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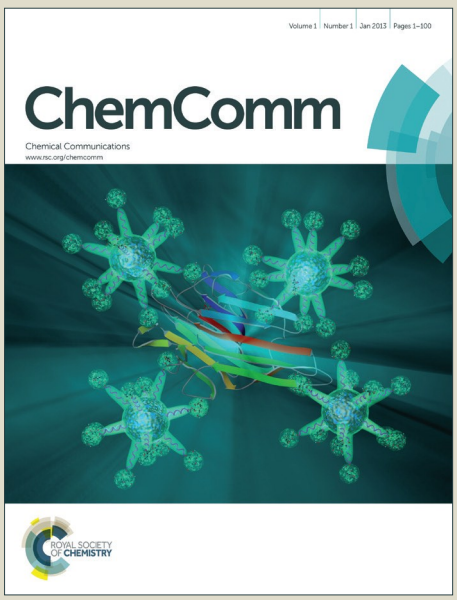

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The Regioselective Iodination of Quinolines, Quinolones, Pyridones, Pyridines and Uracil

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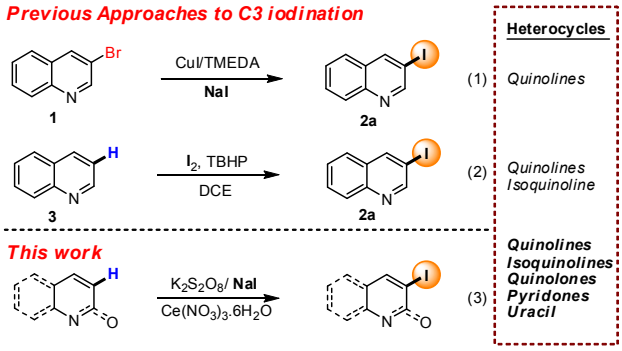
A radical based direct C–H iodination protocol for quinolines, quinolones, pyridones, pyridines, and uracil has been developed. The iodination occurs in a C3 selective manner for quinolines and quinolones. Pyridones and pyrdines undergo C3 and C5 iodination, while dimethyl uracil undergoes C5 iodination. Scope of the method was demonstrated through the rapid synthesis of both electron rich as well as electron poor heteroaromatic iodides. The protocol was found to be scalable and general, while a mechanism has been proposed.

Iodine containing compounds are integral to synthetic organic chemistry. Beyond applications in traditional synthetic methods such as metalation[1] and aromatic nucleophilic substitution,[2] they are now ubiquitous in cross-coupling chemistry.[3] Furthermore, radiolabeled iodide analogues play a vital role in medicinal and radiotherapeutic science.[4] As a consequence, extensive efforts have been made to develop useful protocols for preparing aryl iodides.[5-7] However, their synthesis remains difficult, with limitations relating to the use of expensive transition metals, need for highly polar solvents, prefunctionalization, and modest regioselectivity, plaguing many reported approaches.[8] On contrary to simple aryl iodide, the synthesis of heteroaromatic iodides is increasingly difficult.

Quinoline, pyridone and other nitrogen containing heterocyclic iodides are highly important structural motifs due to their presence in innumerable natural products and pharmaceutical agents.[9] In recent years, much efforts have been devoted towards the regioselective synthesis of iodinated heterocycles.[10-12] Aromatic Finkelstein reaction from bromides (*i.e.* 1) have developed as popular method for accessing iodo-quinolines (2) (eq. 1, Scheme 1).[13] Recently Li *et al.* have disclosed a photo induced metal free Finkelstein reaction to access C3 and C4 iodinated quinoline.[14] Unfortunately, such an approach demands prefunctionalization, and therefore limit generality. Direct regioselective functionalization of heterocycles arguably has the greatest potential to deliver broadly applicable iodination methods. However, selectivity with substrates bearing multiple C–H bonds makes this approach more challenging.



Scheme 1 C3 selective iodination by C–H functionalization

With pyridyl and quinoline, halogenation can be addressed by exploiting the *N*-oxide thereby allowing selective C2 halogenation.[15] While in an orthogonal approach recently reported by Chang and *co-workers* C8 iodination was achievable by rhodium catalyzed C–H iodination of quinoline-*N*-oxide with NIS.[16] While selective C2 and C8 halogenation of quinolines can be achieved, mild regioselective methods for other iodinations remain limited. As part of broader studies on the functionalization of heterocycles[17] in 2013 we commenced studies focused on C3 selective halogenation of quinolines, and related heterocycles. We envisaged a direct radical iodination approach enabled by the mild generation of the iodo radical. It was postulated that such an approach should allow predictable C3 iodination due to the stability of the first formed radical intermediate. Very recently a related concept was communicated by Sun and Jain which allowed the iodination of different quinolone derivatives in a regioselective manner (**3**) (eq. 2, Scheme 1).[10f,g] Stimulated by this report we wish to report our approaches on this topic. While our conditions are related to those of Sun and Jain, we have been able to achieve mild iodination of both electron rich and poor quinolines, as well as pyridones, uracil and pyridines. Mechanistically we believe that *in-situ* generation of the iodo radical leads to selective C3 iodination, although with

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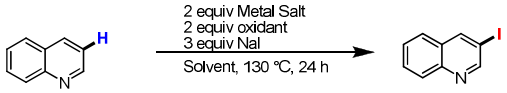
highly electron rich substrates alternate mechanistic pathways are possible.

To achieve selective C3 iodination we commenced by reacting quinoline with $K_2S_2O_8$ and sodium iodide in the presence of $MnSO_4$ in dichloroethane (DCE) heated at 130 °C. Unfortunately, these conditions, and those in which the manganese was replaced by either tin or cobalt failed to provide 3-iodo-quinoline (**2a**) (Table 1, entries 1-3). In contrast the reaction in the presence of either bismuth, nickel or cerium salts gave promising yields of the expected product with $Ce(NO_3)_3.6H_2O$ optimal with 40% yield of **2a** (Table 1, entries 4-6). Addition of 1 equivalent of TFA increased the yield, while an examination of alternate oxidants confirmed that potasium peroxodisulphate was ideal (Table 1, entry 7), although other common oxidants were also viable (Table 1, entries 8-11). Finally, increasing the stoichiometry of sodium iodide to three equivalents increased the yield further to 85% (Table 1, entry 12). Finally, control experiments demonstrated that each reagent is necessary for the formation of 3-iodoquinoline in synthetically useful yields (See SI for detailed optimization).

Table 1 Selected optimization of iodination



3a 2a

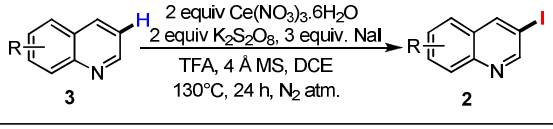
Entry	Metal salt	oxidant	solvent[a]	yield[b]
1	$MnSO_4.H_2O$	$K_2S_2O_8$	DCE	-
2	$SnCl_2.2H_2O$	$K_2S_2O_8$	DCE	-
3	$CoCl_2.6H_2O$	$K_2S_2O_8$	DCE	1
4	$Bi(NO_3)_3.5H_2O$	$K_2S_2O_8$	DCE	30
5	$Ni(NO_3)_2$	$K_2S_2O_8$	DCE	37
6	$Ce(NO_3)_3.6H_2O$	$K_2S_2O_8$	DCE	40
7[c]	$Ce(NO_3)_3.6H_2O$	$K_2S_2O_8$	DCE	62
8[c]	$Ce(NO_3)_3.6H_2O$	TBHP	DCE	61
9[c]	$Ce(NO_3)_3.6H_2O$	$K_2S_2O_8$	1,2,3-TCP	45
10[c]	$Ce(NO_3)_3.6H_2O$	$K_2S_2O_8$	^{t}BuOH	20
11[c]	$Ce(NO_3)_3.6H_2O$	DTBP	DCE	59
12[c,d]	**$Ce(NO_3)_3.6H_2O$**	**$K_2S_2O_8$**	**DCE**	**85(78)[e]**

[a]All reactions performed at 130 °C. [b]GC yield except as noted. [c]1 equiv TFA added. [d]3 equiv NaI. [e]Isolated yield.

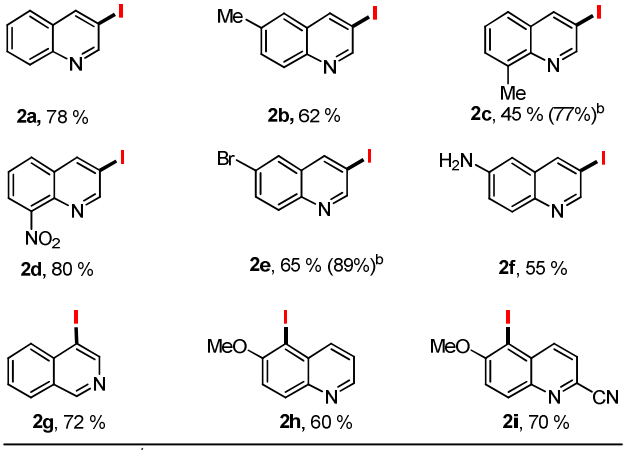
With the optimized reaction condition, the generality of the regioselective iodination was examined with the halogenation of various quinoline derivatives (Table 2). In contrast to the studies of Sun and Li who reported solely the iodination of electron poor substrates our conditions allowed 6-methyl (**2b**, 62%) and 8-methyl (**2c**, 45%), as well as electron deficient 8-NO_2 (**2d**, 80%) iodoquinolines to be prepared in acceptable isolated yields after column chromatography. Similarly 6-bromoquinoline and electron rich 6-amino quinoline gave C3 iodinated **2e** and **2f** in 65% and 55% yields respectively. Isoquinoline gave C4-iodinated product **2g** in 72% yield, as reported by Sun and Li. When the 6-methoxy quinolines were examined the selectivity switches to C5-iodinated products (**2h,** 60% and **2i,** 70%).

Next, we thought to examine the related iodination of *N*-benzyl quinolones (i.e. **4a**) under the optimized reaction condition (Table3). To our delight, we obtained the C3 iodinated *N*-benzyl quinolone derivative **5a** in 65% yield.

Table 2 Scope of iodination for various quinolines[a]



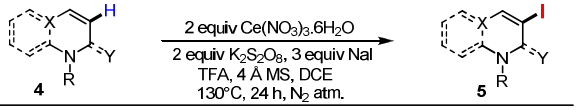
3 2



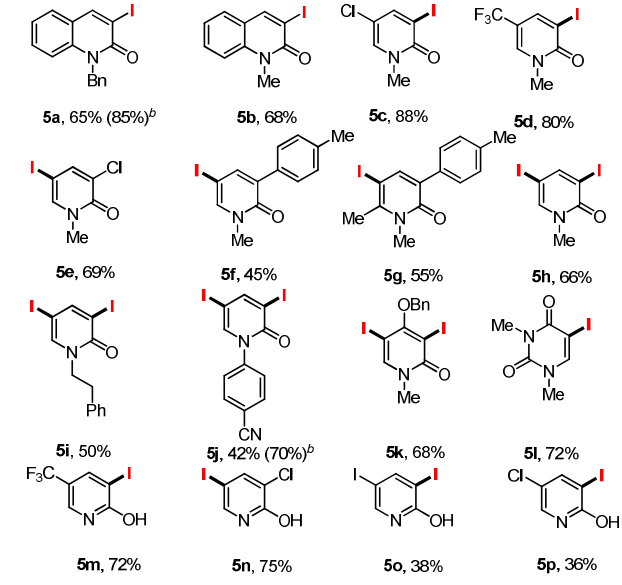
[a]Isolated yield. [b]Yield based on recovered starting material.

Similar results were obtained in the preparation of the *N*-methyl quinolone **5b**, while C5 blocked (Cl, **4c** or CF_3, **4d**) iodinated pyridones (**5c** and **5d**) were also prepared in excellent yield.

Table 3 Scope of the iodination of pyridones, quinolones, uracil and pyridines[a]



4 5



[a]Isolated yield. [b]Yield based on recovered starting material.

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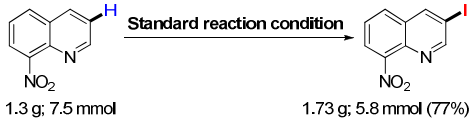
When C3 blocked pyrdiones were subjected to the reaction condition (Cl, **4e;** *p*-tolyl, **4f**) the C5 iodinated products formed smoothly. The reaction was insensitive to steric congestion with the C5 iodinated C6-methyl-C3-*p*-tolyl pyridone prepared in 55% yield.

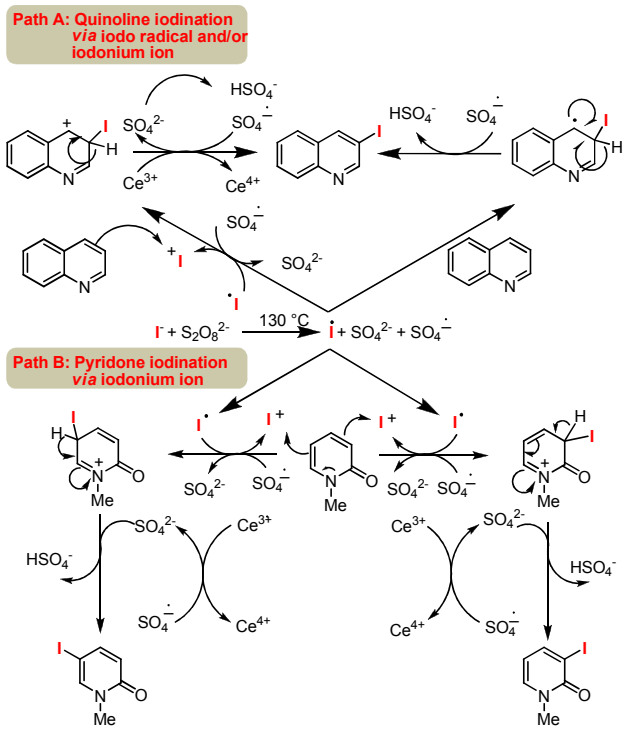
With *N*-phenylethyl, *N*-methyl or *N*-aryl pyridones bearing no additional substituents the diiodinated pyridones **5h**, **5i** and **5j** were prepared in 66, 50 and 42% yields respectively. The electron deficient pyridone **4j** was diiodinated to give **5j** smoothly, while dimethyl uracil (**4k**) provided the product of monoiodination. Finally a series of 2-hydroxy iodopyridines **5m**-**5p** bearing either C3 or C5 substituents were smoothly formed in acceptable yields.

To assess the scalability of the protocol conversion of 8-NO_2 quinoline to 3-iodo-8-nitro quinoline (**2d**) was performed with 1.3 g of substrate. The expected iodide **2d** was obtained in 77% yield, only slightly lower than the yield achieved with the submilimolar scale reaction (Scheme 2).



Scheme 2 Scaled up iodination of 8-nitro quinoline

In order to gain insight into the reaction mechanism, a number of control experiments were performed. When a radical quencher (*e.g.* TEMPO) was introduced this suppressed the iodination reaction with only a trace of the iodinated product of quinoline **2a**. Based on this observation, it may be assumed that one of the steps for iodination is proceeding *via* a radical pathway.



Scheme 3 Plausible mechanism

Previous studies with pyridone demonstrated selective functionalization at C3 position *via* a radical based transformation.[18] The observed C5-functionalized products, as in 6-methoxy quinoline **2h**, likely forms by electrophilic iodination. Therefore, the present protocol can promote iodination reaction both by a radical or electrophilic path. By considering the C3 and C5 selectivity for quinoline and pyridone, a mechanism is proposed in Scheme 3.

Conclusions

In conclusion, a variety of heterocyles can be iodinated in a predictable and selective manner using simple reaction conditions. This method is operationally simple and scalable. Due to high demand of heterocyclic iodides, this protocol is expected to find application in industry and academia.

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