Story of an Age-Old Reagent: An Electrophilic Chlorination of Arenes and Heterocycles by 1-Chloro-1,2-benziodoxol-3-one

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S *Supporting Information*

ABSTRACT: By the use of 1-chloro-1,2-benziodoxol-3-one, an age-old reagent, the practical and efficient chlorination method is achieved. This hypervalent iodine reagent is amenable not only to the chlorination of nitrogen-containing heterocycles but also to selected classes of arenes, BODIPY dyes, and pharmaceuticals. In addition, the advantages, such as easy preparation and recyclable, air- and moisture-stable, in combination with the success in a gram-scale experiment grant this reagent great potential for industrial application.
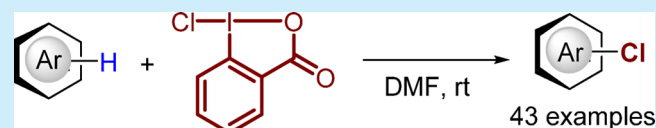
Aryl chlorides are frequently found as a structural motif in natural products[1] and pharmaceuticals,[2] such as the blockbuster drug Abilify (Figure 1). Additionally, they also
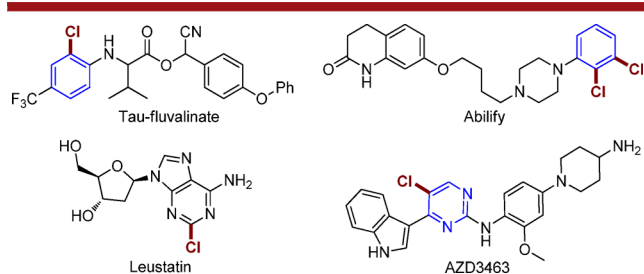

Figure 1. Chlorine containing drugs.

play a very important role in the areas of imaging[3] and material science.[4] The importance of these compounds has prompted substantial efforts for the development of more efficient synthetic strategies, including the invention of new chlorination reagents. Among those efforts, the invention of new reagents based on new molecular structures is a very important direction. However, finding new applications of existing compounds should also not be ignored. In this letter, we present the application of 1-chloro-1,2-benziodoxol-3-one, an age-old reagent, in the direct electrophilic chlorination of heterocycles and arenes (Scheme 1).

A large array of chlorination reagents for the direct aromatic chlorination have been successfully developed. However, these reagents suffer from respective limitations. For example, the often-used NCS (*N*-chlorosuccinimide) and DCDMH (1,3-dichloro-5,5-dimethylhydantoin) were mild and inexpensive. However, lower activity limited their further application.[5] To achieve high activity, reagents such as SO_2Cl_2 and Cl_2 were used; however, these reagents generally give poor regioselectivity (Scheme 1).[6] Toxicity, explosiveness, heat sensitivity, light sensitivity, and moisture sensitivity were the main drawbacks

Scheme 1. Chlorination in Synthetic Chemistry
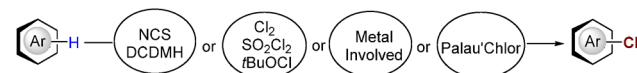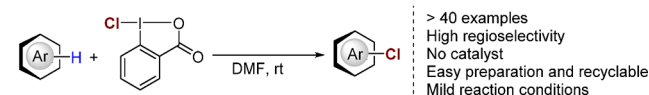

from which other chlorination reagents like PhSeCl,[7] $TiCl_4$/CF_3CO_3H,[8] $SbCl_5$,[9] and *t*-BuOCl.[10] An *ortho*-chlorination reaction was another choice, but the use of strong base and the requirement of a directing group resulted in narrow substrate scope.[11] As a complement to classical methods, chlorination via C–H activation catalyzed by transition-metals provided useful tools with high regioselectivity albeit with limited substrate scope.[12] Recently, a guanidine-based chlorinating reagent CBMG, discovered by Baran group, showed high efficiency and regioselectivity for the chlorination of a variety of enol ether, heterocycles, and sulfonamides.[13] Very recently, Zheng and Yang developed another chlorinating reagent, CFBSA, which exhibited high reactivity and wide substrate scope.[14] However, the development of easily accessible and recyclable chlorinating reagents is still a sustained topic in synthetic chemistry.

Historically, iodobenzene dichloride, synthesized by Willgerodt one century ago,[15] has been used in chlorination.[16] Due to the lack of stability, it has failed to achieve wide application in synthetic chemistry.[16c] However, atom transfer reagents based on hypervalent iodines,[17] such as Togni[18] and Waser[19] reagents, recently have proven important application in organic synthesis. Thanks to the unique cyclic structure, these

Scheme 2. Scope of Chlorination by 1-Chloro-1,2-benziodoxol-3-one[a]
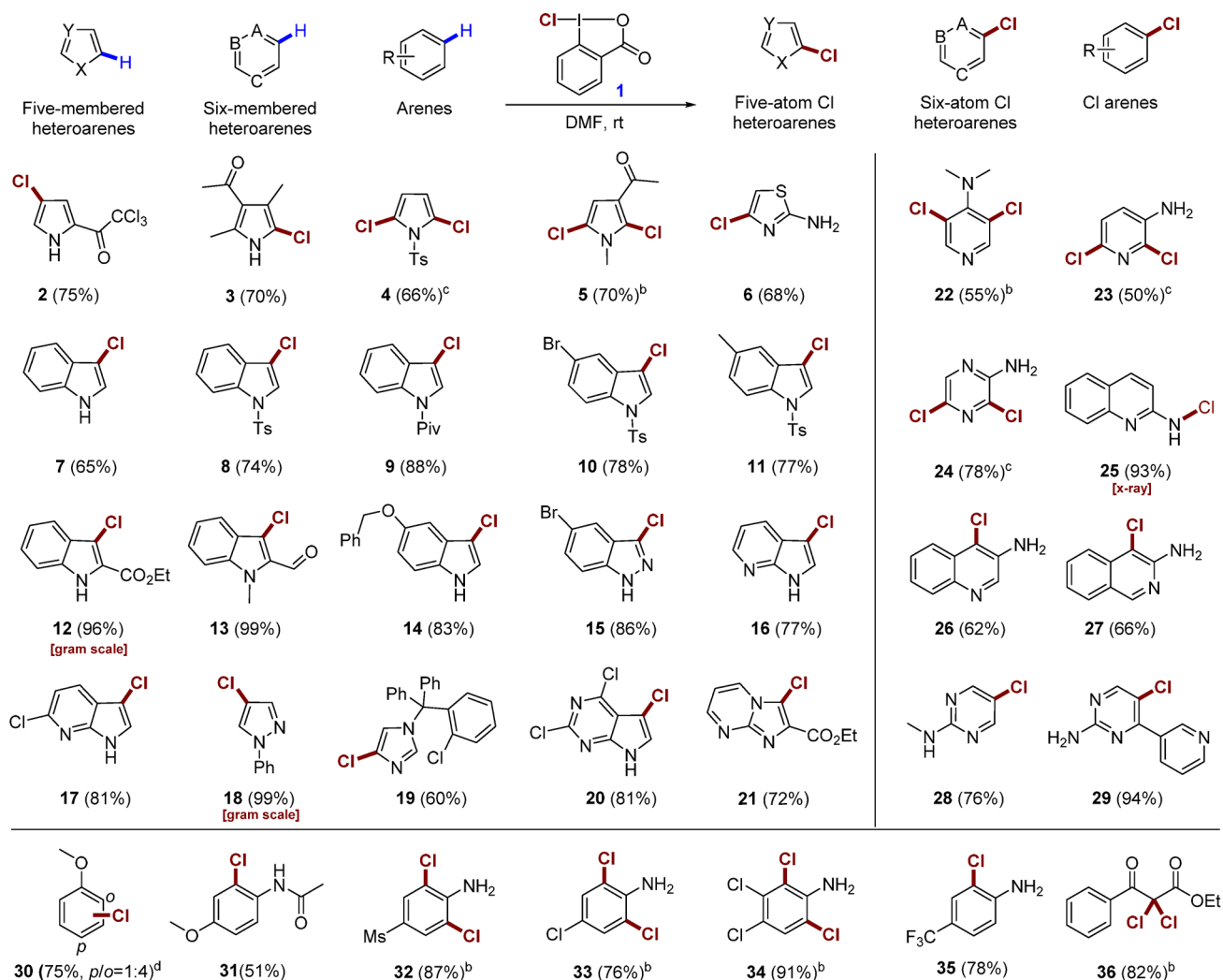
[a]Heterocycles or arenes (1.0 equiv, 0.3 mmol), chlorinating reagent (1.2 equiv, 0.36 mmol), DMF (2 mL), rt, 12 h. Isolated yields. [b]Chlorinating reagent (2.2 equiv, 0.66 mmol). [c]Chlorinating reagent (2.2 equiv, 0.66 mmol), 60 °C. [d]Yields and regioselectivity determined by ^{1}H NMR using 1,3,5-trimethylbenzene as an internal standard.

benziodoxole-derived iodine compounds present an exceptional stability and reactivity.[17d] Inspired by these seminal works, we assume that 1-chloro-1,2-benziodoxol-3-one, discovered in the middle of 20th century,[20] might be a stable and promising chlorine transfer reagent, and the thermal stability of this reagent by differential scanning calorimetry (DSC) showed no thermal events below 150 °C (SI, Tables S2 and S3). To our surprise, this easily accessible and recyclable reagent[18d] did not achieve wide application in chlorination reaction.[21] In this letter, we would like to report the application of this age-old reagent in chlorination of nitrogen-containing heterocycles, arenes, BODIPY dyes, and pharmaceuticals.

In our initial study, we found that by treatment of 1-tosyl-1H-indole with 1.2 equiv of chlorination reagent in DMF (2 mL) at r.t. for 12 h, 3-chloro-1-tosyl-1H-indole **8** was obtained in 74% isolated yield. Next, reaction conditions were screened and DMF gave the best yield in this reaction, affording the product without catalyst or additives (SI, Table S1). Encouraged by the results, we proceeded to investigate the substrate scope. As illustrated in Scheme 2, varieties of heterocycles were successfully chlorinated. Pyrrole (**2–5**),

thiazole (**6**), indole (**7–14**), indazole (**15**), pyrazole (**16, 17**), pyridine (**22, 23**), pyrazine (**24**), quinoline and isoquinoline (**25–27**), pyrimidine (**28, 29**), and other heterocycles (**17–21**) were chlorinated in good to excellent yields, demonstrating the high efficiency and functional group tolerance of this approach. As shown in Scheme 2, this chlorination reagent based on hypervant iodine exhibited good regioselectivity toward the substrates with multiple potential reaction sites. In most cases, single chlorinated products were obtained. In cases where a single chlorinated regioisomer was not observed, bis-chlorination products were formed (**4, 5, 32–34**). 2-(Trichloroacetyl)pyrrole was a versatile and important building block to access either 4- or 5-functionalized pyrrole-2-carboxamides.[22] The commercial availability of **2** is limited and expensive.[23,13] In Baran's work, Palau'chlor proved to be a selective chlorinating reagent, providing **2** in good yield. Under the standard conditions, our chlorination reagent also gave the desired product with good yield. For pyridine (**22, 23**), pyrazine (**24**), quinoline and isoquinoline (**26, 27**), and pyrimidine (**28, 29**) heterocycles, amine or substituted amine group is vital for this reaction. It is interesting that, unlike other heterocycles, by the

treatment of quinolin-2-amine with this chlorinating reagent, *N*-chloroquinolin-2-amine (**25**) was obtained. No chlorination reaction happened without the introduction of these groups in the heterocycles. The chlorinated heterocycles containing amine or substituted amine are versatile and important intermediates.[24] In addition to heterocycles, substituted benzenes also worked smoothly, delivering chlorination products in good to excellent yields (**30–36**). Some of the products were widely used in agrochemistry, for example, compound **34** is the precursor of a pesticide Tau-fluvalinate.[25]

BODIPY derivatives are a class of privileged organic dyes, which are traditionally used as chemosensors, labeling reagent, fluorescent switches, and laser dyes.[26] This chlorinating reagent was also applied in the chlorination of BODIPY dyes. Chlorinated BODIPYs are common precursors for further functionalization.[27,28] This method affords chlorinated BODIPY dyes with good to excellent yields, revealing the potential application of this chlorinating reagent in organic synthesis (Figure 2).
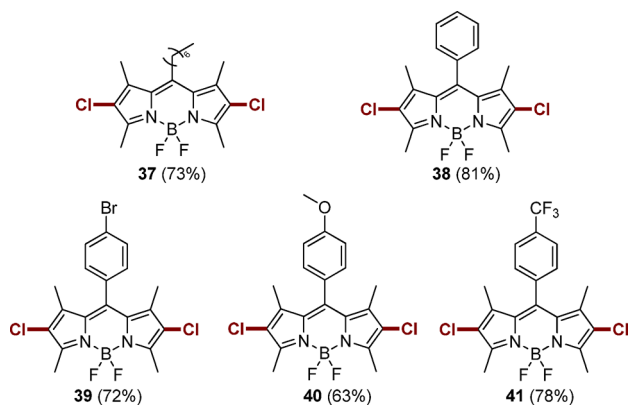

Figure 2. Chlorination of BODIPY dyes. Heterocycles (1.0 equiv, 0.3 mmol), chlorinating reagent (2.2 equiv, 0.66 mmol), DMF (2 mL), rt, 12 h. Isolated yields.

To further demonstrate the utility of this new chlorinating reagent in complex molecule, we applied it to the chlorination of aripiprazole **44**, which has been approved for the treatment of schizophrenia, bipolar, and as an adjunct in clinical depression and is one of the best-selling antipsychotic drugs.[29] Gratifyingly, the monochlorinated aripiprazole **45** was obtained in 96% yield (Scheme 3) at gram scale. For the precursor of aripiprazole **42**, this chlorinating reagent also affords the monochlorinated product **43** with 83% isolated yield. NMR, HRMS, and single crystal X-ray diffraction characterized the structure of compound **43**, which also confirmed the structure of compound **45**.

Scheme 3. Chlorination of Aripiprazole
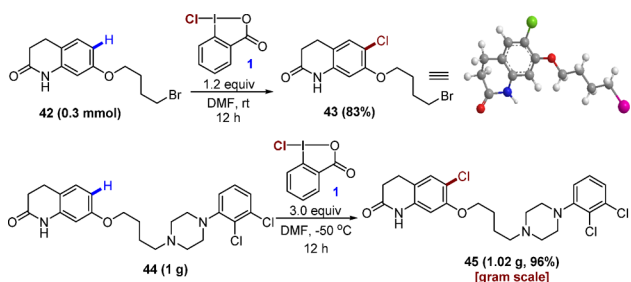
The key feature of our chlorination reagent based on hypervant iodine is easy preparation, postreaction purification, and recyclability. It is worthy to be mentioned that the starting two substrates associated with this chlorination reagent, trichloroisocyanuric acid and 2-iodobenzoic acid, were recyclable. In the first step, the corresponding chloroiodane **1** was obtained in high yield and with excellent purity (Scheme 4)

Scheme 4. Recycle of Chlorinating Reagent
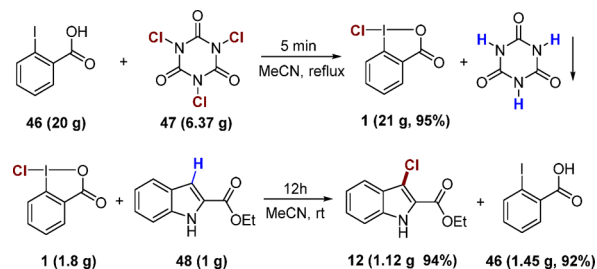
by the stoichiometric use of trichloroisocyanuric acid (2,4,6-trichlorotriazin-1,3,5-trione, TCICA) as chlorine source.[18d,30] The only byproduct, insoluble isocyanuric acid precipitated in the reaction mixture, was recovered by simple filtration. The starting material trichloroisolyanuric acid (TCICA) could be regenerated quantitatively by the treatment of isocyanuric acid with NaOCl solution.[30] In addition, another key intermediate 2-iodobenzoic acid **46** also could be recyclable. As shown in Scheme 4, when ethyl-1*H*-2-carboxylate **48** (1.0 g, 5.30 mmol, 1.0 equiv) was treated with chlorinating reagent (1.8 g, 6.36 mmol, 1.2 equiv) in anhydrous DMF (10.6 mL) under air at room temperature for 12 h, the subsequent chlorination reaction not only afforded the chlorinated product but also regenerated the starting substrate 2-iodobenzoic acid in excellent yield. The resulting mixture was quenched with saturated aqueous NaHCO₃, and after general workup, the crude chlorinated product derived from organic layer was subjected to column chromatography on silica gel to give the desired product with 94% yield. Meanwhile, 1.45 g of 2-iodobenzoic acid obtained from the aqueous phase by simple acidification with HCl (0.3 M), extraction with ethyl acetate, and concentration. The recovery rate of the starting material was 92% based on the amount of chlorinating reagent. Thus, the consumed chlorine source in the whole process is NaOCl, which is very cheap and easy to handle. To gain the information of mechanism, radical scavengers such as TEMPO and BHT were added to the chlorination of ethyl 1*H*-indole-2-carboxylate. As shown in the Supporting Information, the radical scavengers did not block the reaction, which excluded the possibility of radical mechanism.

In conclusion, we have reported an efficient and simple method for the chlorination of arenes and heterocycles by the use of 1-chloro-1,2-benziodoxol-3-one as a chlorination reagent. The reaction shows broad group tolerance and substrate scope. Most importantly, the reaction was easy to handle and the starting substrates were recyclable, which showed great potential in synthetic chemistry. The application of this chlorinating reagent in other transformations is actively underway.

■ ASSOCIATED CONTENT

S Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00547.

Experimental details and spectroscopic data (PDF)
Compound **25** (CIF)
Compound **41** (CIF)
X-ray crystallographic data (PDF)

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Notes

The authors declare no competing financial interest.

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