Amination Reactions

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Synthesis and Structure of Hypervalent Iodine(III) Reagents Containing Phthalimidate and Application to Oxidative Amination Reactions

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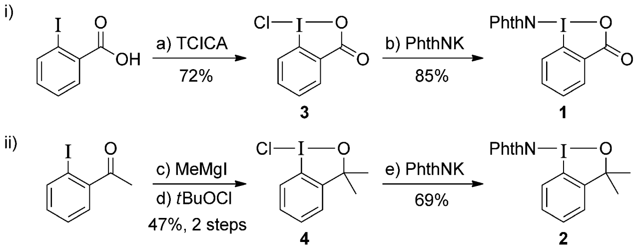
***Abstract:** A new class of hypervalent iodine reagents containing phthalimidate was synthesized, and structurally characterized by X-ray analysis. The benziodoxole-based reagent displays satisfactory solubility in common organic solvents and is reasonably stable in solution as well as in the solid state. The reagent was used for the oxidative amination of the $C(sp^3)$–H bond of N,N-dimethylanilines. In addition, the reagent was also applicable to oxidative amination with rearrangement of trialkylamines as well as enamines that were prepared in situ from secondary amines and aldehydes.*

The incorporation of an amino functional group into an organic molecule by oxidative amination is a powerful strategy for preparing various types of nitrogen-containing compounds, which are promising candidates for use in the synthesis of various biologically active and medicinally important compounds. Recently, hypervalent iodine reagents containing an iodine–nitrogen bond have been reported to be potentially useful for oxidative amination reactions.[1,2] To date, several examples of defined hypervalent iodine reagents containing transferable nitrogen functional groups such as imino, azido, and imido groups have been reported, and they have been used in various oxidative amination reactions. Among them, iminoiodanes (PhI=NTs; Ts = *p*-toluenesulfonyl), a class of compounds that are useful precursors of nitrene in the presence of transition metals, have been the most widely used reagents for the aziridination of alkenes and amination of C–H bonds.[3] Oxidative amination using a hypervalent iodine reagent containing an I–N single bond has received considerable attention in recent decades. In 1994, Zhdankin et al. reported the preparation of isolable azidoiodanes that are stabilized by the formation of five-membered heterocycles, including an iodine(III) center, and demonstrated that they were sufficiently reactive to permit their use in the C–H azidation of dimethylanilines and alkanes.[4–6] Recently, Muñiz and co-workers successfully prepared a new class of hypervalent iodine reagents bearing a bissulfonimide group as a ligand. These compounds have a highly electrophilic iodine(III) center and were applicable for use in the oxidative amination of unsaturated hydrocarbons, including the diamination of alkenes, allylic C–H amination, and the C–H amination of acetylenes.[7] Despite these advances, the use of a hypervalent iodine reagent containing phthalimidate is still very limited, even though it has the potential to introduce a phthalimide moiety into an organic molecule. In 1983, Varvoglis and co-workers synthesized $PhI(NPhth)_2$ (Phth = phthaloyl) by treating $PhI(OCOCF_3)_2$ with potassium phthalimide.[8,9] However, it is thermally stable but undergoes rapid hydrolysis in the presence of moisture in solution, and only a few examples of synthetic applications have been reported so far.[10] Although the formation of *N*-(phenylacetoxyiodo)imido species (PhI(OAc)(NPhth)) was recently proposed for the metal-free oxidative amination of aryl–$C(sp^2)$ and benzylic $C(sp^3)$–H bonds using $PhI(OAc)_2$ with phthalimide, precise structural proof of the intermediate was not obtained.[11] In this context, we recognized that the synthesis of a structurally defined hypervalent iodine reagent containing phthalimidate, which is both stable but reactive under the desired conditions, would be highly desirable for the direct investigation of the reactivity of an iodine(III) reagent containing phthalimidate and for further expanding its synthetic utility. Herein, we report on the synthesis and X-ray structural characterization of benziodoxole-based hypervalent iodine reagents containing phthalimidate, and their use in oxidative amination reactions.

Our initial efforts focused on the synthesis of the hypervalent iodine reagents **1** and **2** (Scheme 1). First, following a known method, chloroiodane **3** was prepared by treating 2-iodobenzoic acid with trichloroisocyanuric acid (TCICA).[12] Subsequently, the reaction of **3** with potassium phthalimide afforded **1** in 85 % yield. In addition, **2** was also synthesized by treating potassium phthalimide with chloroiodane **4**, which was also prepared by a previously reported method.[13] Both **1** and **2** were found to be reasonably stable under ambient



Scheme 1. Syntheses of hypervalent iodine reagents **1** and **2**. a) TCICA, MeCN, 75 °C, 10 min; b) potassium phthalimide, MeCN, RT, 1 h; c) MeMgI, Et_2O, 0 °C to RT, 15 h; then reflux, 1.5 h; d) *t*BuOCl, CH_2Cl_2, 0 °C, 22 h; e) potassium phthalimide, MeCN, RT, 2 h.

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conditions in the solid state and even in solution. Reagent **1** is soluble only in a highly polar solvent such as dimethylsulfoxide, while **2** displayed satisfactory solubility in common organic solvents such as chloroform, dichloromethane, and acetonitrile.[14] Single crystals of **2** suitable for X-ray crystallographic analysis were obtained from a solution of **2** in acetonitrile at ambient temperature. The structural data for **2** clearly revealed that the phthalimidate was bound through its N atom to the hypervalent iodine(III) center, which shows a distorted T-shaped geometry (Figure 1). The length of the I1–N1 bond of 2.197(4) is shorter than that observed in the saccharinylbenziodoxole derivative reported by Zhdankin and co-workers.[15] In the solid state, **2** exists as a monomer without any intermolecular secondary bonding interactions around the iodine center.

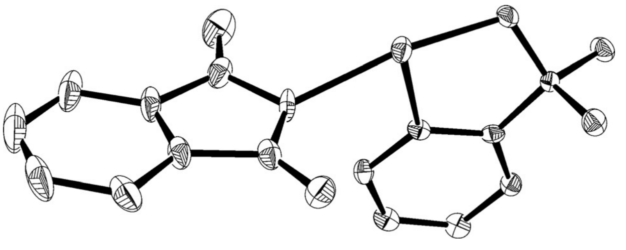
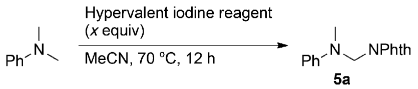


Figure 1. Crystal structure of **2** (hydrogen atoms are omitted for clarity). Thermal ellipsoids are shown at the 30% probability level. Selected bond lengths [Å] and angles [°]: I1-N1 2.197(4), I1-O1 2.064(3), I1-C1 2.113(5), O1-I1-N1 168.04(14); N1-I1-C1 89.13(16), O1-I1-C1 78.91(15), I1-O1-C7 111.1(3).

To illustrate the synthetic utility of these reagents, we investigated the reactivity of **1** and **2** in an oxidative amination reaction (Table 1). When *N*,*N*-dimethylaniline was employed as a model substrate in the reaction with **1** in MeCN at 70 °C, C(sp^3)–H amination occurred to provide **5a** in 62% yield (Table 1, entry 1).[16] Reagent **2** was found to be more efficient than **1**, and **5a** was produced in a high yield when a small excess of **2** was used (Table 1, entries 2 and 3). When the reaction was conducted in the presence of 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO) as a radical inhibitor, the yield of **5a** was dramatically decreased to 13%, thus indicating that the reaction proceeds through a radical pathway involving a one-electron oxidation of the substrate by **2** (Table 1, entry 4).[17] Low yields were obtained when the reaction was performed with $PhI(NPhth)_2$ or a combination of $PhI(OAc)_2$ and phthalimide (Table 1, entries 5 and 6).

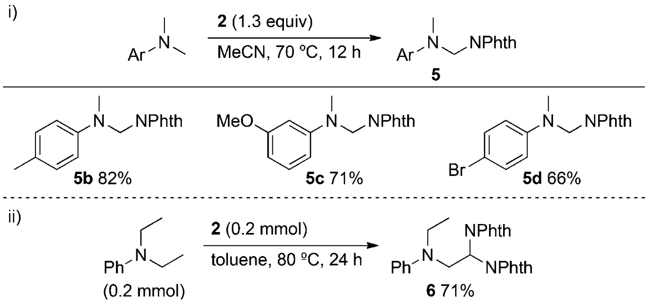
Table 1: Oxidative C–H amination of *N*,*N*-dimethylaniline.[a]



Entry	Hypervalent iodine reagent	Yield [%][b]
1	**1** (1 equiv)	62
2	**2** (1 equiv)	74
3	**2** (1.3 equiv)	83[c]
4[d]	**2** (1.3 equiv)	13
5	$PhI(NPhth)_2$ (1 equiv)	28
6	$PhI(OAc)_2$ (1 equiv) Phthalimide (1 equiv)	38

[a] Reaction conditions: *N*,*N*-dimethylaniline (0.1 mmol), hypervalent iodine reagent (0.1 or 0.13 mmol), MeCN (1 mL), 70 °C, 12 h. [b] Determined by ^1H NMR analysis of crude product using 1,1,2,2-tetrachloroethane as an internal standard. [c] Yield of isolated product. [d] TEMPO (1 equiv) was added.

Oxidative C–H amination using **2** was investigated for a range of *N*,*N*-dialkylaniline derivitives (Scheme 2, reaction i). The reaction of *p*-toluidine afforded the corresponding product **5b** in high yield. A substrate bearing a methoxy group on the phenyl ring also reacted readily, and a bromo substituent was tolerated to give the product **5d**. Interestingly, the use of *N*,*N*-diethylaniline as a substrate for the reaction with **2** in toluene afforded **6**, which has two phthalimide moieties at the β-position to the nitrogen atom (Scheme 2, reaction ii).[18,19]

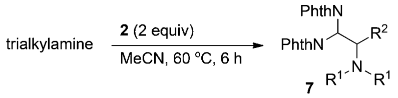


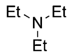
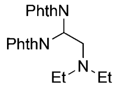
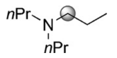
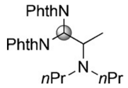
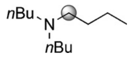
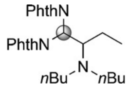
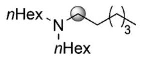
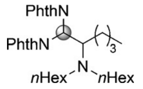
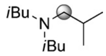
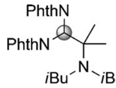
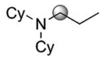
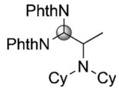
Scheme 2. Oxidative C–H amination of *N*,*N*-dialkylanilines.

To further investigate the applicability of the double imidation reaction to give a product such as **6**, we examined reactions with trialkylamines (Table 2). Treatment of triethylamine with 2 equiv of **2** in acetonitrile at 60 °C for 6 h afforded **7a** containing two phthalimide moieties in 36% yield (Table 2, entry 1), similar to the result of the reaction of *N*,*N*-diethylaniline described above. The reaction of tri-*n*-propylamine provided **7b**, the structure of which was confirmed by NMR spectroscopy and X-ray structural analysis.[20] This result clearly indicates that the reaction includes a rearrangement step (Table 2, entry 2).[18,21] Moreover, the same transformation was observed in reactions using trialkylamines that have a longer alkyl chain (Table 2, entries 3 and 4). The more sterically hindered triisobutylamine also underwent the rearrangement to provide the corresponding amine **7e** with a quarternary carbon atom, albeit in low yield (Table 2, entry 5). The reaction of dicyclohexylpropylamine proceeded selectively at the propyl chain to give **7f** (Table 2, entry 6). Although Tian and Loh reported the copper-catalyzed oxidative rearrangement of tertiary amines under aerobic conditions to provide α-amino acetals,[22] our oxidative amination with rearrangement proceeded under metal-free conditions to provide products that contain amino functional groups.

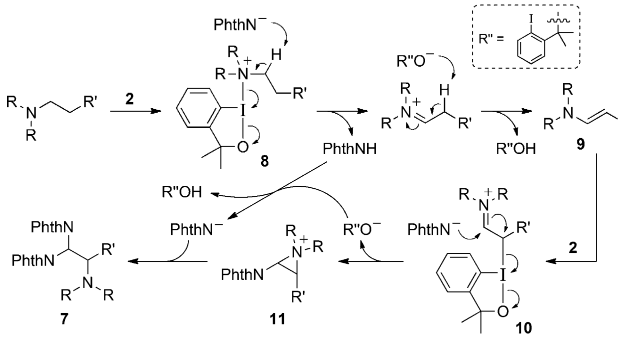
In this oxidative amination with rearrangement of trialkylamines, an enamine that is generated in situ by the oxidation of an amine was predicted to be a reactive intermediate according to a previous report.[22] In addition,

Table 2: Oxidative amination with rearrangement of trialkylamines.[a]



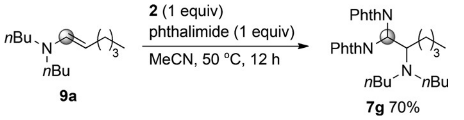
Entry	Trialkylamine	Product		Yield [%][b]
1			**7a**	36
2			**7b**	59
3			**7c**	52
4			**7d**	58
5			**7e**	20
6[c]			**7f**	38

[a] Reaction conditions: trialkylamine (0.1 mmol), **2** (0.2 mmol), MeCN (1 mL), 60 °C, 6 h. [b] Yield of isolated product. [c] The reaction was conducted at 70 °C.

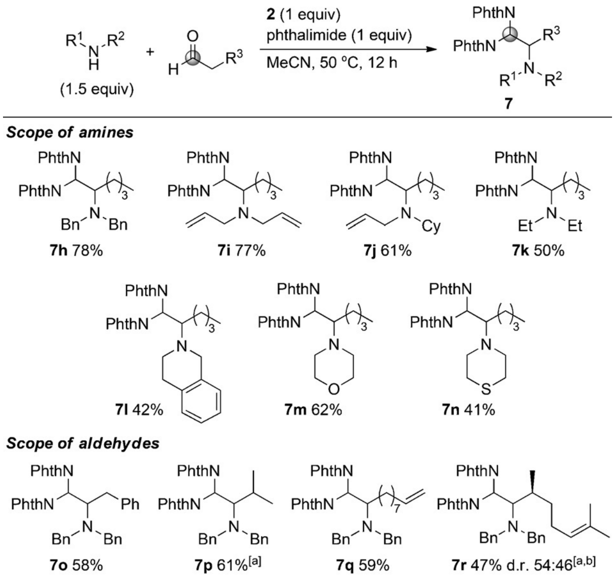


Scheme 3. Plausible reaction mechanism.

when the reaction of tri-*n*-propylamine with **2** was examined in the presence of TEMPO (a radical inhibitor) the yield of **7b** remained essentially the same, thereby indicating that the reaction does not involve the formation of a radical intermediate.[20] A proposed mechanism for the reaction is depicted in Scheme 3. The reaction is initiated by an attack of an amine on an electrophilic iodine center of **2** to form the ammonium intermediate **8**. Proton abstraction by the resulting phthalimidate gives an imminium ion, which is followed by proton abstraction by an alkoxide ($R''O^-$) to provide enamine **9**.[23] Subsequently, the enamine **9** participates in the reaction with **2** to form the C–I bond.[24] The resulting iminium **10** reacts with the phthalimidate, and a subsequent intramolecular cyclization with reductive elimination of the iodobenzene derivative affords the aziridinium intermediate **11**, which would lead to the rearrangement product. Finally, the regioselective opening of **11** probably occurred through the formation of an *N*-phthaloyliminium ion followed by the nucleophilic attack of a phthalimidate, to afford the product **7**.[25] Indeed, when the enamine **9a** (which was prepared separately by reacting hexanal with di-*n*-butylamine) was treated with 1 equiv of **2** and 1 equiv of phthalimide as an additional aminating reagent in MeCN at 50 °C, the corresponding product **7g** was produced in 70 % yield (Scheme 4). This result provides strong support for the mechanism shown in Scheme 3.



Scheme 4. Reaction of an enamine with **2**.



Scheme 5. Oxidative amination with rearrangement of enamines generated in situ from amines and aldehydes. Unless otherwise noted, reaction conditions: amines (0.15 mmol), aldehydes (0.1 mmol), **2** (0.1 mmol), phthalimide (0.1 mmol), MeCN (1 mL), 50 °C, 12 h. Yields are for the isolated products. [a] The reaction was conducted at 60 °C. [b] The d.r. value was determined by ^{1}H NMR analysis.

The oxidative amination was also applicable to reactions in which various types of secondary amines and aldehydes were used as starting materials. These reactions involve the formation of an enamine in situ (Scheme 5).[26] When the reaction of dibenzylamine, hexanal, and **2** in the presence of phthalimide was examined, the corresponding product **7h** was obtained in 78 % yield.[18,27] The use of diallylamine and a bulkier allylcyclohexylamine also provided the corresponding products (**7i** and **7j**) in 77 % and 61 % yield, respectively. A simple aliphatic amine, diethylamine, resulted in a moderate yield of **7k**. Moreover, cyclic secondary amines such as 1,2,3,4-tetrahydroisoquinoline, morpholine, and thiomorpholine were suitable for this transformation to give the products (**7l**–**7n**, respectively) in moderate to good yields.[28] We further investigated the scope of this reaction by using a series of aldehydes.[29] The aldehyde containing a phenyl group at the terminal position provided **7o**, while a β-branched aldehyde provided **7p** in good yield at a higher temperature. The substrate bearing a double bond was well-tolerated in this oxidative rearrangement. In addition, (*S*)-(−)-β-citronellol, derived from natural sources, was also smoothly converted into the product **7r** as a diastereomeric mixture.

In conclusion, novel benziodoxole-based hypervalent iodine reagents containing phthalimidate were prepared and were found to be reasonably stable under ambient conditions in both the solid and solution states. The use of these reagents allowed oxidative amination reactions, including the C(sp^3)−H amination of *N*,*N*-dimethylanilines and oxidative amination with the rearrangement of trialkylamines as well as enamines prepared in situ from secondary amines and aldehydes, to be carried out. Further investigations focused on expanding the utility of the iodine reagents is currently in progress.

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Keywords: amination · amines · hypervalent iodine reagents · phthalimides · rearrangement

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[14] Solubility of **2**: 242 $mg\,mL^{-1}$ in chloroform, 115 $mg\,mL^{-1}$ in dichloromethane, and 6 $mg\,mL^{-1}$ (21 $mg\,mL^{-1}$ at 50 °C) in acetonitrile.

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[18] For details of the optimization of the reaction conditions, see the Supporting Information.

[19] When the reaction of *N*-ethyl-*N*-methylaniline with 2 equiv of **2** was conducted for a competition experiment, the monoaminated product (generated by the reaction at methyl group) and the diaminated product (generated by the reaction at ethyl group)

were obtained in 51% and 7% yields, respectively. See the Supporting Information for details.
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[27] When the reaction was conducted in the presence of TEMPO, the yield of **7h** remained essentially the same. See the Supporting Information for details.
[28] When the reaction using trimethylsilyl-protected diphenylprolinol was carried out, the corresponding product was obtained in 53% yield in a diastereomeric ratio of 86:14. See the Supporting Information for details.
[29] Reactions using α-branched aldehydes, such as isobutyraldehyde and cyclohexanecarbaldehyde, failed to provide the desired products.

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