***E***)[d]
1	4-MeC_6H_4	**a**	76 (93:7)
2	4-$MeOC_6H_4$	**b**	87 (93:7)
3[a]	2-$MeOC_6H_4$	**c**	89 (89:11)
4[b]	3,5-$(MeO)_2C_6H_3$	**d**	45 (93:7)
5[a]	C_6H_5	**e**	40 (94:6)
6[b]	4-BrC_6H_4	**f**	49 (96:4)
7[b]	4-ClC_6H_4	**g**	45 (96:4)
8[b]	4-NCC_6H_4	**h**	n.d.[e]
9[a]	2-naphthyl	**j**	83 (94:6)
10[a]	2-thienyl	**m**	quant. (94:6)
11[a]	2-furyl	**n**	80 (92:8)
12[b]	3-pyridyl	**o**	n.r.[f]
13[a]	$PhCH_2CH_2$	**p**	n.r.[f]

[a]1.0 equiv. of $SnCl_2·2H_2O$ was used. [b]1.5 equiv. of $SnCl_2·2H_2O$ was used. [c]Isolated yield based on **3**.
[d]The ratio of *Z* and *E* isomers was determined by the integral of ^1H NMR. [e]No desired product. [f]No reaction.

2.7 Scanning of amines

Next, the scope of this protocol was expanded to other aliphatic amines such as isobutylamine and *sec*-butylamine, which afforded the corresponding aziridines **3q** and **3r** in moderate to good yields, however, bulkier *tert*-butylamine did not furnish product **3s** while benzylamine afforded product **3t** (Table 6, entries 1–5). In the case of an aromatic amine, no aziridination proceeded (entry 6). Pleasingly, allyl group was well tolerated, facilitating further functionalizations (entry 7). Additionally, it was possible to introduce a hydroxy group on the alkyl group, however decomposition of aziridines **3w** and **3x** to *p*-tolualdehyde was considerably accelerated (entries 8–9). On the other hand, when ethylenediamine was employed to undergo the ring expansion, a complex mixture was obtained (entry 10). The produced crude aziridines were subjected to the next isomerization step without further purification, by which the corresponding β-nitroenamines **8q–x** were furnished in satisfactory yields (Table 1). Regardless of different *N*-substituents in **3**, β-nitroenamines **8** were formed with high *Z*-selectivity.

Table 6. Study on amine scope



Entry	R	Yield (%)	
		3[a]	**8**[b]/(***Z***:***E***)[d]
1	Pr	**3a**: 72	**8a**:76 (93:7)
2	*i*-Bu	**3q**:54	**8q**:73 (93:7)
3[c]	*sec*-Bu	**3r**:31	**8r**:80 (93:7)
4	*t*-Bu	**3s**:0	—
5[c]	Benzyl	**3t**:41	**8t**:86 (92:8)
6	4-MeOC$_6$H$_4$	**3u**:0	—
7	Allyl	**3v**:67	**8v**:82 (92:8)
8	HOCH$_2$CH$_2$	**3w**:30	**8w**:64 (93:7)
9	HOCH$_2$CH$_2$CH$_2$	**3x**:35	**8x**:74 (92:8)
10	H$_2$NCH$_2$CH$_2$	**3y**:cm[e]	—

[a]The yield was determined by ^{1}H NMR using 1,1,2,2-tetrachloroethane as internal standard. [b]Isolated yield based on **3**. [c]1.0 equiv. of SnCl$_2$·2H$_2$O was used. [d]The ratio of *Z* and *E* isomers was determined by the integral of ^{1}H NMR. [e]Complex mixture.

3. Conclusion

In conclusion, we have developed an efficient and highly diastereoselective one-pot synthesis of *trans*-*N*-alkyl-*C*-nitroaziridines **3** upon treatment of nitroalkenes **1** with aliphatic amines **2** and NCS under mild conditions. The resultant aziridines **3** were isomerized into functionalized (*Z*)-β-nitroenamines **8** with high diastereoselectivity through Lewis acid-mediated ring opening and rearrangement. Further efforts about the application of these protocols for synthesizing versatile functionalized compounds is under investigation in our group.

4. Experimental section

4.1 General information

The melting points were determined on SRS-Optimelt Automated Melting Point System, 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 high-resolution mass spectra were measured on an AB SCIEX Triple TOF 4600. The IR spectra were recorded on a JASCO FT/IR-4200 spectrometer. As observed for aziridine **3a**, the isolated yield was considerably diminished compared with NMR yield because of the instability to decompose. Hence, aziridines **3** were subjected to the subsequent reactions without further purification. The yields of unpurified aziridines were determined by ^{1}H NMR using 1,1,2,2-tetrachloroethane as internal standard. Some signals of *E*-isomers of nitroenamines **8** could not be detected in ^{1}H NMR and ^{13}C NMR owing to the low concentration of the compounds in the deuterated solvent. Hence, only spectrum data of *Z*-isomer were shown.

4.2 General procedure for the preparation of nitroalkenes

(*E*)-Aromatic nitrostyrenes **1a**–**k** and **1m**–**o** were successfully synthesized in moderate to good yields upon treatment of aromatic aldehydes with nitromethane or nitroethane in the presence of ammonium acetate.[22]

α-Nitro-β-arylenoate **1l** was prepared through the condensation reaction of *p*-tolualdehyde with ethyl nitroacetate in the presence of dimethylamine hydrochloride.[23]

(*Z*)-nitrostyrene **1e'** was prepared through photoisomerization of the (*E*)-nitrostyrene under the irradiation of a mercury-vapour lamp.[24] It was also confirmed that *Z*-isomer **1e'** did not isomerize to *E*-isomer **1e** under the reaction conditions employed for aziridination.

Aliphatic nitroalkene **1p** was prepared through the condensation reaction of aliphatic aldehyde with nitromethane in the presence of sodium hydroxide followed by MsCl–mediated dehydration.[25]

4.3 General procedure for one-pot synthesis of *trans*-*N*-alkyl-*C*-nitroaziridine 3

trans-2-(4-methylphenyl)-3-nitro-1-propylaziridine (3a)

To a solution of (*E*)-β-nitrostyrenes **1a** (99 mg, 0.61 mmol) and propylamine **2a** (55 μL, 0.67 mmol) in THF (2.5 mL), were added NCS (89 mg, 0.67 mmol) and Cs_2CO_3 (198 mg, 0.61 mmol) successively, and the resultant mixture was stirred at room temperature for 5 h. Then, the solvent was evaporated to afford a reaction mixture as a purple residue, which underwent aqueous workup followed by extraction using CH_2Cl_2. The crude aziridines were obtained as oil after concentration of organic phase, in which aziridine **3a** was included in 72% NMR yield. The mixture was subjected to column chromatography on silica gel to isolate **3a** (eluted with CH_2Cl_2/hexane = 1:2, 41.2 mg, 0.19 mmol, 31% yield) as a yellow oil.

^{1}H NMR ($CDCl_3$) δ 0.89 (t, *J* = 7.2 Hz, 3H), 1.50–1.65 (m, 2H), 2.36 (s, 3H), 2.51–2.64 (m,

2H), 3.85 (d, *J* = 1.2 Hz, 1H), 4.90 (d, *J* = 1.2 Hz, 1H), 7.17 (s, 4H, overlap); ^{13}C NMR ($CDCl_3$) δ 11.6 (CH_3), 21.2 (CH_3), 22.6 (CH_2), 48.3 (CH), 51.9 (CH_2), 75.2 (CH), 128.2 (CH), 128.5 (C), 129.4 (CH), 138.8 (C); IR (ATR/cm^{-1}) ν 1559; HRMS (ESI/TOF) Calcd for $C_{12}H_{16}N_2O_2Na$ [$(M+Na)^+$]: 243.1104, found 243.1100.

***trans*-2-(4-methoxyphenyl)-3-nitro-1-propylaziridine (3b)**

Yellow oil (76.4 mg, 0.32 mmol, 53%). ^{1}H NMR ($CDCl_3$) δ 0.89 (t, *J* = 7.2 Hz, 3H), 1.49–1.64 (m, 2H), 2.50–2.62 (m, 2H), 3.81 (s, 3H), 3.83 (d, *J* = 1.2 Hz, 1H), 4.88 (d, *J* = 1.2 Hz, 1H), 6.89 (d, *J* = 8.4 Hz, 2H), 7.20 (d, *J* = 8.4 Hz, 2H).

***trans*-2-(2-methoxyphenyl)-3-nitro-1-propylaziridine (3c)**

Yellow oil (77.9 mg, 0.33 mmol, 54% yield). ^{1}H NMR ($CDCl_3$) δ 0.90 (t, *J* = 7.2 Hz, 3H), 1.53–1.63 (m, 2H), 2.36–2.42 (m, 1H), 2.58–2.66 (m, 1H), 3.87 (s, 3H), 4.01 (d, *J* = 1.6 Hz, 1H), 4.90 (d, *J* = 1.6 Hz, 1H), 6.89–6.94 (m, 2H), 7.17 (dd, *J* = 1.6, 7.6 Hz, 1H), 7.17 (ddd, *J* = 1.6, 7.6, 7.6 Hz, 1H).

***trans*-2-(3,5-dimethoxyphenyl)-3-nitro-1-propylaziridine (3d)**

Yellow oil (101.9 mg, 0.38 mol, 63% yield). ^{1}H NMR ($CDCl_3$) δ 0.93 (t, *J* = 7.6 Hz, 3H), 1.53–1.67 (m, 2H), 2.58–2.73 (m, 2H), 3.78 (d, *J* = 1.2 Hz, 1H), 3.79 (s, 6H), 4.88 (d, *J* = 1.2 Hz, 1H), 6.43 (s, 3H, overlap); ^{13}C NMR ($CDCl_3$) δ 11.6 (CH_3), 22.6 (CH_2), 48.3 (CH), 52.0 (CH_2), 55.4 (CH_3), 75.2 (CH), 100.5 (CH), 106.1 (CH), 134.5 (C), 161.1 (C); IR (ATR/cm^{-1}) ν 1554; HRMS (ESI/TOF) Calcd for $C_{13}H_{19}N_2O_4$ [$(M+H)^+$]: 267.1339, found 267.1326.

***trans*-3-nitro-2-phenyl-1-propylaziridine (3e)**

Yellow oil (78.3 mg, 0.38 mmol, 63% yield). ^{1}H NMR ($CDCl_3$) δ 0.90 (t, *J* = 7.2 Hz, 3H), 1.52-1.68 (m, 2H), 2.56-2.67 (m, 2H), 3.87 (d, *J* = 1.2 Hz, 1H), 4.93 (d, *J* = 1.2 Hz, 1H), 7.28-7.30 (m, 2H), 7.36-7.39 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 11.6 (CH_3), 22.6 (CH_2), 48.3 (CH), 52.0 (CH_2), 75.2 (CH), 128.2 (CH), 128.7 (CH), 128.8 (CH), 132.0 (C); IR (ATR/cm^{-1}) ν 1558; HRMS (ESI/TOF) Calcd for $C_{11}H_{15}N_2O_2$ [$(M+H)^+$]: 207.1128, found 207.1124.

***trans*-2-(4-bromophenyl)-3-nitro-1-propylaziridine (3f)**

Yellow oil (96.3 mg, 0.34 mmol, 56% yield). ^{1}H NMR ($CDCl_3$) δ 0.92 (t, *J* = 7.2 Hz, 3H), 1.52–1.66 (m, 2H), 2.62–2.73 (m, 2H), 3.78 (d, *J* = 1.2 Hz, 1H), 4.87 (d, *J* = 1.2 Hz, 1H), 7.17 (d, *J* = 8.4 Hz, 2H), 7.50 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 11.6 (CH_3), 22.6 (CH_2), 47.5 (CH), 52.0 (CH_2), 75.1 (CH), 123.0 (C), 129.5 (CH), 131.6 (C), 131.9 (CH); IR (ATR/cm^{-1}) ν 1559; HRMS (ESI/TOF) Calcd for $C_{11}H_{14}BrN_2O_2$ [$(M+H)^+$]: 285.0233, found 285.0222.

***trans*-2-(4-chlorophenyl)-3-nitro-1-propylaziridine (3g)**

Yellow oil (73.9 mg, 0.31 mmol, 51% yield). ^{1}H NMR ($CDCl_3$) δ 0.92 (t, *J* = 7.2 Hz, 3H),

1.50–1.68 (m, 2H), 2.62–2.73 (m, 2H), 3.79 (d, *J* = 1.2 Hz, 1H), 4.87 (d, *J* = 1.2 Hz, 1H), 7.23 (d, *J* = 8.4 Hz, 2H), 7.35 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 11.6 (CH_3), 22.6 (CH_2), 47.4 (CH), 52.0 (CH_2), 75.2 (CH), 129.0 (CH), 129.2 (CH), 131.1 (C), 134.9 (C); IR (ATR/cm^{-1}) ν 1559; HRMS (ESI/TOF) Calcd for $C_{11}H_{14}ClN_2O_2$ [$(M+H)^+$]: 241.0738, found 241.0727.

***trans*-2-(4-cyanophenyl)-3-nitro-1-propylaziridine (3h)**

Yellow oil (42.0 mg, 0.18 mmol, 30% yield). ^{1}H NMR ($CDCl_3$) δ 0.95 (t, *J* = 7.2 Hz, 3H), 1.74 (tq, *J* = 7.2, 7.2 Hz, 2H), 2.83 (t, *J* = 7.2 Hz, 2H), 3.80 (d, *J* = 1.2 Hz, 1H), 4.90 (d, *J* = 1.2 Hz, 1H), 7.42 (d, *J* = 8.4 Hz, 2H), 7.67 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 11.6 (CH_3), 22.7 (CH_2), 47.0 (CH), 52.2 (CH_2), 75.2 (CH), 112.7 (C), 118.2 (C), 128.1 (CH), 132.5 (CH), 139.0 (C); IR (ATR/cm^{-1}) ν 1560; HRMS (ESI/TOF) Calcd for $C_{12}H_{14}N_3O_2$ [$(M+H)^+$]: 232.1081, found 232.1085.

***trans*-2-(2-naphthyl)-3-nitro-1-propylaziridine (3j)**

Yellow oil (97.6 mg, 0.38 mmol, 63% yield). ^{1}H NMR ($CDCl_3$) δ 0.90 (t, *J* = 7.2 Hz, 3H), 1.53–1.67 (m, 2H), 2.59–2.70 (m, 2H), 4.01 (d, *J* = 1.6 Hz, 1H), 5.04 (d, *J* = 1.6 Hz, 1H), 7.35 (dd, *J* = 1.6, 8.4 Hz, 1H), 7.49–7.54 (m, 2H), 7.76 (d, *J* = 1.6 Hz, 1H), 7.83–7.88 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 11.6 (CH_3), 22.7 (CH_2), 48.5 (CH), 52.1 (CH_2), 75.3 (CH), 125.2 (CH), 126.7 (CH), 126.8 (CH), 127.7 (CH), 127.8 (CH), 127.9 (CH), 128.6 (CH), 129.5 (C), 133.0 (C), 133.3 (C); IR (ATR/cm^{-1}) ν 1558; HRMS (ESI/TOF) Calcd for $C_{15}H_{17}N_2O_2$ [$(M+H)^+$]: 257.1285, found 257.1272.

***trans*-3-nitro-1-propyl-2-(2-thienyl)aziridine (3m)**

Yellow oil (44.1 mg, 0.21 mmol, 34% yield). ^{1}H NMR ($CDCl_3$) δ 0.91 (t, *J* = 7.2 Hz, 3H), 1.68–1.76 (m, 2H), 2.60 (t, *J* = 7.2 Hz, 2H), 4.07 (d, *J* = 1.2 Hz, 1H), 4.87 (d, *J* = 1.2 Hz, 1H), 7.03 (dd, *J* = 4.0, 4.4 Hz, 1H), 7.28 (d, *J* = 4.0 Hz, 1H), 7.37 (d, *J* = 4.4 Hz, 1H).

***trans*-2-(2-furyl)-1-propyl-3-nitroaziridine (3n)**

Yellow oil (47.1 mg, 0.24 mmol, 40% yield). ^{1}H NMR ($CDCl_3$) δ 0.89 (t, *J* = 7.2 Hz, 3H), 1.49–1.62 (m, 2H), 2.48–2.54 (m, 1H), 2.61–2.67 (m, 1H), 3.88 (d, *J* = 1.6 Hz, 1H), 5.01 (d, *J* = 1.6 Hz, 1H), 6.41 (dd, *J* = 2.0, 3.6 Hz, 1H), 6.48 (d, *J* = 3.6 Hz, 1H), 7.42 (d, *J* = 2.0 Hz, 1H).

***trans*-3-nitro-1-propyl-2-(3-pyridyl)aziridine (3o)**

Yellow oil (57.4 mg, 0.28 mmol, 46% yield). ^{1}H NMR ($CDCl_3$) δ 0.93 (t, *J* = 7.2 Hz, 3H), 1.60 (tq, *J* = 7.2, 7.2 Hz, 2H), 2.72 (t, *J* = 7.2 Hz, 2H), 3.83 (d, *J* = 1.2 Hz, 1H), 4.95 (d, *J* = 1.2 Hz, 1H), 7.30–7.35 (m, 1H), 7.59 (d, *J* = 8.0 Hz, 1H), 8.60 (s, 2H, overlap); ^{13}C NMR ($CDCl_3$) δ 11.5 (CH_3), 22.5 (CH_2), 45.6 (CH), 52.0 (CH_2), 74.7 (CH), 123.4 (CH), 128.6 (C),

135.2 (CH), 149.4 (CH), 150.0 (CH); IR (ATR/cm^{-1}) ν 1559; HRMS (ESI/TOF) Calcd for $C_{10}H_{14}N_3O_2$ [$(M+H)^+$]: 208.1081, found 208.1078.

***trans*-3-nitro-2-(2-phenylethyl)-1-propylaziridine (3p)**

Colorless oil (92.0 mg, 0.39 mmol, 65% yield). ^1H NMR ($CDCl_3$) δ 0.94 (t, *J* = 7.2 Hz, 3H), 1.56–1.65 (m, 2H), 1.76–1.85 (m, 1H), 1.92–2.00 (m, 1H), 2.49–2.55 (m, 1H), 2.62–2.68 (m, 1H), 2.72–2.87 (m, 3H), 4.20 (d, *J* = 1.2 Hz, 1H), 7.16 (dd, *J* = 1.2, 8.0 Hz, 2H), 7.22 (tt, *J* = 1.2, 8.0 Hz, 1H), 7.30 (dd, *J* = 8.0, 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 11.6 (CH_3), 22.8 (CH_2), 27.7 (CH_2), 33.6 (CH_2), 46.1 (CH), 51.9 (CH_2), 75.5 (CH), 126.5 (CH), 128.2 (CH), 128.7 (CH), 140.1 (C); IR (ATR/cm^{-1}) ν 1555; HRMS (ESI/TOF) Calcd for $C_{13}H_{19}N_2O_2$ [$(M+H)^+$]: 235.1441, found 235.1430.

***trans*-2-(4-methylphenyl)-1-(2-methylpropyl)-3-nitroaziridine (3q)**

Yellow oil (77.5 mg, 0.33 mmol, 54% yield). ^1H NMR ($CDCl_3$) δ 0.90 (d, *J* = 6.8 Hz, 3H), 0.94 (d, *J* = 6.8 Hz, 3H), 1.76–1.95 (m, 1H), 2.36 (s, 3H), 2.36–2.45 (m, 1H), 2.49-2.54 (m, 1H), 3.80 (d, *J* = 1.6 Hz, 1H), 4.89 (d, *J* = 1.6 Hz, 1H), 7.17 (s, 4H, overlap); ^{13}C NMR ($CDCl_3$) δ 20.5 (CH_3), 20.5 (CH_3), 21.2 (CH_3), 28.9 (CH), 48.1 (CH), 57.9 (CH_2), 75.7 (CH), 128.0 (CH), 129.4 (CH), 129.7 (C), 138.8 (C); IR (ATR/cm^{-1}) ν 1557; HRMS (ESI/TOF) Calcd for $C_{13}H_{19}N_2O_2$ [$(M+H)^+$]: 235.1441, found 235.1446.

***trans*-1-(2-butyl)-2-(4-methylphenyl)-3-nitroaziridine (3r)**

Yellow oil (43.8 mg, 0.19 mmol, 31% yield). ^1H NMR ($CDCl_3$) δ 0.74 (t, *J* = 7.2 Hz, 1H), 0.89-0.93 (m, 4H, overlap), 1.20 (d, *J* = 6.0 Hz, 1H), 1.36–1.39 (m, 1H), 1.54-1.66 (m, 1H), 2.35 (s, 3H), 2.56–2.62 (m, 1H), 3.85 (d, *J* = 1.2 Hz, 1H), 4.96 (d, *J* = 1.2 Hz, 1H), 7.17 (s, 4H, overlap); ^{13}C NMR ($CDCl_3$) δ 10.0 (CH_3), 18.6 (CH_3), 21.1 (CH_3), 29.6 (CH_2), 48.2 (CH), 55.9 (CH), 74.6 (CH), 127.9 (CH), 129.3 (CH), 129.4 (C), 138.7 (C); IR (ATR/cm^{-1}) ν 1559; HRMS (ESI/TOF) Calcd for $C_{13}H_{19}N_2O_2$ [$(M+H)^+$]: 235.1441, found 235.1431.

***trans*-2-(4-methylphenyl)-3-nitro-1-(phenylmethyl)aziridine (3t)**

Yellow oil (67.1 mg, 0.25 mmol, 41% yield). ^1H NMR ($CDCl_3$) δ 2.35 (s, 3H), 3.75 (d, *J* = 14.0 Hz, 1H), 3.83 (d, *J* = 14.0 Hz, 1H), 3.99 (d, *J* = 1.2 Hz, 1H), 5.00 (d, *J* = 1.2 Hz, 1H), 7.16 (s, 4H, overlap), 7.27–7.35 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 21.2 (CH_3), 48.9 (CH), 53.5 (CH_2), 74.8 (CH), 127.6 (CH), 128.0 (CH), 128.2 (C), 128.4 (CH), 128.6 (CH), 129.5 (CH), 137.0 (C), 139.1 (C); IR (ATR/cm^{-1}) ν 1559; HRMS (ESI/TOF) Calcd for $C_{16}H_{17}N_2O_2$ [$(M+H)^+$]: 269.1285, found 269.1274.

***trans*-2-(4-methylphenyl)-3-nitro-1-(propene-3-yl)aziridine (3v)**

Yellow oil (88.7 mg, 0.41 mmol, 67% yield). ^1H NMR ($CDCl_3$) δ 2.35 (s, 3H), 3.18 (dd, *J* = 4.8, 14.0 Hz, 1H), 3.28 (dd, *J* = 4.8, 14.0 Hz, 1H), 3.92 (d, *J* = 1.6 Hz, 1H), 4.94 (d, *J* = 1.6

Hz, 1H), 5.14 (dd, J = 1.2, 9.2 Hz, 1H), 5.16 (dd, J = 1.2, 17.2 Hz, 1H), 5.83–5.93 (m, 1H), 7.18 (s, 4H, overlap); ^{13}C NMR ($CDCl_3$) δ 21.2 (CH_3), 48.4 (CH), 52.2 (CH_2), 74.6 (CH), 117.7 (CH_2), 128.0 (C), 128.4 (CH), 129.4 (CH), 133.2 (C), 139.0 (C); IR (ATR/cm^{-1}) ν 1558; HRMS (ESI/TOF) Calcd for $C_{12}H_{15}N_2O_2$ [$(M+H)^+$]: 219.1128, found 219.1117.

***trans*-1-(2-hydroxyethyl)-2-(4-methylphenyl)-3-nitroaziridine (3w)**

Yellow oil (39.6 mg, 0.18 mmol, 30% yield). ^{1}H NMR ($CDCl_3$) δ 2.35 (s, 3H), 2.72 (br s, 1H), 2.73 (t, J = 5.2 Hz, 2H), 3.68–3.86 (m, 2H), 3.87 (d, J = 1.6 Hz, 1H), 5.07 (d, J = 1.6 Hz, 1H), 7.18 (s, 4H, overlap); ^{13}C NMR ($CDCl_3$) δ 21.1 (CH_3), 47.6 (CH), 51.8 (CH_2), 61.4 (CH_2), 75.0 (CH), 127.7 (C), 128.4 (CH), 129.5 (CH), 139.1 (C); IR (ATR/cm^{-1}) ν 1557; HRMS (ESI/TOF) Calcd for $C_{11}H_{15}N_2O_3$ [$(M+H)^+$]: 223.1077, found 223.1066.

***trans*-1-(3-hydroxypropyl)-2-(4-methylphenyl)-3-nitroaziridine (3x)**

Yellow oil (49.9 mg, 0.21 mmol, 35% yield). ^{1}H NMR ($CDCl_3$) δ 1.73–1.77 (m, 2H), 2.25 (br s, 1H), 2.36 (s, 3H), 2.72 (t, J = 6.4 Hz, 2H), 3.74 (t, J = 5.6 Hz, 2H), 3.89 (s, 1H), 4.98 (s, 1H), 7.17 (s, 4H, overlap); ^{13}C NMR ($CDCl_3$) δ 21.2 (CH_3), 31.5 (CH_2), 47.8 (CH_2), 48.4 (CH), 61.2 (CH_2), 74.9 (CH), 127.6 (C), 128.4 (CH), 129.5 (CH), 139.1 (C); IR (ATR/cm^{-1}) ν 1558; HRMS (ESI/TOF) Calcd for $C_{12}H_{17}N_2O_3$ [$(M+H)^+$]: 237.1234, found 237.1228.

4.4 Isomerization of *trans*-*N*-alkyl-*C*-nitroaziridine 3a to β-nitroenamine 8a

(*Z*)-1-(4-methylphenyl)-1-nitro-2-(propylamino)ethene (8a)

To a solution of *trans*-*N*-alkyl-*C*-nitroaziridines **3a** (44 mg, 0.20 mmol) in MeCN (1.5 mL), was added $SnCl_2{\cdot}2H_2O$ (14 mg, 0.06 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, which was treated by column chromatography on silica gel to afford β-nitroenamines **8a** (eluted with CH_2Cl_2, 33.1 mg, 0.15 mmol, 76% yield) as a yellow solid.

Mp 84−86 °C. ^{1}H NMR ($CDCl_3$) δ 1.01 (t, J = 7.2 Hz, 3H), 1.71 (tq, J = 7.2, 7.2 Hz, 2H), 2.36 (s, 3H), 3.38 (dt, J = 6.8, 7.2 Hz, 2H), 7.08 (d, J = 14.0 Hz, 1H), 7.18 (d, J = 8.0 Hz, 2H), 7.25 (d, J = 8.0 Hz, 2H), 9.45−9.55 (br, 1H); ^{13}C NMR ($CDCl_3$) δ 11.0 (CH_3), 21.2 (CH_3), 24.1 (CH_2), 51.6 (CH_2), 122.4 (C), 129.0 (CH), 129.6 (CH), 130.2 (C), 137.7 (C), 148.4 (CH); IR (ATR/cm^{-1}) ν 3288, 1646, 1517; HRMS (ESI/TOF) Calcd for $C_{12}H_{16}N_2O_2Na$ [$(M+Na)^+$]: 243.1104, found 243.1093.

When other aziridines **3** were used, experiments were conducted in a similar way.

(*Z*)-1-(4-methoxyphenyl)-1-nitro-2-(propylamino)ethene (8b)

Yellow solid (41.1 mg, 0.17 mmol, 87%). Mp 122−124 °C; ^{1}H NMR ($CDCl_3$,) δ 1.01 (t, J = 7.2 Hz, 3H), 1.71 (tq, J = 7.2, 7.2 Hz, 2H), 3.37 (dt, J = 6.8, 7.2 Hz, 2H), 3.81 (s, 3H), 6.98 (d,

J = 8.4 Hz, 2H), 7.06 (d, *J* = 14.0 Hz, 1H), 7.22 (d, *J* = 8.4 Hz, 2H), 9.45−9.53 (br, 1H); ^{13}C NMR ($CDCl_3$) δ 11.0 (CH_3), 24.0 (CH_2), 51.6 (CH_2), 55.3 (CH_3), 113.8 (CH), 122.1 (C), 125.5 (C), 131.1 (CH), 148.3 (CH), 159.2 (C); IR (ATR/cm^{-1}) ν 3291, 1643, 1517; HRMS (ESI/TOF) Calcd for $C_{12}H_{17}N_2O_3$ [(M+H)$^+$]: 237.1234, found 237.1232.

(*Z*)-1-(2-methoxyphenyl)-1-nitro-2-(propylamino)ethene (8c)

Yellow oil (41.9 mg, 0.18 mmol, 89%). ^{1}H NMR ($CDCl_3$) δ 1.00 (t, *J* = 7.2 Hz, 3H), 1.70 (tq, *J* = 7.2, 7.2 Hz, 2H), 3.35 (dt, *J* = 6.8, 7.2 Hz, 2H), 3.80 (s, 3H), 6.92 (d, *J* = 8.0 Hz, 1H), 6.96 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.00 (d, *J* = 14.4 Hz, 1H), 7.20 (dd, *J* = 1.6, 8.0 Hz, 1H), 7.33 (ddd, *J* = 1.6, 8.0, 8.0 Hz, 1H), 9.42−9.50 (br, 1H); ^{13}C NMR ($CDCl_3$) δ 11.0 (CH_3), 24.0 (CH_2), 51.5 (CH_2), 55.7 (CH_3), 111.2 (CH), 118.5 (C), 120.5 (CH), 122.1 (C), 130.1 (CH), 132.0 (CH), 149.0 (CH), 157.9 (C); IR (ATR/cm^{-1}) ν 3300, 1646, 1560; HRMS (ESI/TOF) Calcd for $C_{12}H_{17}N_2O_3$ [(M+H)$^+$]: 237.1234, found 237.1240.

(*Z*)-1-(3,5-dimethoxyphenyl)-1-nitro-2-(propylamino)ethene (8d)

Yellow oil (23.6 mg, 0.09 mmol, 45%). ^{1}H NMR ($CDCl_3$) δ 1.01 (t, *J* = 7.2 Hz, 3H), 1.71 (tq, *J* = 7.2, 7.2 Hz, 2H), 3.38 (dt, *J* = 6.8, 7.2 Hz, 2H), 6.42 (t, *J* = 2.4 Hz, 1H), 6.53 (d, *J* = 2.4 Hz, 2H), 7.12 (d, *J* = 14.0 Hz, 1H), 9.47−9.53 (br, 1H); ^{13}C NMR ($CDCl_3$) δ 11.0 (CH_3), 24.0 (CH_2), 51.7 (CH_2), 55.4 (CH_3), 99.9 (CH), 107.9 (CH), 122.3 (C), 134.9 (C), 148.6 (CH), 160.6 (C); IR (ATR/cm^{-1}) ν 3293, 1645, 1559; HRMS (ESI/TOF) Calcd for $C_{13}H_{19}N_2O_4$ [(M+H)$^+$]: 267.1339, found 267.1338.

(*Z*)-1-nitro-1-phenyl-2-(propylamino)ethene (8e)

Yellow oil (16.2 mg, 0.08 mmol, 40%). ^{1}H NMR ($CDCl_3$) δ 1.02 (t, *J* = 7.2 Hz, 3H), 1.72 (tq, *J* = 7.2, 7.2 Hz, 2H), 3.39 (dt, *J* = 6.8, 7.2 Hz, 2H), 7.10 (d, *J* = 13.6 Hz, 1H), 7.28−7.33 (m, 1H), 7.35−7.38 (m, 4H), 9.50−9.56 (br, 1H); ^{13}C NMR ($CDCl_3$) δ 11.0 (CH_3), 24.0 (CH_2), 51.7 (CH_2), 126.8 (C), 127.7 (CH), 128.3 (CH), 129.6 (CH), 133.1 (C), 148.6 (CH); IR (ATR/cm^{-1}) ν 3277, 1646, 1559; HRMS (ESI/TOF) Calcd for $C_{11}H_{15}N_2O_2$ [(M+H)$^+$]: 207.1128, found 207.1131.

(*Z*)-1-(4-bromophenyl)-1-nitro-2-(propylamino)ethene (8f)

Yellow solid (27.8 mg, 0.10 mmol, 49%). Mp 61−62 °C; ^{1}H NMR ($CDCl_3$) δ 1.02 (t, *J* = 7.2 Hz, 3H), 1.73 (tq, *J* = 7.2, 7.2 Hz, 2H), 3.40 (dt, *J* = 6.8, 7.2 Hz, 2H), 7.08 (d, *J* = 14.0 Hz, 1H), 7.24 (d, *J* = 8.4 Hz, 2H), 7.50 (d, *J* = 8.4 Hz, 2H), 9.47−9.55 (br, 1H); ^{13}C NMR ($CDCl_3$) δ 11.0 (CH_3), 24.0 (CH_2), 51.7 (CH_2), 121.5 (C), 121.7 (C), 131.1 (CH), 131.5 (CH), 132.0 (C), 148.3 (CH); IR (ATR/cm^{-1}) ν 3268, 1637, 1539; HRMS (ESI/TOF) Calcd for $C_{11}H_{14}BrN_2O_2$ [(M+H)$^+$]: 285.0233, found 285.0235.

(*Z*)-1-(4-chlorophenyl)-1-nitro-2-(propylamino)ethene (8g)

Yellow solid (21.3 mg, 0.09 mmol, 45%). Mp 77−79 °C; ^{1}H NMR ($CDCl_3$) δ 1.02 (t, *J* = 7.2 Hz, 3H), 1.72 (tq, *J* = 7.2, 7.2 Hz, 2H), 3.40 (dt, *J* = 6.8, 7.2 Hz, 2H), 7.08 (d, *J* = 14.0 Hz, 1H), 7.30 (d, *J* = 8.8 Hz, 2H), 7.34 (d, *J* = 8.8 Hz, 2H), 9.48−9.54 (br, 1H); ^{13}C NMR ($CDCl_3$) δ 11.0 (CH_3), 24.0 (CH_2), 51.7 (CH_2), 121.5 (C), 128.5 (CH), 130.9 (CH), 131.5 (C), 133.6 (C), 148.3 (CH); IR (ATR/cm^{-1}) ν 3280, 1642, 1539; HRMS (ESI/TOF) Calcd for $C_{11}H_{14}ClN_2O_2$ [$(M+H)^+$]: 241.0738, found 241.0749.

(*Z*)-1-(2-naphthyl)-1-nitro-2-(propylamino)ethene (8j)

Yellow solid (42.3 mg, 0.17 mmol, 83%). Mp 82−85 °C; ^{1}H NMR ($CDCl_3$) δ 1.02 (t, *J* = 7.2 Hz, 3H), 1.72 (tq, *J* = 7.2, 7.2 Hz, 2H), 3.40 (dt, *J* = 6.8, 7.2 Hz, 2H), 7.21 (d, *J* = 14.0 Hz, 1H), 7.45−7.49 (m, 2H), 7.56 (dd, *J* = 1.2, 8.4 Hz, 1H), 7.71 (d, *J* = 1.2 Hz, 1H), 7.78−7.83 (m, 3H), 9.54−9.60 (br, 1H); ^{13}C NMR ($CDCl_3$) δ 11.0 (CH_3), 24.1 (CH_2), 51.7 (CH_2), 122.5 (C), 126.2 (CH), 126.3 (CH), 127.6 (CH), 127.7 (CH), 127.8 (CH), 127.8 (CH), 127.9 (CH), 130.7 (C), 132.7 (C), 133.2 (C), 148.8 (CH); IR (ATR/cm^{-1}) ν 3295, 1643, 1560; HRMS (ESI/TOF) Calcd for $C_{15}H_{17}N_2O_2$ [$(M+H)^+$]: 257.1285, found 257.1283.

(*Z*)-1-nitro-2-propylamino-1-(2-thienyl)ethene (8m)

Yellow oil (42.5 mg, 0.20 mmol, quant.). ^{1}H NMR ($CDCl_3$) δ 1.03 (t, *J* = 7.2 Hz, 3H), 1.74 (tq, *J* = 7.2, 7.2 Hz, 2H), 3.44 (dt, *J* = 6.8, 7.2 Hz, 2H), 6.99 (dd, *J* = 3.6, 5.2 Hz, 1H), 7.03 (d, *J* = 3.6 Hz, 1H), 7.30 (d, *J* = 5.2 Hz, 1H), 7.43 (d, *J* = 14.0 Hz, 1H), 9.74−9.80 (br, 1H); ^{13}C NMR ($CDCl_3$) δ 11.0 (CH_3), 23.9 (CH_2), 51.9 (CH_2), 117.6 (C), 123.8 (CH), 125.7 (CH), 126.2 (CH), 134.8 (C), 148.3 (CH); IR (ATR/cm^{-1}) ν 3288, 1646, 1559; HRMS (ESI/TOF) Calcd for $C_9H_{13}N_2O_2S$ [$(M+H)^+$]: 213.0692, found 213.0691.

(*Z*)-1-(2-furyl)-1-nitro-2-(propylamino)ethene (8n)

Yellow solid (31.1 mg, 0.16 mmol, 80%). Mp 63−64 °C; ^{1}H NMR ($CDCl_3$) δ 1.03 (t, *J* = 7.2 Hz, 3H), 1.75 (tq, *J* = 7.2, 7.2 Hz, 2H), 3.47 (dt, *J* = 6.8, 7.2 Hz, 2H), 6.44 (dd, *J* = 1.6, 3.6 Hz, 1H), 6.81 (dd, *J* = 0.8, 3.6 Hz, 1H), 7.31 (dd, *J* = 0.8, 1.6 Hz, 1H), 7.68 (d, *J* = 14.4 Hz, 1H), 9.82−9.90 (br, 1H); ^{13}C NMR ($CDCl_3$) δ 10.9 (CH_3), 23.9 (CH_2), 52.1 (CH_2), 107.6 (CH), 111.6 (CH), 116.4 (C), 140.1 (CH), 145.8 (C), 147.7 (CH); IR (ATR/cm^{-1}) ν 3255, 1653, 1559; HRMS (ESI/TOF) Calcd for $C_9H_{13}N_2O_3$ [$(M+H)^+$]: 197.0921, found 197.0916.

(*Z*)-1-(4-methylphenyl)-2-[(2-methylpropyl)amino]-1-nitroethene (8q)

Yellow oil (34.1 mg, 0.15 mmol, 73%). ^{1}H NMR ($CDCl_3$) δ 1.00 (d, *J* = 6.8 Hz, 6H), 1.91 (triple septet, *J* = 6.4, 6.8 Hz, 1H), 2.36 (s, 3H), 3.22 (dt, *J* = 6.4, 6.4 Hz, 2H), 7.05 (d, *J* = 14.0 Hz, 1H), 7.18 (1H, *J* = 8.0 Hz, 2H), 7.25 (1H, *J* = 8.0 Hz, 2H), 9.50−9.59 (br, 1H); ^{13}C NMR ($CDCl_3$) δ 19.7 (CH_3), 21.2 (CH_3), 29.7 (CH), 57.6 (CH_2), 122.3 (C), 129.0 (CH), 129.6

(CH), 130.2 (C), 137.6 (C), 148.7 (CH); IR (ATR/cm^{-1}) ν 3281, 1643, 1517; HRMS (ESI/TOF) Calcd for $C_{13}H_{19}N_2O_2$ [(M+H)$^+$]: 235.1441, found 235.1431.

(*Z*)-2-(2-butylamino)-1-(4-methylphenyl)-1-nitroethene (8r)

Yellow solid (37.4 mg, 0.16 mmol, 80%). Mp 68−70 °C; ^{1}H NMR ($CDCl_3$) δ 0.99 (t, *J* = 7.2 Hz, 3H), 1.35 (d, *J* = 6.4 Hz, 3H), 1.61−1.69 (m, 2H), 2.36 (s, 3H), 3.37 (dtq, *J* = 6.4, 6.8, 7.2 Hz, 1H), 7.11 (d, *J* = 14.0 Hz, 1H), 7.18 (d, *J* = 8.0 Hz, 2H), 7.26 (d, *J* = 8.0 Hz, 2H), 9.40−9.48 (br, 1H); ^{13}C NMR ($CDCl_3$) δ 10.3 (CH_3), 21.2 (CH_3), 21.3 (CH_3), 30.5 (CH_2), 57.7 (CH), 122.1 (C), 129.0 (CH), 129.6 (CH), 130.3 (C), 137.6 (C), 146.9 (CH); IR (ATR/cm^{-1}) ν 3276, 1638, 1517; HRMS (ESI/TOF) Calcd for $C_{13}H_{19}N_2O_2$ [(M+H)$^+$]: 235.1441, found 235.1442.

(*Z*)-1-(4-methylphenyl)-1-nitro-2-[(phenylmethyl)amino]ethene (8t)

Yellow solid (45.7 mg, 0.17 mmol, 86%). Mp 92−94 °C; ^{1}H NMR ($CDCl_3$) δ 2.35 (s, 3H), 4.57 (d, *J* = 6.0 Hz, 2H), 7.12 (d, *J* = 14.0 Hz, 1H), 7.16−7.42 (m, 9H), 9.60−9.68 (br, 1H); ^{13}C NMR ($CDCl_3$) δ 21.2 (CH_3), 53.3 (CH_2), 123.2 (C), 127.5 (CH), 128.5 (CH), 129.1 (CH), 129.2 (CH), 129.6 (CH), 130.0 (C), 136.1 (C), 137.8 (C), 147.7 (CH); IR (ATR/cm^{-1}) ν 3287, 1640, 1517; HRMS (ESI/TOF) Calcd for $C_{16}H_{17}N_2O_2$ [(M+H)$^+$]: 269.1285, found 269.1284.

(*Z*)-1-(4-methylphenyl)-1-nitro-2-[(propene-3-yl)amino]ethene (8v)

Yellow solid (35.6 mg, 0.16 mmol, 82%). Mp 88−90 °C; ^{1}H NMR ($CDCl_3$) δ 2.35 (s, 3H), 4.01 (dd, *J* = 5.6, 5.6 Hz, 2H), 5.30 (dd, *J* = 0.8, 8.8 Hz, 1H), 5.33 (dd, *J* = 0.8, 17.2 Hz, 1H), 5.87-5.97 (m, 1H), 7.05 (d, *J* = 13.6 Hz, 1H), 7.18 (d, *J* = 8.0 Hz, 2H), 7.24 (d, *J* = 8.0 Hz, 2H), 9.38−9.46 (br, 1H); ^{13}C NMR ($CDCl_3$) δ 21.2 (CH_3), 51.5 (CH_2), 118.7 (CH_2), 123.1 (C), 129.0 (CH), 129.6 (CH), 130.0 (C), 132.8 (CH), 137.8 (C), 147.8 (CH); IR (ATR/cm^{-1}) ν 3292, 1637, 1518; HRMS (ESI/TOF) Calcd for $C_{12}H_{15}N_2O_2$ [(M+H)$^+$]: 219.1128, found 219.1128.

(*Z*)-2-[(2-hydroxyethyl)amino]]-1-(4-methylphenyl)-1-nitroethene (8w)

Yellow solid (28.3 mg, 0.13 mmol, 64%). Mp 96−98 °C; ^{1}H NMR ($CDCl_3$) δ 2.34 (s, 3H), 2.97−3.02 (br, 1H), 3.52 (dt, *J* = 5.6, 5.6 Hz, 2H), 3.83 (dt, *J* = 4.4, 5.6 Hz, 2H), 7.14 (d, *J* = 8.4 Hz, 2H), 7.17 (d, *J* = 15.2 Hz, 1H), 7.23 (d, *J* = 8.4 Hz, 2H), 9.58−9.66 (br, 1H); ^{13}C NMR ($CDCl_3$) δ 21.2 (CH_3), 52.1 (CH_2), 61.5 (CH_2), 122.4 (C), 129.0 (CH), 129.6 (CH), 129.9 (C), 137.7 (C), 149.8 (CH); IR (ATR/cm^{-1}) ν 3296, 1642, 1517; HRMS (ESI/TOF) Calcd for $C_{11}H_{15}N_2O_3$ [(M+H)$^+$]: 223.1077, found 223.1073.

(*Z*)-2-[(3-hydroxypropyl)amino]-1-(4-methylphenyl)-1-nitroethene (8x)

Yellow oil (34.9 mg, 0.15 mmol, 74%). ^{1}H NMR ($CDCl_3$) δ 1.80−1.85 (br, 1H), 1.92 (tt, *J* = 5.6, 5.6 Hz, 2H), 2.36 (s, 3H), 3.59 (dt, *J* = 5.6, 6.4 Hz, 2H), 3.81 (dt, *J* = 4.8, 5.6 Hz, 2H),

7.12 (d, J = 14.0 Hz, 1H), 7.18 (d, J = 7.6 Hz, 2H), 7.25 (d, J = 7.6 Hz, 2H), 9.62−9.70 (br, 1H); ^{13}C NMR ($CDCl_3$) δ 21.2 (CH_3), 32.7 (CH_2), 47.0 (CH_2), 59.4 (CH_2), 122.4 (C), 129.0 (CH), 129.5 (CH), 130.1 (C), 137.7 (C), 148.8 (CH); IR (ATR/cm^{-1}) ν 3373, 1646, 1517; HRMS (ESI/TOF) Calcd for $C_{12}H_{16}N_2O_3Na$ [$(M+Na)^+$]: 259.1053, found 259.1060.

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