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Hypervalent Iodine(III)-Mediated Regioselective Cyanation of Quinoline *N*-Oxides with Trimethylsilyl Cyanide

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Abstract. A regioselective cyanation of quinoline *N*-oxides with trimethylsilyl cyanide was developed by using (Diacetoxyiodo) benzene (PIDA) as mediated hypervalent iodine(III) reagent under metal-free and base-free reaction conditions to obtain 2-cyanoquinolines. The efficient PIDA reagent could play the role of an activator of the substrates and an accelerator of N-O bond cleavage. The reaction system featured a wide range of substrate suitability and high yields. The procedure was enlarged gram-scale to synthesize the tuberculosis (TB) inhibitor. Finally, according to some experimental results, a plausible mechanism for the cyanation reaction is proposed.

Keywords: Cyanation; Metal-free; PIDA; Quinoline *N*-oxides; Trimethylsilyl cyanide

Introduction

N-containing heterocycle compounds are widely used in pharmaceuticals, agricultures and material sciences.[1] Functionalized quinoline derivatives as important *N*-containing heterocycle compounds are increasingly utilized in pharmaceutical chemistry, particularly in the fields of antimalarial and anticancer activities.[2] Meanwhile, cyanide as a common functional group that plays an important role in chemistry, biology and medicine.[3] The nitrile group also possess multifunctional applications as intermediates in organic synthesis because it can be easily converted into various functional groups, such as amines, amides, carboxylic acids and heterocyclic compounds, etc.[4] Some derivatives of 2-cyano quinoline/pyridine are important structural units in pharmaceutical, natural products and preclinical drug candidates. (**Figure 1**).[5] Therefore, synthesis of derivatives of 2-cyano quinoline/pyridine has attracted more attention.

Regioselective cyanation is an important synthetic strategy to get 2-cyano quinolines. Over the past years, the synthesis of 2-cyano quinolines were commonly to use cyanation of 2-haloquinolines or quinoline diazonium salt with CuCN, namely the Sandmeyer and the Rosenmund-von Braun reactions (**Scheme 1a**).[6-7] Traditional synthetic approaches have a few limitations, such as the requirement of higher reaction temperature and the use of stoichiometric amounts of toxic CuCN. Another common method involves the transition-metal-catalyzed C-H bond cyanation of quinoline.[8] In 2004, Tagawa and co-workers reported the Pd-catalyzed direct C-H activation and cyanation of quinoline *N*-oxides by using trimethylsilyl cyanide as cyanation reagent and DDQ as oxidant (**Scheme 1b**).[9] However, the author only investigated the reaction of 4-substituted quinoline *N*-oxides, and the reaction of quinoline *N*-oxides with electron-withdrawing groups at the 4-position did not proceed at all.

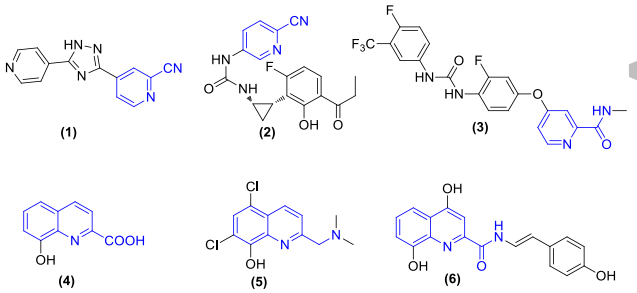

Figure 1. Representative bioactive derivatives of 2-cyano quinoline/pyridine. (1) Topiroxostat (anti-gout); (2) MIV-150 (anti-HIV); (3) Regorafenib (anti-cancer); (4) TB inhibitor; (5) PBT2 (anti-AD); (6) perspicamides A.

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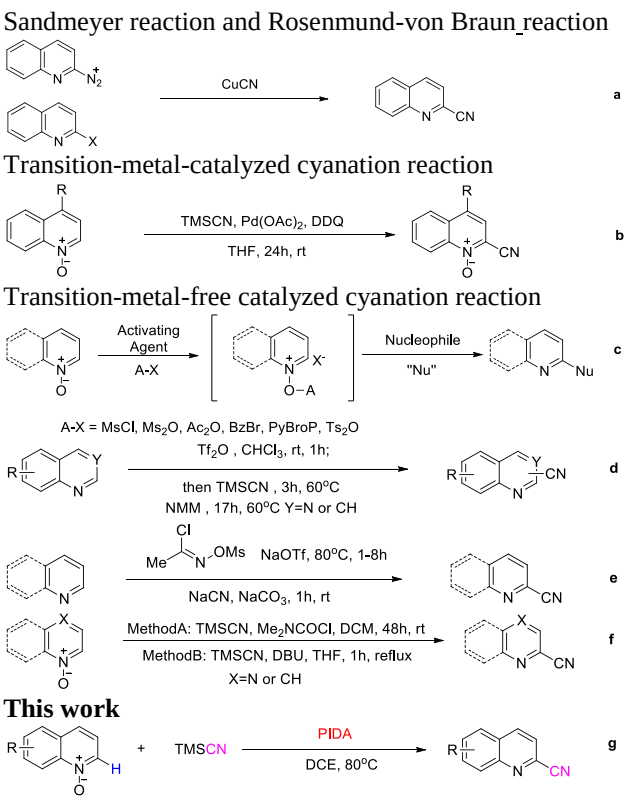
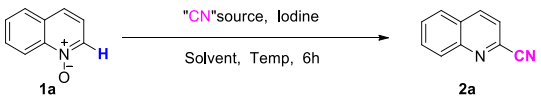


Scheme 1. Strategies for C2-cyanation of quinolines.

In most of the cases, expensive transition metals may pollute the product, thereby limiting their applications, especially in the pharmaceutical industry and advanced functional material. Thus, it is necessary to develop the method of transition-metal-free catalyzed cyanation reaction.[10] A metal-free approach for regioselective C-2 functionalization of quinolines or pyridines involves initial oxidation to quinoline/pyridine *N*-oxides, followed by *O*-activation and nucleophilic substitution (**Scheme 1c**).[11] In 2017, Paton *et al*. reported the cyanation of 6-ring *N*-containing heterocycles by using a triflic anhydride (Tf_2O) / *N*-methylmorpholine (NMM) system with trimethylsilyl cyanide as the cyano-group source. Moreover, triflic anhydride (Tf_2O) was found to be predominant as an activator. Nonetheless, the reaction had other isomers with poor regioselectivity (**Scheme 1d**).[12] In 2017, P. S. Fier reported that cyanation of pyridine used NaCN as an cyanation reagent with α-chloro *O*-methanesulfonyl aldoximes as an activator under mild conditions (**Scheme 1e**).[13] However, NaCN as a toxic cyanation reagent was required. In 1983, Fife reported *N,N*-dimethylcarbamoyl chloride could be used as an activation reagent for the cyanation of the pyridine *N*-oxides with TMSCN in dichloromethane. In addition, Miyashita *et al*. reported that DBU was an effective base for the cyanation of the quinoxaline/ quinazoline *N*-oxides with TMSCN in 1992 (**Scheme 1f**).[14] Reaction A requested harsh acylating reagent *N,N*-dimethylcarbamoyl chloride and long reaction time. Reaction B requires that its substrates are mainly suitable for quinoxaline/ quinazoline *N*-oxides. Iodine reagent as an eco-friendly and inexpensive reagent could induce functional groups to the 2-position of quinoline *N*-oxides derivatives.[15] In 2017, Yu and colleagues reported that quinoline *N*-oxides and sulfonamides were induced by $PhI(OAc)_2$ (PIDA) and PPh_3 to synthesize 2-sulfonamideyl quinoline. Nevertheless, a stoichiometric amount of phosphorus reagent was necessary for the successful intermolecular sulfamidation. [15c] In addition, $PhI(OAc)_2$ has become one of the most popular research topics in organic synthesis. Herein, we developed a highly regioselective synthesis of 2-cyanoquinoline derivatives by the $PhI(OAc)_2$-mediated N-O bond disruption and direct cyanation of quinoline *N*-oxide substrates by using TMSCN as cyano source (**Scheme 1g**). The method avoided using the transition-metal, phosphorus reagent and base additives.

Results and Discussion

Table 1. Screening of the reaction conditions[a)]



Entry	Iodine (equiv)	"CN" source	Solvent	T (°C)	Yield (%)[b)]
1	$PhI(OAc)_2$ (1)	TMSCN	DME	80	45
2	$PhI(OTf)_2$ (1)	TMSCN	DME	80	35
3	IBX (1)	TMSCN	DME	80	trace
4	I_2 (1)	TMSCN	DME	80	n,d.[c)]
5	$PhI(OAc)_2$ (2)	TMSCN	DME	80	58
6	$PhI(OAc)_2$ (3)	TMSCN	DME	80	60
7	$PhI(OAc)_2$ (4)	TMSCN	DME	80	57
8	$PhI(OAc)_2$ (3)	TMSCN	DMF	80	28
9	$PhI(OAc)_2$ (3)	TMSCN	DMSO	80	23
10	$PhI(OAc)_2$ (3)	TMSCN	MeOH	80	n,d.
11	$PhI(OAc)_2$ (3)	TMSCN	Toluene	80	65
12	$PhI(OAc)_2$ (3)	TMSCN	DCE	80	73
13	$PhI(OAc)_2$ (3)	TMSCN	DCE	30	25
14	$PhI(OAc)_2$ (3)	TMSCN	DCE	50	46
15	$PhI(OAc)_2$ (3)	TMSCN	DCE	100	58
16	$PhI(OAc)_2$ (3)	$K_4Fe(CN)_6$	DCE	80	n,d
17	$PhI(OAc)_2$ (3)	PhCOCN	DCE	80	12
18	--	TMSCN	DCE	80	n,d
19	PIFA(3)	TMSCN	DCE	80	trace

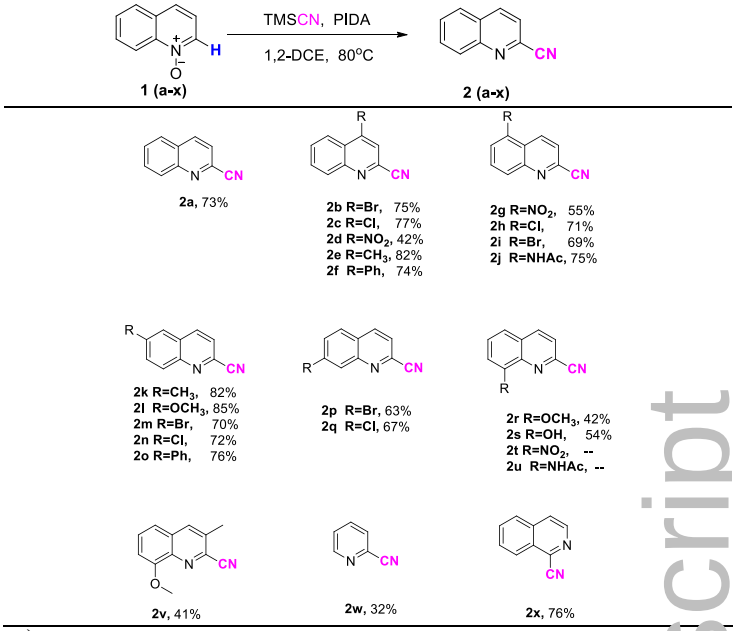
[a)] Reaction conditions: 1a (0.1 mmol), TMSCN (3.0 equiv) and iodine (3 equiv) in solvent (5 ml) for 6 hours. [b)] Isolated yield after purification by column chromatography. [c)] n.d. = not detected.

Quinoline *N*-oxide (**1a**) and TMSCN were selected as an initial model reaction to screen various reaction conditions. The experimental results were summarized in **Table 1**. Quinoline *N*-oxide (1 equiv) was initially chosen as the model substrate to react with TMSCN (3 equiv) in the presence of $PhI(OAc)_2$ (1 equiv) in 1,2-dimethoxyethane at 80 °C under an air atmosphere. Much to our delight, the reaction proceeded to give

access to the desired cyanation product **2a** with a low yield (45%, **Table 1**, entry 1). Encouraged by this result, we planned to employ different iodine reagents, cyanide sources, tempretures and solvents to search for the optimal reaction conditions. The use of $PhI(OTf)_2$ or 2-iodoxybenzoic acid (IBX) as hypervalent iodine compounds to instead of $PhI(OAc)_2$ result in significant decline in yield or traces (35% and traces, respectively; **Table 1**, entries 2-3). Even when I_2 was used, no reaction was observed (**Table 1**, entry 4). Therefore, $PhI(OAc)_2$ should be a good catalyst. When loading of $PhI(OAc)_2$ was increased, yields of **2a** was increased significantly to 50% and 60% (**Table 1**, entries 5-6). While loading of 4 equivalents $PhI(OAc)_2$, yield of **2a** only gave 57% (**Table 1**, entry 7). Next, other different solvents were examined towards the same reaction. The use of polar aprotic solvents DMF (28%) and DMSO (23%) gave relatively low yields of **2a** (**Table 1**, entries 8-9). While the use of protic solvent MeOH did not produce anything (**Table 1**, entry 10). Finally, the use of nonpolar solvents toluene and DCE gave relatively good yields of **2a** (**Table 1**, entries 11-12), wherein, DCE gave the most significant increase of product in 73% yields. Upon a comparison of different reaction temperatures, we found that 80 °C is to be optimal (**Table 1**, entries 13-14). However, a continued increase in temperature to 100°C failed to improve the reaction, which was probably due to fast decomposition of $PhI(OAc)_2$. (**Table 1**, entry 15). Other inorganic and organic cyanide source like $K_4Fe(CN)_6$ and PhCOCN did not become effective cyanide sources (not detected and 12%, respectively; **Table 1**, entries 16-17) under optimized condition. No product was obtained in the absence of $PhI(OAc)_2$ (**Table 1**, entry 18). The result emphasized the importance of $PhI(OAc)_2$ in this transformation. PIFA was used in the optimization of reaction conditions to afford the trace amount of product (**Table 1**, entry 19). Under the optimal reaction conditions, the PIFA is apt to decompose because of the high reaction temperature. Thus, the optimized conditions for the cyanation of the quinoline *N*-oxide involved 3.0 equiv of $PhI(OAc)_2$ as the catalyst and 3.0 equiv of TMSCN as the cyanating reagent in DCE at 80°C for 6 h.

With an optimized general procedure in hand, the substrate scope of the cyanation was investigated (**Table 2**), the current catalytic system was suitable for a wide range of substituted quinoline *N*-oxides (**1a-1x**). First, compound **1a** without substituent group gave desired product **2a** with 73% yield. Then, starting from C-4 functionalized quinoline *N*-oxides (**2b-2f**), a remarkable compatibility for produce was found. Particularly, the electron-donating substituents (-Me, **2e**, 82%) were more favorable to the reaction compared with electron-poor substituents ($-NO_2$, **2d**, 42%). Quinoline *N*-oxides bearing electron-donating and electron-withdrawing substituents (such as, -Me, -OMe, -Ph, -NHAc, -Cl, -Br and $-NO_2$) at the C-5, 6 positions of quinoline ring (**2g-2o**) all underwent cyanation smoothly at the 2-position. Substrates that

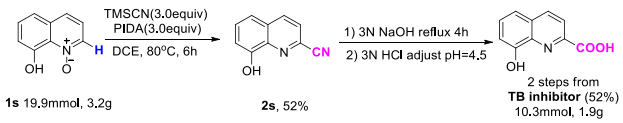
Table 2. Substrate scope of quinoline *N*-oxides with TMSCN[a)]



[a)] Reaction conditions: Compound 1 (0.1 mmol), TMSCN (3.0 equiv) and $PhI(OAc)_2$ (3.0 equiv) in DCE (5 ml) for 6 hours. Isolated yield after purification by column chromatography. No reaction is denoted by "--".

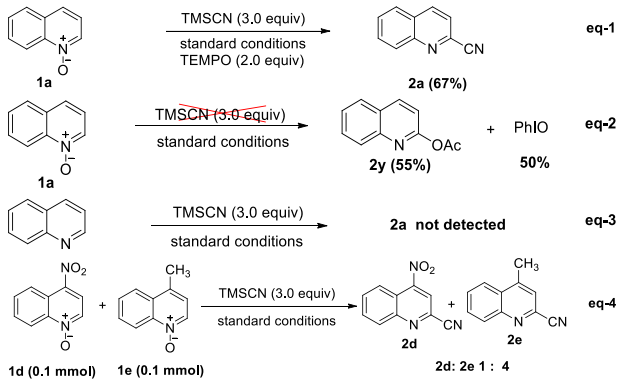
contained electron-withdrawing groups (-Cl, -Br and $-NO_2$) at the C-5 and C-6 position afforded the corresponding products (**2g-2i** and **2m-2n**) in 55-72% yield. However, Quinoline *N*-oxides attached electron-donating substitutents at the C-5 and C-6 positions, including -NHAc, -Me and -OMe, the yields of the target products **2j-2l** increased with improvement of electron-donating ability of these groups. These outcomes indicated that changing the electron density in the substituents on the quinoline *N*-oxides had a remarkable influence on the efficiency of the reaction. Medium yields could be obtained for halogen substituents at 7-position of quinoline ring (-Cl, **2q**, 67% and -Br, **2p**, 63%). Furthermore, the survival of a halogen substituent offered a great opportunity to further functionalize the products. Notably, the relatively low yield of **2r** and **2s** were attributed to the steric effect of the 8-methoxy and hydroxy groups in quinoline *N*-oxide substrate. Unfortunately, **2t** and **2u** were not converted into their target products. **2t** outcome indicated that the strong electron-withdrawing effect and large steric hindrance at the 8-nitro group of quinoline ring restrained the process of reaction seriously. **2u** outcome was attributed to the steric effect and intramolecular hydrogen bonding interaction of the 8-acetyl amino group in quinoline *N*-oxide substrate. In the next experiment, polysubstituted quinoline *N*-oxides (**1v**) provided the desired product in 41% (**2v**) yield, suggesting that the methyl at the 3-position of quinoline *N*-oxide did not display an obvious steric hindrance effect in this course. To our excitement, pyridine *N*-oxide (**1w**) and isoquinoline *N*-oxide (**1x**) could proceed efficiently

and afford the corresponding products in 32% and 76% yields respectively. Compared with the optimized protocol, pyridine *N*-oxide (**1w**) were generally less reactive for nucleophilic attack.[16]

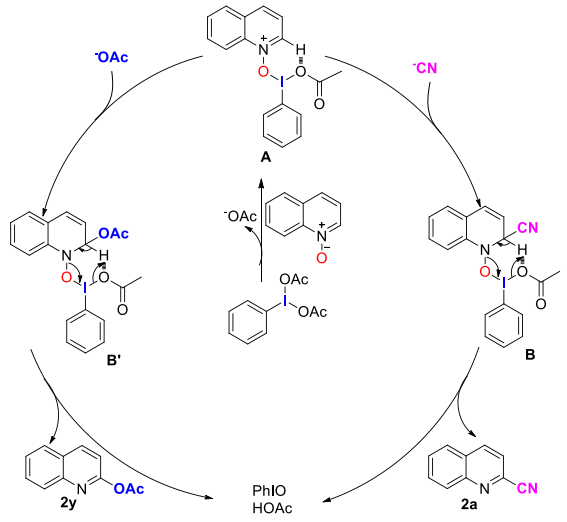


Scheme 2. Synthesis of the TB inhibitor in gram-scale.

In order to further demonstrate the synthetic utility of this cyanation reaction, a gram-scale reaction was carried out to the synthesis of the TB inhibitor.[5c, 17] As illustrated in **Scheme 2**, **1s** and TMSCN were chosen to the optimized reaction conditions and subjected to hydrolysis to obtain the TB inhibitor with 52% yield. Compared with other protocols,[18] this scheme had the features of mild reaction conditions, simple operation and easy availability of raw materials.



Scheme 3. Control experiments in the search for a reaction mechanism.



Scheme 4. Proposed reaction mechanisms.

More control experiments were designed to gain an insight into the reaction mechanism. When the radical scavenger TEMPO was employed in the reaction mixture, product **2a** was produced in 67% yield (**Scheme 3**, **eq-1**), indicating that the reaction possibly involved a non-radical pathway. Without the TMSCN, 2-acetoxyquinoline (**2y**) and PhIO were obtained under the standard conditions (**Scheme 3**, **eq-2**) (The compound data of NMR and IR were in the Supporting Information). This result indicated that $PhI(OAc)_2$ was decomposed into acetoxyl anion under the reaction conditions, and $PhIOAc^+$ might react with the oxygen atom in the quinoline *N*-oxide (**1a**). When quinoline was used to take the place of quinoline *N*-oxide as the reactant under the standard reaction conditions (**Scheme 3**, **eq-3**), the reaction did not proceed, which suggested that the N-O group played a crucial role in this reaction system. Furthermore, to compare the reactivity of the electronically different quinoline *N*-oxides, a ratio of equimolar *N*-oxides with electron-withdrawing groups (**1d**) and electron-donating groups (**1e**) were processed by TMSCN under standard conditions (**Scheme 3**, **eq-4**). The intermolecular competition reaction provided **2d**:**2e** in 1:4 ratio. This implied that the reaction might favour for an electrophilic reagent to attack the quinoline *N*-oxide.

On the basis of these experimental results and literatures,[19] a plausible mechanism for this metal-free induced cyanation of quinoline *N*-oxide is proposed in **Scheme 4**. Initially, $PhI(OAc)_2$ attacks the oxygen atom in the quinoline *N*-oxide (**1a**) to form intermediate **A**. Next, the intermediate **A** can transform into dearomatized intermediate **B** (or **B'**) through regioselective nucleophilic attacks of cyanide ion (or acetate ion) at α-carbon of quinoline. Finally, the resulting intermediate **B** (or **B'**) underwent deprotonation/ aromatization to give the 2-cyano product (or 2-acetoxy product) and deliver the HOAc and PhIO.

Conclusion

In summary, we have developed a mild, efficient and metal-free system for the highly regioselective cyanation of the quinoline *N*-oxides and other *N*-containing heterocycle *N*-oxides system. This cyanation method was induced by the efficient and economical $PhI(OAc)_2$ reagent, and it proceeded the N-O bond disruption to form 2-cyano quinoline derivatives. Moreover, this reaction used an organic and less toxic TMSCN as a cyanation reagent. Furthermore, the procedure was extended to synthesize the TB inhibitor in gram-scale. Finally, a plausible mechanism for this PIDA induced cyanation of quinoline *N*-oxides is proposed on the basis of some experimental results and literatures. Further exploration of the other functionalization with quinoline *N*-oxides is underway in our laboratory.

Experimental Section

1. General Procedure for Synthesis of quinoline *N*-oxides

Representative Procedure: To a mixture of quinoline (1.3 g, 10.0 mmol) in AcOH (20 mL) was added H_2O_2 (30 wt%, 1.40 mL) at room temperature. The reaction mixture was stirred at 70 °C for 36 h, and then was cooled to room temperature. The product was extracted with dichloromethane (3 × 20 mL), and the combined organic layers were dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue obtained was purified via silica gel chromatography (eluent: ethyl acetate/methanol = 8/1) to afford quinoline *N*-oxide (**1a**) as a yellowish solid (1.3 g, 90%).

2. General procedure for the synthesis of 2-cyanoquinolines

Representative Procedure: A 10 mL screw-cap vial charged with quinoline *N*-oxides (58.1 mg, 0.4 mmol), TMSCN (119.1 mg, 1.2 mmol), PIDA (386.5 mg, 1.2 mmol) and anhydrous DCE (6 ml), the mixture was stirred at 80 °C temperature for 6-7 h. After completion of the reaction, the solution was extracted with dichloromethane (3×20 mL). Organic layers were combined and dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude material was separated on a silica gel column with petroleum ether/ethyl acetate (1/5) as the eluent to get product quinoline-2-carbonitrile (**2a**) as a white solid (45.0 mg, 73%).

Acknowledgements

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FULL PAPER

Hypervalent Iodine(III)-Mediated Regioselective Cyanation of Quinoline *N*-Oxides with Trimethylsilyl Cyanide

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