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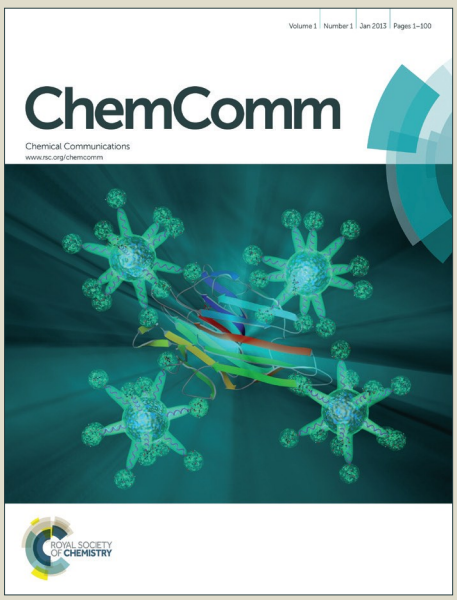

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An Atom Economical Method for Quinoline Derivatives Direct from Substituted o-Nitrotoluenes

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A highly efficient one-pot procedure for the preparation of substituted quinolines from substituted o-nitrotoluenes with electron-withdrawing groups and olefins (acrylic esters and acrylonitriles) using a cesium catalyst has been developed. A plausible [2 + 4] cycloaddition mechanism is proposed. This method uses nitroaromatic compounds as the starting materials to give quinoline derivatives in good to high yields under mild conditions and with no transition metal catalysis. It provides an atom economical pathway for the synthesis of quinoline derivatives which could be used in industrial processes.

Quinoline and its derivatives are key skeletons in numerous organic compounds, many of which have important applications.[1] The quinoline unit is frequently used as a core structure for the design of modern pharmaceuticals and related compounds such as antibacterials,[2,3] anticancer agents,[4] antifungals,[5,6] antimalarials,[7,8] and antischizophrenia drugs.[9] Functionalized quinolines are also important photo-sensitive materials and have been applied to analyses,[10] the dye industry,[11] organic electroluminescent devices,[12] and optical recording media.[13] Owing to the vast array of uses, there continues to be an intense focus on the synthesis of substituted quinolines.

Quinoline and its derivatives can be formed in three ways: a) the formation of the benzene and pyridine rings at the same time;[14] b) the cyclization of the benzene ring after the formation of the pyridine ring;[15] and c) the cyclization of the pyridine ring after the formation of the benzene ring. There are only a few examples of the construction of quinoline and its derivatives by methods a and b. Only method c is commonly used to produce quinoline and its derivatives.

Method c has been used to develop many synthetic methods to prepare quinolines derivatives with different properties.[1c] Generally, there are four types of intermediates that are associated with the c method (Fig. 1, a). Usually, these intermediates are generated from functionalized anilines which are synthesized from nitrobenzene or substituted nitrobenzenes and α,β-unsaturated carbonyl compounds at elevated temperatures under strongly acidic conditions.[10a,16,17] The use of palladium,[18] rhodium,[19] ruthenium,[20] copper[21] and gold[22] metal-catalyzed approaches have significantly lessened the harsh conditions. However, these methods are still limited because they lack generality and have limited functional-group tolerance.

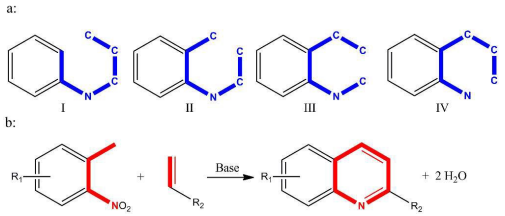


Fig. 1 Comparison of the traditional and this work's synthetic protocols for quinoline derivatives. Important frameworks associated with the traditional methods (a), model reaction for this work's method (b). R_1 = -ether, -NO_2, -COOEt, -CN, -CF_3 or 4-((3-nitrophenyl)sulfonyl)-; R_2 = -COOEt or , -CN.

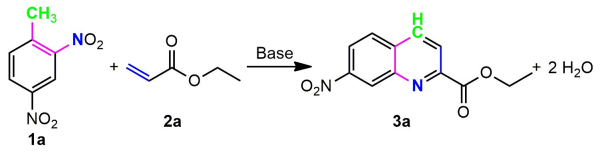
Up until now, both the traditional procedures and the newly developed metal catalysis methods began with aniline or substituted aniline which originates from nitrobenzene compounds. If a direct synthetic method that started with aromatic nitro compounds could be established for the construction of quinoline derivatives, it would be more efficient since the synthetic pathway would be significantly shortened and the costs would be reduced. This is in line with the modern concept of atom economy.[23] So, a simple and direct transformation of nitrobenzene or substituted nitrobenzene to quinoline and its derivatives is very desirable.

Herein, a one-pot, highly efficient method for the construction of substituted quinolines from substituted *o*-nitrotoluene derivatives and acrylic esters or acrylonitriles using a cesium catalyst is reported (Fig. 1, b). This new strategy results in quinoline derivates with electron withdrawing groups in an atom economical way. Achieving these compounds by traditional routes requires complex synthetic methods. Thus, this could be an attractive procedure for quinoline derivates that could be used in industrial processes.

Our investigation started with the reaction of 2,4–dinitrotoluene (**1a**) and ethyl acrylate (**2a**) with 2 equiv of 1,4-

diazabicyclo[2.2.2]octane (DABCO) or NEt_3 as a base in THF at 65 °C (Table 1, entries 1 and 2). A low yield of ethyl 7-nitroquinoline-2-carboxylate (**3a**) (less than 10%) was obtained. The 1,4-Michael type addition product, ethyl 4-(2,4-dinitrophenyl)but-3-enoate, was not observed. The reaction did not proceed without a base present. When the base was changed to an inorganic base, such as Na_2CO_3, K_3PO_4, K_2CO_3 or KOH, the product yields of **3a** increased to 32%, 38%, 51%, and 81% respectively after 12 h of reaction (entries 3-6). The highest yield of **3a** (83%) was obtained when Cs_2CO_3 was used as the base (entry 8). Solvent and the amount of base screening showed that the optimal result could be obtained with Cs_2CO_3, **1a**, and **2a** in a mole ratio of 2:1:3 in THF at 65 °C.

Table 1 Optimization of the conditions for the reaction of 2,4–dinitrotoluene (**1a**) with acrylic ethyl ester (**2a**).



Entry	Base	Ratio[a]	Solvent	Temp.(°C)	Time (h)	Yield (%)[b]
1	DABCO	2:1:3	THF	65	24	<10
2	Et_3N	2:1:3	THF	65	24	<10
3	-	0:1:3	THF	65	24	nr
4	Na_2CO_3	2:1:3	THF	65	12	32
5	KOH	2:1:3	THF	65	12	81
6	K_3PO_4	2:1:3	THF	65	12	38
7	K_2CO_3	2:1:3	THF	65	12	51
8	Cs_2CO_3	2:1:3	THF	65	12	83
9	Cs_2CO_3	2:1:3	$CHCl_3$	60	12	68
10	Cs_2CO_3	2:1:3	DCE	83	12	13
11	Cs_2CO_3	2:1:3	Toluene	110	12	58
12	Cs_2CO_3	2:1:1	THF	65	12	14
13	Cs_2CO_3	2:1:2	THF	65	12	39
14	Cs_2CO_3	1:1:3	THF	65	24	66
15	Cs_2CO_3	3:1:3	THF	65	24	82

[a] Molar ratio of base:**1a**:**2a**. [b] Isolated yields.

Next, the scope and limitations of this reaction for the synthesis of quinoline derivatives were examined using the optimized reaction conditions and the results are shown in Table 2. A variety of substituted *o*-nitrotoluenes with electron-withdrawing groups proved to be very efficient substrates under the optimized reaction conditions. When **2a** was reacted with *o*-nitrotoluenes with substituents such as -NO_2 (**1a**), -CN (**1b**), -COOEt (**1c**) or (3-NO_2-Ph)SO_2- (**1d**), at the 4-position, the desired 6-substituted-quinoline-2-carboxylic acid ethyl esters **3a**, **3b**, **3c**, and **3d** were obtained in isolated yields of 83%, 74%, 82%, and 81%, respectively.

A -NO_2 group at the 6-position of *o*-nitrotoluene (**1e**) also reacted with **2a** but a yield of only 66% of the desired product **3e** was obtained. When a -NO_2 group was at the 6-position and a –COOEt or a –CON(CH_3)$_2$ group was at the 4-position, the desired products **3f** (86% yield) and **3g** (73% yield) were produced. When o-nitrotoluene contained -NO_2 at the 4-position and another -NO_2 group at the 6-position, or another group (such as –CON(CH_3)$_2$, –COOEt, -CF_3 or –CH_3) at the 5-postiton, the reaction still progressed smoothly and gave the desired products in good yield (**3h**-80%, **3i**-81%, **3j**-80%, **3k**-79%, **3l**-82%, and **3m**-88%).

A substitution on the methyl group of **1** had almost no influence on the reaction with **2a**; thus, 2,4-dinitroethylbenzene (**1n**) reacted with **2a** to give ethyl 4-methyl-7-nitroquinoline-2-carboxylate (**3n**) in 79% yield. Substrates **1o**, **1p**, and **1q**, gave quinoline derivatives **3o**, **3p**, and **3q** in yields of 63%, 67%, and 68% respectively. If methyl and nitro groups were situated on the electron deficient aromatic ring, for example, 4-methyl-3-nitroquinoline (**1r**), the reaction with **2a** proceeded smoothly to give the desired product (**3r**) in 91% yield. However, substrates without an electron-withdrawing group on the arene ring did not react with **2a** to give the desired quinoline derivatives even with a stronger base such as *t*-BuOK. These results clearly demonstrate the importance of an electron-withdrawing substituent in forming the transition state that finally leads to the quinoline ring.

The substituted o-nitrotoluenes, **1a**, **1b**, **1d**, **1e**, and **1k-1r** also reacted with acrylonitrile (**2b**) to give substituted quinoline-2-carbonitrile products (**4a** (66%), **4b** (66%), **4d** (66%), **4e** (66%), **4k-4r** (65%-93%) under similar reaction conditions (Table 3). The isolated yields of these reactions are comparable with those for the reactions with **2a**.

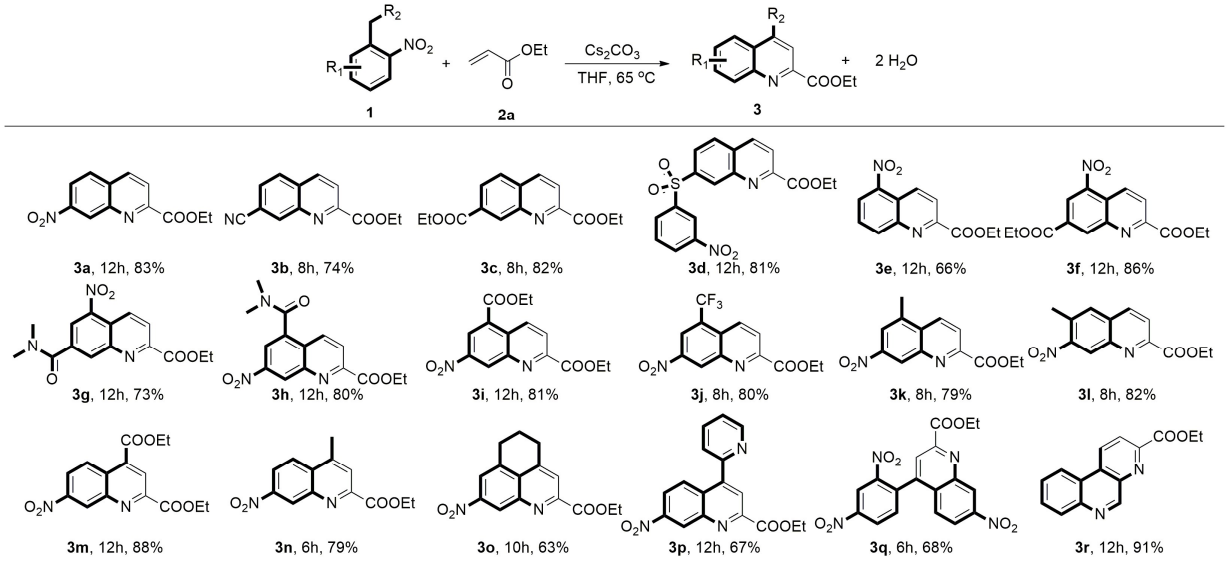
The formation of unexpected quinoline derivatives in the reaction between the substituted o-nitrotoluenes and olefins inspired us perform more experiments to uncover the reaction mechanism. It is known that o-nitrotoluene (**1a**) easily transforms to its nitronate isomer (**7**) (Scheme 1)[24] and that when Cs_2CO_3 is present in the reaction system, this isomer can be further stabilized by forming a Cs salt (**8**). Initially, we suspected a two-step mechanism where a 1,4-Michael type addition of the methylene anion **8** to the olefin produced **14** as an important intermediate and then the carbanion attacked the nitrogen cation of the nitro group. However, the attempt to trap the proposed key intermediate **14** by a reaction of **1a** with acrylic ethyl ester failed.

Instead **1a** quickly converted to **3a** in high yield and no key intermediates were observed during or after the reaction by either NMR or TLC, indicating that the key intermediate **14** may only form in very low concentrations and that it quickly converts to product **3a**. To further demonstrate the possibility of a two-step mechanism, compound **14** was prepared by cross-coupling 1-bromo-2,4-dinitrobenzene with (4-ethoxy-4-oxobutyl)zinc(II) bromide using a palladium catalyst (see the Supporting Information). Then, **14** was reacted with 2 equiv of Cs_2CO_3 in THF. However, the desired ethyl 7-nitroquinoline-2-carboxylate (**3a**) was not observed when the reaction was conducted at 65 °C even for 24 h. When a stronger base such as *t*-BuOK was used in combination with Cs_2CO_3, the reaction gave a complex product mixture and **3a** could not be isolated from the reaction system. Based on these results, the hypothesis of a two-step mechanism was eliminated.

So, a one-step mechanism involving a [2 + 4] cycloaddition of nitronate **8** to olefin **2** is proposed (Scheme 1). First, a [2 + 4] cycloaddition of nitronate **8**, an analogue of 1,3-butadiene, to olefin **2** gives cyclic compound **9**. A hydrogen transfer reaction in **9** then gives **10** as an intermediate which contains two hydroxyl groups connected to the same atom. Dehydration of **10** gives nitrone analogue **11**. Intermediate **11** has nitrogen oxide structure **12** as its resonance form. A proton transfer in **12** then gives **13** as an intermediate. The allylic proton is then attacked by the base and after the release of a water molecule, the quinoline derivative is formed as the final product.

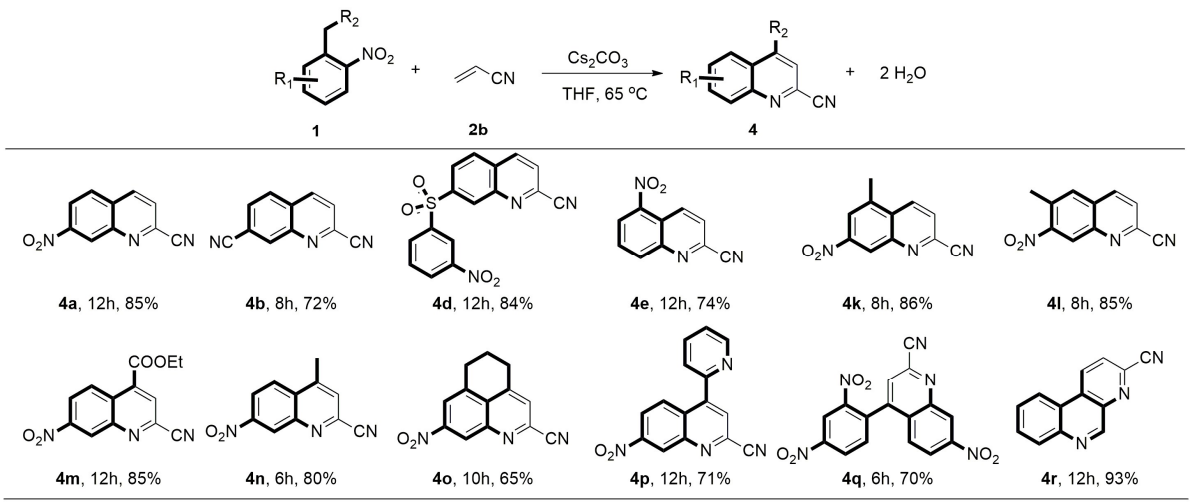
In conclusion, a new strategy for the direct synthesis of quinoline derivatives from substituted o-nitrotoluene was developed based on a Cs2CO3 catalyzed [2 + 4] cycloaddition protocol. This is a one-step procedure to produce quinolone building blocks under mild reaction conditions using o-nitrotoluene as the starting materials. Water molecules are the

Table 2 Synthesis of quinoline derivates via the reaction of substituted o-nitrotoluenes with acrylic ethyl ester.[a,b]

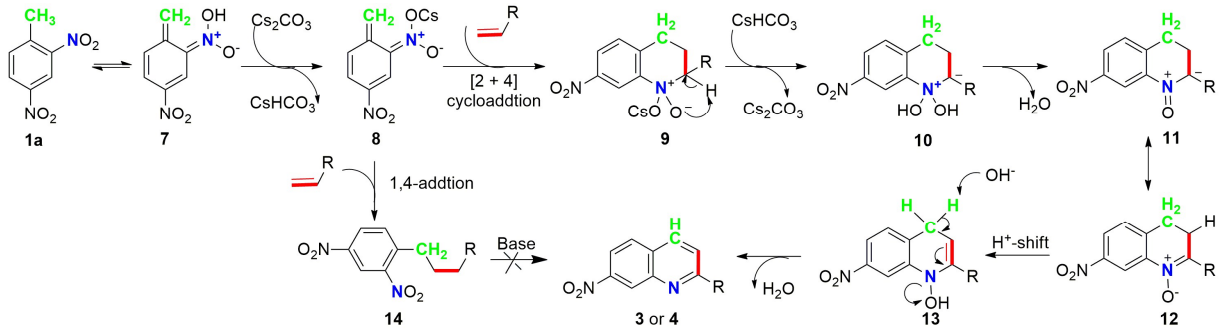


[a]Conditions: **1a** (1.0 mmol), **2a** (3.0 mmol), $CsCO_3$(2.0 mmol), THF (5.0 mL). [b]Isolated Yield.

Table 3 Synthesis of quinoline derivates via the reaction of substituted o-nitrotoluenes with acrylonitrile.[a,b]



[a]Conditions: **1a** (1.0 mmol), **2b** (3.0 mmol), $CsCO_3$(2.0 mmol), THF (5.0 mL). [b]Isolated Yield.



Scheme 1 The proposed reaction mechanism for the synthesis of quinoline derivates via the reaction of substituted o-nitrotoluenes with an olefin.

only fragments lost in these reactions, so this represents an atom economical process for the construction of functionalized quinoline derivatives. The unusual 1,4-cycloaddition of nitronate to an olefin provide an opportunity to generate ring compounds containing C-N bonds directly from *o*-nitrotoluene derivatives under mild reaction conditions. This method might be extended to *o*-nitrotoluene or *o*-nitrotoluenes with electron donating groups by employing special bases to stabilize the nitronate intermediates. Additional studies of this type as well as the application of this method to pharmaceutical syntheses are ongoing in our laboratory. Considering the growing interest for functionalized quinoline derivates in pharmaceutical and material sciences, this method should find numerous applications in the laboratory as well as in industrial fields due to its mild reaction conditions and expensive commercial starting materials.

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Notes and references

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