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Copper-Catalyzed Synthesis of 3-NO_2 Quinolines from *o*-Azidobenzaldehyde and Nitro-olefins and its Application in the Concise Synthesis of Quindolines

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Abstract. An efficient copper-catalyzed cyclization of *o*-azidobenzaldehyde and nitro-olefins was developed. This reaction proceeds under solvent-free conditions and displays broad functional group compatibility and affords 3-nitroquinolines in good to excellent yields. The synthetic utility of this strategy is illustrated by the concise construction of quindolines in only three steps, which renders the reaction more practical.

Keywords: copper-catalyzed; solvent-free reaction; 3-NO_2 quinolines; quindolines

Quinoline represents a fundamental and abundant class of nitrogen-containing heterocycles.[1] Among them, the substituted quinolines containing nitrogen atom at 3-position are prevalent in natural products,[2] such as quindoline, cryptolepine and jusbetonin. Moreover, these quinoline derivatives are also known to possess a wide range of biological activities,[3] including inhibitory activities toward EGFR-TK[3b] or bis-amide HDAC[3c], antibacterial, and antituberculosis activities[3d] **(**Figure 1). Besides, 3-nitroquinoline compounds could also serve as a precursor for the direct construction of quinoline derivatives containing nitrogen atom at the 3-position, especially in some quinoline natural alkaloid.[4] However, the approaches to synthesize 3-nitroquinoline compounds remain rare and, as a result, become a challenge in the research area of quinoline synthesis.[5] In general, the direct nitration of quinolones was considered as the most direct synthetic method, but this process often affords 3-nitroquinoline *N*-oxides as the major nitrification product. Moreover, the cycloaddition between 2-aminobenzaldehyde and nitro-olefins in alkaline conditions followed by oxidation using 2,3-dicyano-5,6-dichlorobenzoquinone (DDQ) or silica gel could serve as alternative methods for 3- nitroquinolines synthesis,[5c] but the 2-aminobenzaldehyde could readily undergo self-condensation, which resulted in poor yields and limited applications.[6] Therefore, the development of effective methods for the facile construction of 3-nitroquinoline is highly desirable.

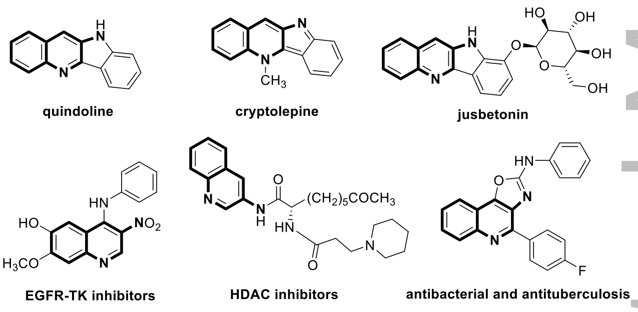
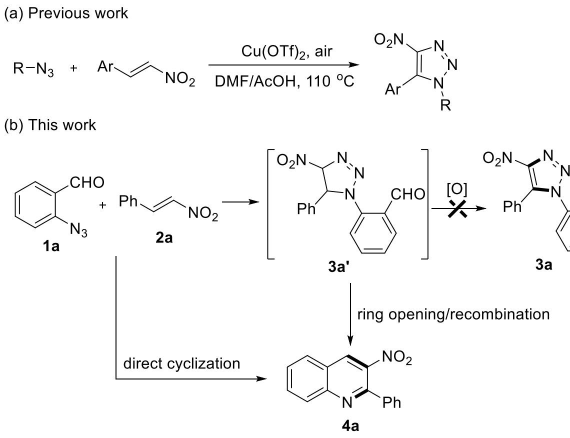


Figure 1. Biologically active compounds with 3-position nitrogen-containing quinoline moiety

We are interested in the synthesis and applications of novel 1,2,3-triazoles and related heterocycles.[7] Previously, we have developed a copper-catalyzed [3+2] cycloaddition/oxidation reaction between nitro-olefins and organic azides to afford 1,4(-NO_2),5-trisubstituted 1,2,3-triazoles *via* the inhibition of the elimination of HNO_2 (Scheme 1a).[7a] *o*-Azidobenzaldehyde is a bifunctional synthon, which has been employed to construct diverse *N*-heterocycles through C-N and C-C bond formation.[8] In the following study, *o*-azidobenzaldehyde (**1a**) was designed to be used as an azide source to react with nitro-olefins (Scheme 1b). If the reaction were carried out at inert atmosphere, the oxidative aromatization process would be inhibited and the desired 3-nitroquinoline (**4a**) could be formed *via* a ring-opening/six-member ring recombination of triazoline (**3a'**). Indeed, the ring-opening of the 1,2,3-triazoline strategy has been used to synthesize other nitrogen-containing heterocycles.[9] Alternatively, **1a** may also react with **2a** directly to produce the target product **4a** *via* a tandem cyclization. Herein, we report a copper-catalyzed synthesis of 3-NO_2 substituted quinolines by using a formal [4+2] cycloaddition between *o*-azidobenzaldehyde and nitro-olefins, and the application in the concise synthesis of quindoline and their derivatives.

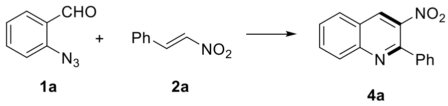
Scheme 1. The synthetic design of 3-NO_2 quinolines



To test the above hypothesis, *o*-azidobenzaldehyde (**1a**) and *β*-nitrostyrene (**2a**) were chosen as model substrates for the optimization of the reaction conditions (Table 1). Firstly, the reaction was performed by using $Cu(OTf)_2$ as the catalyst, DMF and AcOH (glacial acetic acid, 25%) as the mixed solvent at 110 °C under Ar (argon) atmosphere (entry 1). Although the formation of a complex mixture of products was observed, the desired NO_2-substituted quinoline (**4a**) was still obtained with 10% isolated yield. To improve the yield further, various reaction parameters were evaluated systematically, including metal salts, temperatures and solvents. When the AcOH was removed from the reaction condition, the yields of **4a** improved slightly (entry 2). Next, various metal salts were screened against the reaction (entries 3-9). Obviously, the catalytic efficiencies of the copper(I) salts were higher than others, and CuI exhibited good catalytic performance giving **4a** with 72% isolated yield. Altering the temperature of the reaction led no further improvements (entries 10-12). Other solvents (e.g., DMSO, toluene, CH_3CN) were tested as well, however, no better results were achieved (entries 13-15). Pleasantly, the addition of molecular sieves could reduce the byproducts effectively and afforded 76% yield of **4a** in DMF (entry 16). In addition, considering the low boiling point of *o*-azidobenzaldehyde, a solvent-free strategy was also tested (entries 17-18). The reaction rate was greatly accelerated and completed in 2h with the yield up to 88%. Decreasing the loading of CuI let to a slight improvement in the yield of **4a** (entry 18). And the reaction did not work without the addition of catalyst.

With the optimal reaction conditions in hand (Table 1, entry 18), the scope of this reaction was subsequently examined (Table 2). The nitrostyrenes containing either electron-donating groups (e.g., CH_3 and OCH_3) or electron-withdrawing groups (e.g., Cl, F, NO_2 and Br) were well tolerated. The electron-donating groups gave slight lower yields than the electron-withdrawing ones. The yields were decreased when 2-position substituted nitrostyrene were chosen as reaction partners (**4e, 4f, 4g, 4h, 4i** and **4j**). It was speculated that the decreased yields may be caused by the steric hindrances. Additionally, furyl-substituted nitro-olefin was also suitable for this transformation (**4k**, 78%). Other substituted *o*-azidobenzaldehydes were also viable substrates for this reaction and gave the products with satisfied yields (**4l-4y**). It was found that 4,5-dimethoxy substituted *o*-azidobenzaldehyde which bearing electron-rich substituents was more reactive than the other azides.

Table 1. Optimization of the reaction conditions[a]



Entry	Catalyst (5%)	Solvent	Temp (°C)	Yield of 4a (%)[b]
1	$Cu(OTf)_2$	DMF/AcOH	110	10
2	$Cu(OTf)_2$	DMF	110	15
3	$Ce(OTf)_2$	DMF	110	0
4	$AlCl_3$	DMF	110	<5
5	$FeCl_3$	DMF	110	0
6	$ZnCl_2$	DMF	110	<5
7	$CuSO_4$	DMF	110	<5
8	CuI	DMF	110	72
9	CuCl	DMF	110	65
10	CuI	DMF	120	67
11	CuI	DMF	100	61
12	CuI	DMF	90	<5
13	CuI	DMSO	110	66
14	CuI	toluene	110	70
15	CuI	CH_3CN	110	69
16[c]	CuI	DMF	110	76
17[c]	CuI	neat[d]	110	88
18[c]	**CuI**[e]	**neat**[d]	**110**	**91**
19	-	neat	110	0

[a] Reaction conditions: *o*-azidobenzaldehyde **1a** (0.6 mmol, 1.2 equiv), nitrostyrene **2a** (0.5 mmol, 1 equiv), catalyst (0.025 mmol, 5 mol%) and solvent (2 mL) were heated under Ar for 10 hours.

[b] Isolated yields.

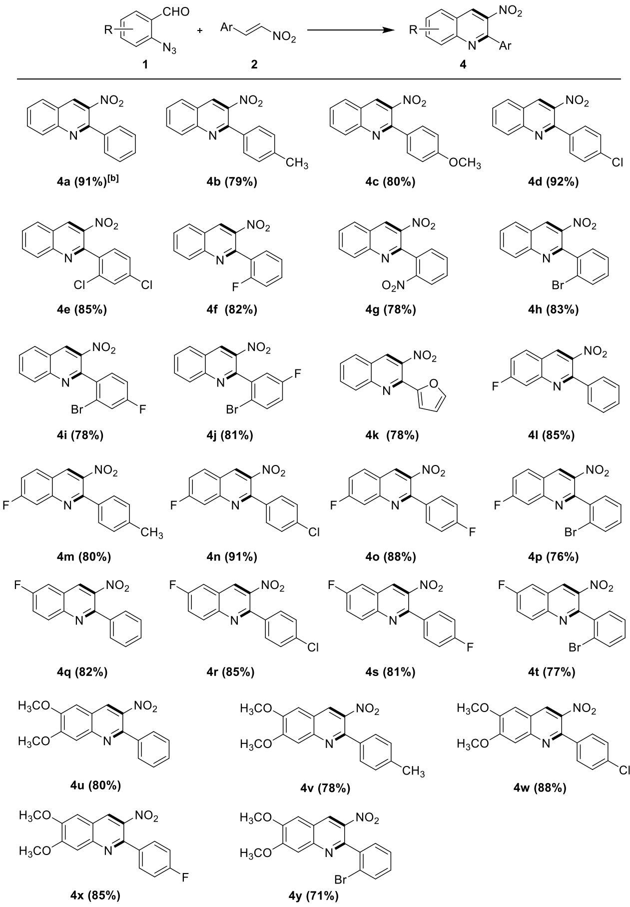
[c] 100 % w/w of crushed 4Å MS was used.

[d] Solvent-free conditions: *o*-azidobenzaldehyde **1a** (1.2 mmol, 1.5 equiv), nitrostyrene **2a** (0.8 mmol, 1 equiv), catalyst (0.06 mmol, 5 mol%) were under Ar for 2 hours.

[e] 1 mol% CuI was used.

To gain some insights into the mechanism of this transformation, several control experiments were performed as shown in Scheme 2. First, the reaction was carried out in DMF, *o*-aminobenzaldehyde (**5**) was also observed with the formation of product **4a** (Scheme 2a). We suspected that **5** might be the reaction intermediate, which was reacted with nitroalkenes *via* Michael addition/cyclization/dehydration/oxidation to give **4a**.

Table 2. Substrate scope[a]

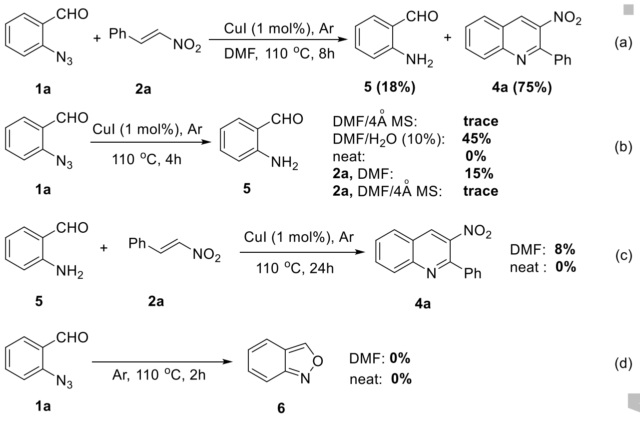


[a] Reaction conditions: *o*-azidobenzaldehyde **1** (1.2 mmol), nitrostyrene **2** (0.8 mmol), CuI (0.008 mmol), 100 % w/w of crushed 4Å MS, 110 °C under Ar atmosphere.

[b] Isolated yields.

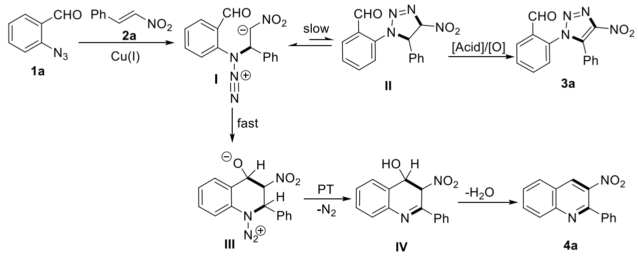
So the routes of **1a** to **5** and **5** to **4a** were investigated individually. It was found that water is indispensable in the conversion of **1a** to **5**, probably water might serve as reductive species and hydrogen source (Scheme 2b). On the other hand, **5**, **2a** and CuI(1%) were heated in DMF or neat reaction conditions, low yields (8% and 0%) of **4a** were obtained within 24h, whereas the use of **1a** could be completed in 8h with 75% yield of **4a** (Scheme 2c, 2a). This result suggests that the reaction does not proceed through the intermediate **5**. It also explains that the addition of molecular sieves can improve the reaction yield obviously. Another possibility is that the reaction proceeds *via* a nitrene thermolysis mechanism. The nitrene could be trapped by **2a** directly[10] or further formed benzisoxazole (**6**) intermediate[11] to give **4a**, meanwhile it also could be converted to **5** by hydrogen abstraction.[12] However, directly heating of **1a** in DMF or neat reaction condition, **6** was not observed in 2h (Scheme 2d). By contrast, the gas was generated and product was observed immediately in the presence of **2a** and CuI (1%) and the reaction could be completed within 2h (Table 1, entry 18). These results suggested that the release of nitrogen occurred after the cyclization of **1a** and **2a**. Furthermore, the triazoline intermediate **3a'** could not be observed under standard reaction conditions, other attempts (such as no addition of catalyst, shorten the reaction time) to form the triazoline intermediate **3a'** also failed.

Scheme 2. Control experiments



According to the results mentioned above and the previously reported work,[13] a plausible reaction pathway for the reaction was proposed. The nitroalkene is firstly nucleophilic attacked by the azide group in **1a** to form the intermediate **I**, which could be cyclized in two ways. One way is to form triazoline **II**, which could endure oxidative aromatization to form NO_2-substituted triazole **3a**. This path could be promoted by external oxidant and acids. While the other way is to attack aldehyde group to yield intermediate **III**, it then undergoes proton transfer (PT)[9] and releases nitrogen gas to give intermediate **IV**. Finally, the target product **4a** is formed along with the elimination of H_2O (Scheme 3). Because there were not triazoline or NO_2-substituted 1,2,3-triazole formed, we proposed that the anion attack to the azide group is much slower than to the aldehyde group due to the linear structure of azide group (the high energy of the cyclic transition state) in this case, 3-NO_2 quinolines may be formed *via* direct cyclization.

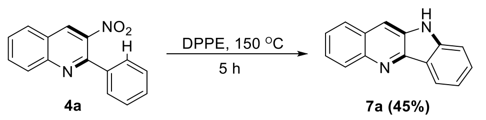
Scheme 3. Plausible reaction pathway



This method can be applied in the formal total synthesis of some important natural products, such as quindolines and cryptolepines (Figure 1). Actually, there are mainly three approaches to obtain quindolines.[14] The use of indoles as starting materials is fundamental to the synthesis of quindoline. However, the diversity of strategies within this approach is rather limited.[14-15] Another way which is started from halogen or amino substituted quinolines usually requires obtaining the coupled intermediates by noble metal (e.g., Pd) catalysts.[16] The introduction of nitrogen source on the quindoline is very tricky which requires multi-step conversion and restricted reactant. Other methods[17] (using benzonitrile, 2-nitrophenylacetic acid, ect.) require long reaction routes with unsatisfied yields or harsh reaction conditions (high temperature, noble metal catalysts or inconvenient starting materials).

The Cadogan reduction of 2-nitrobiphenyls by trivalent phosphorus reagents has been recognized as a general route to carbazoles and other nitrogen-containing heterocycles.[18] Thus, different phosphorus reagents and solvent were tested (see *Supporting Information*). However, it was found that the product was very difficult to purify when PPh_3 was used, due to the strong hydrogen bonding between the product and PPh_3O.[18b, 18d, 19] Hereby, 1,2-bis(diphenyl-phosphino)ethane (DPPE) was used as phosphorus reagents directly at 150 °C under Ar atmosphere in solvent- free conditions[17b] and the quinoline **4a** was successfully converted into quindoline **7a** with 45% isolated yield (Scheme 4).

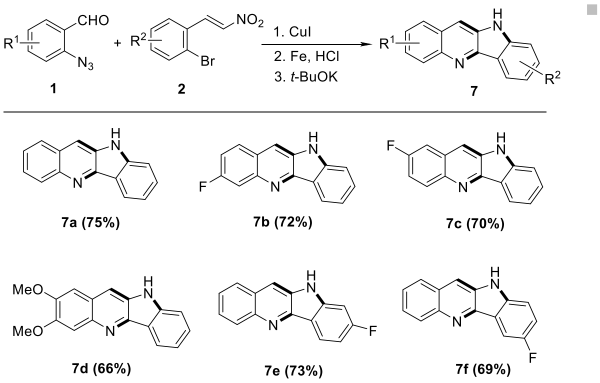
Scheme 4. Cadogan reaction synthesis nature product quindoline **7a**



In order to improve the isolated yield and simplify the purification process, an alternative sequential strategy was also developed (Table 3). Firstly, the cyclization of 1-bromo-2-(2-nitrovinyl)benzene, *o*-azidobenzaldehyde and CuI (1 mol%) were heated in the Ar atmosphere. Then, the nitro group of the obtained quinoline was in-situ reduced to amino group by using iron or zinc/acid system. After the simple extraction and evaporation, the obtained crude product could be converted to the corresponding quindoline (**7a**) smoothly through intramolecular coupling in alkaline condition with 75% overall yield. Some other quindoline analogues were also obtained in this way with satisfied overall yields (66 - 73%).

In conclusion, we have developed an efficient copper-catalyzed synthesis of 3-nitroquinolines from *o*-azidobenzaldehydes and nitro-olefins in good to excellent yields. The solvent-free reaction conditions reduced reaction time and eliminated the formation of some byproducts. The reaction did not involve the formation of the benzisoxazole intermediate and avoided the high temperature or harsh reaction conditions. Remarkably, these 3-NO_2 quinolines could be further used for high-efficient synthesis of quindolines and their derivatives, which rendered this method more practical.

Table 3. Synthesis of quindoline **7** and the analogues



Reaction conditions:
1. CuI (1 mol%), 100 % w/w of crushed 4Å MS, 110 °C;
2. Fe (4 eq), HCl (0.1 M), EtOH/H_2O = 4:1, reflux;
3. *t*-BuOK (2.5 equiv), DMSO, 130 °C.

Experimental Section

o-Azidobenzaldehyde **1a** (1.2 mmol), nitro-olefin **2a** (0.8 mmol), CuI (0.008 mmol), 100 % w/w of crushed 4Å MS were mixed well in a 10 mL round bottle without solvent, and the bottle was immersed in an oil bath of 110 °C under Ar atmosphere. The reaction was cooled after 2h and the residue was subjected to column chromatography on silica gel using petroleum ether/ethyl acetate (10:1) as eluents to afford the desired products **4a** as a pale yellow solid.

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