

Chemical Science

Volume 11
Number 4
28 January 2020
Pages 901–1180

rsc.li/chemical-science



ISSN 2041-6539

EDGE ARTICLE

Yunfei Du *et al.*

A new hypervalent iodine(III/V) oxidant and its application to the synthesis of 2*H*-azirines

Cite this: *Chem. Sci.*, 2020, 11, 947

All publication charges for this article have been paid for by the Royal Society of Chemistry

Received 2nd November 2019

Accepted 5th December 2019

DOI: 10.1039/c9sc05536c

rsc.li/chemical-science

A new hypervalent iodine(III/V) oxidant and its application to the synthesis of 2*H*-azirines†

Guangtao Zhang,^a Yuanxun Wang,^a Jun Xu,^a Jiyun Sun,^a Fengxia Sun,^b Yilin Zhang,^c Chenglin Zhang^a and Yunfei Du^{*,a}

The reaction of *o*-nitroiodobenzene and *m*CPBA in acetic acid was found to afford a novel hypervalent iodine compound, in the structure of which both iodine(III) and iodine(V) moieties coexist. The nitro groups at the *ortho* phenyl positions were found to be crucial in stabilizing this uncommon structure. This novel hypervalent iodine(III/V) oxidant is proved to be effective in realizing the synthesis of 2-unsubstituted 2*H*-azirines *via* intramolecular oxidative azirination, which could not be efficiently achieved by the existing known hypervalent iodine reagents.

Introductions

In the past several decades, hypervalent iodine chemistry has witnessed prosperous development in organic synthesis.¹ On one hand, organic chemists are making use of the existing hypervalent iodine oxidants to discover new organic reactions.² On the other hand, many endeavors have been devoted to the development of novel hypervalent iodine oxidants, seeking new versatile applications in important synthetic transformations.³ In this regard, designing novel hypervalent iodine compounds and discovering their new application continue to be an important research topic of hypervalent iodine chemistry.

The existing hypervalent iodine reagents can be generally classified into iodine(III) and iodine(V) based on the valence of the iodine atom. The existing hypervalent iodine(III) reagents include phenyliodine diacetate (PIDA), phenyliodine bis(trifluoroacetate) (PIFA), iodosylbenzene (PhIO), [hydroxyl(tosyloxy)iodo]benzene (HTIB, Koser reagent),⁴ PhICl₂,⁵ TolIF₂,⁶ diaryl iodonium salts,⁷ Togni's reagents,⁸ μ -oxobis(trifluoroacetoxyiodobenzene) (μ -oxo BTI),⁹ cyano(trifluoromethylsulfonyloxy)iodobenzene (Stang's reagent),¹⁰ 1-phenyl-2-(phenyl- λ^3 -iodaneylidene)-2-((trifluoromethyl)sulfonyl)ethan-1-one (Shibata reagent II),¹¹ iodosodilactone,^{1e} *etc.*¹² The more widely studied hypervalent iodine(V) reagents mainly include 2-iodoxybenzoic acid (IBX),¹³ Dess–Martin periodinane

(DMP),¹⁴ Hara reagent,¹⁵ pentafluorophenyliodine tetrafluoride (PFITF),¹⁶ 2-iodoxybenzenesulfonic acid (IBS),¹⁷ iodine pentafluoride,¹⁸ iodoxybenzene,¹⁹ and diaryliodosyl salts²⁰ (Fig. 1). It is evident that all these hypervalent iodine compounds, which bear one single iodine atom center or multinuclear iodine centers (such as polymeric PhIO, μ -oxo BTI, and Zefirov's reagent²¹), all have a sole valence number of either I(III) or I(V) present in their chemical structure. To the best of our knowledge, there is no report on a hypervalent iodine compound that bears both I(III) and I(V) moieties in its chemical structure. In this communication, we reported such a new hypervalent iodine compound bearing concurrently I(III) and I(V) moieties and its preliminary application in the synthesis of 2-unsubstituted 2*H*-azirines, which could not be efficiently achieved by the existing known hypervalent iodine reagents.

Iodoxybenzenes, as a class of hypervalent iodine(V) oxidants, have found useful applications in organic synthesis.²² For example, in the presence of diaryl selenium can selectively oxidize the allylic position of olefins to form an α,β -unsaturated ketone.^{22a} It can also convert a cyclic ketone compound to an α,β -unsaturated ketone *via* dehydrogenative oxidation.^{22c,23} With regard to their synthesis, iodoxybenzenes can be generally prepared through two methods: one is the oxidation of aryl iodine(I) after reacting with an oxidant like peracetic acid (Saltzman's work), oxone (Zhdankin's work), *m*CPBA (Kropp's work), 3,3-dimethyldioxirane (Serri's work) or potassium peroxomonosulfate (Zhdankin's work),²⁴ while the other is to use aryl iodine(III) as a substrate, which is further oxidized by sodium hypochlorite to form iodoxybenzene *via* an iodosylbenzene intermediate.^{24c,25} However, to the best of our knowledge, neither of the two methods reported the synthesis of *o*-nitroiodoxybenzene, an unusual hypervalent iodine(V) reagent bearing a strong electron-withdrawing *ortho*-nitro substituent. It was not until 2018 that Powers and coworkers reported that *o*-nitroiodoxybenzene could be synthesized from

^aSchool of Pharmaceutical Science and Technology, Tianjin University, Tianjin 300072, China. E-mail: duyunfeier@tju.edu.cn

^bCollege of Chemical and Pharmaceutical Engineering, Hebei University of Science and Technology, Shijiazhuang 050018, China

^cC. Eugene Bennett Department of Chemistry, West Virginia University, Morgantown, West Virginia 26506-6045, USA

† Electronic supplementary information (ESI) available: Experimental procedure, characterization data of all new compounds and NMR spectra. CCDC 1950436. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c9sc05536c



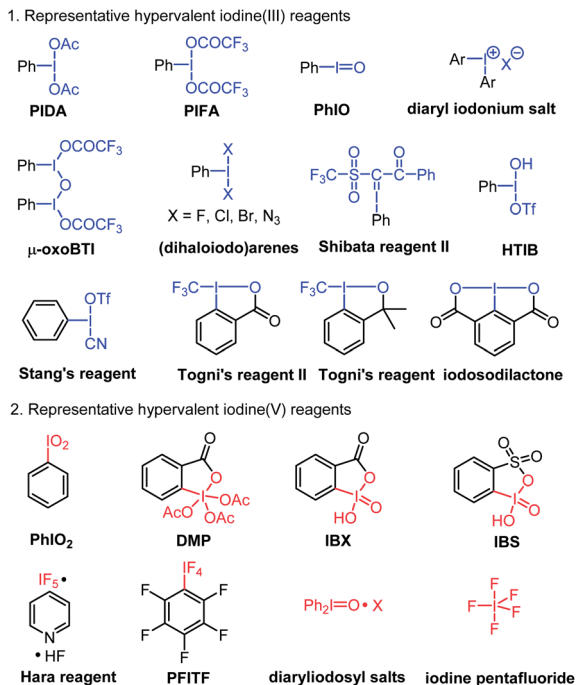


Fig. 1 The existing hypervalent iodine(III) and iodine(V) reagents.

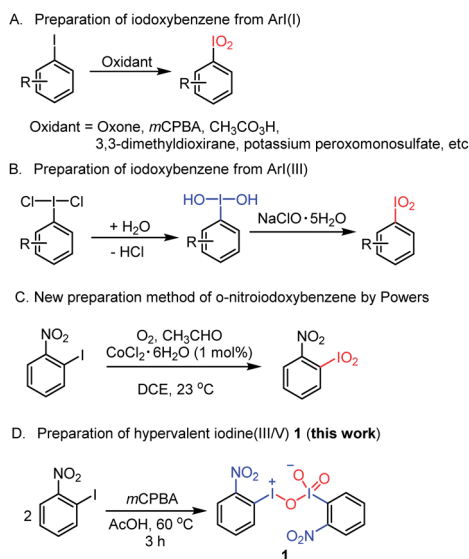


Fig. 2 Existing methods for the synthesis of iodoxybenzene and its derivatives vs. the serendipitous access to the first hypervalent iodine(III/V) oxidant.

o-nitrobenzene mediated by cobalt(II) chloride hexahydrate under an O₂ atmosphere (Fig. 2C).²⁶

Results and discussion

At the outset of the study, we were interested to synthesize *o*-nitroiodoxybenzene according to the literature as shown in Fig. 2A.²² Unfortunately we did not get the desired product (*o*-nitroiodoxybenzene) by this method. So, we were interested to

further optimize the oxidants and the solvents (see ESI, Table 2†). To our surprise, when *o*-nitroiodobenzene reacted with *m*CPBA in acetic acid at 60 °C for 3 h, a hypervalent iodine(III/V) **1**,²⁷ rather than the expected *o*-nitroiodoxybenzene, was formed as an orange solid (the structure was undoubtedly confirmed by X-ray analysis) (Fig. 2D). A careful literature survey indicated that this could represent the first hypervalent iodine compound containing both I(III) and I(V) moieties in its chemical structure.

The solid state of molecule **1** was established by single-crystal X-ray crystallography (for crystallographic details, see Tables 3–9 in the ESI†). The X-ray data revealed that four crystallographically independent molecules are present in one crystal unit cell. Molecule **1** assembles in an unusual “scissor” manner as a result of intermolecular I(2)⋯O(5) and I(1)⋯O(4) interactions (Fig. 3A). The crystal structure of **1** is uncommon among the known hypervalent iodine structures that have been characterized to date, with a pentavalent I(2) atom and a trivalent I(1) atom coexisting in one molecule *via* connection of an O(3) atom^{17,28} (Fig. 3B).

The I(2)–O(3) bond length is 2.447 Å. Analyses of the electron density at BCPs and the Mayer bond order revealed that the I(2)–O(3) bond in molecule **1** was a relatively weak bond compared to the I–O bonds in other hypervalent iodine reagents (see ESI, Fig. S1†).

The I(2)–O(4) bond length and I(2)–O(5) bond length are 1.773 Å and 1.788 Å respectively. The pentavalent I(2) forms an intramolecular I⋯O interaction with one of the nitro oxygen atoms O(6) at a distance of 2.788 Å (Fig. 3B), which was revealed previously.²⁹ In addition, DFT calculations were performed with ORCA 4.1.2 software.³⁰ The comparison of ρ_{bcip} and the Mayer bond order of I₂–O₃ bonds in the hypervalent iodine molecule with or without nitro groups was summarized, which showed that the I₂–O₃ bond became weaker when the nitro groups in molecule **1** were deleted (see ESI, Fig. S3A†). Multiwfn and VMD programs were used to generate a molecular electrostatic potential surface.³¹ The electro-positive regions (surface maxima) around I(III) or I(V) atoms displayed electrostatic interaction with the oxygen atoms of nitro groups (see ESI, Fig. S3B†). The calculation results indicated that nitro groups could strengthen I₂⋯O₃ bonds in molecule **1**. Thus, nitro groups played an essential role in molecule **1**.

Moreover, the attractive interaction between I(2) and O(6) was demonstrated by the presence of a bond path and a BCP(1) along the bond path in ‘atoms in molecules’ analysis (Fig. 3C). Additionally, the pentavalent I(2) also forms an intermolecular I⋯O interaction with an O(5) atom in another molecule at a distance of 2.534 Å, thereby producing a hexacoordinated complex with pseudooctahedral geometry around iodine atoms (Fig. 3A).

In general, the geometry of the trivalent I(1) center is consistent with that of the reported *o*-nitrophenylhydroxyiodonium molecule, with a strong interaction formed between the iodine atom and one of the oxygen atoms from the nitro group on the *ortho*-position of the phenyl ring.²⁹ In molecule **1**, the distance between I(1) and O(2) in the nitro group (2.638 Å) is slightly longer than that in the *o*-nitrophenylhydroxyiodonium molecule (2.510 Å), but is much



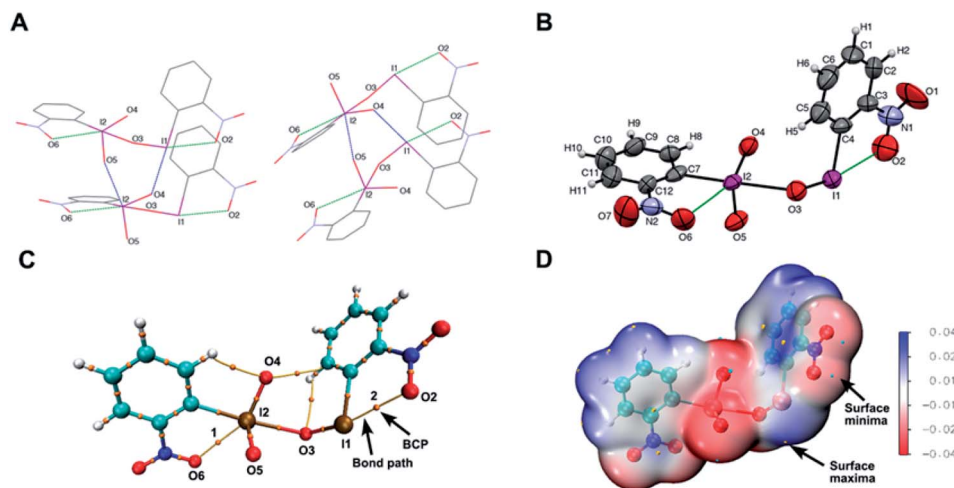


Fig. 3 X-ray crystallographic structure and quantum mechanics studies of molecule **1**. The intermolecular I \cdots O interactions were indicated by a blue dashed line, and the intramolecular I \cdots O secondary bonding was indicated by a green dashed line. (A) The wireframe diagram of an independent crystal unit cell of **1**. (B) The ORTEP diagram (50% probability level) of an individual molecule **1**. (C) The 'atoms in molecules (AIM)' analysis of molecule **1**. The bond critical points (BCPs) were represented by orange spheres, and the bond paths connecting the nuclei with critical points were represented by yellow lines. (D) Molecular electrostatic potential surfaces computed for molecule **1** (unit: a.u.).

shorter than the sum of the respective vdW radii (3.530 Å), indicating a strong interaction between the iodine atom and nitro group.²⁹ Similar to the attractive interaction between I(2) and O(6), I(1) and O(2) interaction was also found with the presence of a bond path and a BCP(2) (Fig. 3C). The computed electrostatic potential surfaces of molecule **1** showed the electrostatic attraction between hypervalent iodine atoms I(1) or I(2) (surface maxima) and nitro oxygen atoms O(2) or O(6) (surface minima) (Fig. 3D and S1†). The I(1)–O(3) bond is 1.861 Å in length, which is shorter than that (1.901 Å) observed in a *o*-nitrophenylhydroxyiodonium molecule.²⁹ Moreover, the 5-membered ring O(2)–N(1)–C(3)–C(4)–I(1) is nearly coplanar with a small dihedral angle N(1)–O(2)–I(1)–C(4) of about 3.55°. The bond angle O(2)–I(1)–O(3) is about 164.44° and distorted from optimal T-shaped geometry same as that in the *o*-nitrophenylhydroxyiodonium molecule (Fig. 3B). The trivalent I(1) also maintains an intermolecular I \cdots O interaction with an O(4) atom from another molecule at a distance of 2.696 Å, creating a tetracoordinated complex with pseudo-square-planar geometry about iodine (Fig. 3A).³²

A possible reaction mechanism was proposed for the formation of this new hypervalent iodine(III/V) compound **1** (Fig. 4). First, the reaction of *o*-nitroiodobenzene with *m*CPBA afforded the iodine(III) intermediate **A**, in which the nitro substituent at the *ortho* position of *o*-nitroiodobenzene played a crucial auxiliary role. With the abstraction of a proton, **A** was converted to I(III) species **B**. Next, the intermolecular reaction between two molecules of **B** led to the formation of the iodine(III/III) intermediate **C**. Similarly, assisted by the "free" adjacent nitro group, **C** was further oxidized by *m*CPBA to give the iodine(III/V) intermediate **D**. Finally, **D** was converted to the titular iodine(III/V) **1** *via* the removal of one proton.

Next, we were interested to investigate the applicability of this newly discovered hypervalent iodine(III/V) oxidant. As our

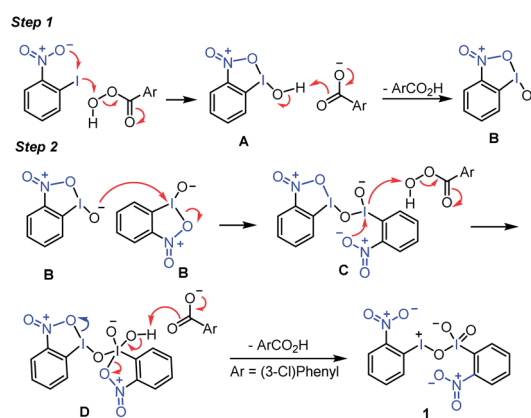


Fig. 4 Proposed mechanism for the synthesis of iodine(III/V) **1**.

research interest focuses on constructing heterocyclic skeletons using various hypervalent iodine reagents,^{1b,33} we first investigated whether this novel hypervalent iodine(III/V) oxidant could be used to realize conversions that are not readily achievable by other hypervalent iodine reagents.

2*H*-Azirines³⁴ are an important class of N-containing heterocycles and have received extensive attention because of their occurrence in natural products and application as building blocks in various useful transformations. Several synthetic strategies, including the classical Neber reaction,³⁵ pyrolysis or photolysis of vinyl azide,³⁶ elimination of aziridine derivatives,³⁷ the Swern oxidation reaction,³⁸ intramolecular ring contraction reactions³⁹ and intermolecular aziridination,⁴⁰ have been reported for the synthesis of this privileged class of heterocycles.⁴¹ In 2009, we found that the reaction of enamine substrates with PIDA in DCE could enable a convenient intramolecular aziridination, leading to the formation of 2*H*-azirine



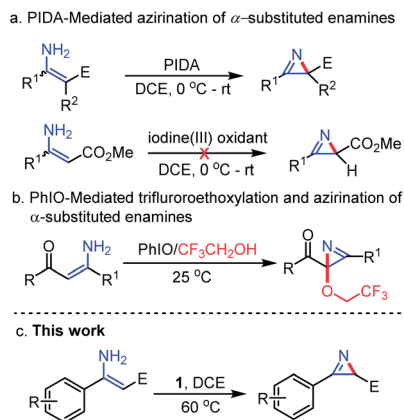


Fig. 5 Existing methods for the construction of $2H$ -azirine skeletons mediated by hypervalent iodine reagents.

compounds in satisfactory to good yield⁴² (Fig. 5a). However, substrate scope study indicated that this method could not be applied to β -unsubstituted enamines bearing a β -methoxycarbonyl group ($E = \text{CO}_2\text{Me}$), albeit such a type of substrate could be converted to trifluoroethoxylated $2H$ -azirines through reaction with PhIO in trifluoroethanol (TFE), *via* an oxidative trifluoroethoxylation followed by an azirination reaction⁴³ (Fig. 5b). Since β -unsubstituted $2H$ -azirines bearing an ester moiety are basic skeletons commonly seen in naturally occurring (*S*)-(+)-dysidazirin⁴⁴ compounds, it is equally desirable to develop a method that can efficiently achieve the direct intramolecular azirination of β -unsubstituted enamines.⁴⁴ To our delight, we found that this newly discovered hypervalent iodine(III/V) is able to realize this expected azirination, demonstrating the unusual properties of this hypervalent iodine oxidant (Fig. 5c).⁴⁵

The initial reactivity assay employed a simple α -substituted enamine **2a** as the model substrate to optimize the reaction parameters. The results are summarized in Table 1. First, when substrate **2a** was treated with iodine(III/V) **1** in DCE at room temperature for 5 h, only a trace amount of the desired product **3a** was obtained (Table 1, entry 1). To our delight, elevating the reaction temperature to 60 °C led to the formation of product **3a** in a much higher yield of 47% (Table 1, entry 2). Solvent screening revealed that compared to the protic solvents such as MeOH and AcOH, aprotic solvents, especially DCE, were found to be ideal for this specific reaction, as the yield of the product could reach 80% (Table 1, entries 3–9). We also investigated the dosage of the oxidant and the best result was obtained when 0.7 equivalent of the oxidant was added (Table 1, entry 8). Further attempts to improve the reaction outcome by using Lewis acids as an additive proved to be unfruitful (Table 1, entries 10 and 11). Also, in light of our previous work and structural analysis of **1**, we attempted to complete the synthesis of $2H$ -azirines in a one-pot protocol. Unfortunately, no $2H$ -azirine product was observed under these conditions, probably because the strong oxidizing power of *m*CPBA preferentially acts on the model substrate (Table 1, entry 12). Further tuning of the reaction by reacting *o*-nitroiodobenzene with *m*CPBA in AcOH, followed by a reaction with substrate **2a**, only led to the formation of the desired product **3a** in 26% yield (Table 1, entry 13). These results implied that the one-pot protocol utilizing the *in situ* generation of compound **1** for efficient synthesis of $2H$ -azirines was not feasible.

With the optimized conditions in hand, substrate scope study was carried out by using this newly discovered hypervalent iodine(III/V) reagent on a series of α -substituted enamines. It was found that a variety of substituents on the phenyl ring could be well tolerated during the reaction. With

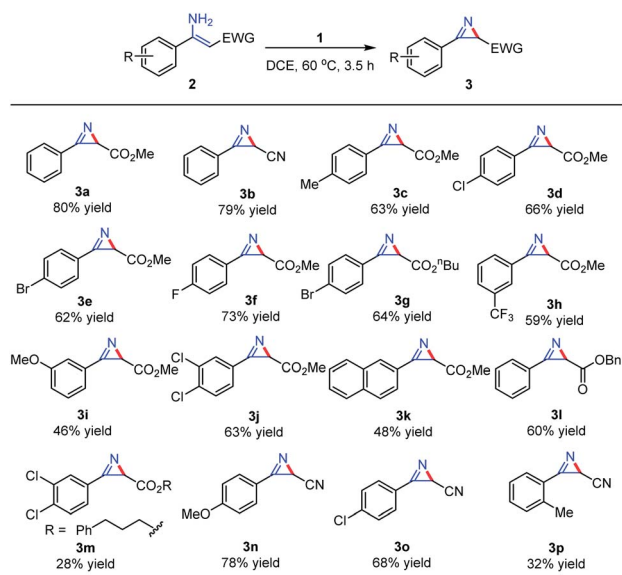
Table 1 Optimization of the reaction conditions^a

Entry	Oxidant (equiv.)	Additive	Solvent	Temp. (°C)	Time [h]	Yield ^b [%]
1	1 (0.5)	None	DCE	rt	5	Trace
2	1 (0.5)	None	DCE	60	3.5	47
3	1 (0.7)	None	EtOAc	60	4	57
4	1 (0.7)	None	Toluene	60	4	70
5	1 (0.7)	None	MeCN	60	4	53
6	1 (0.7)	None	MeOH	60	3.5	19
7	1 (0.7)	None	PhCl	60	3.5	55
8	1 (0.7)	None	DCE	60	3.5	80
9	1 (0.7)	None	AcOH	60	3	55
10 ^e	1 (0.7)	BF ₃ ·Et ₂ O	DCE	60	3	76
11 ^e	1 (0.7)	TBSOTf	DCE	60	3	73
12 ^c	1 (0.7)	None	AcOH	60	2	N.D.
13 ^d	1 (0.7)	None	AcOH	60	5.5	26

^a Reaction conditions: **2a** (1.0 mmol), **1** (0.7 mmol), DCE (5 mL), and stirred at 60 °C for 3.5 h. ^b Isolated yield. ^c **2a** (1.0 mmol), *o*-nitroiodobenzene (2.0 mmol), *m*CPBA (2.2 mmol), and AcOH (5 mL). ^d *o*-Nitroiodobenzene (2.0 mmol), *m*CPBA (2.2 mmol), AcOH (5 mL), stirred at 60 °C for 3 h, and then added **2a** (1.0 mmol) and stirred at the same temperature for another 2.5 h. ^e 2.0 equiv. of the additive was used.



Table 2 Synthesis of 2*H*-azirine derivatives through iodine(III/V) 1-mediated azirination of enamines^{a,b}



^a Reaction conditions: **2** (1.0 mmol), **1** (0.7 mmol), DCE (5 mL), and stirred at 60 °C for 3.5 h. ^b Isolated yield.

regard to the substituent effect of the R group, substrates bearing electron-withdrawing groups or electron-donating groups at the *para*-position of the phenyl ring both gave the corresponding products in good yields (**2b–g**, **2i–o**), with the substrates bearing electron-withdrawing groups affording a better outcome (**2d–2f** vs. **2c**). A lower yield was obtained for substrates containing substituents at the *meta* position of the phenyl ring (**2h–i**), while for the substrate bearing an *ortho*-substituent methyl group on the phenyl ring, the desired 2*H*-azirine product was only afforded in a much lower yield (**3p**) (Table 2).

We also proposed a possible reaction pathway for the formation of a 2*H*-azirine product using this novel hypervalent iodine(III/V) oxidant (Fig. 6). First, the reaction of the enamine

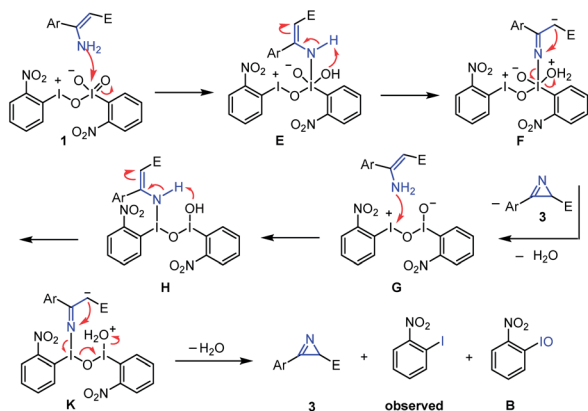


Fig. 6 Proposed mechanism for the synthesis of 2*H*-azirines.

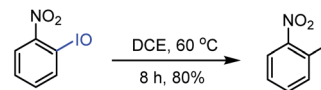


Fig. 7 Control experiment.

substrate with hypervalent iodine(III/V) **1** afforded enamine intermediate **E** via the formation of an N–I(V) bond.⁴⁶ Then enamine **E** was isomerized into imine **F**, which underwent intramolecular azirination to give 2*H*-azirine product **3**, with the concurrent generation of hypervalent iodine(III/III) **G**. Following the reaction of this intermediate **G** with one more molecule of the enamine substrate, enamine intermediate **H** was formed via the formation of an N–I(III) bond. Similarly, enamine intermediate **H** was converted of 2*H*-azirine product **3** via isomerization and intramolecular azirination, with the formation of *o*-nitroiodobenzene and *o*-nitroiodosylbenzene as by-products. It is worth noting that *o*-nitroiodosylbenzene is not stable under the conditions and was converted to *o*-nitroiodobenzene, which can be supported by the result of a control experiment: when a solution of *o*-nitroiodosylbenzene⁴⁷ in DCE was heated at 60 °C for 8 h, *o*-nitroiodobenzene was obtained in a yield of 80% (Fig. 7).

Conclusions

In summary, we have reported for the first time a new hypervalent iodine oxidant containing both I(III) and I(V) moieties in its chemical structure. Computational experiments were carried out to reveal that the nitro group at the *ortho* phenyl position is crucial in stabilizing this new structure. This novel hypervalent iodine(III/V) oxidant can be applied to the synthesis of 2-unsubstituted 2*H*-azirines, which cannot be successfully achieved by other traditional hypervalent iodine reagents. Further application of this hypervalent iodine(III/V) oxidant is currently under study in our lab.

Conflicts of interest

The authors declare no conflict of interest.

Acknowledgements

We acknowledge the National Natural Science Foundation of China (#21472136) for financial support. Computational support was provided by the Special Program for Applied Research on Super Computation of the NSFC-Guangdong Joint Fund (the second phase) under Grant No. U1501501.

Notes and references

- (a) L. F. Silva Jr and B. Olofsson, *Nat. Prod. Rep.*, 2011, **28**, 1722; (b) A. Yoshimura and V. V. Zhdankin, *Chem. Rev.*, 2016, **116**, 3328; (c) R. M. Moriarty, *J. Org. Chem.*, 2005, **70**, 2893; (d) V. V. Zhdankin and P. J. Stang, *Chem. Rev.*, 2008, **108**, 5299; (e) J. Tian, W. C. Gao, D. M. Zhou and C. Zhang,



- Org. Lett.*, 2012, **14**, 3020; (f) U. Farid and T. Wirth, *Angew. Chem., Int. Ed.*, 2012, **51**, 3462; (g) N. O. Ilchenko, M. Hedberg and K. J. Szabo, *Chem. Sci.*, 2017, **8**, 1056; (h) Y. Tamura, T. Yakura, Y. Shirouchi and J. Haruta, *Chem. Pharm. Bull.*, 1986, **34**, 1061; (i) M. W. Justik, in *PATAI'S Chemistry of Functional Groups [online]*, John Wiley & Sons, Ltd, New York, 2009, pp. 1–88.
- 2 (a) J. D. Haupt, M. Berger and S. R. Waldvogel, *Org. Lett.*, 2019, **21**, 242; (b) L. Wang, H. Li and L. Wang, *Org. Lett.*, 2018, **20**, 1663; (c) S. R. Kandimalla, S. P. Parvathaneni, G. Sabitha and B. V. S. Reddy, *Eur. J. Org. Chem.*, 2019, 1687; (d) I. Colomer, C. Batchelor-McAuley, B. Odell, T. J. Donohoe and R. G. Compton, *J. Am. Chem. Soc.*, 2016, **138**, 8855; (e) D. Bhattacharjee, S. Ram, A. S. Chauhan, Yamini, Sheetal and P. Das, *Chem.–Eur. J.*, 2019, **25**, 5934.
- 3 (a) J. Kalim, T. Duhail, T.-N. Le, N. Vanthuyne, E. Anselmi, A. Togni and E. Magnier, *Chem. Sci.*, 2019, **10**, 10516; (b) G.-X. Li, C. A. Morales-Rivera, F. Gao, Y. Wang, G. He, P. Liu and G. Chen, *Chem. Sci.*, 2017, **8**, 7180; (c) J. Qurban, M. Elsherbini, H. Alharbia and T. Wirth, *Chem. Commun.*, 2019, **55**, 7998; (d) A. Yoshimura, M. T. Shea, C. L. Makitalo, M. E. Jarvi, G. T. Rohde, A. Saito, M. S. Yusubov and V. V. Zhdankin, *Beilstein J. Org. Chem.*, 2018, **14**, 1016; (e) Y. Wang, H. Yuan, H. Lu and W.-H. Zheng, *Org. Lett.*, 2018, **20**, 2555.
- 4 Z. Begum, G. Bhavani, B. Sridhar and B. V. S. Reddy, *Synthesis*, 2018, **50**, 4089.
- 5 P. Ajda, J. Markus, S. Stojan, Z. Marko, I. Jernej and J. A. Gladysz, *J. Org. Chem.*, 2009, **74**, 3133.
- 6 J. Hu, B. Xing and C. Ni, *Angew. Chem., Int. Ed.*, 2018, **57**, 9896.
- 7 J. L. Dektar and N. P. Hacker, *J. Org. Chem.*, 1990, **55**, 639.
- 8 (a) S. Kyrill, K. Raffael and T. Antonio, *J. Org. Chem.*, 2010, **40**, 7678; (b) S. Kawamura, D. Sekine and M. Sodeoka, *J. Fluorine Chem.*, 2017, **203**, 115; (c) E. Patrick, G. Sebastian and T. Antonio, *Chem.–Eur. J.*, 2010, **12**, 2579.
- 9 (a) J. Gallos, A. Varvoglis and N. W. Alcock, *J. Chem. Soc., Perkin Trans. 1*, 1985, **1985**, 757; (b) T. Dohi, T. Uchiyama, D. Yamashita, N. Washimi and Y. Kita, *Tetrahedron Lett.*, 2011, **52**, 2212.
- 10 P. J. Stang, B. L. Williamson and V. V. Zhdankin, *J. Am. Chem. Soc.*, 1991, **113**, 5870.
- 11 Y.-D. Yang, A. Azuma, E. Tokunaga, M. Yamasaki and N. Shibata, *J. Am. Chem. Soc.*, 2014, **44**, 8782.
- 12 (a) S. V. Kohlhepp and T. Gulder, *Chem. Soc. Rev.*, 2016, **45**, 6270; (b) T. Hokamp, L. Mollari, L. C. Wilkins, R. L. Melen and T. Wirth, *Angew. Chem., Int. Ed.*, 2018, **57**, 8306; (c) M. Bedin, A. Karim, M. Reitti, A. C. C. Carlsson, F. Topic, M. Cetina, F. F. Pan, V. Havel, F. Al-Ameri, V. Sindelar, K. Rissanen, J. Grafenstein and M. Erdélyi, *Chem. Sci.*, 2015, **6**, 3746; (d) W. C. Agosta, *Tetrahedron Lett.*, 1965, **6**, 2681.
- 13 P. J. Stevenson, A. B. Treacy and M. Nieuwenhuyzen, *J. Chem. Soc., Perkin Trans. 2*, 1997, 589.
- 14 D. B. Dess and J. C. Martin, *J. Org. Chem.*, 1983, **15**, 4155.
- 15 S. Hara, M. Monoi, R. Umemura and C. Fuse, *Tetrahedron*, 2012, **68**, 10145.
- 16 W. Breuer and H. J. Frohn, *J. Fluorine Chem.*, 1987, **34**, 443.
- 17 I. A. Mironova, P. S. Postnikov, R. Y. Yusubova, A. Yoshimura, T. Wirth, V. V. Zhdankin, V. N. Nemykin and M. S. Yusubov, *Beilstein J. Org. Chem.*, 2018, **14**, 1854.
- 18 T. Birchall, R. D. Myers, H. D. Waard and G. J. Schrobilgen, *Inorg. Chem.*, 1982, **21**, 1068.
- 19 A. R. Katritzky, J. K. Gallos and H. D. Durst, *Magn. Reson. Chem.*, 1989, **27**, 815.
- 20 F. M. Beringer and P. Bodlaender, *J. Org. Chem.*, 1968, **33**, 2981.
- 21 N. S. Zefirov, V. V. Zhdankin, V. V. Dan'kov and A. S. Koz'min, *J. Org. Chem. USSR*, 1984, **20**, 401.
- 22 (a) D. H. R. Barton and D. Crich, *Tetrahedron*, 1985, **41**, 4359; (b) R. Gleiter and G. Mueller, *J. Org. Chem.*, 1988, **53**, 3912; (c) T. Iida, S. Nishida, F. C. Chang, T. Niwa, J. Goto and T. Nambara, *Chem. Pharm. Bull.*, 1993, **41**, 763.
- 23 H. Künzer, G. Sauer and R. Wiechert, *Tetrahedron*, 1989, **45**, 6409.
- 24 (a) N. Soldatova, P. Postnikov, A. A. Troyan, A. Yoshimura, M. S. Yusubov and V. V. Zhdankin, *Tetrahedron Lett.*, 2016, **57**, 4254; (b) J. G. Sharefkin and H. Saltzman, *Org. Synth.*, 1963, **43**, 65; (c) R. I. Davidson and P. J. Kropp, *J. Org. Chem.*, 1982, **47**, 1904; (d) N. Taneja and R. K. Peddinti, *Tetrahedron Lett.*, 2016, **57**, 3958; (e) A. Bravo, F. Fontana, G. Fronza, F. Minisci and A. Serri, *Tetrahedron Lett.*, 1995, **36**, 6945; (f) A. Watanabe, K. Miyamoto, T. Okada, T. Asawa and M. Uchiyama, *J. Org. Chem.*, 2018, **83**, 14262; (g) M. S. Yusubov, A. A. Zagulyaeva and V. V. Zhdankin, *Chem.–Eur. J.*, 2009, **15**, 11091.
- 25 (a) R. Bell and K. J. Morgan, *J. Chem. Soc.*, 1960, **1960**, 1209; (b) M. S. Yusubov, K. W. Chi, J. Y. Park, R. Karimov and V. V. Zhdankin, *Tetrahedron Lett.*, 2006, **47**, 6305; (c) A. A. Mironova, V. V. Orda, L. M. Yagupolskii and I. I. Maletina, *Synthesis*, 1983, **1983**, 456; (d) L. Troiangautier, J. D. Winter, P. Gerbaux and C. Moucheron, *J. Org. Chem.*, 2013, **78**, 11096.
- 26 A. Maity, S.-M. Hyun, A. K. Wortman and D. C. Powers, *Angew. Chem., Int. Ed.*, 2018, **57**, 7205.
- 27 (a) Compound **1** tends to decompose into *o*-nitroiodobenzene if stored in air at room temperature. It is necessary to have compound **1** stored under a N₂ atmosphere and at lower temperature (<3 °C); (b) It is worth noting that compound **1** is relatively stable in MeOH, as the use of MeOH/CH₂Cl₂ for column purification does not bring about any obvious decomposition. We tried to dissolve compound **1** in ethanol, *p*-methoxybenzyl alcohol, and *p*-chlorophenylethanol. However, the poor solubility of **1** allowed it to be well stored in these alcoholic solvents at room temperature for more than one day. However, an obvious decomposition of compound **1** into *o*-nitroiodobenzene was observed if it was dissolved in benzyl alcohol and stirred for 10 minutes at room temperature.
- 28 M. S. Yusubov, D. Y. Svitich, A. Yoshimura, V. N. Nemykin and V. V. Zhdankin, *Chem. Commun.*, 2013, **49**, 11269.



- 29 V. A. Nikiforov, V. S. Karavan, S. A. Miltsov, S. I. Selivanov, E. Kolehmainen, E. Wegelius and M. Nissinen, *ARKIVOC*, 2003, **6**, 191.
- 30 F. Neese, *Wiley Interdiscip. Rev.: Comput. Mol. Sci.*, 2012, **2**, 73.
- 31 (a) T. Lu and F. Chen, *J. Comput. Chem.*, 2012, **33**, 580; (b) W. Humphrey, A. Dalke and K. Schulten, *J. Mol. Graphics*, 1996, **14**, 33.
- 32 We carried out structural remodeling of all-iodine(III) and all-iodine(V) agents and performed DFT calculations. The results indicated that the values of ρ_{bcip} and Mayer bond order of the $\text{I}_2 \cdots \text{O}_3$ bond of the mixed valent agent molecule **1** were significantly higher than those of all-iodine(III) and all-iodine(V) agents. Therefore, it could exist in the unusual mixed valent form **1**. Please see ESI, Fig. S2† for details.
- 33 (a) I. Tellitu and E. Dominguez, *Synlett*, 2012, **23**, 2165; (b) W. Thomas, *Angew. Chem., Int. Ed.*, 2005, **36**, 3656; (c) E. A. Merritt and B. Olofsson, *Angew. Chem., Int. Ed.*, 2009, **48**, 9052.
- 34 (a) T. W. Miller, E. W. Tristram and F. J. Wolf, *J. Antibiot.*, 1971, **24**, 48; (b) E. O. Stapley, D. Hendlin, M. Jackson, A. K. Miller, S. Hernandez and J. M. Mata, *J. Antibiot.*, 1971, **24**, 42.
- 35 (a) D. F. Morrow, M. E. Butler and E. C. Y. Huang, *J. Org. Chem.*, 1965, **30**, 579; (b) D. J. Cram and M. J. Hatch, *J. Am. Chem. Soc.*, 1953, **75**, 33; (c) P. W. Neber and A. V. Friedolsheim, *Justus Liebigs Ann. Chem.*, 1926, **449**, 109; (d) P. W. Neber and A. Uber, *Justus Liebigs Ann. Chem.*, 1928, **467**, 52.
- 36 G. Smolinsky, *J. Org. Chem.*, 1962, **27**, 3557.
- 37 (a) J. C. Guillemain, J. M. Denis, M. C. Lasne and J. L. Ripoll, *Tetrahedron*, 1988, **4**, 4447; (b) F. A. Davis, G. V. Reddy and H. Liu, *J. Am. Chem. Soc.*, 1995, **117**, 3651; (c) R. G. Kostyanovskii, G. K. Kadorkina, S. V. Varlamov, I. I. Chervin and I. K. A. Romero-Maldonado, *Chem. Heterocycl. Compd.*, 1988, **24**, 387.
- 38 L. Gentilucci, Y. Grijzen, L. Thijs and B. Zwanenburg, *Tetrahedron Lett.*, 1995, **36**, 4665.
- 39 R. R. Sauers, L. M. Hadel, A. A. Scimone and T. A. Stevenson, *J. Org. Chem.*, 1990, **55**, 4011.
- 40 (a) Y. Zhang, X. Zhao, C. Zhuang, S. Wang, D. Zhang-Negrerie and Y. Du, *Adv. Synth. Catal.*, 2018, **360**, 2107; (b) J. Sun, X. Zhen, H. Ge, G. Zhang, X. An and Y. Du, *Beilstein J. Org. Chem.*, 2018, **14**, 1452.
- 41 (a) F. Palacios, A. M. O. de Retana, E. M. de Marigorta and J. M. de los Santos, *Eur. J. Org. Chem.*, 2001, **2001**, 2401; (b) F. Palacios, A. M. O. de Retana, E. M. de Marigorta and J. M. de los Santos, *Org. Prep. Proced. Int.*, 2002, **34**, 219.
- 42 X. X. Li, Y. F. Du, Z. D. Liang, X. K. Li, Y. Pan and K. Zhao, *Org. Lett.*, 2009, **11**, 2643.
- 43 X. Q. Sun, Y. R. Lyu, D. Zhang-Negrerie, Y. F. Du and K. Zhao, *Org. Lett.*, 2013, **15**, 6222.
- 44 C. E. Salomon, D. H. Williams and D. J. Faulkner, *J. Nat. Prod.*, 1995, **58**, 1463.
- 45 We also investigated other commonly used iodine(III) and iodine(V) reagents including PIDA, PIFA, PhIO, IBX, DMP and PhIO₂ to see if they are also effective for this azirination process. The results implied that the reactivity of iodine(III/V) **1** is superior to that of the other iodine(III) or (IV) reagents. See the ESI† for details.
- 46 An alternative mechanistic pathway involving the formation of a C–I intermediate was also provided in the ESI.† It is worth noting that the DFT calculations supported a mechanistic pathway involving the formation of an I–N intermediate. See the ESI† for details.
- 47 T. Baba, S. Takahashi, Y. Kambara, A. Yoshimura, V. N. Nemykin, V. V. Zhdarkin and A. Saito, *Adv. Synth. Catal.*, 2017, **359**, 3860.

