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Synthesis, characterization, and initial reaction study of two new bicyclic hypervalent iodine(III) reagents

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ABSTRACT

The synthesis of two new bicyclic hypervalent iodine(III) reagents **5** and **6** is described along with their corresponding X-ray crystal structures for the first time. A detailed comparison in the bond lengths and bond angles of reported bicyclic hypervalent iodine(III) reagents is also presented. Furthermore, an initial study shows that these two hypervalent iodine(III) reagents could promote the dipeptide coupling reaction.

During the past decades, the chemistry of hypervalent iodine reagents has attracted significant research interest.[1] Various types of hypervalent iodine(III) compounds (λ3-iodanes) have been reported and some of them have been applied for diverse useful oxidative transformations due to their high chemoselectivity, mild reaction conditions, and environmentally benign nature. Among these reagents, monocyclic or bicyclic hypervalent iodine(III) compounds represent an especially important class of reagents, which facilitate diverse organic transformations. Monocyclic hypervalent iodine(III) reagents derived from 2-iodobenzoic acid such as 1-(*tert*-butylperoxy)-1,2-benziodoxol-3(1*H*)-one,[2] 1-azido-1,2-benziodoxol-3(1*H*)-one,[3] Togni reagent,[4] and 1-chloro-1,2-benziodoxol-3(1*H*)-one[5] have been well studied and applied in the synthetic chemistry. As for the bicyclic ones, several reagents have also been reported due to their unique structural characters, and examples include (dialkoxy)iodinanes and (dilactone)iodinanes (Fig. 1). In 1982, Martin and co-workers reported the synthesis of dialkoxyiodinanes **1** and **2**, which bore two hexafluoroisopropyl ether rings,[6] and the X-ray analysis of (dialkoxy)iodinane **2** indicated the two five-membered ether rings were not exactly coplanar.[7] However, because of the complicated synthesis routes, there is no report about their synthetic utility. In 1965, Agosta firstly reported the preparation of iodosodilactone **3** and **4**, which were hardly soluble in organic solvent except DMSO;[8] quite recently, the X-ray crystal structure of iodosodilactone **3** was obtained by Zhang and co-workers, and it was found that **3** could

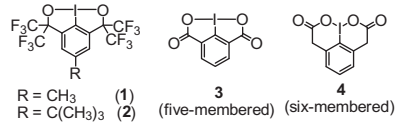

Figure 1. Examples of bicyclic hypervalent iodine(III) reagents.

be functioned as an efficient coupling reagent to promote the direct esterification, direct amidation, and peptide coupling without racemization.[9]

As the continuous research in bicyclic hypervalent iodine reagents, herein, we report the synthesis of two new types of bicyclic hypervalent iodine(III) reagents (Fig. 2): one is the (dialkoxy)iodinane **5** bearing two symmetric isopropyl ether rings; the other is the lactone-ether-mixed iodinane **6**, including a five-membered ether ring and a five-membered lactone ring. These two reagents are readily accessed from the commercially available materials, and both of their X-ray structures are disclosed for the first time.

The synthesis route for iodinane **5** began with the esterification of the commercially available 2-iodoisophthalic acid (**7**), which gave dimethyl 2-iodoisophthalate (**8**) in 90% yield. When subject-

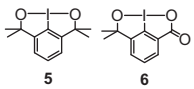

Figure 2. Two new kinds of bicyclic hypervalent iodine(III) reagents.

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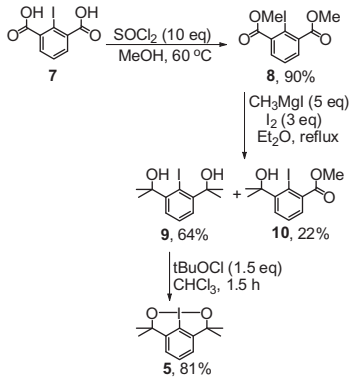
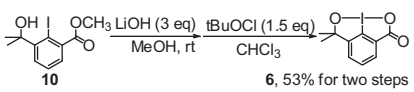


Scheme 1. Synthesis of iodinane **5**.

ing **8** to the conventional protocol for the preparation of tertiary alcohol,[10] the reaction of **8** with methyl Grignard reagent resulted in the loss of the iodine atom in the diol product. Therefore, the additional molecular iodine was required to trap the generated phenyl cation. The desired diol **9** was produced in 64% yield, along with a minor product, methyl 3-(2-hydroxypropan-2-yl)-2-iodobenzoate (**10**),[11] which could serve as the precursor of iodinane **6**. After the diol **9** reacted with *tert*-butyl hypochlorite (*t*BuOCl), the (dialkoxy)iodinane **5** was afforded in 81% yield (Scheme 1).[12] Iodinane **5** is a stable compound, which could be stored for several months at room temperature without any detectable decomposition. Starting from the benzoate **10**, the other bicyclic iodinane **6** could be readily accessed after hydrolysis with LiOH followed by the oxidation with *t*BuOCl (Scheme 2).[13]

These two bicyclic hypervalent iodine(III) compounds are identified on the basis of NMR spectroscopic data, high resolution mass spectrometry, and single crystal X-ray analysis. ^{13}C NMR analysis indicated a downfield shift of the signal for the carbon atom attached to the iodine atom: the shift from δ 94.2 ppm to δ 105.5 ppm in the iodinane **5**, and the shift from δ 90.7 ppm to δ 115.2 ppm in the iodinane **6**, which are consistent with what is observed in other hypervalent iodine(III) compounds.[14] It was noted that there was a 10-ppm motion to the downfield in the bicyclic hypervalent iodine(III) compounds when an ether ring is replaced by a lactone ring (Fig. 3).

Both of these two bicyclic iodinanes have good solubility in commonly organic solvents such as dichloromethane (**5**, 4 mg/mL; **6**, 2.8 mg/mL) and ethyl acetate (**5**, 4.5 mg/mL; **6**, 4.4 mg/mL). The single crystal of iodinane **5** was grown from the mixed solvent of dichloromethane and ethyl acetate, and the single crystal of iodinane **6** was obtained in the solvent of dichloromethane. As is observed in iodosodilactone **3**, these two crystal structures have roughly coplanar geometry. For the structure of **5** (Fig. 4), the five-membered rings are slightly distorted from planarity (torsion angles O1–I1–C1–C2 = 9.27(15)°, O2–I1–C1–C6 = 8.10(16)°); when one of the ether rings is replaced by the lactone ring, just as the structure of iodinane **6** (Fig. 5), the lactone ring bends more slightly (torsion angle O1–I1–C1–C6 = 8.77(19)°, O2–I1–C1–C2 = 2.67(19)°). And, as for the iodosodilactone **3** bearing two lactone rings, all of the lactone atoms are almost coplanar (torsion angles 0.4(4)° and 0.5(4)° respectively).



Scheme 2. Synthesis of iodinane **6**.

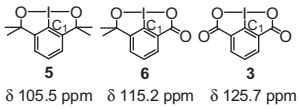


Figure 3. NMR signals of the carbon atom attached to the iodine atom.

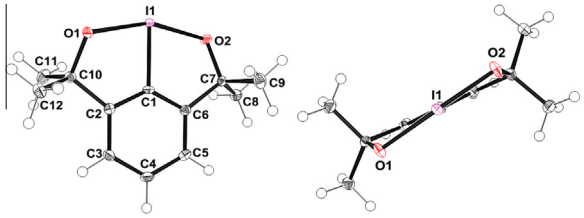


Figure 4. X-ray crystal structure of iodinane **5**.

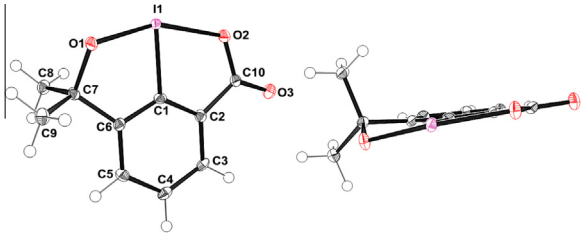
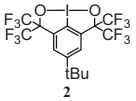
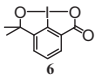
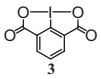


Figure 5. X-ray crystal structure of iodinane **6**.

Table 1
Selected intramolecular bond lengths and bond angles of bicyclic hypervalent iodine(III) reagents

Entry	Structure	O–I–O angle/°	I–O bond length/Å	Ref.
1		158.2(1)	2.113(3) 2.077(3)	7
2		157.46(6)	2.0919(15) 2.0994(15)	This work
3		156.28(9)	2.047(2) 2.212(3)	This work
4		155.21(14)	2.126(4) 2.141(4)	9

The O–I–O angle is also an important parameter in the structural analysis of hypervalent iodine reagents. To give a clear comparison, the O–I–O angles of existing bicyclic hypervalent iodine(III) reagents are listed in Table 1. A slightly greater deviation from 180° is found when all the fluorine atoms are replaced by hydrogen atoms (Table 1, entry 1 vs entry 2). The change of ring system from an ester ring to a lactone ring also affects the O–I–O angle, which becomes smaller when the lactone ring is introduced (entry 2 vs entry 3; entry 3 vs entry 4).

Another structural parameter, the O–I bond lengths of iodinane **5** and **6**, are also revealed according to the X-ray analysis (Table 1). Compared with bicyclic iodinane **2**, the intramolecular I–O bonds in the compound **5** are more equal (entry 1 vs entry 2). And, introducing a lactone ring would break this balance. For example, the intramolecular I–O bond length in the lactone ring of compound **6** is 2.212(3) Å, which is longer than the I–O bond length in the ether ring (2.074(2) Å). A comparison of the intramolecular I–O

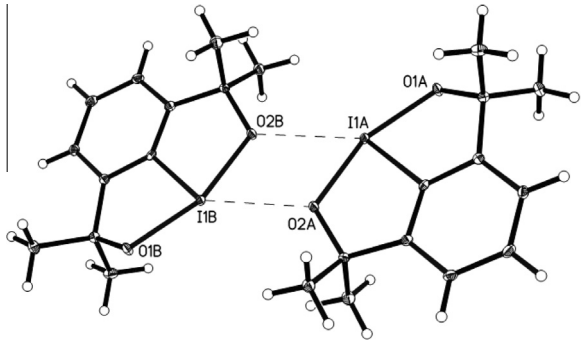


Figure 6. Intermolecular interaction between **5** and its neighboring molecule.

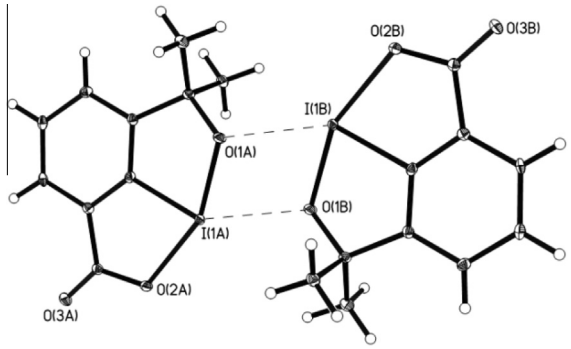


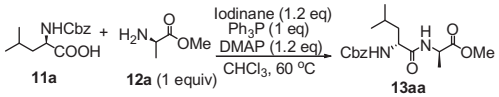
Figure 7. Intermolecular interaction between **6** and its neighboring molecule.

bonds with the known bicyclic hypervalent iodine(III) reagents is given in Table 1. The I–O bond lengths in the five-membered rings, regardless of an ether ring or a lactone ring, are generally found in the range of 2.07 Å to 2.22 Å.

Both of the molecules **5** and **6** are aggregated in the solid state to form dimmers held together by intermolecular I···O secondary bonds, which is consistent with what is observed in other hypervalent iodine compounds.[7] In the iodinane **5** (Fig. 6), the distance between the iodine atom and its nearest oxygen atom of the neighbor molecule (I···O 2.89 Å) is shorter than the intermolecular I···O secondary bond in the iodinane **2** (I···O 3.00 Å). As for iodinane **6** (Fig. 7), although two ring types exist, only one type of the intermolecular I···O secondary bond, linking the iodine atom and the oxygen atom in the ether ring of the neighbor molecule (I···O 2.79 Å), is observed, while the bond distance (3.81 Å) between the iodine atom and the oxygen atom in the nearest lactone ring is out of the sum of van der Waals radii (3.5 Å).[15] However, when both of two ether rings were replaced by the lactone rings, there are two types of intermolecular secondary bonding found in the iodosodilactone **3**. One is the interaction between the iodine atom and the oxygen atom in the cycle of a neighboring lactone ring (I···O 3.17 Å), and the other secondary bond is between the iodine atom and the carbonyl oxygen of the neighboring lactone ring (I···O 2.84 Å). Accordingly, the molecules of iodosodilactone **3** are linked together via two I–O secondary bonds and hydrogen bonds to form a dense network, which led to the poor solubility different from iodinane **5** and **6**.

Since the iodosodilactone **3** could function as a coupling reagent for dipeptide coupling reaction,[9] compound **5** and **6** were also examined for the dipeptide coupling reaction by using N-Cbz-leucine and glycine methyl ester under the standard conditions (1.2 equiv of oxidant, 1 equiv of Ph_3P, 1.2 equiv of DMAP, $CHCl_3$, 60 °C). All of these three bicyclic reagents could promote the dipeptide coupling reaction, while the iodinane **5** and **6** were not as efficient as iodosodilactone **3** (Table 2, entries 2 and 3 vs entry 1). Even though the reaction time was prolonged to 24 h, the starting materials were still not consumed. Furthermore, the reaction was also tested at higher temperature, while no better results were obtained (entries 4 and 5). Compared with iodosodilactone **3**, the iodine center was more electron rich in compound **5** or **6**, which may cause their weak reactivity for the present transformation. It was noted that there was no detectable racemization in these coupling reactions mediated by three bicyclic hypervalent iodine(III) reagents.

Table 2
Synthesis of dipeptide Z-L-Leu-L-Ala-OMe using three bicyclic hypervalent iodine(III) reagents[a]



Entry	Iodinane	Yield[b] (%)	Time (h)	D/DL[c] (%)
1	3	84	6	<0.1
2	6	70 (86)[d]	24	<0.1
3	5	58 (80)[d]	24	<0.1
4[e]	6	69 (88)[d]	10	<0.1
5[e]	5	55 (82)[d]	10	<0.1

[a] Reaction conditions: **11a** (1.0 mmol), **12a** (1.0 mmol), Iodinane (1.2 mmol), DMAP (1.2 mmol), Ph_3P (1.0 mmol), in $CHCl_3$ (10 mL), 60 °C.
[b] Isolated yield.
[c] The optical purity of products was determined by HPLC.
[d] The data in the parentheses are the chemical yields based on the recovery of **11a**.
[e] The reaction was run at 80 °C in EtOAc.

In conclusion, two new bicyclic hypervalent iodine(III) reagents **5** and **6** have been successfully prepared and characterized by spectroscopy and single crystal X-ray analysis. By the structural comparison with other reported bicyclic hypervalent iodine(III) reagents, the unique structural features of these two iodinanes are disclosed. Furthermore, these two bicyclic hypervalent iodine(III) reagents are readily available and soluble in common organic solvents, rendering them the oxidative potential in organic synthesis. In an initial reactivity study, these two bicyclic reagents can promote the dipeptide coupling reaction without racemization. The further reactivity exploration of two reagents is currently in progress.

Supplementary data

Crystallographic data for the structural analysis of **5** and **6** have been deposited in the Cambridge Crystallographic Data Centre (CCDC No. 959777 and 959973). Copies of this information can be obtained free of charge via www.ccdc.cam.ac.uk.

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.03.034.

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11. To the solution of **8** (1.3 g, 4 mmol) in toluene (10 mL) was added the freshly prepared Methyl Grignard reagent (20 mL) at 100 °C. After the addition was complete, the reaction mixture was stirred at reflux for 1 h. And then the solution of iodine (3 g, 12 mmol) in diethyl ether (15 mL) was added dropwise. The reaction mixture was stirred at reflux for another 15 min, and quenched with satd aqueous $Na_2S_2O_3$ (10 mL) and satd aqueous $NaHCO_3$ (10 mL). The resulted mixture was extracted with EtOAc (3 × 20 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by chromatography (PE/EtOAc, 1:5) to give **9** and **10**. Compound **9**: 64% yield; pale yellow solid; mp 142–144 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.51 (d, 2H, J = 8.0 Hz), 7.26 (t, 1H, J = 8.0 Hz), 3.09 (br s, 2H), 1.84 (s, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 149.8, 127.9, 126.4, 94.2, 75.4, 30.9. Compound **10**: 22% yield; colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.62 (dd, 1H, J = 10.0, 1.6 Hz), 7.23 (t, 1H, J = 10.0 Hz), 7.07 (dd, 1H, J = 10.0, 1.6 Hz), 3.83 (s, 3H), 1.67 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.2, 149.8, 142.7, 128.0, 127.9, 126.5, 90.4, 73.9, 52.6, 29.6.
12. To the solution of **9** (240 mg, 0.75 mmol) in chloroform (8 mL) was added the freshly prepared *t*BuOCl (122 mg, 1.1 mmol). The reaction was stirred at room temperature until **9** was completely consumed. After the solvent was removed in vacuo, the crude product was purified by chromatography to give iodinane **5**. Yield: 81%; white solid; mp: 169–171 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.53 (t, 1H, J = 7.6 Hz), 7.19 (d, 2H, J = 7.6 Hz), 1.46 (s, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 147.7, 132.0, 123.5, 105.5, 75.5, 29.7; IR (neat) ν: 3426, 2967, 1420, 1355, 1208, 1154, 944, 885, 856, 803; HRMS (MALDI) m/z calcd for $C_{12}H_{16}IO_2$ $[M+H]^+$: 319.0189, found: 319.0187.
13. To the solution of compound **10** (160 mg, 0.5 mmol) in anhydrous methanol (5 mL) was added LiOH (36 mg, 1.5 mmol), and the mixture was stirred at room temperature for 24 h. After **10** was completely consumed, the solvent was removed in vacuo, and the solid residue was dissolved in water (5 mL) and extracted with EtOAc (3 × 10 mL). The organic layer was dried over anhydrous Na_2SO_4, concentrated to give a crude acid product, which was used directly for the next step. The crude acid was dissolved in chloroform (5 mL), and the freshly prepared *t*BuOCl (81 mg, 0.75 mmol) was added dropwise. The resulted mixture was stirred at room temperature for 3 h, and then the solvent was removed in vacuo. The crude product was purified by chromatography (PE/EtOAc, 1:5) to give iodinane **6**. Yield: 53%; white solid; mp: 192–194 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.18 (d, 1H, J = 7.2 Hz), 7.76 (t, 1H, J = 7.6 Hz), 7.44 (d, 1H, J = 7.6 Hz), 1.60 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 165.2, 146.8, 133.2, 130.1, 129.4, 128.8, 115.2, 85.4, 29.9; IR (neat) ν: 3384, 3058, 2966, 1668, 1280, 1249, 1199, 1148, 825, 769; HRMS (MALDI) m/z calcd for $C_{10}H_{10}IO_3$ $[M+H]^+$: 304.9669, found: 304.9665.
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