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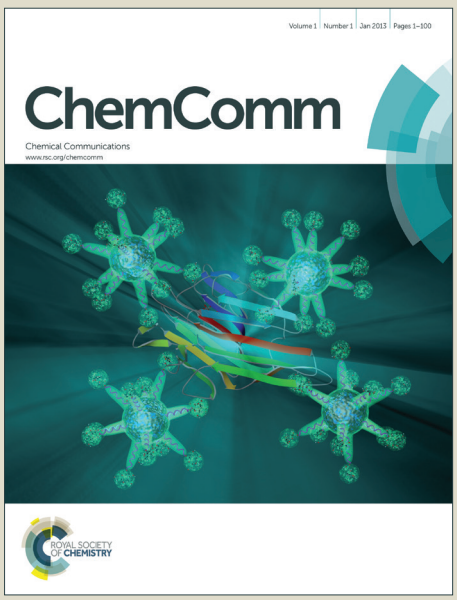

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Metal-Free Synthesis of *N*-Fused Heterocyclic Iodides via C-H Functionalization Mediated by *tert*-Butylhydroperoxide

Received 00th January 20xx,
Accepted 00th January 20xx
DOI: 10.1039/x0xx00000x

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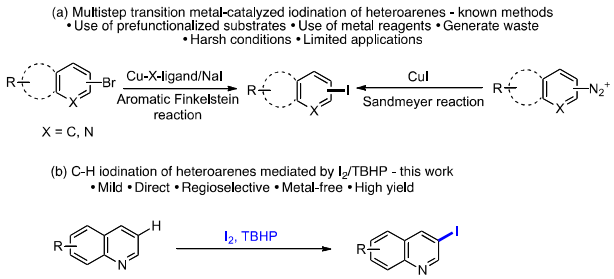
Direct, regioselective and metal-free synthesis of fused *N*-heterocyclic iodides is reported. This regioselective C-H functionalization is mediated by *tert*-butylhydroperoxide (TBHP), via dual activation of molecular iodine and heterocyclic substrate, resulting in the *in situ* generation of electrophilic iodine species (I^+), and free radical(s) $^tBuO^\cdot$ or $^tBuOO^\cdot$, driving the iodination reaction.

(Hetero)aryl iodides are versatile synthons in organic synthesis, useful for generating diversity in bioactive molecules. Higher reactivity of aryl iodides compared to aryl bromides and aryl chlorides, and their ease in undergoing an oxidative addition reaction due to a weaker carbon–iodine bond, makes them valuable precursor in the transition metal-catalyzed transformations.[1] The aryl iodides are also susceptible to photolytic cleavage at the carbon–iodine bond, and this property has been elegantly exploited in various reports.[2] In addition, (hetero)aryl iodides have found applications in thyroid disease, anticancer treatment, X-ray imaging, and several pharmacokinetics studies.[3]

Despite wide applications, (hetero)aryl iodides are expensive and have limited commercial availability, compared to their bromide or chloride counterparts. Traditional approaches to the synthesis of (hetero)aryl iodides include, (i) widely used direct iodination reaction of inactivated aromatic C-H bond that requires strong Lewis acids or protonic acids conditions, but have limited application to heterocycles, and are generally non-regioselective,[4] and (ii) Sandmeyer reaction, which has a prerequisite of an aromatic nitro or amino group and later generation of diazonium salt (scheme 1).[5] Buchwald et al. recently reported an aromatic Finkelstein reaction to synthesize (hetero)aryl iodides from the corresponding bromides via a trans-halogenation reaction using a copper catalyst and a bidentate ligand.[6] Although elegant, these methods have limited functional group tolerance or substrates scope, and (hetero)aryl iodides are obtained in multistep synthesis. In the Sandmeyer and aromatic Finkelstein reactions, the iodination at a specific position is governed by the electronic factors, and position of nitro, amino and bromo groups of the substrates. More recently, directing group-assisted C-H iodination at the *ortho*-position to the directing group, catalyzed by palladium, rhodium, and other transition metals have been reported.[7]

The generalized methods of C-H bromination and chlorination of the six membered *N*-fused heterocycles can not be extended to include iodination.[8] Therefore, direct C-H iodination of *N*-fused heterocycles is a significant challenge, and has often been unsuccessful or limited due to several factors, including poor regioselectivity, harsh reaction conditions and over-iodination.[9] The known methods for the direct C-2 iodination of *N*-fused heterocycles often requires metalation-based approaches.[10]



Scheme 1. Approaches to regioselective iodination of (hetero)arenes

Quinolines and structurally related heterocycles are one of the most explored groups of compounds in drug discovery. This ring system is present in a number of naturally occurring bioactive molecules, and has application in material science.[11] In our continuing work on quinolines as bioactive compounds,[12] we were interested in synthesizing C-3 iodinated quinolines and other related heterocycles under mild reaction conditions upto multigram scale. However, to the best of our knowledge, there is no generalized report on the direct regioselective C-3 iodination of quinolines and related heterocycles. Herein, we report the first metal-free, direct and regioselective C-H iodination of *N*-fused heterocycles using inexpensive molecular iodine. The reaction proceeds via a dual activation strategy mediated by *tert*-butylhydroperoxide (TBHP). The regioselectivity of the C-H iodination is easily predictable (β-position to nitrogen) and is not affected by the electronic and steric factors; a major limitation of the reported C-H iodination protocols.[4e]

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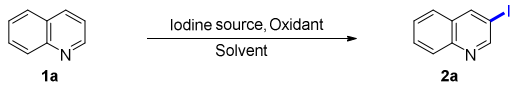
Electronic Supplementary Information (ESI) available: [Experimental procedures, product characterization, copies of ^1H and ^{13}C NMR.
See DOI: 10.1039/x0xx00000x

Table 1. Optimization of the reaction[a]



Entry	Oxidant (equiv.)	Iodine source	Temp.	Solvent	**2a** (% Yield)[b]
1	Oxone (3)	I_2	RT	MeCN	n.r.[c]
2	*m*-CPBA (3)	I_2	RT	MeCN	n.r.[c]
3	H_2O_2(3)	I_2	RT	MeCN	n.r.[c]
4	$(NH_4)_2S_2O_8$ (3)	I_2	RT	MeCN	n.r.[c]
5	$PhI(OAc)_2$ (3)	I_2	RT	MeCN	n.r.[c]
6	$PhI(OCOCF_3)_2$ (3)	I_2	RT	MeCN	n.r.[c]
7	TBHP (3)	I_2	RT	MeCN	23
8	TBHP (3)	I_2	80 °C	MeCN	34
9	TBHP (6)	I_2	80 °C	MeCN	67
10	TBHP (8)	I_2	80 °C	MeCN	92
11	TBHP (8)	I_2	90 °C	MeCN	87
12	DTBP(8)	I_2	80 °C	MeCN	82
13	TBHP (8)	NIS	80 °C	MeCN	81
14	TBHP (8)	TBAI	80 °C	MeCN	n.r.[c]
15	TBHP (8)	I_2	80 °C	DMF	n.r.[c]
16	TBHP (8)	I_2	80 °C	$CHCl_3$	74
17	TBHP (8)	I_2	80 °C	DMSO	78

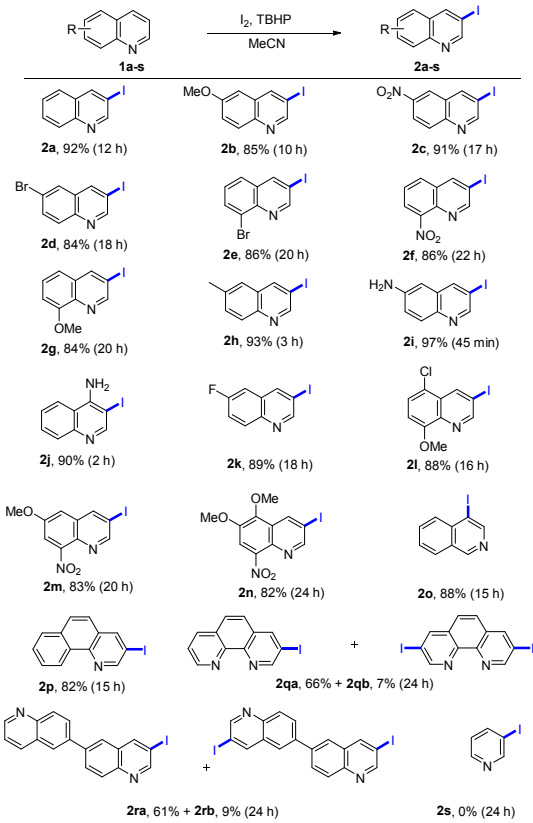
[a]All reactions were performed with substrate **1a** (0.1 mmol), I_2 (1.2 equiv.), solvent (2 mL). [b]isolated yield. 30% (w/w) H_2O_2 solution was used. 70% (v/v) solution of TBHP in water was used. Reactions monitored by TLC up to 12 h. [c]No reaction.

The investigation began with the screening of a number of oxidants at room temperature while using quinoline (**1a**) as a model substrate and molecular iodine as the iodinating reagent in MeCN; however, no iodination was observed (table 1, entries 1-6). The first success was observed when 70% TBHP in water (3 equiv.) was used as an oxidant in the presence of I_2 (1.2 equiv.) in MeCN (2 mL) to afford regioselectively 3-iodoquinoline (**2a**) in 23% yield after 12 h, along with the unreacted starting material (table 1, entry 7). Heating the reaction mixture at 80 ˚C, while keeping the reagents ratio intact as described above afforded 3-iodoquinoline (**2a**) in 34% yield, without any change in the regioselective nature of the reaction (table 1, entry 8). Increasing the stoichiometry of TBHP to six equivalents resulted in even higher conversion and yield of the product (table 1, entry 9). Finally, the use of 8 equivalents of TBHP at 80 ˚C afforded 3-iodoquinoline (**2a**) in 92% yield (table 1, entry 10). Further attempts to vary the stoichiometry of iodine and TBHP, and temperature of the reaction did not improve yield of the product. The use of di-*tert*-butylperoxide (DTBP) as the oxidant under the optimized conditions produced **2a** in 82% yield (table 1, entry 12). The use of electrophilic iodinating reagent (NIS) afforded **2a** in 81% yield (table 1, entry 13), while the use of tetrabutylammonium iodide (TBAI) resulted in no reaction (table 1, entry 14). The use of alternate solvents such as DMF, $CHCl_3$ and DMSO did not offer any advantage over MeCN as the solvent medium of the reaction (table 1, entries **15-17**). To determine the catalytic nature of the reaction, an experiment was conducted wherein catalytic amount of TBHP (20 mol%) and $AgNO_3$ (20 mol%) was used in the presence of I_2 (1.2 equiv.), resulting in trace formation of the product, and thereby indicating that the high stoichiometry of TBHP is a desirable factor in the reaction.

With the optimized conditions, the substrate scope of the reaction with various substituted quinolines and structurally related heterocycles was investigated (table 2). As seen clearly, electron-withdrawing groups, electron-donating groups, and reactive functional groups were well tolerated during the iodination reaction. The electron-donating group containing quinolines, generally prone to over iodination underwent facile regioselective C-H activation to afford C-3 heteroaryl iodides (table 2, entries **2b**, **2g-j**). The 8-substituted quinolines (table 2, entries **1e-g, 1l-n**) were also regioselectively iodinated at the C-3 position.

As expected, the presence of electron-donating methoxy group, electron-withdrawing nitro group and electron-neutral bromo group containing quinolines due to their reduced reactivity, took longer time for the completion of reaction (table 2, entries **2e-g**). Pre-halogenated quinolines were iodinated without difficulty, although position of the halogen group affected the kinetics, resulting in increased reaction time (table 2, entries **2d-e, 2k-l**). The reactive benzylic protons were also tolerated under these conditions (table 2, entry **2h**).[13] Multi-substituted quinolines were also successfully C-3 iodinated, but reaction took between 16-24 hours, due to the less reactivity of substrates owing to the steric hindrance (table 2, entries **2l-n**).

Table 2. Substrate scope of the iodination reaction

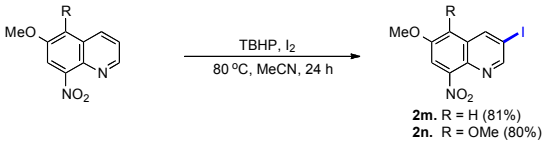


Substrate (0.25 mmol), I_2 (1.2 equiv.), TBHP (8 equiv.), MeCN (4 mL), 80 ˚C; reaction time in parentheses.

It was observed that any type of substitution at the C-8 position of the ring reduces the reactivity of quinolines,

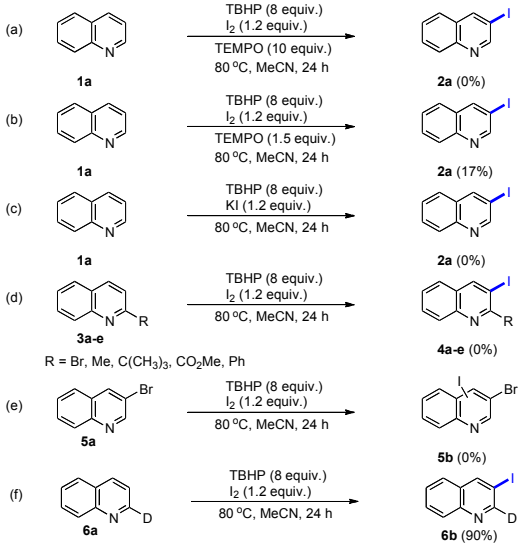
possibly due to the steric hindrance. Remarkably, highly reactive amino group was tolerated under these conditions as exemplified by the successful iodination of 6-amino- and 4-aminoquinolines (table 2, entries **2i-j**). It is important to note that 4-aminoquinolines constitute an essential class of antimalarial drugs, amply illustrated by the widely used chloroquine, and these intermediates provide interesting scaffolds for derivatization, in the quest for new antimalarials.[11,14] Similarly, 8-nitroquinoline and 6-methoxy-8-nitroquinoline were selectively iodinated in high yields (table 2, entries **2f, 2m**). Noticeably, 6-methoxy-8-nitroquinoline (**2m**) is an intermediate for the marketed antimalarial drug primaquine. Therefore, these iodinated quinolines have previously untapped applications in the possible derivatization and radiolabeling studies.

Next, the scope of other structurally related heterocycles was investigated under the optimized reaction conditions. Isoquinoline, benzo[*h*]quinoline, phenanthroline, and bisquinoline were regioselectively iodinated under these conditions in high yields (table 2, entries **2o-r**). In the case of substrates containing two reactive sites (table 1, entries **1q-r**), both mono- and di-iodinated products were obtained. However, increasing the stoichiometry of iodine (2.4 equiv.) and TBHP (16 equiv.) exclusively afforded diiodinated products. Tunable fluorophores and one of the most widely used bidentate ligand phenanthrolines and its iodinated derivatives (table 2, entries **2qa-b**) have potential application in the synthesis of designer phenanthrolines.[15] The extension of this protocol on the iodination of pyridine (table 2, entry **2s**) was unsuccessful, and is the subject of future investigation. To the best of our knowledge, a number of substituted or unsubstituted *N*-fused heterocycles (table 2, entries **1c-i**, **1k-n**, **1p-r**) are iodinated for the first time, further amplifying the utility of the reaction. The reaction was successfully applied to achieve gram scale iodination of medicinally important intermediates (**1m**-**n**), in identical yields, albeit in a slightly longer reaction time (Scheme 2).

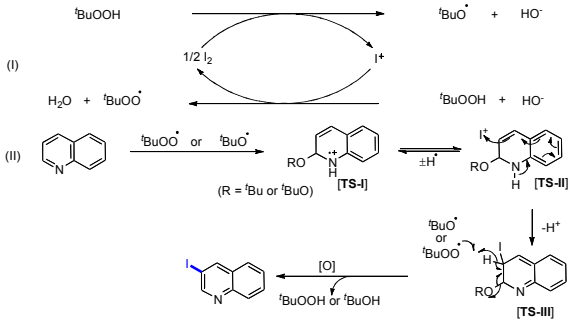


Scheme 2. Gram scale experiments

The mechanism of the reaction was investigated by conducting a series of control experiments (scheme 3). The radical trapping experiments with the varying stoichiometry of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), under the optimized reaction conditions resulted in no product formation (scheme 3a), and a drastic reduction in the yield (scheme 3b). Thus, as anticipated, this reaction is possibly radical by nature, wherein the generation of free radical is mediated by TBHP. When reaction was tried with KI (source of nucleophilic I^-), no product formation was observed (scheme 3c). In another control experiment, iodination of a number of C-2 substituted substrates failed, indicating that the regioselectivity of the reaction is possibly controlled via the C-2 position (scheme 3d). It may be noted that the designed C-2 substituents in scheme 3d are used to block C-2 position of the substrates, thereby making it inaccessible for free radical initiated reaction. No iodination of 3-bromoquinoline was observed under the optimized conditions confirming the absolute regioselectivity of the reaction (scheme 3e). We noted the iodination of quinoline-2-*d* (**6a**) at the C-3 position in high yield, without any loss of deuterium atom at the C2 position (scheme 3f). We have also carried out a time-dependent NMR study on **1a** and **6a** to obtain mechanistic insights of the reaction by taking aliquots from reaction mixture at various time intervals. The presence of both substrate and product signals were traced in the ^{1}H NMR study (see SI). To study the primary kinetic isotope effect (KIE), H/D KIE measurement with **1a** and quinoline-3-*d* was carried out resulting in the k_H/k_D ratio of 2.53. The secondary KIE measurement (k_H/k_D) ratio of 0.83 was observed with the experiment of **1a** and quinoline-2-*d* (**6a**) (see SI).



Scheme 3. Mechanistic investigation by control experiments



Scheme 4. A plausible reaction mechanism

Upon the basis of the control experiments and some earlier reports, a plausible catalytic cycle of the C-H activation reaction is depicted in scheme 4.[16] The electrophilic I^+ species were generated from I_2 in the presence of TBHP (scheme 4, equation I). It is proposed that the *in situ* generated alkoxy or

peroxy radical(s) reacts with the C2 position of **1a**, and results in radical cationic TS-I. Addition of $H^{\cdot}$ to TS-I results in TS-II. The C3 position of the quinoline ring is activated by the electron movement (mesomeric effect) and reacts with the electrophilic I^{+} (TS-III). Under the oxidative conditions, and the loss of a proton and alkoxy/peroxy radical produced **2a** (equation II).

In conclusion, we report a regioselective C-H iodination reaction of *N*-fused heterocycles under mild conditions, using molecular iodine and TBHP. To the best of our knowledge, this is the first generalized metal-free, direct and regioselective C-3 iodination protocol of *N*-fused heterocycles. This protocol provides direct and easy access to several inaccessible C-3 iodinated quinolines, and structurally related heterocycles in excellent yields. A number of control experiments provided a plausible mechanism of this C-H functionalization reaction. As discussed earlier, these *N*-fused heterocyclic iodides constitute a group of synthetically demanding and medicinally important compounds having great potential in further functionalization.

Acknowledgement

Krishna K. Sharma thanks University Grant commission (UGC), New Delhi for the award of Senior Research Fellowship.

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