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ARTICLE

An efficient iodine pentoxide-triggered iodocarbocyclizations for the synthesis of iodooxindoles in water

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Ming-Zhong Zhang,*[a] Xin Wang,[a] Ming-Ying Gong,[a] Lin-Chen,[a] Wen-Bing Shi,*[a] Shu-Hua He,[a] Yong Jiang[a] and Tieqiao Chen*[b]

An efficient iodocarbocyclization of alkenes for the synthesis of iodooxindoles has been developed. This reaction proceeds in a chemoselective manner and shows excellent tolerance of various functional groups, including a chemosensitive hydroxymethyl group. Nonmetal inorganic iodine pentoxide was used as both the oxidant and iodine source, making this protocol very practical. On the basis of experimental observations, a plausible electrophilic reaction mechanism was proposed.

Introduction

Iodocyclization reactions are very important reactions in organic chemistry, since they can play an important role in building carbocycles, heterocycles and natural products.[1] In addition, some of the iodocyclized products are bioactive.[2] Thus, in recent years, cyclizations involving iodonium-induced activation of prefunctionalized alkyne and alkene substrates have gained significant prominence. These reactions generally allow the generation of polysubstituted molecules (e.g., indoles, isoquinolines, isocoumarins, quinolones, oxazolones, and furans, etc.) from simple skeletons in one step, providing the chance for further functionalization via cross-coupling.[3-8]

3,3'-Disubstituted oxindoles, bearing a functional group at the C_3-position, are an important class of heterocycles that can be used for synthesizing biologically active molecules.[9,10] Traditional procedures for their preparation rely on a radical C-H functionalization process, whereas these radical reactions have their advantages and disadvantages.[11] The introduction of an iodine atom was shown to induce the cyclization of activated alkenes, involving the simultaneous formation of both C-I and C-C bonds, thus arising as a fascinating strategy for producing 3,3'-disubstituted oxindoles. In 2011, a phenyliodine diacetate (PIDA)-promoted iodocarbocyclization of alkenes leading to iodinated oxindoles was reported.[12] Using organohypervalent iodine reagent as an oxidant faces the drawback of generating organic waste (e.g., iodobenzene), which lowers the overall atom efficiency of the reaction. In 2014, Guo et al. reported a metal-free $(NH_4)_2S_2O_8$-mediated halocarbocyclization for the synthesis of halogenated oxindoles by using NH_4X (X = Cl, Br, I) as the halide source.[13] This report was followed by Ye et al. by using $K_2S_2O_8$/KX (X = Cl, Br, I) as a similar oxidative halogenation system.[14] Although some advances have been made, these oxidative methods suffered from the following drawbacks: (1) narrow substrate scope and/or limited functional group tolerance, were exposed in iodocarbocyclization; (2) large amounts of organic by-products and environmentally deleterious waste (e.g., SO_4^{2-}) were frequently brought about when stoichiometric amounts of strong oxidants, i.e., persulfates, were used. Therefore, developing a new oxidative iodination system to accomplish a similar transformation that can exploit more efficient and sustainable approaches to iodooxindoles would be highly desirable.

Nonmetal inorganic iodine pentoxide (I_2O_5) is widely used as a reliable single-electron oxidant in radical reactions due to its safe, clean, and environmental friendly characters.[15] For example, in 2014, Liu group pioneeringly employed I_2O_5 as an initiator to realize the radical trifluoromethylation/cyclization of alkenes with Langlois reagent for producing trifluoromethylated 3,3'-disubstituted oxindoles.[16,17] Almost at the same time, Liu demonstrated that I_2O_5 can be both a radical promoter and an iodine source for generating β-CF_3 alkyl/alkenyl iodides.[18] Inspired by these findings, we envisaged that the iodocarbocyclization of alkenes to yield valuable iodinated 3,3'-disubstituted oxindoles could be potentially realized by using I_2O_5 as an iodine source. Herein, we communicate an efficient iodine pentoxide-triggered iodocarbocyclization (Scheme 1). This reaction proceeds via an electrophilic process and produces O_2 and H_2O as the green by-products. Most importantly, under the reaction conditions, various functional groups, including these electron-withdrawing and chemosensitive ones, were well-tolerated, leading to the

[a] School of Chemistry and Chemical Engineering, Yangtze Normal University, Chongqing 408100, China; E-mail: mingzhongzhang2010@126.com; wenbingshi@hotmail.com
[b] State Key Laboratory of Marine Resource Utilization in South China Sea, College of Materials and Chemical Engineering, Hainan University, Haikou 570100, China; chentieqiao@hnu.edu.cn

† Footnotes relating to the title and/or authors should appear here.
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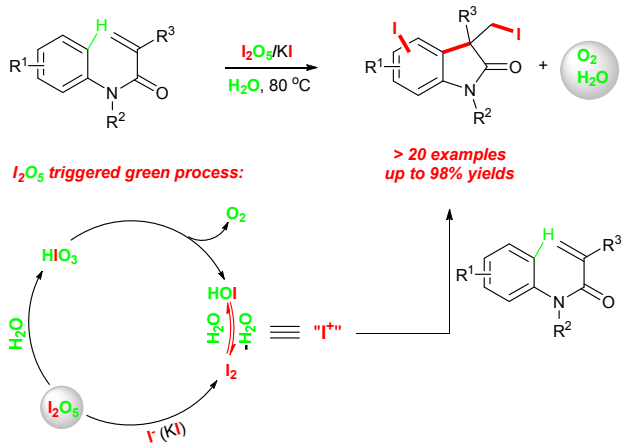
generation of the corresponding iodooxindoles in good to excellent yields (up to 98% yields). Moreover, the reaction can be carried out on large scales to produce the desired iodooxindoles without significant decrease of the efficiency. Preliminary mechanistic studies reveal that iodine pentoxide plays a dual role (both the oxidant and iodine source) in this iodocarbocyclization, which is mechanistically distinct from other oxidative ones. The present protocol provides an efficient and practical method for creating the synthetically useful halooxindoles.[9]

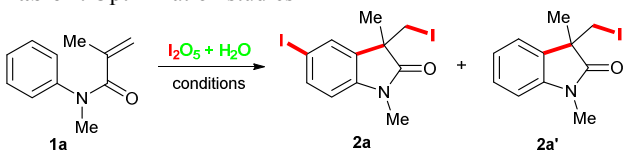


Scheme 1. An efficient iodine pentoxide-triggered iodocarbocyclization.

Results and discussion

We commenced our study by investigating the reactivity of *N*-arylacrylamide **1a**, and the obtained results were compiled in Table 1. An initial experiment employing 3.0 equiv of I_2O_5 as the iodine source, H_2O as the solvent, and the reaction provided the cyclic product **2a'** in 12% yield (entry 1). Changing the solvent to H_2O-CH_3CN or H_2O-DCE produced only a trace amount of the mixed products **2a** and **2a'** (entries 2 and 3). Elevating the temperature to 80 °C improved the efficiency of the reaction (entry 4); however, we noted that a further rise in the temperature failed in improving the reaction efficiency, whereas some unknown by-products were produced within a relatively short reaction time (10 h, entry 5). To our delight, the main product **2a** was produced in 55% yield with the addition of 20 mol% of KI in the present reaction system (entry 6). Encouraged by this result, we expected to obtain diiodooxindole **2a** as a single product. Satisfyingly, when the reaction was performed with 1.0 equiv of KI in I_2O_5/H_2O system, the single product **2a** was produced in 83% yield (entry 7). Further attempts to improve the yields by lowering the reaction temperature were futile (entries 8 and 9). However, a decrease of reaction time lead to a clean reaction, and the desired product **2a** was isolated in 85% yield (12 h, entry 10). Both the loadings of I_2O_5 and KI were systematically optimized, and the experimental results revealed that a combination of 2.2 equiv of I_2O_5 and 1.2 equiv of KI gave the highest yield of **2a** (92%, entry 16 *vs* entries 11-15 and entry 17). Subsequently, other iodine anion sources such as NaI and NH_4I were tested, the results showed that KI was the best choice for this reaction (entry 16 *vs* entries 18 and 19). It should be noted that when the

Table 1. Optimization studies[a]



Entry	I_2O_5 (equiv)	Additive (equiv)	Temp (°C) /Time (h)	Yield[b] (%) 2a	2a'
1	3.0	None	60/24	Trace	12
2[c]	3.0	None	60/24	Trace	Trace
3[d]	3.0	None	60/24	Trace	Trace
4	3.0	None	80/24	19	24
5	3.0	None	100/10	20	25
6	3.0	KI (0.2)	80/24	55	9
7	3.0	KI (1.0)	80/24	83	0
8	3.0	KI (1.0)	60/24	75	Trace
9	3.0	KI (1.0)	RT/24	60	5
10	3.0	KI (1.0)	80/12	85	0
11	2.5	KI (1.0)	80/12	87	0
12	2.2	KI (1.0)	80/12	90	0
13	2.0	KI (1.0)	80/12	86	0
14	1.5	KI (1.0)	80/12	75	Trace
15	2.2	KI (0.5)	80/12	50	31
16	2.2	KI (1.2)	80/12	92	0
17	2.2	KI (1.5)	80/12	91	0
18	2.2	NaI (1.2)	80/12	89	0
19	2.2	NH_4I (1.2)	80/12	85	0
20	2.2	I_2 (1.2)	80/12	87	0
21[e]	2.2	KI (1.2)	80/16	83	0
22[f]	2.2	KI (1.2)	80/24	86	0

[a] General reaction conditions: **1a** (0.2 mmol), H_2O (1 mL); RT = Room temperature. [b] Isolated yields based on **1a**. [c] H_2O/CH_3CN (1:1, 1 mL). [d] H_2O/DCE (1:1, 1 mL). [e] **1a** (0.35g, 2 mmol) and H_2O (10 mL). [f] **1a** (1 g, 5.7 mmol) and H_2O (15 mL).

reaction was performed using 1.2 equiv of I_2 as an iodine source in the presence of I_2O_5, 87% yield of **2a** was produced (entry 20).[19] Therefore, the optimal reaction conditions were found to be 2.2 equiv of I_2O_5 and KI (1.2 equiv), using H_2O as the solvent at 80 °C for 12 h. To demostrate the feasibility of the optimized I_2O_5-triggered protocol, we performed the model iodocarbocyclization of *N*-arylacrylamide **1a** on large scales. At first, a 2-mmol scale iodocarbocyclization of **1a** is successfully performed with I_2O_5 and KI, giving the desired product **2a** in satisfactory yield (16 h, entry 21). Moreover, treatment of 1 g (5.7 mmol) of **1a** with 2.2 equiv of I_2O_5 and 1.2 equiv of KI in H_2O at 80 °C afforded the single product **2a** in 86% yield (24 h, entry 22). Obviously, the present iodine pentoxide-triggered system leads to the highly efficient and chemoselective

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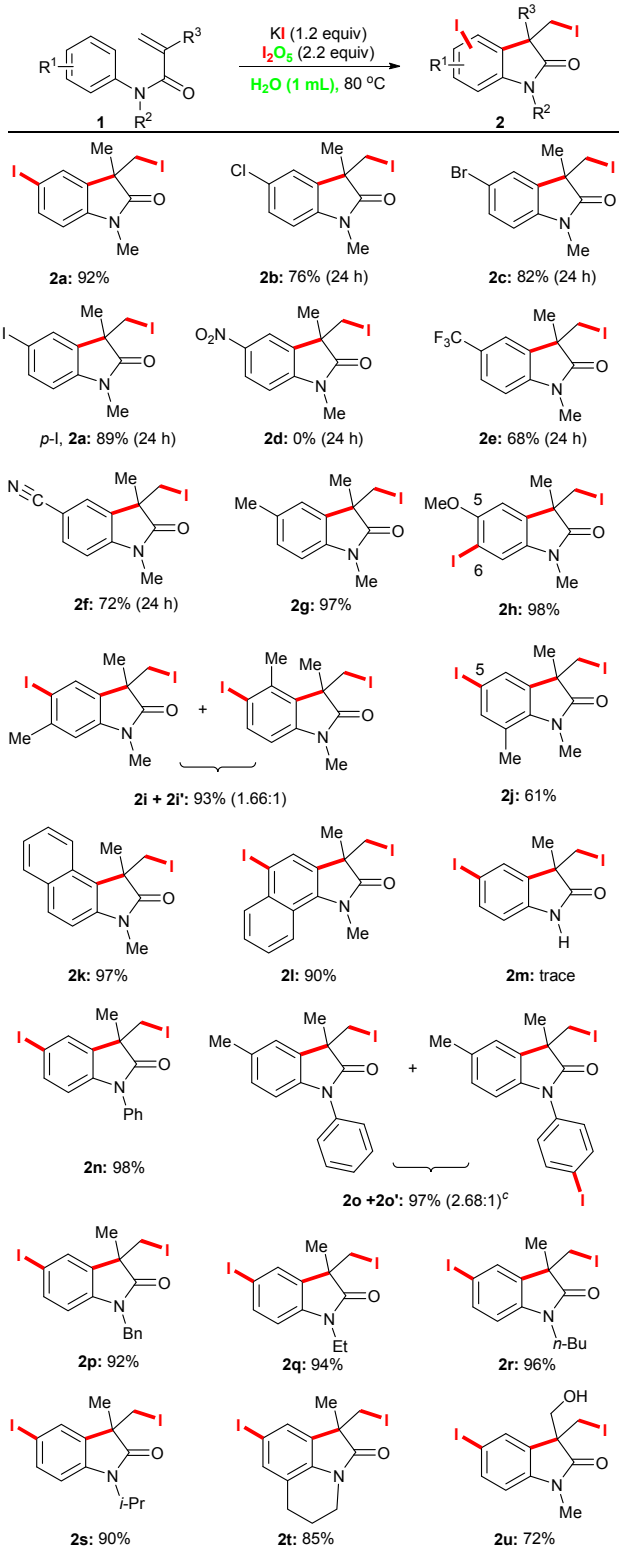
Table 2. Substrate scope for iodine pentoxide-triggered iodocarbocyclization[a,b]



[a] General reaction conditions: **1** (0.2 mmol), I_2O_5 (2.2 equiv), KI (1.2 equiv) and H_2O (1 mL) at 80 °C for 12 h. [b] Isolated yields. [c] conversion, 100%; yield was determined by TLC analyse; the ratio of **2o** and **2o'** was determined by ^{1}H NMR.

formation of the diiodooxindoles.

With the optimized protocol in hand, the substrate scope of this iodocarbocyclization was explored. As shown in Table 2, substrates with halo-substituents (Cl, Br, and I) on the *para*-position of the aromatic ring served well, delivering the iodooxindoles in good to high yields. The *para*-NO_2-substituted substrate did not work in this reaction. Other substrates with the strong electron-withdrawing groups, as exemplified by *para*-CF_3 and *para*-CN substituted derivatives, underwent cyclization readily under the reaction conditions, yielding the desired products **2e** and **2f** in 68% and 72% yields, respectively. Substrates containing electron-donating groups exhibited excellent reactivity in this reaction. For instance, *para*-methyl and *para*-methoxy reactants gave excellent yields of 97% and 98%, respectively (products **2g** and **2h**). Worth noting is that the *para*-methoxy-substituted alkene furnished the product with phenyl ring C_6-position being iodinated exclusively, which is in sharp contrast to an iodobenzene diacetate-mediated reaction with lower chemoselectivity.[12] A substrate bearing a methyl group on the *meta*-position of phenyl ring could also be cyclized to produce the corresponding product in an excellent yield although with inevitable regioisomers (**2i/2i'** in a ratio of 1.66:1). The steric hindrance seemed to have an unfavorable impact on the conversion since the *ortho*-methyl-substituted substrate produced the desired **2j** with a decreased yield. Naphthylanilides also underwent cyclization in this system to selectively provide the iodinated oxindoles in excellent yields. The substituent effect at the N atom (R^2) was also investigated. It was found that except for a *N*-hydrogen atom substituted alkene, other *N*-substituted substrates with phenyl, benzyl, ethyl, *n*-butyl, and isopropyl all proved to be productive partners. Particularly worth noting is that when the *para*-position of one benzene ring in *N*-arylacrylamide was occupied with a methyl group, the reaction proceeded smoothly to deliver the cyclic products **2o** and **2o'** in 97% yield (the ratio of **2o**/**2o'** was ca. 2.68:1), and a small amount of pure **2o'** could be separated from its mixture. In addition, a tetrahydroquinoline derivative was also compatible with the reaction conditions and provided the desired product **2t** in 85% yield. To our satisfaction, the monosubstituted olefin (R^3 position) with a chemosensitive hydroxymethyl group also showed good reactivity in this reaction (**2u**, 72%).

To understand the mechanism of this transformation, some information has been gathered. First, the reaction proceeded well in the presence of 2.0 equiv of radical scavengers such as TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) and BHT (2,6-di-tert-butyl-4-methylphenol), which may exclude a radical mechanism for this transformation (Scheme 2a). Second, when *para*-fluoro-substituted alkene **3** was employed as a substrate, the iodohydroxylated product **5**, which was produced from the classic electrophilic addition mechanism, was isolated in 64% yield (Scheme 2b, for details, see the Supporting Information). Similarly, with the addition of 2.0 equiv of ethene-1,1-diyldibenzene **6** under the standard conditions, apart from **2a**, 28% yield of the iodohydroxylated product **7** was also obtained (Scheme 2c, for details, see the Supporting Information). The above results clearly suggested that the reaction should be an electrophilic process. Third, under the standard reaction conditions, monoiodinated product **2a'** was converted to the corresponding **2a** with excellent yield (99%, Scheme 2d), implying that the cyclization process probably occurred prior to the substitution of the aromatic ring.

Since the formation of molecular iodine was confirmed by observing the color changes of the reaction mixture (Figure S1), we further conducted a series of control experiments to verify the potential activated iodine species and iodine sources in our

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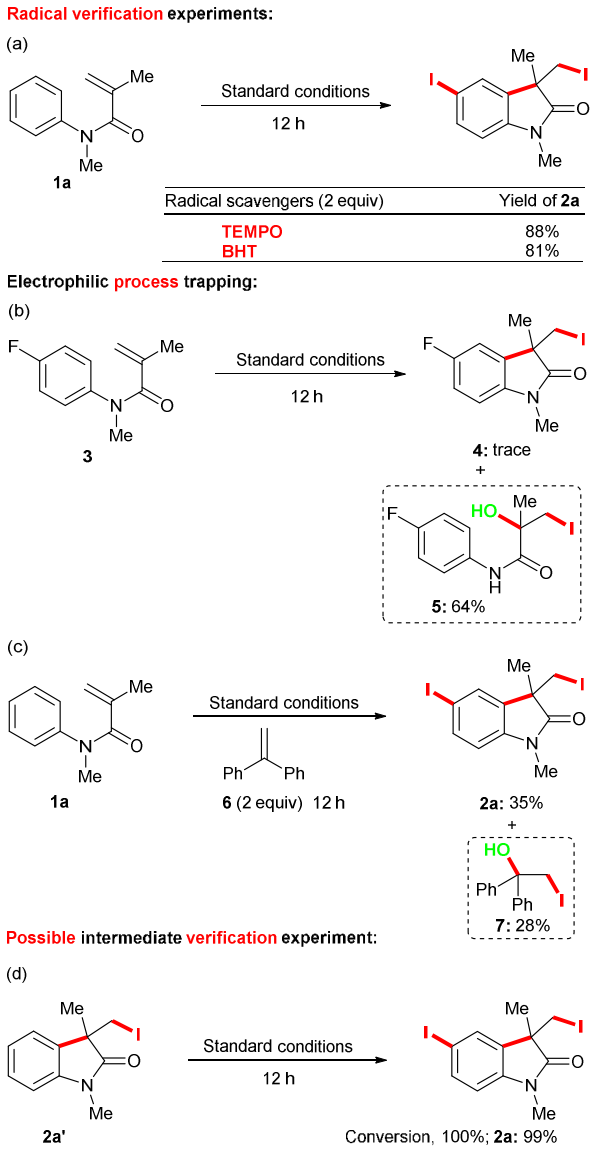
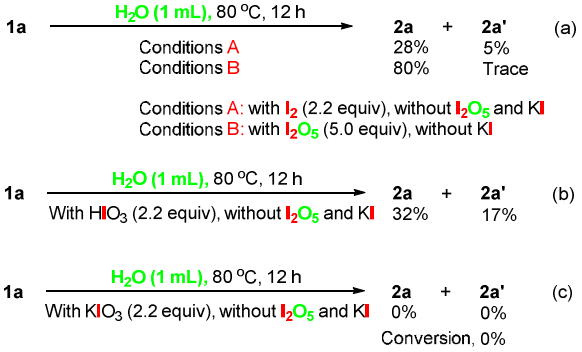
reaction system. Replacement of I_2O_5 and KI with 2.2 equiv of I_2 gave a 33% yield of the mixture products **2a** and **2a'** (Scheme 3a; Conditions A). Moreover, when 5.0 equiv of I_2O_5 was employed to react with **1a** in the absence of KI, in addition to excellent yield of **2a** was obtained (Scheme 3a; Conditions B), the solid iodine could also be observed from the reaction tube (Figure S1).[20] The above results coupled with previous optimization studies using 3.0 equiv of I_2O_5 (Table 1, entries 4 and 5), suggesting that I_2O_5 can be an iodine source and the molecular iodine is presumably an activated iodine species in this reaction. It should be noted that when readily available HIO_3, which was known as a hydrated form of I_2O_5,[21] was used as an iodine source instead of I_2O_5 and KI under otherwise identical reaction conditions, products **2a** and **2a'** were isolated in 49% total yield; however, addition of 2.2 equiv of KIO_3 to replace HIO_3 completely quenched the reaction (Scheme 3b, c). The above results suggested that this reaction presumably proceeded via HIO_3 as another activated iodine species.

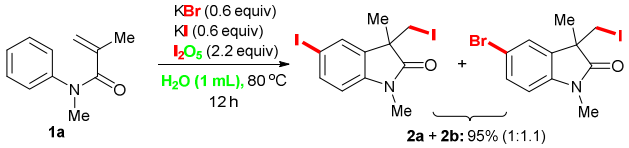


Scheme 2. Experiments for mechanistic studies.



Scheme 3. The potential activated iodine species and iodine sources verification experiments.

To further probe the mechanism, an additional competition experiment was also performed. As shown in Scheme 4, when 0.6 equiv of both KBr and KI were used as the halide source, the reaction gave a 95% yield of an inseparable mixture of diiodooxindole **2a** and iodobromooxindole **2b** (the ratio of **2a**/**2b** was ca. 1:1.1), implying that I_2O_5 could be an oxidant for the generation of I_2 in this iodocarbocyclization.[22]



Scheme 4. Competition experiment using KBr and KI.

Based on our experimental results as well as other reports, a plausible reaction mechanism was proposed and shown in Scheme 5. The oxidation of the iodine ion with iodine pentoxide (I_2O_5) generates molecular iodine, which is further transformed in water into HOI and HI reversiblely.[22] Since I_2O_5 can be easily hydrated into iodic acid (HIO_3) in water, we propose the activated HOI could also be generated from HIO_3 through a decomposition process and released O_2.[23] Once this unstable species (HOI) is formed, it will be captured by the Π electron of alkene **1a** to produce an iodonium ion intermediate **A**.[24] Further evidence was provided by the nucleophilic trapping by water using alkenes **3** and **6** (products **5** and **7**). Reasonably, similar electrophilic process can also be directly engaged by molecular iodine, since the reaction rate constant between iodine and water is very small. The subsequent intramolecular electrophilic cyclization and proton elimination processes occurred successively, generating the monoiodinated product **2a'**. Finally, electrophilic iodination on the aromatic ring in intermediate **2a'** by an activated iodine species take place to yield the desired diiodooxindoles **2a**. For the iodocarbocyclization reaction studied in the present contribution, we assumed the I_2O_5-triggered mechanism involving the generation of O_2 and H_2O as the green appendants.

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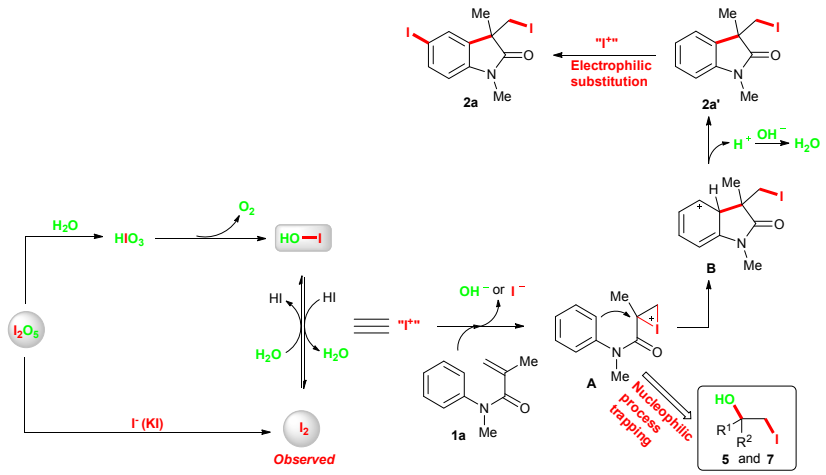

Scheme 5. Proposed mechanism.

Conclusions

In summary, we have developed a highly efficient iodine pentoxide-triggered iodocarbocyclization. This transformation proceeded via an electrophilic process under transition metal-free conditions, realizing C-H activation, C-I and C-C bonds formation in one pot to produce the synthetically useful iodinated oxindoles. The use of readily available I_2O_5 as both the oxidant and iodine source succeeded in avoiding the generation of environmentally deleterious wastes. Valuable functional groups such as halo (Cl, Br and I), methoxy, trifluoromethyl, and even the chemosensitive hydroxymethyl group were well tolerated. The gram-scale iodocarbocyclization well demonstrated the potential synthetic application of this highly efficient method in organic synthesis. Further studies on the mechanism and applications are ongoing in our laboratory.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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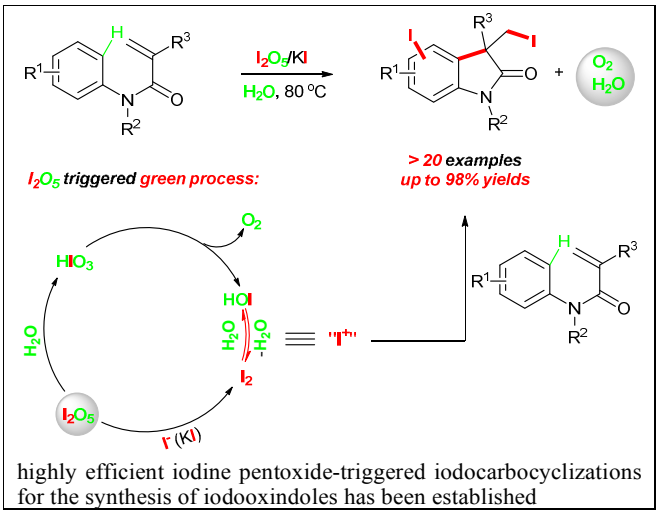

highly efficient iodine pentoxide-triggered iodocarbocyclizations for the synthesis of iodooxindoles has been established