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Synthesis of Spirooxindoles from *N*-Arylamide Derivatives via Oxidative C(sp^2)−C(sp^3) Bond Formation Mediated by PhI(OMe)$_2$ Generated in Situ

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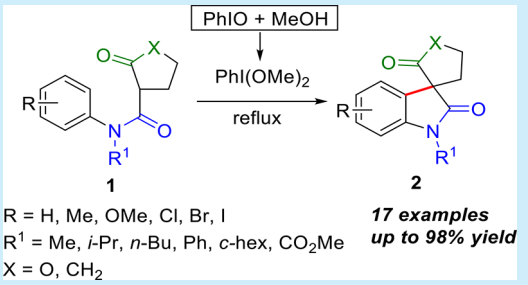
Supporting Information

ABSTRACT: A class of novel spirooxindole compounds (**2**) were readily synthesized, in a metal-free environment, from *N*-arylamide derivatives (**1**) via intramolecular oxidative cyclization. Direct oxidative C(sp^2)−C(sp^3) bond formation was realized with the least-studied PhI(OMe)$_2$ as an oxidant, formed in situ from the reaction between PhIO and MeOH.



The past several decades have witnessed rapid development of hypervalent iodine chemistry, with many hypervalent iodine (iodine(III), iodine(V)) reagents being developed and applied in various synthetic transformations.[1] Among them, those where the I atom bears two carboxylate substituents, in addition to the aryl group, e.g., phenyliodine(III) *bis*(trifluoroacetate) (PIFA), phenyliodine(III) diacetate (PIDA), and their derivatives, have been extensively studied.[2] Besides, iodosobenzene (PhIO), Koser's reagent, aryliodoodium salts, and PhIX$_2$ (X = F, Cl, Br, N$_3$) types of hypervalent iodine(III) reagents[3−6] have also been extensively investigated, with their particular favorable reaction systems being identified. On-going research in the field of hypervalent iodine oxidants including utilizing Togni's reagent,[7] Stang's reagent,[8] and iminoiodanes (Figure 1).[9] Searching for such new nonmetal oxidants and establishing new, efficient applications are, obviously, highly desirable activities.

It was reported by Hill[10] in 1982 that PhIO could be converted to phenyliodine(III) dimethoxide (PhI(OMe)$_2$) upon treatment with MeOH, likely via solvolysis. However, virtually no further report was found in the literature involving PhI(OMe)$_2$ nor the PhIO−MeOH system since then. As a hypervalent reagent, PhI(OMe)$_2$ demonstrates the potential to enable certain organic transformations playing the role of an oxidant. As a continuation of our research interest in discovering new reactions for constructing novel organic compounds mediated by hypervalent iodine reagents,[11a−c,12a−c] we set out to explore such possibilities in PhI(OMe)$_2$. We assume that the reinvestigation on PhI(OMe)$_2$ should be desirable because this "forgotten" hypervalent reagent may realize some transformations that might not be readily achieved by existing hypervalent iodine reagents.

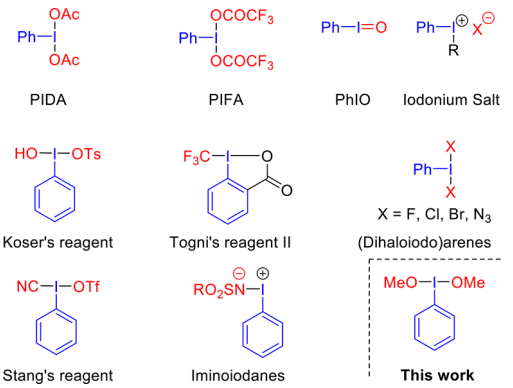


Figure 1. Representative hypervalent iodine(III) reagents.

Carbon−carbon bond-forming reactions play a very important role in organic synthesis.[13] Hypervalent iodine reagents have also been vastly applied to the construction of C(sp^2)−C(sp^2)[14] and C(sp^2)−C(sp)[11] bonds under metal-free conditions. However, a literature survey indicated that hypervalent iodine(III)-mediated C(sp^2)−C(sp^3)[12] bond-forming reactions are the least-exploited. In 2001, Kita and co-workers[12a] reported that α-(aryl)alkyl-β-dicarbonyl substrates **A** could undergo PIFA-mediated C(sp^2)−C(sp^3) bond formation, leading to the synthesis of spirooxindole compounds **B** (Scheme 1a). In our previous work,[12b] we applied PIFA in a cascade annulation reaction of 1,3-diketone **C**, enabling the dual oxidative C(sp^2)−C(sp^3) bond formations to

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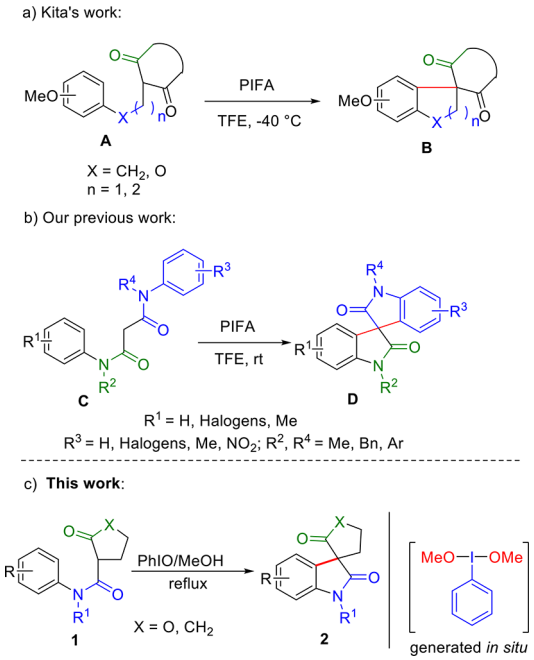
Scheme 1. Oxidative C(sp^2)−C(sp^3) Bond Formation Reactions



afford spirooxindole **D** (Scheme 1b). In this work, we report a convenient synthesis of spirooxindoles **2** from *N*-arylamide derivatives **1** via oxidative C(sp^2)−C(sp^3) bond formation mediated by PhI(OMe)$_2$ generated in situ (Scheme 1c).

Substrate **1a** was used as model substrate to test the reaction of converting *N*-methyl-2-oxo-*N*-phenyltetrahydrofuran-3-carboxamide (and derivatives) to the hitherto undocumented spiroheterocycle **2a** via iodine(III)-mediated oxidative C(sp^2)−C(sp^3) bond formation. Much to our delight, treating **1a** with PIFA in TFE under Kita's conditions[12a] or those developed in a previous report,[12b] we were able to obtain the desired product, albeit the yield was low. However, when the reaction was performed at 65 °C, **2a** was afforded in 40% yield. The solvent including TFE, DCM, MeCN, and MeOH (Table 1, entries 1−4) were also tested, the result of which showed that MeOH was the most suitable solvent for the reaction. With an attempt to further improve the yield, we introduced $NaHCO_3$ (Table 1, entry 5) to the reaction to neutralize the generated TFA. However, no improvement in yield was attained. Conjecturing that the lower yield might be due to the side reactions caused by the presence of the powerful oxidant of PIFA, we continued our studies by switching to less-potent hypervalent iodine(III) oxidants. To our satisfaction, when PIDA was applied, the yield was improved to 56% (Table 1, entry 7), and with PhIO, **2a** was afforded in a gratifying yield of 81% (Table 1, entry 8). Further studies with PhIO as the oxidant showed that the dosage had to be at least 3 equiv to ensure complete consumption of the substrates, and the reaction was very sluggish at room temperature (Table 1, entry 18) and the reaction at 65 °C (the reflux temperature of MeOH) provided the best yield. Solvent-screening studies showed that all nonalcohol solvents, e.g., MeCN, toluene, DMF, DCE, THF (Table 1, entries 9−13), impeded the transformation, while all alcohol solvents, including EtOH, isopropanol, TFE, and HFIP (Table 1, entries 14−17) all facilitate the reaction, although to a lesser level than MeOH. We also introduced Lewis acids including $BF_3{\cdot}Et_2O$ and $FeCl_3$

Table 1. Optimization of the PhIO/MeOH-Mediated Cyclization Reaction Conditions[a]

entry	oxidant (equiv)	solvent	temperature (°C)	time (h)	yield[b] (%)
1	PIFA (1.5)	TFE	65	2	40
2	PIFA (1.5)	TFE	rt	3	30
3	PIFA (1.5)	DCM	reflux	5	NR
4	PIFA (1.5)	MeOH	reflux	3	43
5[c]	PIFA (1.5)	MeOH	reflux	3	41
6	PIFA (1.5)	MeCN	65	3	35
7	PIDA (1.5)	MeOH	reflux	3	56
8	**PhIO (3.0)**	**MeOH**	**reflux**	**3**	**81**
9	PhIO (3.0)	MeCN	65	4	trace
10	PhIO (3.0)	toluene	65	5	NR
11	PhIO (3.0)	DMF	65	3	NR
12	PhIO (3.0)	DCE	65	3	NR
13	PhIO (3.0)	THF	65	4	10
14	PhIO (3.0)	TFE	65	3	18
15	PhIO (3.0)	HFIP	reflux	3	15
16	PhIO (3.0)	*i*-PrOH	65	3	20
17	PhIO (3.0)	EtOH	65	3	35
18	PhIO (3.0)	MeOH	rt	24	trace
19	PhIO (2.0)	MeOH	reflux	3	55
20	PhIO (1.5)	MeOH	reflux	3	30
21[d]	PhIO (1.5)	MeOH	reflux	5	28
22[e]	PhIO (1.5)	MeOH	reflux	5	51

[a]Reaction conditions: **1a** (1.0 mmol), PhIO (3.0 mmol), MeOH (5 mL), stirred at reflux (65 °C) for between 2 and 24 h. Abbreviations used: TFE, tetrafluoroethylene; DCM, dichloromethane; MeCN, acetonitrile; MeOH, methyl alcohol; DMF, dimethylformamide; THF, tetrahydrofuran; HFIP, hexafluoro-2-propanol; *i*-PrOH, isopropyl alcohol; EtOH, ethyl alcohol; rt, room temperature. [b]Isolated yield. [c]$NaHCO_3$ (3.2 mmol) was added. [d]$BF_3{\cdot}Et_2O$ (10% mmol) was added. [e]$FeCl_3$ (10% mmol) was added.

to promote the reaction. However, we were disappointed to find that no improvement could be achieved in each case (Table 1, entries 21 and 22). On the basis of the fact that the reaction does not occur in nonalcoholic reaction, we postulated that the effective oxidant might not be the original PhIO, but the PhI(OMe)$_2$ species, generated in situ from PhIO and MeOH. A reaction was then performed, by following Hill's method,[10] between PhIO and MeOH. As expected, PhI(OMe)$_2$ was obtained as a white crystalline after crystallization in *n*-hexane at −22 °C and was finely characterized by nuclear magnetic resonance (^{1}H NMR, ^{13}C NMR) and high-resolution mass spectroscopy (HRMS) analysis (see the Supporting Information for details).

However, PhI(OMe)$_2$ was found to be unstable at room temperature and was gradually decomposed back to PhIO and MeOH.[10] This might account for the fact that at least 3 equiv of PhIO was required to realize a full conversion of the reaction. When substrate **1a** was treated with pure PhI(OMe)$_2$ in DCE, the desired product was obtained in 60% yield (Scheme 2). This result indicates that PhI(OMe)$_2$ might be involved in the reaction as the intermediate of oxidant. What we had observed was a two-step process in a one-pot reaction.

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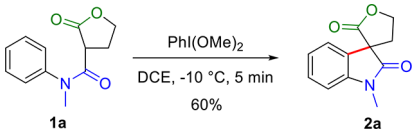
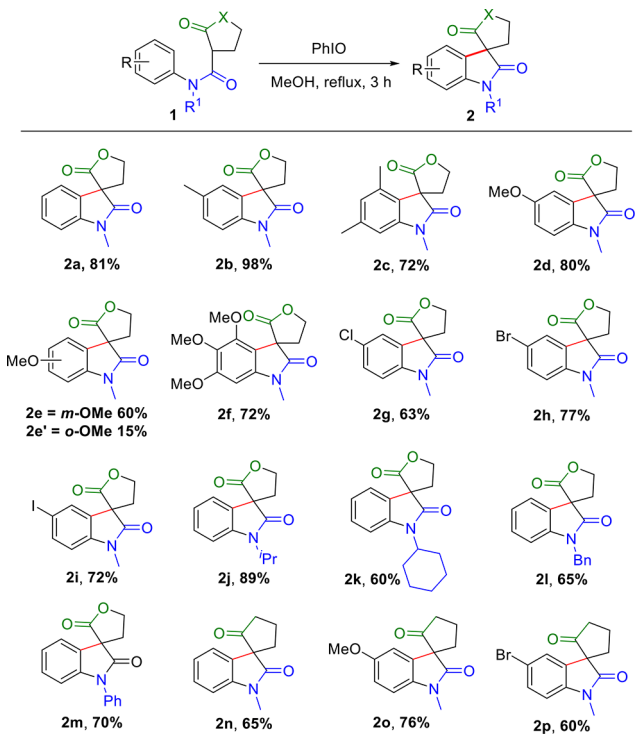
Scheme 2. PhI(OMe)$_2$-Mediated Intramolecular Oxidative Cyclization of 1a in DCE at Low Temperature



Under the optimal conditions (Table 1, entry 7), we explored the substrate scope with different substituents on a series of *N*-arylamide derivatives by this newly established method (Scheme 3). Results showed that the method was

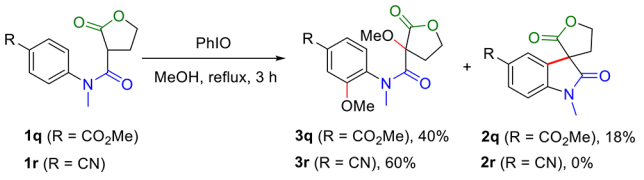
Scheme 3. Synthesis of Spirooxindoles[a,b]



[a]Reaction conditions: **1** (1.0 mmol), PhIO (3.0 mmol), MeOH (5 mL), stirred at reflux (65 °C) for 3 h. [b]Isolated yield.

applicable across a wide range of *N*-methyl-*N*-phenylamide type of substrates and all the corresponding products were obtained smoothly in good to excellent yield. Substrates bearing electron-donating groups such as methyl and methoxyl substituent (Scheme 3, **1b**−**1f**) in *para*-, *meta*-, or *ortho*-positions were converted to the expected spirooxindoles **2b**−**2f** in satisfactory yields. Notably, the reaction involving the substrate bearing *meta*-methoxyl afforded two inseparable regioisomeric products **2e** and **2e′**, with yields of 60% and 15%, respectively. Besides, substrates bearing electron-withdrawing groups including chloro, bromo, and iodo substituents also afforded the desired product **2g**−**2i** in satisfactory yields. For the R^1 substituent, isopropyl, benzyl, and cyclohexyl groups were all well-tolerated during the reaction. In addition, the substrates on the *N* atom can also be extended to an aryl group, as the N-arylated product **2l** could be obtained in 70% yield. Finally, the method could be extended to substrates with the lactone moiety being replaced with a cyclopentanonyl group, as spirooxindoles **2n**−**2p** were all obtained in moderate yields. However, when a substrate bearing an electron-withdrawing methoxycarbonyl substituent in the phenyl ring was subjected to the standard conditions, the reaction afforded the dimethoxylated product **3q** as the major product, with the desired product **2q** being obtained in only 18% yield. Furthermore, when the substrate bearing a strong electron-withdrawing cyano group was applied, the reaction afforded the dimethoxylated product **3r** as the sole product (Scheme 4). Disappointingly, when the substrate bearing a strong electron-withdrawing nitro group was used, no desired cyclized or dimethoxylated product was obtained (not shown).

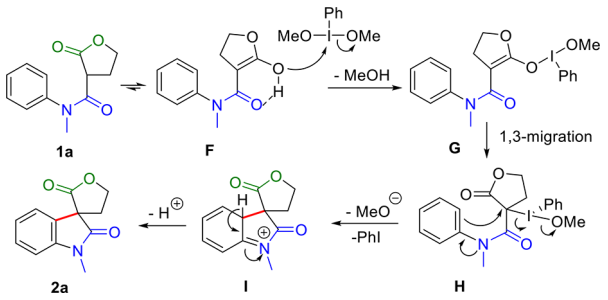
Scheme 4. PhIO/MeOH-Mediated Reaction of *N*-Arylamide Derivatives Bearing Electron-Deficient Substituents[a,b]



[a]Reaction conditions: **1** (1.0 mmol), PhIO (3.0 mmol), MeOH (5 mL), stirred at reflux (65 °C) for 3 h. [b]Isolated yield.

We performed mechanistic studies on the direct *N*-arylamide of **1a** to elucidate the reaction mechanism in Scheme 5, using **1a** as the starting substrate. First, substrate **1a**

Scheme 5. Proposed Reaction Mechanism



is tautomarized into its enol form **F**, which could be understood as stabilized by the internal hydrogen bonds. Nucleophilic attack on the iodine center of PhI(OMe)$_2$[15] by the enol of intermediate **F** afforded the O−I enol form **F**, which could be regarded as being stabilized by the internal hydrogen bonds. Nucleophilic attack on the iodine center of PhI(OMe)$_2$ by the enol of intermediate **F** afforded the O−I intermediate **G**, which was converted to the I−C intermediate **H** via 1,3-migration.[16] Intramolecular cyclization then occurred in **H**, furnishing the formation of the C−C bond, with the concomitant release of phenyliodine and methoxide, affording the iminium salt **I**. Finally, aromatization was realized via the abstraction of a proton from **I**, giving the title product **2a**.

In summary, we have discovered a novel, metal-free synthetic method to construct a novel class of compounds of spiroheterocyclic skeletone with the application of a "forgotten" PhI(OMe)$_2$ via intramolecular oxidative C(sp^2)−C(sp^3) bond formation. We hope this method may rekindle the exploration of PhI(OMe)$_2$ (or the PhIO/MeOH system) as an oxidant in other novel organic transformations.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03741.

Experimental procedures, data of compounds characterization (PDF)

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Notes

The authors declare no competing financial interest.

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