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

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The reaction of o-nitroiodoxybenzene and mCPBA 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 2H-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. On one hand, organic chemists are making use of the existing hypervalent iodine oxidants to discover new organic reactions. 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. 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(tri-furoacetate) (PIFA), iodosylbenzene (PhIO), [hydroxyl(tosyloxy) iodo]benzene (HTIB, Koser reagent), PhICl2, Togni’s reagents, PhIO, cyano(trifluoromethyl)sulfonylox)iodobenzene (Stang’s reagent), 1-phenyl-2-(phenyl-3-iodaneylidene)-2-[(trifluoromethyl)sulfonyl]ethan-1-one (Shibata reagent II), iodosodialcetone, etc. The more widely studied hypervalent iodine(III/V) reagents mainly include 2-iodoxybenzoic acid (IBX), Dess–Martin periodinane (DMP), Hara reagent, pentafluorophenylidone tetrafluoride (PFITF), 2-iodoxybenzenesulfonic acid (IBS), iodine pentafluoride, iodosylbenzene, and diaryl iodosylsulfonyl inorganic salts. Togni’s reagents, μ-oxobis(trifluoroacetoxyiodobenzene) (μ-oxo BTI), Togni’s reagents, μ-oxobis(trifluoroacetoxyiodobenzene) (μ-oxo BTI), cyanotri(1-fluoromethylsulfonyl)oxy)iodobenzene (Stang’s reagent), 1-phenyl-2-(phenyl-3-iodaneylidene)-2-[(trifluoromethyl)sulfonyl]ethan-1-one (Shibata reagent II), iodosodialcetone, etc.

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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. 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 mCPBA in acetic acid at 60 °C for 3 h, a hypervalent iodine(III/V) oxidant 1,27 rather than the expected o-nitroiodobenzene, 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) atom17,28 (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_BCP and the Mayer bond order of I_2–O_3 bonds in the hypervalent iodine molecule with or without nitro groups was summarized, which showed that the I_2–O_3 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 I_2–O_3 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 pseudoctahedral 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 further optimized.
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⋯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(ω/ν) compound 1 (Fig. 4). First, the reaction of o-nitroiodobenzene with mCPBA afforded the iodine(ω) 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(ω) species B. Next, the intermolecular reaction between two molecules of B led to the formation of the iodine(ω/ν) intermediate C. Similarly, assisted by the “free” adjacent nitro group, C was further oxidized by mCPBA to give the iodine(ω/ν) intermediate D. Finally, D was converted to the titular iodine(ω/ν) 1 via the removal of one proton.

Next, we were interested to investigate the applicability of this newly discovered hypervalent iodine(ω/ν) oxidant. As our research interest focuses on constructing heterocyclic skeletons using various hypervalent iodine regents,18,33 we first investigated whether this novel hypervalent iodine(ω/ν) oxidant could be used to realize conversions that are not readily achievable by other hypervalent iodine reagents.

2H-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 azirination, leading to the formation of 2H-azirine...
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(m/n) 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 mCPBA preferentially acts on the model substrate (Table 1, entry 12). Further tuning of the reaction by reacting α-nitroiodobenzene with mCPBA 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(m/n) 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

![Fig. 5 Existing methods for the construction of 2H-azirine skeletons mediated by hypervalent iodine reagents.](image)

Table 1  Optimization of the reaction conditions

| Entry | Oxidant (equiv.) | Additive | Solvent | Temp. (℃) | Time [h] | Yield [%] |
|-------|------------------|----------|---------|-----------|----------|-----------|
| 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*   | 1 (0.7)          | BF₃·Et₂O| DCE     | 60        | 3        | 76        |
| 11*   | 1 (0.7)          | TBSOTf   | DCE     | 60        | 3        | 73        |
| 12*   | 1 (0.7)          | None     | AcOH    | 60        | 2        | N.D.      |
| 13*   | 1 (0.7)          | None     | AcOH    | 60        | 5.5      | 26        |

* Reaction conditions: 2a (1.0 mmol), 1 (0.7 mmol), DCE (5 mL), and stirred at 60 °C for 3.5 h. † Isolated yield. ‡ 2a (1.0 mmol), α-nitroiodobenzene (2.0 mmol), mCPBA (2.2 mmol), and AcOH (5 mL). § α-Nitroiodobenzene (2.0 mmol), mCPBA (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. ¶ 2.0 equiv. of the additive was used.
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 2H-azirine product was only afforded in a much lower yield (3p) (Table 2).

Table 2 Synthesis of 2H-azirine derivatives through iodine(m/v) 1-mediated azirination of enamines.

| Substrate | Yield (%) | Reaction Condition |
|-----------|-----------|--------------------|
| 2a        | 80        | DCE, 60 °C, 3.5 h   |
| 2b        | 75        | DCE, 60 °C, 3.5 h   |
| 2c        | 65        | DCE, 60 °C, 3.5 h   |
| 2d        | 66        | DCE, 60 °C, 3.5 h   |
| 2e        | 62        | DCE, 60 °C, 3.5 h   |
| 2f        | 73        | DCE, 60 °C, 3.5 h   |
| 2g        | 59        | DCE, 60 °C, 3.5 h   |
| 2h        | 48        | DCE, 60 °C, 3.5 h   |
| 2i        | 65        | DCE, 60 °C, 3.5 h   |
| 2j        | 32        | DCE, 60 °C, 3.5 h   |

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

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(m/v) oxidant can be applied to the synthesis of 2H-azirines, which cannot be successfully achieved by other traditional hypervalent iodine reagents. Further application of this hypervalent iodine(m/v) oxidant is currently under study in our lab.

Conflicts of interest

The authors declare no conflict of interest.

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