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Heterocyclic Iodoniums for the Assembly of Oxygen-Bridged Polycyclic Heteroarenes with Water as the Oxygen Source

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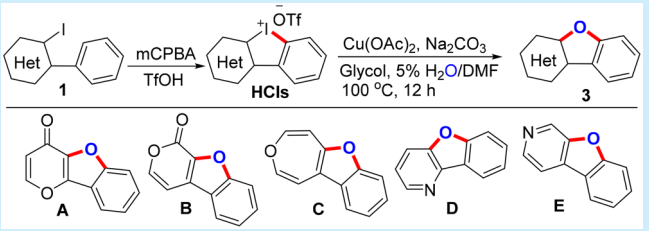
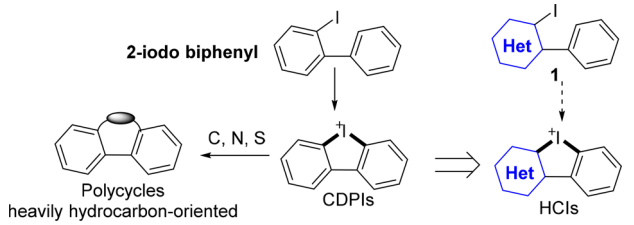
Supporting Information

ABSTRACT: A diverse set of novel heterocyclic iodoniums was synthesized for the first time. The reactions of these unique iodoniums with environmentally benign water as the oxygen source provided structurally complex oxygen-incorporated heteropolycycles that are essential motifs in natural products and biologically active compounds. The transformation only required low-cost copper acetate. Further derivatization of the obtained polycycles expanded the structural diversity, which is important in the building of chemical libraries for drug discovery.



The past five years have witnessed significant advancements in the synthetic chemistry field of cyclic diphenyl iodoniums (CDPIs). Due to the unique triple-ring system of CDPIs, it is naturally used to build complex polycyclic arenes. CDPIs can react with various nucleophiles including reactive carbon,[1] nitrogen,[2] and sulfur,[3] leading to the formation of polycyclic frameworks (Scheme 1). These obtained polycycles

Scheme 1. Concept of HCIs for Synthesis of Polycycles[a]



[a]Bold bonds indicate the structural feature of iodoniums.

are often heavily hydrocarbon-oriented and lipophilic.[4] In the drug discovery field, heterocyclic frameworks with a considerable number of heteroatoms are in demand to gain the druggability of pharmacologically active compounds.[5] Such heterocyclic compounds may favor interactions with protein targets by forming essential hydrogen bonds and $\pi-\pi$ stacking patterns, increasing their binding affinity to the targets. Meanwhile, the heterocycles exhibit better performance in terms of water solubility, a key drug property that is indispensable for their bioavailability. Thus, the evolution of CDPIs into cyclic iodoniums that are sided by heterocyclic aryls would be promising for the construction of polycyclic heteroarenes (Scheme 1). However, such heterocyclic iodoniums (HCIs) are rarely reported.[6] Therefore, the synthesis of *ortho*-iodo heteroaryl-aryls **1** that might be precursors of HCIs has to be developed. Moreover, the reactivity of HCIs also remains to be fully explored.

In our previous work using CDPIs, two phenyls siding by a central hypervalent iodine ion likely have equal electronic richness, and the iodine positions in the precursor 2-iodobiphenyls are not essential (Scheme 1). However, heteroaryls have varied electron properties in the precursors **1** and **1′** for the synthesis of HCIs (Figure 1). We envisioned that positioning iodide in the heteroaryl ring could be more viable to make HCIs due to the electronic richness of the opposite phenyl. Therefore, a series of heteroaryl phenyl compounds **1** were designed. To our delight, using the standard conditions to synthesize CDPIs in our previous work,[2a] a structurally diverse set of novel HCIs could be easily obtained by oxidizing **1** with *m*CPBA under strong acidic conditions (Figure 1). Thus, three major types of novel HCIs containing heterocyclic motifs including flavone (**2a−2g**), isoquinoline (**2h−2k**), and quinoline (**2l−2r**) were constructed for the first time. Meanwhile, other iodoniums fusing dibenzo-oxepine (**2s**, **2t**), coumarin (**2u**), and thioflavone (**2v**) were also prepared. Furthermore, the structures of cyclic iodomiums **2a** and **2u** were unambiguously clarified by X-ray crystallographic analysis (Figures S1, S2).[7] Our work demonstrated the availability of such novel cyclic heteroaryl iodoniums. These unique iodoniums might be ready for potential transformations to build complex poylcyclic frame-

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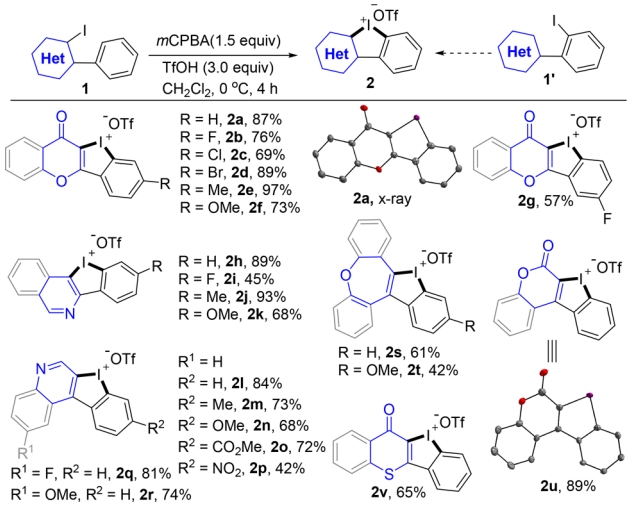

Figure 1. Synthesis of HCIs **2**. Note: The counteranions in the ORTEP drawings of **2a** and **2u** are omitted for clarity.

works that are core structural features in natural products and biologically active compounds.[8]

In recent decades, oxygen-bridged heteropolycycles have received considerable attention from the research community due to their natural occurrence and potential pharmacological activities (Figure 2a). For example, terpyridine as well as

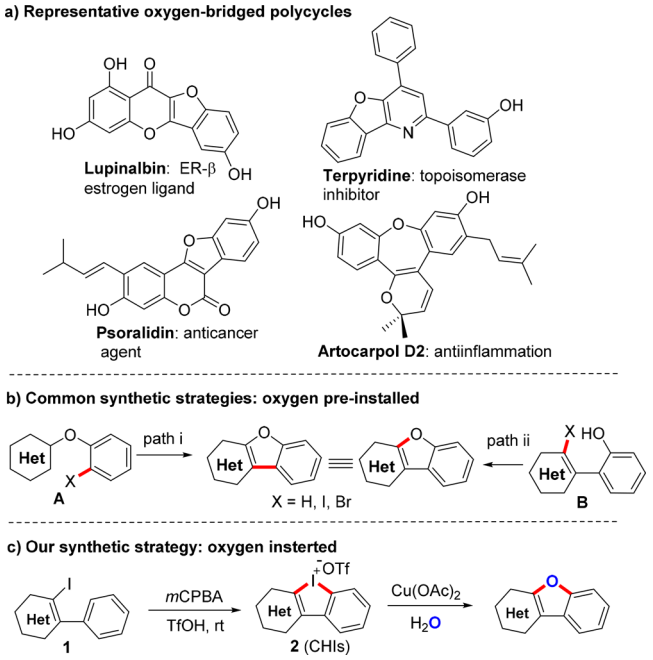

Figure 2. Oxygen-bridged polycyclic heteroarenes and their synthetic strategies.

naturally occurring lupinalbin A, psoralidin, and artocarpol D2 have exhibited excellent biological activities.[9] A variety of synthetic methods have been developed to construct these special oxygen-containing polycycles over the past few years.[10] Intramolecular carbon−carbon bond formation in diaryl ethers[11] and carbon−oxygen bond formation in 2-biary alcohols[12] are common strategies (Figure 2b). Although these synthetic methods enabled the efficient assembly of the wanted oxygen-bridged polycyclic frameworks, they suffered from some disadvantages, for example, requirement of harsh conditions such as high temperature and strong bases or acids, or use of costly transition-metal catalysts. Thus, the development of other efficient synthetic methods for structurally diverse oxygen-containing heteropolycycles is in high demand.

Our research group and others have realized the insertion of heteroatoms nitrogen and sulfur into the common CDPIs, leading to the formation of carbazoles and dibenzothiophenes.[2a,c,3,13] However, the oxygen insertion remained to be investigated, likely due to the low reactivity of oxygen functional groups. Indeed, 2-propanol was even used as solvent in the reactions involving CDPIs in our previous work. When using strong basic sodium alkoxide and sodium phenoxide as nucleophiles, both cyclic and acyclic diphenyliodoniums could react with these hydroxyl species.[14] Recently, 2-aminobenzoic was reported to be *O*-arylated by CDPIs.[15] Water is undoubtedly the most environmentally benign oxygen source.[16] The reaction of our new prepared HCIs with a water molecule to form oxygen-bridged polycycles would be valuable and challenging (Figure 2c). Meanwhile, the reactivity of HCIs also remained to be investigated.

Our investigation commenced on the reaction of HCI **2a** with water. With low cost $Cu(OAc)_2$ (20%) as the catalyst and Na_2CO_3 as the base, the desirable oxygen-bridged polycycle **3a** was obtained at a refluxing temperature in 2-propanol, albeit at 39% (Table S1, entry 1). A preliminary screening of copper catalysts was then conducted, indicating that all the screened copper species, regardless of their valence, mediated the transformation at a similar efficacy (Table S1, entries 1−3). The screening of additional ligands did not make a substantial improvement (Table S1, entries 4−7). However, further study found the reaction performed in DMF with 3 equiv of glycol as a ligand at 100 °C could improve the yields significantly (Table S1, entries 8−10). Compared to other bases, such as Cs_2CO_3, K_2CO_3, and NaOH, Na_2CO_3 proved the best in terms of yields (Table S1, entries 11−13). The copper catalyst could be further decreased to 10% without an obvious sacrifice in yields (Table S1, entry 14). However, no reaction was detected in the absence of copper catalysts (Table S1, entry 15), indicating that copper played an essential role in the transformations. Notably, the success of the transformation required the addition of an appropriate amount of water (Table S1, entry 16).

Since polycyclic heteroarenes demonstrate various biological properties, it is highly valuable to derivatize them to provide more structural resources. While our currently designed HCIs have a broad structural diversity (Figure 1), the translation of our initial effort to other HCIs could enrich the structure features of polycyclic heteroarenes (Figure 3). Like **2a**, the other flavone-containing HCIs **2b**−**2g** reacted smoothly with water under the standard conditions, leading to the formation of a diverse set of polycycles **3b**−**3g** that resemble the natural product lupinalbin A. Notably, halogens (F, Cl, and Br) were well-tolerated in the current conditions. The incorporation of fluorine (**3b**) might show increased metabolic stabilities and better pharmacokinetic properties compared to the non-fluorinated analogues.[17] Synthetically, both chlorinated and brominated species (**3c**, **3d**) could undergo further modifications to broaden the structural complexity. The motifs of isoquinoline as well as quinoline are frequently found in polycyclic heteroarenes. These nitrogen-incorporating HCIs **2h**−**2r** reacting with water enabled the construction of isoquinoline- or quinoline-fused benzofurans **3h**−**3r** that

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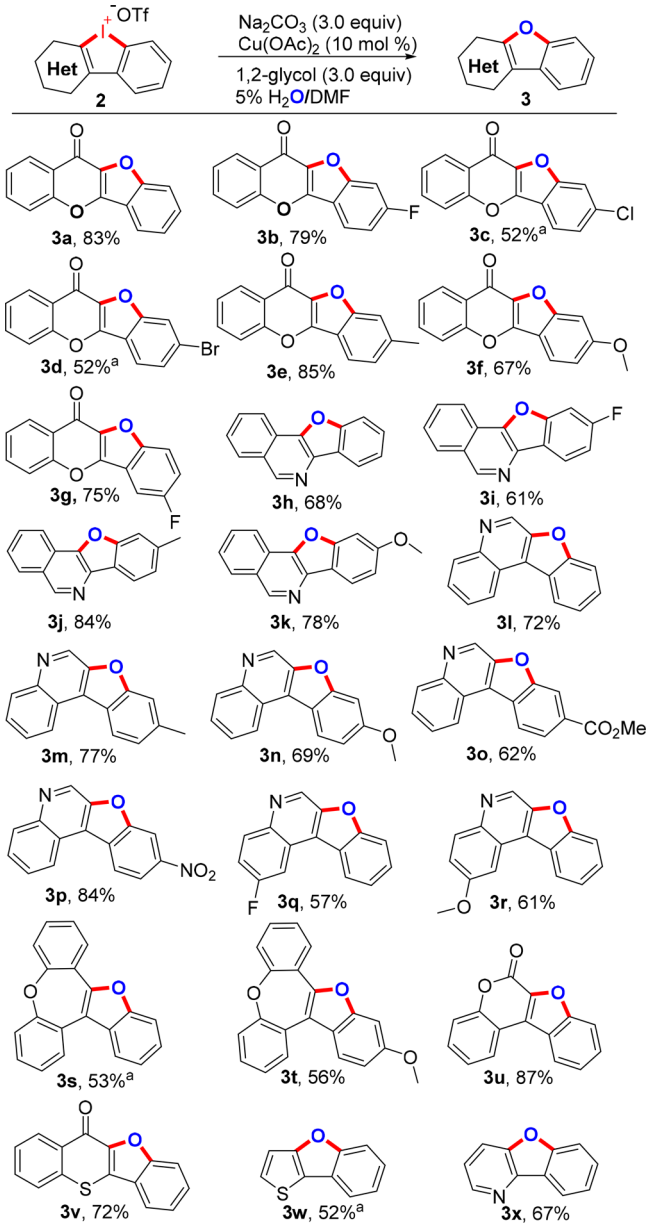
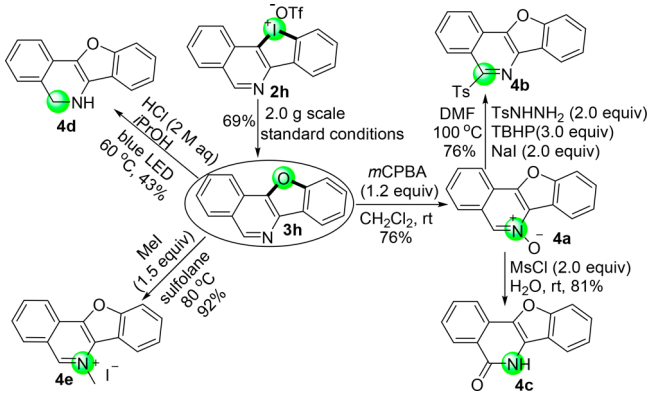


Figure 3. Conversion of HCIs to oxygen-bridged polycyclic heteroarenes. Reaction conditions: HCI **2** (0.35 mmol), 5% H_2O/DMF (1.8 mL, 0.2 M), Ar, 100 °C, 12 h.

might have pharmacological activities.[18] Moreover, the reaction scope was broadened to more complex dibenzooxepine-fused HCIs (**2s**, **2t**) to provide artocarpol D2-like compounds **3s**−**3t**. Meanwhile, the insertion of oxygen from water into the coumarin-fused HCI **2u** facilitated the formation of **3u** in a good yield. Thioflavone-containing HCI **2v** proved to be a suitable substrate to afford **3v**. Another sulfur-containing HCI **2w** also reacted with water smoothly for the synthesis of thienobenzofuran **3w**. Finally, the pyridine-fused HCI **2x** gave the desired product (**3x**) in moderate yield.

To our delight, the reaction of HCI **2h** with water was even performed in a 2 g scale, providing **3h** smoothly, suggesting the potential for large-scale production of oxygen-incorporated polycycles. Further diversification of **3h** was performed to obtain more complex heterocyclic compounds **4** (Scheme 2). Via the oxidation by *m*CPBA, **3h** was readily converted to the quinoline *N*-oxide **4a**. Subsequently, a tosyl functional group

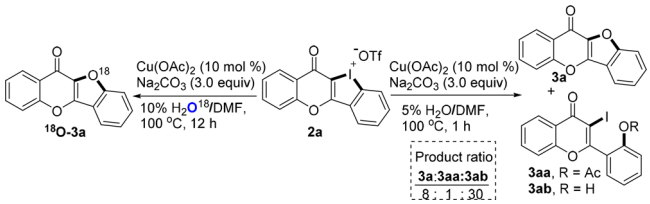
Scheme 2. Scale-up Synthesis and Late Stage Diversification of 3h



could be installed in **4a**, resulting in the formation of **4b** in a good yield.[19] The treatment of **4a** with MsCl enabled the generation of the lactam **4c**.[20] Meanwhile, subjection of **3h** to a reductive reaction condition provided **4d**.[21] The isoquinolinium **4e** could be generated while **3h** was treated with methyl iodide. The consequent anticancer evaluation found that **4e** at single-digit micromolar concentrations substantially inhibited the growth of various cancer cells including pancreatic (PANC-1), breast (BT549), lung (A549), and colon (HCT-116) cancers as well as leukemia (HL-60) (Table S2). Further biological study of its action mechanism is underway.

In order to gain more insight into the mechanism of this transformation, some control experiments were conducted (Scheme 3). While HCI **2a** was subjected to the standard

Scheme 3. Control Experiments for the Mechanistic Study



conditions but in a short reaction time, the desired product **3a** as well as the hydroxyl intermediate **3ab** was detected by HRMS (Figure S3). Surprisingly, a trace of **3aa**, the acetate form of **3ab**, was also identified. The appearance of **3aa** implied that acetate group from the copper catalyst might be involved in the transformation, further verified by our observation that the reaction mediated by CuI with additional NaOAc dramatically increased the yield (Figure S4). While the reaction was carried out in the presence of ^{18}O-labeled water, ^{18}O-**3a** was detected as a major product (Figure S5), indicating that the origin of incorporated oxygen atom came from the water.

In summary, we have successfully developed a series of novel heterocyclic iodoniums with structural diversity and complexity. Further transformation of these unique iodoniums with water as the oxygen source into oxygen-incorporated polycyclic heteroarenes is accomplished using low-cost $Cu(OAc)_2$. A variety of complex polycycles containing a heterocyclic motif such as flavone, quinoline, isoquinoline, coumarin, and oxepine are finally obtained in moderate to good yields. The present method is general and straightforward for the diversity-

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oriented synthesis of polycyclic arenes, providing a complementary strategy to the reported synthetic routes. Further studies on the applications of this method for developing cytotoxic anticancer drugs are ongoing in our group.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01969.

Full experimental procedures and copies of ^{1}H, ^{13}C NMR spectra (PDF)

Accession Codes

CCDC 1581869−1581870 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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