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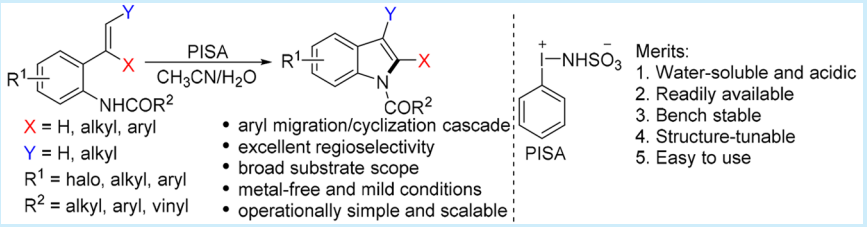
# Water-Soluble Hypervalent Iodine(III) Having an I−N Bond. A Reagent for the Synthesis of Indoles

Hai-Dong Xia, Yan-Dong Zhang, Yan-Hui Wang, and Chi Zhang*

State Key Laboratory of Elemento-Organic Chemistry, Collaborative Innovation Center of Chemical Science and Engineering (Tianjin), College of Chemistry, Nankai University, Tianjin 300071, China

Supporting Information




**ABSTRACT:** A readily accessible and bench-stable water-soluble hypervalent iodine(III) reagent (*p*henyl*i*odonio)sulfam*a*te (PISA) with an I−N bond was synthesized, and its structure was characterized by X-ray crystallography. With PISA, various indoles were synthesized via C−H amination of 2-alkenylanilines involving an aryl migration/intramolecular cyclization cascade with excellent regioselectivity in aqueous $CH_3CN$. Notably, using this new method as the key step, not only two drug molecules, indometacin and zidometacin, but also another bioactive molecule, pravadoline, were synthesized.



Hypervalent iodine reagents have recently attracted considerable research attention owing to their versatile reactivity, low toxicity, easy handling, ready availability, and high stability.[1] Nevertheless, the design of new hypervalent iodine reagents with unprecedented reactivity and the ability to mediate difficult chemical transformations is of interest to synthetic chemists. In addition, although many hypervalent iodine reagents are soluble in organic solvents at ambient or high temperature, only a few water-soluble hypervalent iodine reagents have been reported. The main strategy for the synthesis of such reagents is introducing a hydrophilic group such as potassium sulfonate, carboxyl, or trimethylammonium on the phenyl ring, as reported by Zhdankin et al.,[2a] Kirsch et al.,[2b] Vinod et al.,[2d] and our group (Figure 1a). This strategy requires the use of risky reagents such as concentrated or fuming $H_2SO_4$ and usually requires multistep synthesis, which restricts the practical application of these reagents. Thus, we become interested in tuning the water solubility of the new hypervalent iodine reagent by rational ligand design. The development of organic reactions mediated by water-soluble hypervalent iodine reagents in aqueous media is desirable for several reasons. First, water molecules can coordinate with the iodine center of these reagents to enhance their thermal stability and maintain their high oxidizing ability in water, as has been shown for aquo(hydroxy)-$\lambda^3$-iodane−[18]crown-6 complexes.[3] Second, when water-soluble hypervalent iodine reagents are employed for reactions in aqueous organic media, they can exhibit reactivity different from that of their organic-soluble parent molecules.[2c] Third, the development of aqueous organic reactions mediated by water-soluble hypervalent iodine reagents can be expected to broaden the application scope of hypervalent iodine reagents in organic synthesis. Herein, we report a new water-soluble hypervalent iodine(III) reagent (phenyliodonio)sulfamate (PISA) having an I−N bond (Figure 1b).

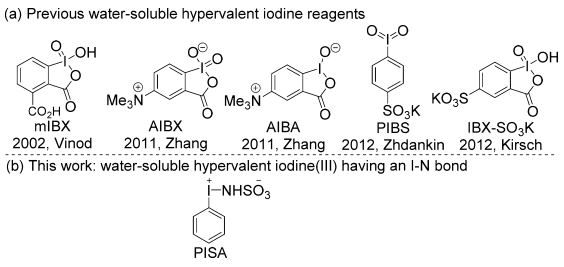



**Figure 1.** Representative water-soluble hypervalent iodine reagents: (a) existing reagents; (b) our newly developed reagent PISA.

Most of the previously reported water-soluble hypervalent iodine reagents are iodine(V) reagents which are synthesized by introducing a hydrophilic group on the phenyl ring through multistep reactions. In addition, all of the water-soluble hypervalent iodine reagents reported to date have I−O bonds; no water-soluble hypervalent iodine reagents with I−N bonds have yet been reported. In order to explore a novel reaction mediated by hypervalent iodine reagents in strongly acidic aqueous media, we envisaged the synthesis of a first strongly acidic water-soluble hypervalent iodine reagent with an I−N bond by introducing a hydrophilic group as a ligand in

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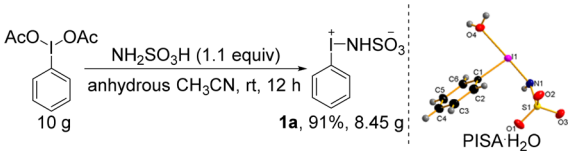
a single-step reaction. To synthesize one such reagent, we chose $NH_2SO_3H$ as the ligand. The specific reasons are as follows: (a) because the sulfonic acid group is hydrophilic, introduction of a $NH_2SO_3H$ ligand would impart good water solubility; (b) the strong acidity of $NH_2SO_3H$ ($pK_a$ = 1.45 at 95 °C[4]) would make the reagent acidic, allowing it to retain its oxidative ability even in the absence of an added Brønsted or Lewis acid.

We adopted a ligand-exchange approach for the synthesis of PISA. We were delighted to find that the reaction of $PhI(OAc)_2$ with $NH_2SO_3H$ (1.1 equiv) in anhydrous $CH_3CN$ [0.5 M of $PhI(OAc)_2$] proceeded smoothly at room temperature: PISA (**1a**) was obtained in 91% yield within 12 h as a colorless solid after filtration and washing with diethyl ether (Scheme 1) (For optimization of the synthesis conditions, see Table S1.) Notably, PISA could be prepared on a large scale (8.45 g) without diminishment of the yield. The solid showed good solubility in water (up to 0.21 M at room temperature), and a saturated aqueous solution of PISA had a pH of 2.05. The oxidation potential of PISA was 1.67 V, and it could be stored at ambient temperature for at least 2 months.

**Scheme 1. Synthesis of PISA (1a)**

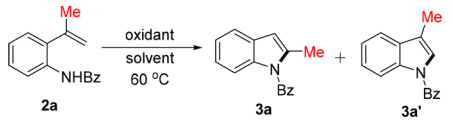



A single crystal of PISA·$H_2O$ was grown from $CH_3CN/H_2O$ at room temperature (Scheme 1). X-ray crystallography showed that PISA·$H_2O$ is a zwitterionic species in which the oxygen atom of water is bound to the iodine(III) center, forming a linear N(1)–I(1)···O(4) triad (bond angle 178.60°). PISA·$H_2O$ has the T-shaped structure that is typical of other commonly used hypervalent iodine(III) reagents, including $PhI(OAc)_2$. The close contact between I(1) and the oxygen atom of water (O(4), 2.4912 Å) can stabilize PISA in water, as has been observed for aquo(hydroxy)-$\lambda^3$-iodane–[18]crown-6 complexes by Ochiai and Miyamoto.[3] The unique structure of PISA shows that it is both a donor and an acceptor of hydrogen bonding. The hydrogen bonding between PISA and $H_2O$ can considerably improve the solubility of PISA in water. The strong acidity of PISA is mainly due to the effective delocalization of negative charge of the resulting nitrogen anion through interaction with strongly electron-withdrawing groups $I^+$ and $SO_3^-$.

With the newly developed hypervalent iodine reagent in hand, we turned to explore its utility for the synthesis of indoles, important and valuable heterocycles, in aqueous media. Intramolecular oxidative C–H amination of 2-alkenylanilines has been considered as one of the most straightforward and powerful routes toward the indole skeleton since the pioneering work of the Hegedus group.[5] Zheng et al. and Youn et al., respectively, reported substituted indole synthesis via C–H amination of 2-alkenylanilines involving a migratory process ($\beta$- to $\alpha$-carbon relative to phenyl) by using $[Ru(bpz)_3](PF_6)_2$/visible light, DDQ, or $Ag_2CO_3$.[6] Excitingly, herein, an inverse migratory process ($\alpha$- to $\beta$-carbon) was first discovered in the synthesis of 2-substituted indole via C–H amination of 2-alkenylanilines with PISA in aqueous $CH_3CN$. More interestingly, we also accomplished the first synthesis of 2,3-disubstituted indoles by means of an aryl migration/intramolecular cyclization cascade. In this reaction, PISA acted both as an oxidant and as a Brønsted acid.

We began by exploring the reaction of *N*-(2-(prop-1-en-2-yl)phenyl)benzamide (**2a**) with PISA (1.5 equiv) in anhydrous $CH_3CN$ at 60 °C under Ar (Table 1, entry 1). Surprisingly, the reaction formed (2-methyl-1*H*-indol-1-yl)(phenyl)methanone (**3a**, 65%) along with 10% of (3-methyl-1*H*-indol-1-yl)-(phenyl)methanone (**3a′**), an isomer of **3a**. Inspired by this result, we optimized the reaction conditions for the synthesis of **3a**. When the reaction was performed under open-flask conditions, **3a** was obtained in 71% yield (entry 2). Another iodine(III) reagent such as PhI = NTs, $PhI(OAc)_2$, or PhIO was employed, giving **3a′** as the only product (entries 3–5). When $PhICl_2$ was used instead of PISA, the reaction gave **3a′** as the major product (75%), along with a 15% yield of **3a** (entry 6). A reaction in the presence of PIFA gave **3a** in a yield of only 31% (entry 7). We also tested hypervalent iodine(V) reagent IBX and found that the reaction did not proceed (entry 8). When the reaction was performed in as-supplied $CH_3CN$ (that is, $CH_3CN$ that was not anhydrous), **3a** was exclusively obtained in 84% yield, implying that traces of $H_2O$ played a critical role in improving the yield and selectivity of **3a** (entry 9). After screening other reaction conditions including $CH_3CN/H_2O$ solvent systems, reaction solvent, the amount of PISA, and reaction temperature (for details, see Table S2), we obtained the optimal reaction conditions for 2-methylindole synthesis as follows: 1.5 equiv of PISA in anhydrous $CH_3CN$ (0.1 M of **2a**) containing 1.5 equiv of $H_2O$ at 60 °C for 2 h

**Table 1. Optimization of Reaction Conditions for 2-Methylindole Synthesis[a]**




| entry | oxidant (1.5 equiv) | solvent | $H_2O$ (equiv) | time (h) | isolated yield (%) 3a | 3a′ |
|---|---|---|---|---|---|---|
| 1[b] | PISA | $CH_3CN$ | | 5 | 65 | 10 |
| 2 | PISA | $CH_3CN$ | | 5 | 71 | 6 |
| 3 | PhI = NTs | $CH_3CN$ | | 5 | 0 | 42 |
| 4 | $PhI(OAc)_2$ | $CH_3CN$ | | 5 | 0 | 80 |
| 5 | PhIO | $CH_3CN$ | | 5 | 0 | 42 |
| 6 | $PhICl_2$ | $CH_3CN$ | | 5 | 15 | 75 |
| 7 | PIFA | $CH_3CN$ | | 5 | 31 | 0 |
| 8 | IBX | $CH_3CN$ | | 5 | 0 | 0 |
| 9[c] | PISA | $CH_3CN$ | | 5 | 84 | 0 |
| 10 | PISA | $CH_3CN$ | 1.5 | 2 | 88 | 0 |
| 11[d] | PIFA | $CH_3CN$ | 1.5 | 5 | 43 | 0 |
| 12 | AIBA | $CH_3CN$ | 1.5 | 4 | 0 | 0 |
| 13 | mIBX | $CH_3CN$ | 1.5 | 4 | 0 | 0 |
| 14 | AIBX | $CH_3CN$ | 1.5 | 4 | 0 | 0 |
| 15 | PIBS | $CH_3CN$ | 1.5 | 4 | 0 | 0 |
| 16 | IBX-$SO_3K$ | $CH_3CN$ | 1.5 | 4 | 0 | 0 |

[a]Reaction conditions, unless otherwise stated: **2a** (0.3 mmol), solvent (3 mL), 60 °C, open flask. [b]The reaction was conducted under Ar. [c]The reaction was carried out with as-supplied $CH_3CN$ (not anhydrous). [d]1.5 equiv of $NH_2SO_3H$ was used.



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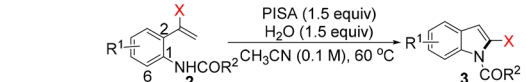
(entry 10). A reaction using 1.5 equiv of PIFA and $NH_2SO_3H$ only gave 43% of **3a**, indicating that PISA was indispensable for the efficient synthesis of **3a** (entry 11). When other water-soluble hypervalent iodine reagents, such as AIBA (3-oxo-5-(trimethylammonio)-1$\lambda^3$-benzo[*d*][1,2]iodaoxol-1(3*H*)-olate), mIBX (1-hydroxy-1,3-dioxo-1,3-dihydro-1$\lambda^5$-benzo[*d*][1,2]-iodaoxole-4-carboxylic acid), AIBX (5-trimethylammonio-1,3-dioxo-1,3-dihydro-1$\lambda^5$-benzo-[*d*][1,2]iodoxol-1-ol anion), PIBS (potassium 4-iodylbenzenesulfonate), and IBX-$SO_3K$ (potassium 1-hydroxy-1,3-dioxo-1,3-dihydro-1$\lambda^5$-benzo[*d*]-[1,2]iodaoxole-5-sulfonate), were subjected to the standard reaction conditions (entries 12−16), **3a** was not detected. These results confirm the unique reactivity of PISA.

With the optimal reaction conditions established, we explored the generality of the method by testing various substrates **2** (Scheme 2). When X was alkyl, phenyl, or hydrogen, the reaction gave 2-substituted indoles **3a−g** as the sole products; that the formation of 3-substituted indoles was not observed demonstrates the excellent regioselectivity of this method. Furthermore, we could also obtain good to high yields of 2-methylindoles with different substituents on the phenyl ring (**3h−n**), and the Cl and Br atoms can serve as handles for the construction of more complex molecules. Heteroaromatic motifs such as furyl and thienyl were compatible with the reaction conditions as well, giving desired products **3o** and **3p** in high yields. Considering that the bioactivities of *N*-protected indoles vary with the protecting group,[7] we next investigated the effects of various *N*-protecting groups on the formation of 2-substituted indoles (**3q−v**). An acryloyl group, which is susceptible to oxidation, was also compatible (**3v**).

Surprisingly, when the trisubstituted alkene (*E*)-*N*-(2-(pent-2-en-2-yl)phenyl)benzamide (**2w**) was used as the substrate, 2,3-disubstituted indole **3w** was obtained in 69% yield via cyclization; this transformation constitutes a formal interchange of the methyl and ethyl groups (eq 1).

**Scheme 2. Substrate Scope of PISA-Mediated Synthesis of 2-Substituted Indoles on a 0.3 mmol Scale***

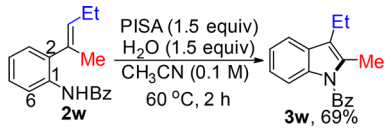



**3a**, X = Me, 88%, 2 h
**3b**, X = Et, 73%, 2 h
**3c**, X = *n*-pentyl, 77%, 3 h
**3d**, X = cyclopropyl, 72%, 12 h
**3e**, X = cyclohexyl, 70%, 5 h
**3f**, X = Ph, 62%, 2.5 h[a]
**3g**, X = H, 63%, 9 h[b]

**3h**, $R^1$ = 5-F, 65%, 2 h
**3i**, $R^1$ = 6-Cl, 80%, 2 h
**3j**, $R^1$ = 5-Br, 83%, 2.5 h
**3k**, $R^1$ = 6-$CF_3$, 78%, 3 h
**3l**, $R^1$ = 6-Me, 77%, 2.5 h
**3m**, $R^1$ = 7-Cl, 57%, 12 h[c]
**3n**, $R^1$ = 5-Ph, 83%, 2 h
**3o**, $R^1$ = 5-furyl, 77%, 2 h[d]
**3p**, $R^1$ = 5-thienyl, 75%, 2 h

**3q**, $R^2$ = 1-naphthyl, 65%, 1.5 h
**3r**, $R^2$ = 2-thienyl, 75%, 2 h
**3s**, $R^2$ = 2-furyl, 81%, 2.5 h
**3t**, $R^2$ = $PhCH_2$, 72%, 2.5 h
**3u**, $R^2$ = Me, 57%, 1 h
**3v**, $R^2$ = vinyl, 61%, 2 h

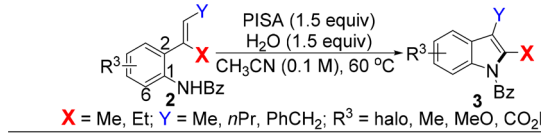
*Isolated yields are reported. [a]One hour after the start of the reaction, a solution of concd HCl (3 equiv) in $CF_3CH_2OH$ was added to the reaction mixture, which was then stirred at 60 °C for an additional 1.5 h. The conversion of **2f** was 90%, and the yield of **3f** was based on this conversion. [b]The oxidant was 4-$NO_2C_6H_4I^+NHSO_3^-$ (**1b**, 1.5 equiv). The conversion of **2g** was 91%, and the yield of **3g** was based on this conversion. [c]The reaction was carried out at 60 °C for the first 2 h and then at reflux temperature for another 10 h. The conversion of **2m** was 93%, and the yield of **3m** was based on this conversion. [d]The oxidant was **1b** (1.5 equiv).

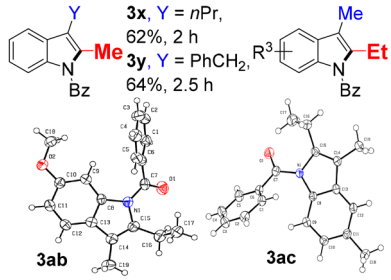



(1)

Inspired by this significant finding, we evaluated some additional trisubstituted alkenes (Scheme 3). When (*E*)-trisubstituted alkenes **2x−z** were subjected to the standard reaction conditions, the desired 2,3-disubstituted indoles (**3x−z**) were obtained in good to high yields with excellent regioselectivity. We confirmed the *E* configuration of **2ah** by means of X-ray crystallography (data available in SI) and also obtained NOESY spectra of (*E*)- and (*Z*)-**2ac** (spectra available in SI). To confirm the structures of **3w−z**, we deprotected them with $N_2H_4{\cdot}H_2O$ to give the corresponding known compounds (see the SI). In addition, substrates bearing either electron-donating or electron-withdrawing substituents on the phenyl ring were converted smoothly to the corresponding 2,3-disubstituted indoles (**3aa−ag**) in satisfactory yields. The reaction of **2ah**, which has a methyl group at C-6 of the phenyl ring, furnished **3ah** in 68% yield, although a prolonged reaction time (11.5 h) was required, owing to steric hindrance. A gram-scale reaction of **2ah** (1.4 g) afforded **3ah** in 61% yield. The structures of **3ab** and **3ac** were confirmed by X-ray crystallography.

**Scheme 3. Substrate Scope of PISA-Mediated Synthesis of 2,3-Disubstituted Indoles on a 0.3 mmol Scale***




**3z**, $R^3$ = H, 67%, 4 h
**3aa**, $R^3$ = 5-MeO, 60%, 4 h
**3ab**, $R^3$ = 6-MeO, 70%, 2 h
**3ac**, $R^3$ = 5-Me, 66%, 2 h
**3ad**, $R^3$ = 6-F, 75%, 4 h
**3ae**, $R^3$ = 5-Cl, 56%, 3.5 h[a]
**3af**, $R^3$ = 6-Br, 61%, 4 h
**3ag**, $R^3$ = 6-$CO_2$Me, 72%, 6 h[b]
**3ah**, $R^3$ = 7-Me, 68%, 11.5 h

*Isolated yields are reported. [a]2.5 equiv of PISA was used. The conversion of **2ae** was 91%, and the yield of **3ae** was based on this conversion. [b]The conversion of **2ag** was 75%, and the yield of **3ag** was based on this conversion.

To demonstrate the synthetic utility of this novel method, we used it as the key step in the preparation of two nonsteroidal anti-inflammatory drug molecules: Indometacin (**8**) and zidometacin (**9**) (Scheme 4). A reaction of 1.4 g of **2ai** was also conducted, giving **3ai** in 71% yield. The overall yields of Indometacin and zidometacin were 39% and 16%, respectively.

In addition, deprotection of **3a** provided 2-methylindole (**10**, 95% yield), which is a key intermediate in a previously reported synthesis of the analgesic agent pravadoline (**11**) (Scheme S1).[8]

To study the mechanism of the formation of various indoles, we conducted a series of control experiments (Scheme 5). At room temperature (instead of 60 °C), the reaction of substrate **2a** gave *N*-(2-(2-oxopropyl)phenyl)benzamide (**12**) in 96%



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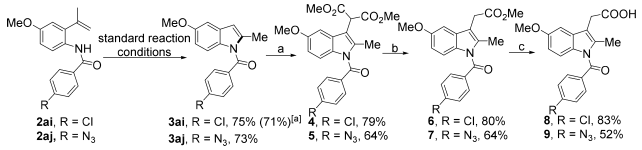
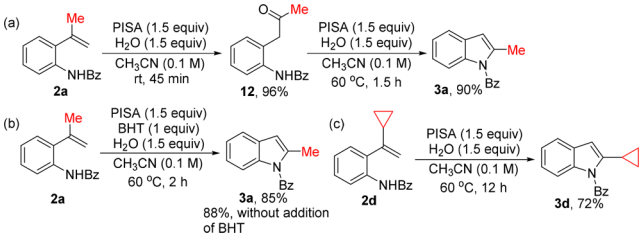
**Scheme 4. Synthesis of Indometacin (8) and Zidometacin (9)***




*Reaction conditions: (a) $Cu(acac)_2$, $N_2C(COOMe)_2$, toluene; (b) LiCl, DMF/$H_2O$ for **6**, DMSO/$H_2O$ for **7**, reflux; (c) LiI, pyridine, reflux. [a]The yield in parentheses was obtained from 1.4 g of **2ai**.

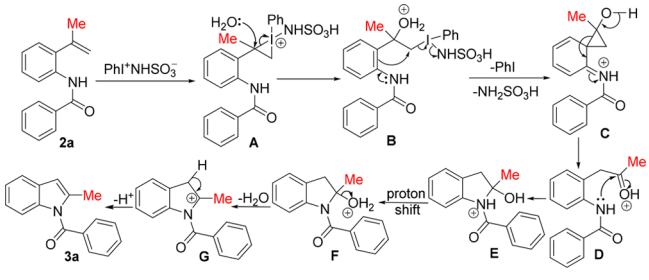
**Scheme 5. Control Experiments**




yield. Subjecting **12** to the standard reaction conditions afforded 2-substituted indole **3a** in 90% yield, suggesting the intermediacy of **12**. A radical-capture experiment involving the reaction of **2a** in the presence of 2,6-di-*tert*-butyl-4-methylphenol (BHT) smoothly produced **3a** in 85% yield, and a radical clock experiment performed with **2d** under the optimal reaction conditions generated **3d** in 72% yield as the sole product; the product of cyclopropyl ring opening was not detected. These results suggest that a radical intermediate was not involved in the reaction.

On the basis of the above-described control experiments and literature precedents,[9] we propose the mechanism involving an aryl migration/intramolecular cyclization cascade shown in Scheme 6. First, nucleophilic attack on PISA by the substrate

**Scheme 6. Proposed Reaction Mechanism**




double bond forms iodonium ion **A**, which is then opened by $H_2O$ selectively at the benzylic carbon to afford intermediate **B**. Nucleophilic attack of the phenyl ring of **B** on the carbon center of the newly formed hypervalent iodine(III) species affords spiro intermediate **C** and is accompanied by dearomatization of **B** and the release of iodobenzene and $NH_2SO_3H$. Then, in the key step, ring opening of spiral intermediate **C** proceeds exclusively and smoothly under the driving force of rearomatization to give **D** (protonated **12**). Release of a proton from **D**, forms methyl ketone **12**, the intermediacy of which was confirmed by the control experiment shown in Scheme 5a. From **D**, indole formation occurs, accompanied by the release of $H_2O$.[10]

In summary, we report the synthesis of PISA, a novel acidic water-soluble hypervalent iodine(III) reagent with one I–N bond and a high oxidation potential. We found that a series of indoles could be synthesized with excellent regioselectivity in aqueous $CH_3CN$ with PISA. In this reaction, PISA acted both as an oxidant and as a Brønsted acid, and water could act as a catalyst to enhance the efficiency and selectivity of the reaction. The method described herein was utilized for rapid synthesis of the bioactive molecules indometacin, zidometacin, and pravadoline. The unique reactivities of PISA, which differ from those of previously reported water-soluble hypervalent iodine reagents (such as AIBA and mIBX), are currently being explored further in our laboratory.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01615.

Experimental procedures and characterization of products (PDF)

### Accession Codes

CCDC 1547807, 1811512–1811513, and 1817528 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.

## ■ AUTHOR INFORMATION


### Corresponding Author

*E-mail: zhangchi@nankai.edu.cn.

### ORCID

Chi Zhang: 0000-0001-9050-076X


### Notes

The authors declare no competing financial interest.

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