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Regioselective, Molecular Iodine-Mediated C3 Iodination of Quinolines

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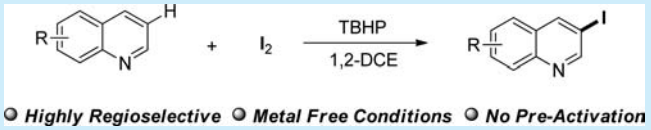
Supporting Information

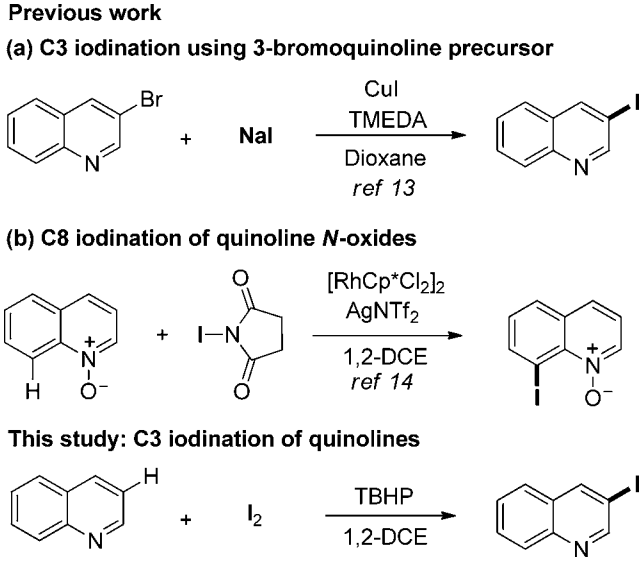
ABSTRACT: A novel and convenient method has been developed for the regioselective iodination of quinolines at their C3 position under metal-free conditions. Iodinated quinolines, which are popular building blocks in organic and medicinal chemistry, can be prepared in gram quantities and good yields using this method and further derivatized to give increasingly complex compounds. Preliminary mechanistic studies have shown that this reaction most likely occurs via a radical intermediate.



Quinolines are an important class of nitrogen-containing heterocycles that can be found in a wide range of interesting compounds, including natural products,[1] medicinal agents,[2] and functional materials.[3] In light of their numerous applications, considerable research effort has been directed toward the development of efficient methods for the regioselective functionalization of quinolines at various positions.[4] Traditional routes for the functionalization of quinolines have focused predominantly on the reactions of halo-quinoline substrates, such as transition-metal-catalyzed cross-coupling and nucleophilic aromatic substitution (S_NAr) reactions, which have been used extensively with a high level of success.[5] For this reason, there has been growing interest in the development of new methods for the incorporation of chloro,[6] bromo,[7] and iodo[8] substituents onto quinoline rings. However, progress in this area has been limited by over-halogenation and poor regioselectivity. An improved strategy has been developed for the halogenation of quinolines via the corresponding *N*-oxides. However, the exposure of *N*-oxides to prolonged periods of heating raises important safety concerns regarding the thermal stability and C2 selectivity of the corresponding halogenated quinolines during these halogenation reactions. Baran et al.[9] recently reported an elegant method for the regioselective C2-bromination of fused azine *N*-oxides using *n*-Bu_4NBr as a nucleophilic bromide source. From a synthetic practicality viewpoint, rapid, efficient, and practical access to halogenated quinolines, especially complementary methods other than C2 halogenation, are still highly desired.

Indeed, reports pertaining to the catalytic activation of quinolines at sites other than C2 are scarce.[10] With the exception of the work reported by Fagnou and co-workers,[11] very few C8 alkenylation, arylation, amidation, and borylation reactions have been disclosed based on a N−O directing group.[12] Quinoline iodides are fundamental building blocks in synthetic chemistry, where they are used for a wide range of important transformations. However, the facile iodination of quinolines under mild conditions remains a long-standing issue in chemistry. The Finkelstein reaction is a well- established method for the construction of aryl iodides, including C3 iodinated quinolines (Scheme 1a).[13] In 2014, Chang et al.[14] made a significant breakthrough in the C8 iodination of quinoline *N*-oxides using a Rh(III) catalyst and NIS (Scheme 1b). Most recently, Li et al.[15] disclosed an elegant photo-induced process for the metal-catalyst-free iodination of aromatic compounds, including the C3 and C4 iodination of quinoline, under mild conditions. The lack of mild and scalable methods for the regioselective iodination of quinolines recently

Scheme 1. Iodination of Quinolines (*N*-Oxides) at Different Positions



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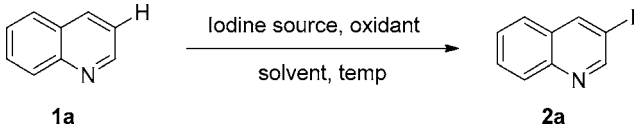
came to our attention when we attempted to prepare 3-aminoquinolines as potential drug candidates. As part of our continued interest in the development of new methods for the formation of C−X (X = C, N, S, I) bonds,[16] we present herein a novel route for the iodine-mediated C3 iodination of quinolines through a radical pathway. Notably, this method proceeded smoothly on gram scale, where it provided facile access to a C−I bond that was subsequently converted to a C−N bond via a Pd(II)-catalyzed reaction.

The commercially available quinoline **1a** was initially screened against a variety of different iodination agents to identify the best reagent for the selective C3 iodination of this substrate (Table 1). The reaction of **1a** with molecular iodine and TBHP (70% in water) in MeOH at 120 °C for 24 h gave the desired product **2a** in 70% yield (Table 1, entry 1). *n*-Bu_4NI and KI, which could both serve as radical initiators for the decomposition of TBHP to give the corresponding *tert*-butoxyl and *tert*-butylperoxy radicals, were also tested, but no **2a** could be detected (Table 1, entries 3 and 4). When Selectfluor and KI were used as the oxidant and iodine source, respectively, the desired product **2a** was obtained in only 17% yield (Table 1, entry 5). Based on this result, we investigated the use of the electrophilic iodine source, IBr. Surprisingly, IBr failed to afford any of the desired product **2a** (Table 1, entry 6). A variety of different solvents were also screened in this reaction (Table 1, entries 7−11). DCE was identified as the optimum solvent for this catalytic system, with the desired product **2a** being isolated in 89% yield (Table 1, entry 11). Water and DMSO performed poorly as solvents for this reaction (Table 1, entries 7 and 8). In contrast, CH_3CN and THF gave good results, with the desired product **2a** being isolated in satisfactory yields of 78% and 71%, respectively. When the reaction temperature was reduced to 80 °C, there was a significant decrease in the yield of **2a** (Table 1, entry 12). Further screening revealed that TBHP was critical to the success of the reaction, with no **2a** being detected when TBHP was omitted from the reaction (Table 1, entry 14). Taken together, these results revealed that the optimum reaction conditions for the C3 iodination of quinoline were molecular iodine and TBHP in DCE at 120 °C for 24 h (Table 1, entry 11).

With the optimized reaction conditions in hand (Table 1, entry 11), we proceeded to investigate the scope of the reaction using a variety of different quinoline derivatives (Scheme 2). The presence of an electron-donating or -withdrawing group on the quinoline ring had very little impact on the success of the transformation, with methyl, methoxyl, fluoro, chloro, bromo, ester, and nitro groups being well tolerated at the C6 position to give the corresponding C3 iodinated products in good to

Table 1. Screening of Reaction Conditions[a]

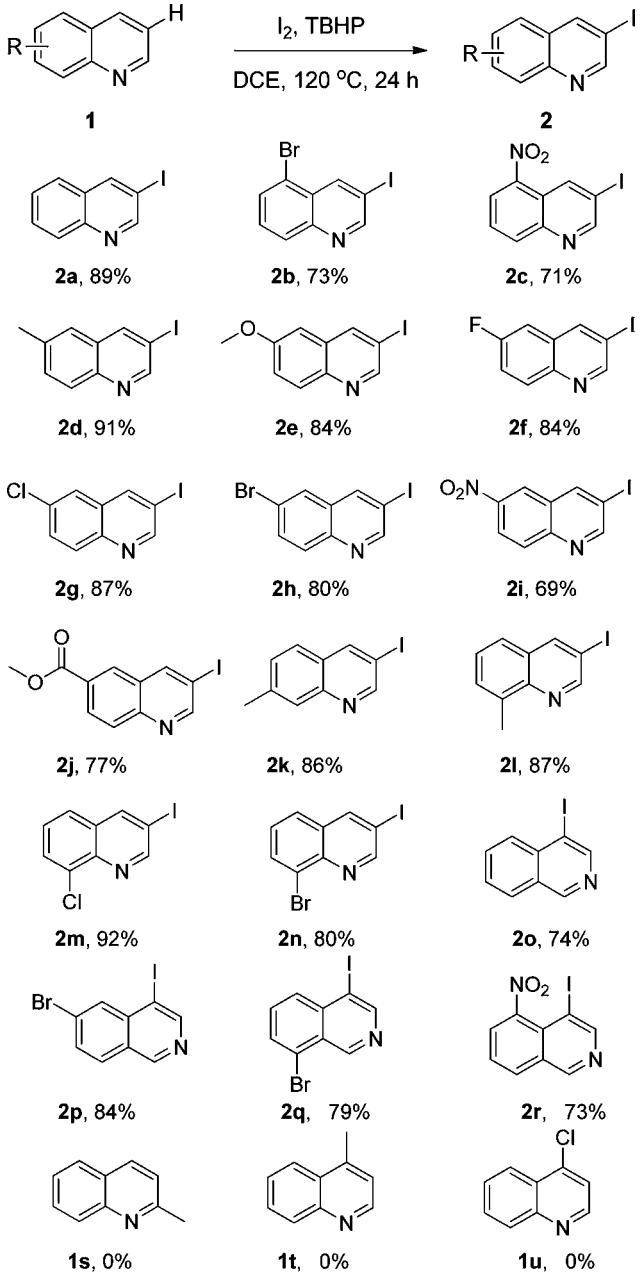


1a **2a**

entry	iodine source (1 equiv)	oxidant (3 equiv)	solvent (3 mL)	yield (%)[b]
1	I_2	TBHP	CH_3OH	70
2	I_2	H_2O_2	CH_3OH	23
3	*n*-BuNI	TBHP	CH_3OH	0
4	KI	TBHP	CH_3OH	0
5	KI	Selectfluor	CH_3OH	17
6	IBr	TBHP	CH_3OH	0
7	I_2	TBHP	H_2O	0
8	I_2	TBHP	DMSO	0
9	I_2	TBHP	CH_3CN	78
10	I_2	TBHP	THF	71
11	I_2	TBHP	DCE	89
12	I_2	TBHP	DCE	46[c]
13	I_2	TBHP	DCE	0[d]
14	I_2	no	DCE	0

[a]Reaction conditions: **1a** (0.5 mmol), iodine source (1.0 mmol), oxidant (1.5 mmol), and solvent (2.0 mL) at 120 °C for 24 h. [b]Yield of isolated product. [c]Reaction was performed at 80 °C. [d]Reaction was performed at 20 °C.

Scheme 2. Iodination of Various Quinoline Derivatives[a,b]



[a]Reaction conditions: **1** (0.5 mmol), molecular iodine (1.0 mmol), TBHP (1.5 mmol), and DCE (2.0 mL) at 120 °C for 24 h. [b]Yield of isolated product.

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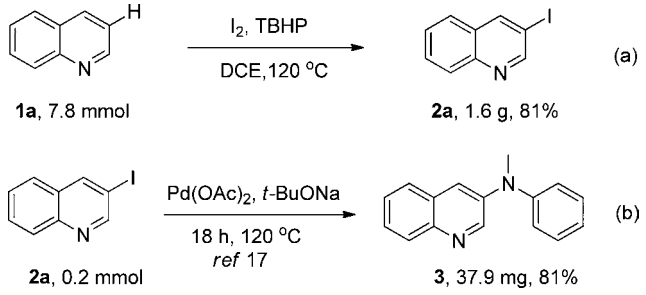
high yields (69−91%). 5-Bromoquinoline (**1b**), 5-nitroquinoline (**1c**), 7-methylquinoline (**1k**), 8-methylquinoline (**1l**), 8-chloroquinoline (**1m**), and 8-bromoquinoline (**1n**) also reacted with unprecedented efficiency to give the corresponding iodinated products in 71−92% yield. However, quinolines bearing a substituent at their 2- or 4-position such as 2-methylquinoline (**1s**), 4-methyl-quinoline (**1t**), or 4-chloroquinoline (**1u**) failed to afford the desired iodinated product under the same conditions, presumably because of steric hindrance at C3. Isoquinoline (**1o**), 8-bromoisoquinoline (**1p**), 8-bromoisoquinoline (**1q**), and 5-nitroisoquinoline (**1r**) were also subjected to the optimized conditions and afforded the C4 iodinated products **2o**, **2p**, **2q**, and **2r**, respectively, in 73−84% yields.[17] Although the substrate scope of this reaction is limited, the results of this work are still significant considering that excellent C3 selectivity of quinolines and C4 selectivity of isoquinolines were achieved and Cl, Br, and I can be converted into various functional groups under ambient conditions.

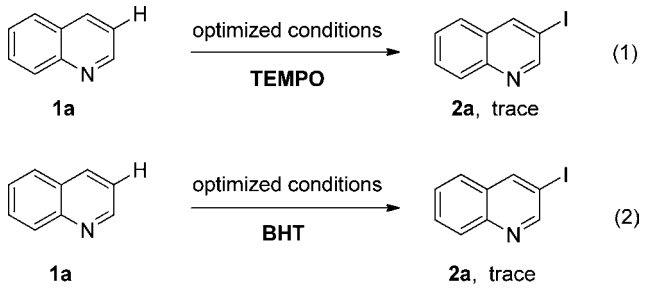
To demonstrate the practicality of this approach, we conducted the gram-scale iodination of quinoline (**1a**) under the optimized conditions, which gave the desired product 3-iodoquinoline (**2a**) in 81% yield (Scheme 3a). The C−I bond

Scheme 3. Gram-Scale Iodination of Quinoline



of 3-iodoqunilone (**2a**) was subsequently converted to a C−N bond following its reaction with *N*-methylaniline in the presence of $Pd(OAc)_2$, which gave the *N*-methyl-*N*-phenylquinolin-3-amine **3** in good yield. Notably, this compound represents a common structural motif found in many pharmaceutically active molecules (Scheme 3b).[18]

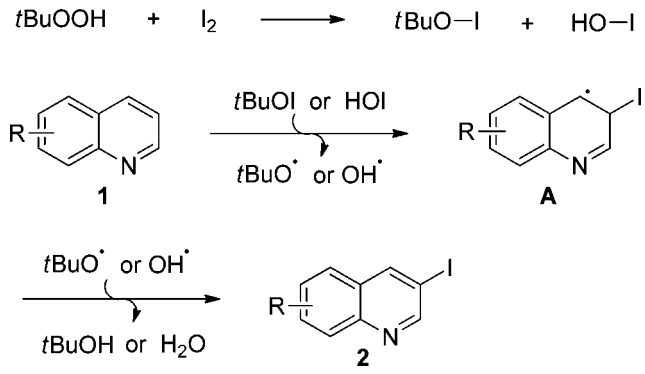
To probe the mechanism of this reaction, we investigated the impact of the addition of the radical inhibitors BHT (2,6-di-*tert*-butyl-4-methylphenol) and TEMPO (2,2,6,6-tetra- methylpiperid-idine-*N*-oxyl). In both cases, the reaction was almost completely suppressed, with only trace amounts of the desired product being identified, even after an extended reaction time (eqs 1 and 2). These results therefore suggested that this



reaction most likely proceeds via a free radical process. Given that KI and n-Bu_4NI did not work as iodinating reagents in this reaction, we speculate that this reaction does not involve an iodide ion as an active intermediate during the iodination procedure. Considering that the electron density at the C3 position of quinoline is slightly higher than those at the C2 and C4 sites, we propose a radical pathway to explain the regioselective of this iodination reaction for the C3 position.

The initial reaction of *t*BuOH with molecular iodine would lead to the formation of *t*BuOI and HOI. The iodination reaction could then proceed via a homolytic attack involving *t*BuOI and HOI to generate intermediate **A**, followed by *tert*-butoxyl or hydroxy radical-induced abstraction of a hydrogen atom from the C3 position to give the final product **2** (Scheme 4).

Scheme 4. Plausible Catalytic Cycle



In summary, we have developed a novel and convenient process for the regioselective iodination of quinolines at the C3 position in the presence of molecular iodine and TBHP. This method is operationally simple and shows good functional group compatibility. Furthermore, the reaction was used for the gram-scale synthesis of 3-iodoquinoline, which was subsequently derivatized under conventional Buchwald−Hartwig amination conditions. Preliminary mechanistic studies suggest that a radical intermediate is likely involved in this process. Further work toward expanding on this protocol is currently underway, and the results will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01857.

Experimental procedures and details of the characterization of all of the new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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NOTE ADDED AFTER ASAP PUBLICATION

This paper was published ASAP on August 3, 2015. The structures of compounds **2o**, **2p**, **2q**, and **2r** were incorrectly reported. The manuscript now describes the compounds correctly in the text and Scheme 2 shows the correct structures. Reference 17 has been added. A revised Supporting Information file contains the correct structures for these compounds. The revised paper was reposted on August 28, 2015.

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