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Metal-Free Chemoselective Oxidation of 4-Methylquinolines into Quinoline-4-Carbaldehydes

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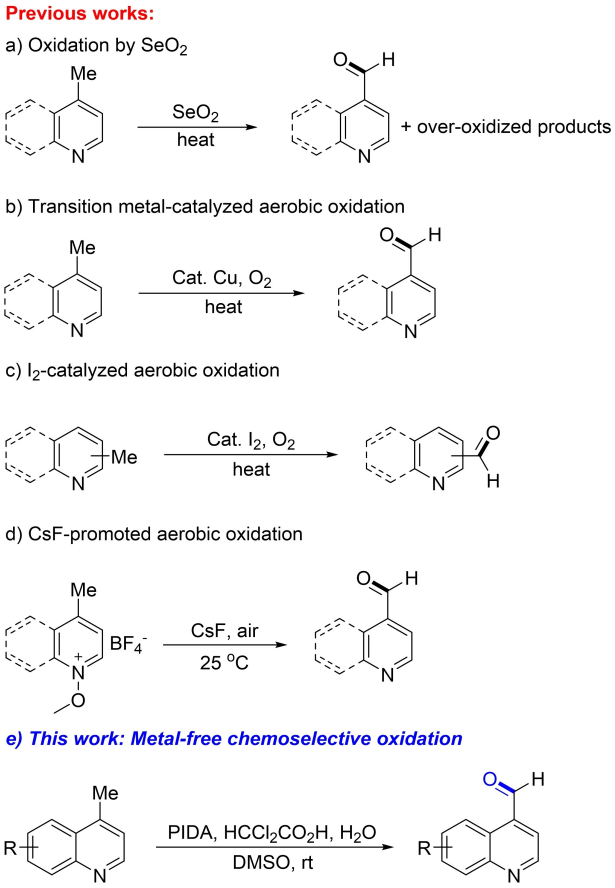
Abstract: A convenient protocol for the synthesis of quinoline-4-carbaldehydes *via* chemoselective oxidation of 4-methylquinolines using hypervalent iodine(III) reagents as oxidant is described. This method highlights metal-free and mild reaction conditions, nice yield, good functional group tolerance, and high chemoselectivity.

Heteroaromatic aldehydes are important skeletons of natural products.[1] Furthermore, highly reactive formyl group can be converted into various useful functional groups conveniently.[2] Due to this property, heteroaromatic aldehydes are frequently used as key precursors to synthesize various biologically active molecules, such as quinine,[3] mefloquine[4] and camptothecin[5] derivatives. Thus, an efficient and practical method for the synthesis of heteroaromatic aldehydes is always utility in synthetic chemistry.

Direct oxidation of methylheteroarenes provides a convenient and straightforward route for the synthesis of heteroaromatic aldehydes. However, compared to the less reactive methylheteroarenes, the corresponding heteroaromatic aldehyde products are more easily to be over-oxidized into acids.[6] Therefore, it is quite challenging to avoid over-oxidation of the aldehyde products under oxidative conditions. Oxidation of methyl-substituted *N*-heteroaromatics using selenium dioxide as oxidant is a classical protocol to synthesize the corresponding aldehydes (Scheme 1a).[7] However, the reaction condition is harsh, which limit substrate scope and chemoselectivity. In addition, a serious drawback of this method is the toxicity of selenium dioxide.[8] As a green, cheap and highly abundant oxidant, molecular oxygen is widely used in catalytic oxidation process.[9] In the last few years, several methods for transition metal-catalyzed aerobic oxidation of methyl-substituted *N*-heteroaromatics have been developed (Scheme 1b).[10] But the metal residue severely limits their application in industrial synthesis. Chen and Itoh groups reported I_2-catalyzed aerobic oxidation of methyl-substituted *N*-heteroaromatics to form the corresponding aldehydes (Scheme 1c).[11] Despite these methods avoid the use of any transition metal catalyst, they still require high reaction temperature. Very recently, Wu and coworkers developed a novel protocol to access *N*-heteroaromatic aldehydes by the oxidation of pre-functionalized quinolines under room temperature (Scheme 1d).[12] However, the extra two pre-processing steps disfavor convenience and practicality of this method. The above previous works have shown that new methods for the chemoselective oxidation of methylheteroarenes under metal-free conditions at room temperature are highly desired. Herein, we wish to report a metal-free chemoselective oxidation of 4-methylquinolines into the corresponding aldehydes using phenyliodine(III) diacetate (PIDA) as the oxidant (Scheme 1e).



Scheme 1. Oxidation of methylheteroarenes into heteroaromatic aldehydes.

Initially, 4-methylquinoline **1a** was chosen as the model substrate for this oxidation reaction. PIDA was applied as the oxidant and HCF_2CO_2H was used as the additive. The first attempt was carried out in DMSO in the presence of 2 equiv. of

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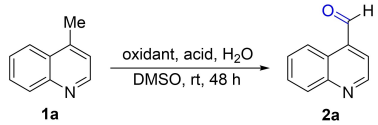
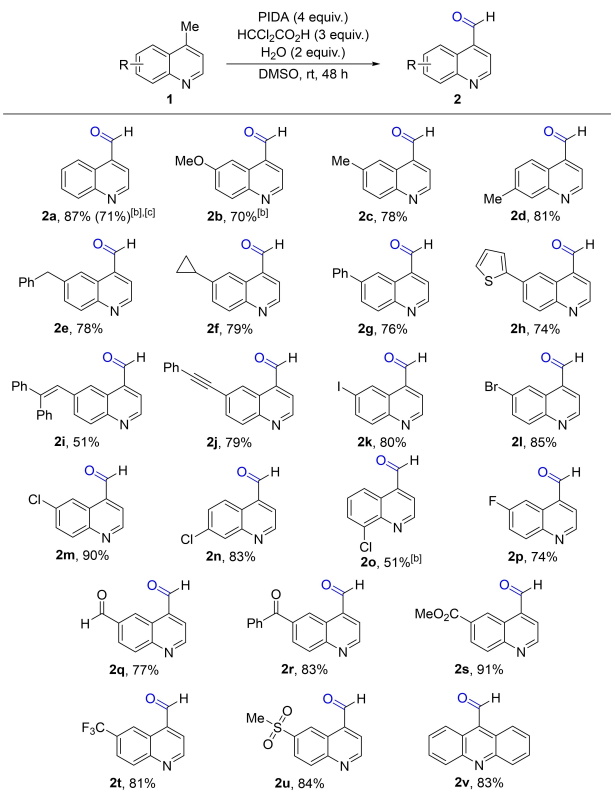
Table 1. Optimization of the reaction conditions.[a]



1a 2a

entry	oxidant [equiv.]	acid [equiv.]	H_2O [equiv.]	NMR yield [%][b]
1	PIDA (2)	HCF_2CO_2H (2)	2	46 (17)[c]
2	PIFA (2)	HCF_2CO_2H (2)	2	25 (62)[c]
3	PhIO (2)	HCF_2CO_2H (2)	2	24 (33)[c]
4	DMP (2)	HCF_2CO_2H (2)	2	28 (19)[c]
5	Togni II (2)	HCF_2CO_2H (2)	2	1 (28)[c]
6	PIDA (2)	$HCCl_2CO_2H$ (2)	2	49 (25)[c]
7	PIDA (2)	CF_3CO_2H (2)	2	46 (38)[c]
8	PIDA (2)	CCl_3CO_2H (2)	2	2 (70)[c]
9	PIDA (2)	CH_3CO_2H (2)	2	2 (92)[c]
10	PIDA (2)	HCO_2H (2)	2	2 (91)[c]
11	PIDA (2)	$PhCO_2H$ (2)	2	6 (76)[c]
12	PIDA (1)	$HCCl_2CO_2H$ (2)	2	15 (64)[c]
13	PIDA (4)	$HCCl_2CO_2H$ (2)	2	86 (5)[c]
14	PIDA (4)	$HCCl_2CO_2H$ (1)	2	27 (40)[c]
15	PIDA (4)	$HCCl_2CO_2H$ (3)	2	91 (87)[d]
16	PIDA (4)	$HCCl_2CO_2H$ (5)	2	86 (4)[c]
17	PIDA (4)	$HCCl_2CO_2H$ (3)	1	75 (15)[c]
18	PIDA (4)	$HCCl_2CO_2H$ (3)	3	88 (2)[c]

[a] All reactions were carried out using **1a** (0.5 mmol), oxidant, acid, and H_2O in anhydrous DMSO (2.5 mL) at rt for 48 h. [b] Yield was determined by ^1H NMR analysis of the crude reaction mixture using CH_2Br_2 (0.5 mmol) as internal standard. [c] Recovered yield of **1a**. [d] Isolated yield of **2a**.



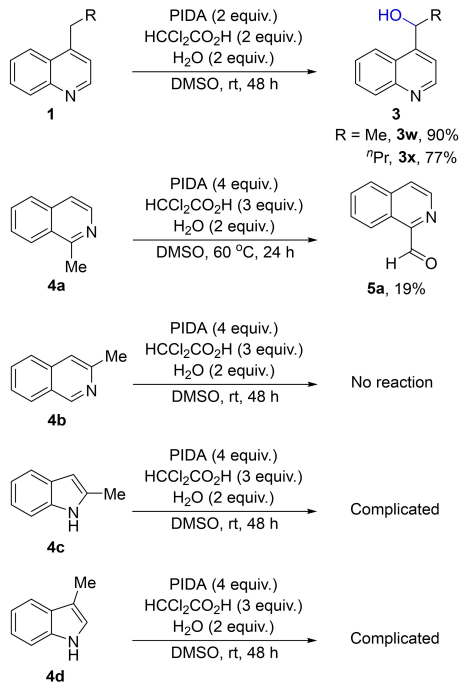
Scheme 2. Substrate scope. [a] All reactions were carried out using **1** (0.5 mmol), PIDA (4 equiv.), $HCCl_2CO_2H$ (3 equiv.) and H_2O (2 equiv.) in anhydrous DMSO (2.5 mL) at rt for 48 h. Isolated yield was reported. [b] The reaction was carried out for 96 h. [c] Gram-scale reaction.

H_2O at room temperature for 48 h, affording the desired product quinoline-4-carbaldehyde **2a** in 46% NMR yield (Table 1, entry 1). Subsequently, a series of hypervalent iodine reagents were investigated. Disappointingly, other oxidants were less effective (Table 1, entries 2–5). Thus, PIDA was chosen as the oxidant for further optimization. Next, the screening of carboxylic acids revealed that $HCCl_2CO_2H$ was more favorable (Table 1, entries 6–11). Decreasing the amount of PIDA to 1 equiv. resulted in a diminished yield (Table 1, entry 12). Increasing the amount of PIDA to 4 equiv. led to much higher yield (Table 1, entry 13). Next, we reduced the amount of $HCCl_2CO_2H$ to 1 equiv.. The yield was sharply decreased (Table 1, entry 14). Then, we improved the amount of $HCCl_2CO_2H$ (Table 1, entries 15 and 16). The best result was observed when 3 equiv. of $HCCl_2CO_2H$ was applied, affording **2a** in 87% isolated yield (Table 1, entry 15). Finally, the amount of H_2O was investigated, but no further improvement was observed (Table 1, entries 17 and 18). Thus, Condition A (**1**, PIDA (4 equiv.), $HCCl_2CO_2H$ (3 equiv.), H_2O (2 equiv.), DMSO, and rt) was applied as the optimized condition for further studies.

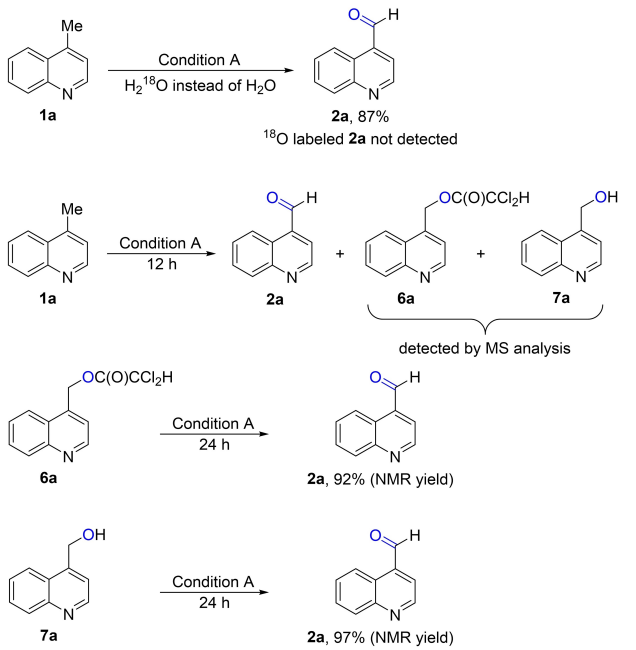
With the optimized conditions in hand, we next explored the substrate scope of this reaction. As shown in Scheme 2, a series of 4-methylquinoline substrates were tested under Condition A. Substrates with a strong electron donating group (**1b**) or a weak donating group (**1c**–**1j**) afforded the corresponding products in moderate to good yields. Delightedly, selective oxidation took place only at the C4 position when another methyl (**1c** and **1d**) or active benzyl (**1e**) located at benzene ring of quinoline. The active cyclopropane ring (**1f**) was intact under Condition A. Substrates with an aryl (**1g**) or a heteroaryl (**1h**) were suitable for accessing the desired products. Unsaturated functional groups, such as alkenyl (**1i**) and alkynyl (**1j**), were also tolerant. Halogen-substituted reactants (**1k**–**1p**) could be converted into the desired products in moderate to excellent yields. Strong electron withdrawing group substituted 4-methylquinolines (**1q**–**1u**) showed good reactivity, yielding the corresponding products in good to excellent yields. Gratifyingly, a variety of potentially sensitive functional groups, such as formyl (**1q**), benzoyl (**1r**), methoxycarbonyl (**1s**), trifluoromethyl (**1t**), and methylsulfonyl (**1u**), were all well tolerated in this transformation. Furthermore, the reaction of 9-methylacridine (**1v**) also formed the desired product in 83% isolated yield.

Then, we investigated the reactivities of other 4-alkylquinolines under the standard conditions (Scheme 3). To our delight, 4-ethylquinoline (**1w**) and 4-butylquinoline (**1x**) could be oxidized into the corresponding benzylic alcohol (**3w** and **3x**), respectively. Next, some other methylheteroarenes were tested under Condition A. Disappointingly, only 1-methylisoquinoline (**4a**) could be oxidized into the desired aldehyde (**5a**) in a very low yield. 3-Methylisoquinoline (**4b**), 2-methyl-1*H*-indole (**4c**) and 3-methyl-1*H*-indole (**4d**) gave no desired product at all.

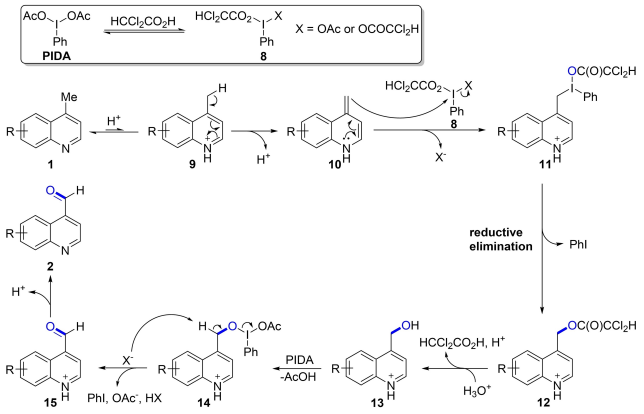
The bioactivities of quinoline-4-carbaldehydes have been well-studied. For example, **2a** has been found to be a highly bioactive molecule in many fields.[13] Thus, we felt quite interested in exploring the potential antineoplastic activity of such compounds. Our results[14] showed that **2a** and cisplatin



Scheme 3. Substrate scope of other alkylheteroarenes.



Scheme 4. Preliminary mechanism study.



Scheme 5. Plausible mechanism.

suppressed the growth of OCI-LY 3 with IC_{50} values of 1.87 μM and 0.85 μM, respectively. Obviously, **2a** effectively decreased cell viability of OCI-LY 3, which was comparable to the classic chemotherapeutic drug-cisplatin. Next, we wanted to explore whether this method could be used to synthesize quinoline-4-carbaldehydes in gram-scale, so as to provide a tool for other researchers to carry on anti-tumor studies using these compounds as potential drugs. Thus, a gram-scale reaction using **1a** (10 mmol, 1.434 g) was performed, and the desired product **2a** was obtained in 71% isolated yield (Scheme 2). This result showed that this method highlights great synthetic value.

To get insight into the reaction mechanism, several experiments were carried out (Scheme 4). Firstly, to determine oxygen atom source of the product **2a**, 2 equiv. of $H_2{}^{18}O$ instead of H_2O was added into the reaction mixture. The result showed that no ^{18}O labeled **2a** was formed (for details, see Supporting Information), which suggested the oxygen atom of the newly formed carbonyl group should not from H_2O. Thus, we assumed that the role of H_2O was just for hydrolysis step (*vide infra*). Then, MS analysis of the reaction mixture was carried out when **1a** was reacted under Condition A for 12 h. **6a** and **7a** were detected (for details, see Supporting Information). These results suggested that **6a** and **7a** might be two key intermediates of this reaction. Next, **6a** and **7a** were employed under Condition A, yielding **2a** in 92% and 97% NMR yield, respectively. These results support our hypothesis.

On the basis of the experimental results and related literature reports, a plausible reaction mechanism is proposed (Scheme 5). Firstly, the exchange of one or two dichloroacetic acid with the acetoxyl group on PIDA affords hypervalent iodine(III) **8**.[15] Meanwhile, protonation of substrate **1** gives intermediate **9** which then undergoes deprotonation to generate intermediate **10**.[16] Subsequently, intermediate **11** is obtained *via* nucleophilic attack of **10** to **8**. **11** undergoes reductive elimination to produce the dichloroacetic ester **12** and PhI.[17] The resulting **12** can be hydrolyzed into the benzylic alcohol **13** by acid catalysis. The nucleophilic substitution reaction between **13** and PIDA occurs to result in species **14**. Then, **14** is converted into aldehyde **15** *via* an anion X^--induced I–O bond cleavage. Finally, the desired product **2** is formed by a deprotonation process.

In summary, we have developed a simple and practical acid-induced chemoselective oxidation of 4-methylquinolines to afford the corresponding aldehydes using PIDA as oxidant at room temperature under metal-free conditions. This transformation is excellent tolerant for a variety of functional groups. We believe this mild oxidation method provides an attractive alternative for synthesis of *N*-heteroaromatic aldehydes. Further investigations of this strategy are currently in progress.

Acknowledgements

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: oxidation · aldehyde · hypervalent iodine(III) · metal-free · quinoline

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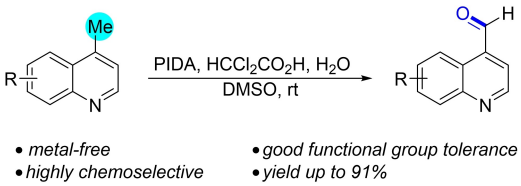

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Metal-Free Chemoselective Oxidation of 4-Methylquinolines into Quinoline-4-Carbaldehydes

A metal-free chemoselective oxidation of 4-methylquinolines into the corresponding aldehydes using phenyliodine(III) diacetate as the oxidant. This mild oxidation method provides an attractive alternative for synthesis of *N*-heteroaromatic aldehydes.