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Formation of Spirooxindoles Iodonium from N-Substituted 3-Oxopentanediamides via Phenyliodine Bis(trifluoroacetate)-Mediated Oxidative Cascade Reactions

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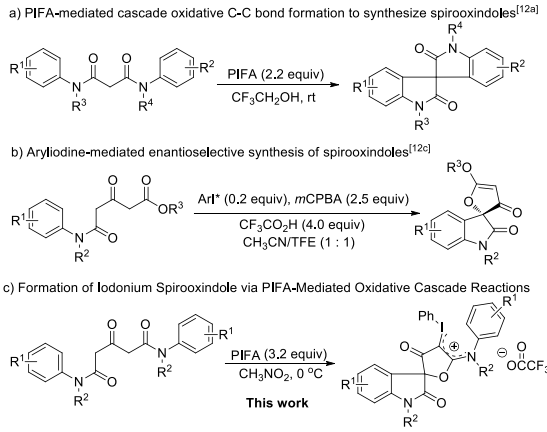
Abstract. The reaction of N-substituted 3-oxopentanediamides with phenyliodine bis(trifluoroacetate) (PIFA) was found to give a novel class of spirooxindole iodonium compounds under metal-free conditions. The reaction is postulated to undergo a cascade process involving an oxidative C-O bond formation, an oxidative C-C bond formation and a final iodination step.

Keywords: hypervalent iodine(III) reagent; cascade reaction; C(sp^3)–C(sp^2) bond formation; C(sp^2)–O bond formation; spirooxindoles iodonium

Cascade reactions,[1] during which several bonds are formed in one pot without reagents added or intermediates isolated, are powerful approaches in organic synthesis. Numerous cascade reactions have been discovered for the formation of polycyclic heterocycles, a class of compounds known playing key roles in various interesting biological activities.[2] However, literature survey shows that the majority of the existing methods rely on the transition-metal-mediated C–H functionalization, arguably the most commonly adopted and applicable strategy nowadays.[3] Due to the issue of heavy metal residue, there is a need for the development of the transition-metal-free method as an alternative method for construction of the polycyclic heterocyclic skeletons.

Hypervalent iodine reagents, a class of non-metal oxidants, have been widely used in the construction of various heterocyclic compounds in the past decade due to their ready availability, high reactivity,[4a-g] and mild toxicity.[4h-l] In most of these reactions, a single bond of C–N,[5] C–O,[6] C–C,[7] C–S,[8] N–N,[9] N–O,[10] or N–S[11] is formed during the oxidative coupling step. Not many cascade reactions have been reported, and even less in forming polyheterocycles[12,4k,l] or spiroheterocycls.[13] In 2012, our group reported PIFA-mediated intramolecular cascade oxidative C–C bond formations which converted N_1,N_3-diphenylmalonamides to spirooxindoles (Scheme 1a).[13a] Later our study found that diverse spirofurooxindole derivatives could be formed from ethyl 3-oxopentanioate monoamide derivatives by chiral aryl iodine-mediated cascade C−O and C–C oxidative bond formations (Scheme 1b).[13c] Inspired by the results of this work, we envisaged a parallel reaction of the amide version of ethyl 3-oxopentanioate monoamide where the ester substituent was replaced with an *N*-aryl amide moiety.



Scheme 1. Oxidative Cascade Reactions Mediated by Hypervalent Iodine Reagent

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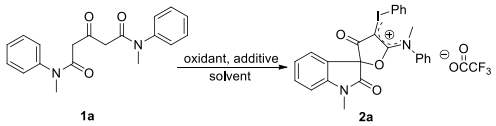
We prepared compound **1a** (N_1,N_5-dimethyl-3-oxo-N_1,N_5-diphenylpentanediamid) and had it subjected to the conditions used for the construction of spirofurooxindoles. To our delightful surprise, 1 equivalent of **1a** with 2.2 equivalents of PIFA in 2,2,2-trifluoroethanol (TFE) afforded an iodonium spirooxindole compound, **2a**, in 35% yield. Although the product was not what we had expected, it was an iodonium compound reportedly to exhibit significant activities against microorganisms and other potential applications.[4a,n,14] Thus, we set out to investigate a series of iodonium polyheterocycles which, to our knowledge, had never been reported in previous literature.

Table 1. Optimization of the Reaction Conditions.[a]

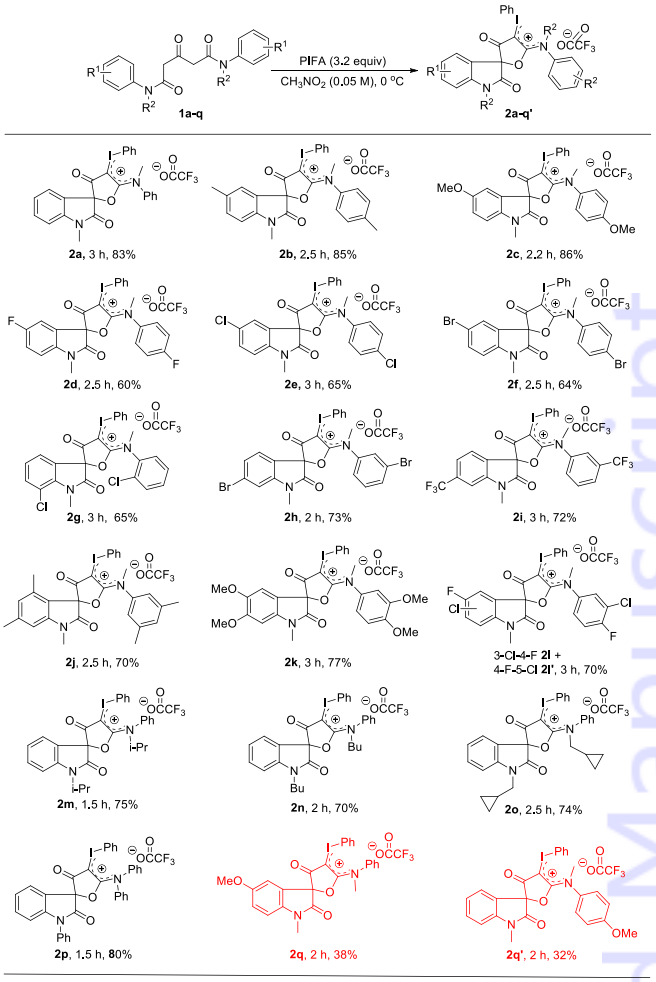


Entry	Oxidant	Additive	Solvent	T	Time / h	Yield[b](%)
1[c]	PIFA	none	TFE	rt	0.5	35
2	PIFA	none	CH_3CN	rt	0.5	58
3[d]	PIFA	$BF_3{\cdot}Et_2O$	CH_3CN	rt	0.5	40
4[d]	PIFA	TMSOTf	CH_3CN	rt	0.5	43
5[d]	PIFA	TEA	CH_3CN	rt	0.5	53
6[d]	PIFA	K_2CO_3	CH_3CN	rt	0.5	55
7	PIFA	none	CH_3NO_2	rt	0.5	70
8	PIFA	none	DCM	rt	0.5	63
9	PIFA	none	DMF	rt	0.5	50
10	PIFA	none	MeOH	rt	0.5	47
11	**PIFA**	**none**	**CH_3NO_2**	**0 °C**	**3**	**82**
12	PIFA	none	CH_3NO_2	-10 °C	4	80
13[e]	PIDA	none	CH_3NO_2	0 °C	3	62
14[e]	PhIO	none	CH_3NO_2	0 °C	3	NR

[a] All reactions were carried out with **1a** (2 mmol) and oxidant (6.4 mmol) in solvent (40 mL) unless otherwise stated. [b] Isolated yield. [c] 2.2 equiv of PIFA was used. [d] 0.2 equiv of additive was used. [e] 1.1 equiv of TFA was added.

Aiming to gain further insight of the newly discovered transformation, we set out to optimize the reaction conditions by using substrate **1a**. Increasing the dosage of the oxidant to 3.2 equivalents showed a positive impact as the yield was improved to 58% (Table 1, entry 2). Two additives, $BF_3{\cdot}Et_2O$ and TMSOTf were applied, but both led to slightly decreased yield due to the formation of some unidentified byproducts (Table 1, entries 3−4). Bases

Table 2. Synthesis of Spirooxindoles iodonium via PIFA-Mediated Oxidative Cascade Reaction.[a]



[a] All reactions were carried out by treating substrate **1** (2 mmol) with PIFA (3.2 equiv) in CH_3NO_2 (40 mL, c = 0.05 M) under air unless other state. [b] Isolated yield.

such as TEA and K_2CO_3 (Table 1, entries 5 and 6) were found to have little effect on the yield. Screening of a series of other solvents, including CH_3NO_2, DCM, DMF and MeOH revealed that CH_3NO_2 was the most suitable solvent (Table 1, entries 7−10). Control experiment identified 0 °C as the ideal temperature for the reaction (Table 1, entries 11-12). Finally, other hypervalent iodine reagents were applied for comparison, which showed the less potent $PhI(OAc)_2$ giving a considerably lower yield (Table 1, entry 13) and iodosobenzene (PhIO), failed to afford the desired product (Table 1, entry 14).

Under the optimized conditions (Table 1, entry 11), the scope and generality of this novel cascade reaction was tested (Table 2). First, the electronic nature of the phenyl ring of the amide moiety was studied. The results showed that substrates with both electron-donating (Me, and OMe) and electron-

withdrawing (halogen) groups at the *para* position of the aniline ring could be well converted to the desired products in 60-86% yields (**2b−f**), although lower yields were consistently observed for substrates containing electron-deficient amides. *ortho*-Substituted substrates bearing a Cl group was also well tolerable under the reaction conditions (**2g**). All substrates (Br, CF_3 and Dimethyl) at the *meta*-position of the aniline ring were readily converted into the corresponding desired products in good yields (**2h-j**). Also, substrate **1k** with methoxyl substituents at the 3- and 4-positions of the *N*-aryl moiety was converted to the product **2k**, while **1l** delivered expected regioisomeric products **2l** and **2l'** in an overall yield of 70%. Steric hindrance was not found in cases **1m−p**, as the corresponding spirooxindoles iodoniums were all obtained in similar satisfactory yields. Aiming to test the selectivity of the transformation and improve the diversity of the substrates, we synthesized an asymmetric amide (**1q**) and carried out the reactions under the standard conditions. Fortunately, a mixture of two isomers were isolated in 38% and 32% yields, respectively.

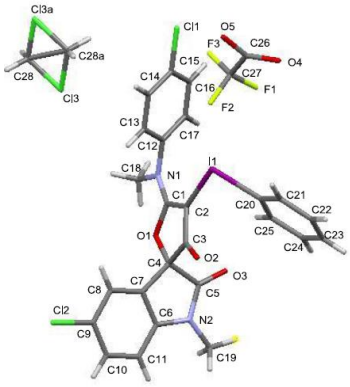
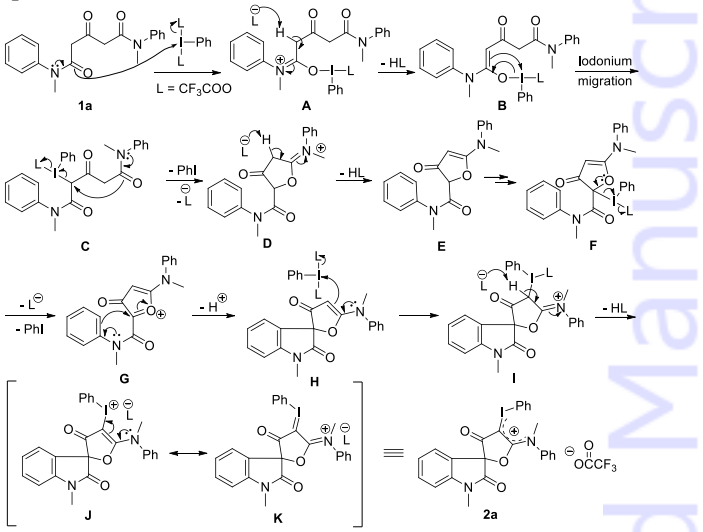


Figure 1. X-ray structure of **2e**.

The structure of the spirooxindole moiety was undoubtedly confirmed through the X-ray crystallographic analysis of **2e**,[15] a dichlorofunctionalized analogue of **2a**. X-ray structural data of bond lengths: I_1–C_2 (2.070 Angstrom (or 207.0 pm)), C_2–C_1 (139.3 pm) and C_1–N_1 (132.5 pm) bonds and bond angles: N_1–C_1–C_2 (132.0°), C_1–C_2–I_1 (131.45°), and C_2–I_1–C_{20} (93.25°) suggest double bond nature of both the C_2–C_1 and C_1–N_1 bonds and slightly shortened single bond of C-I while comparing to that in a classical iodonium salt.[16,4b]

Based on the results from previous report[17] and our own work,[18,13a,c] a plausible mechanistic pathway for this oxidative cascade process has been proposed. As depicted in Scheme 2, the reaction starts with a nucleophilic attack of the carbonyl oxygen of the anilide on the hypervalent iodine center leading to the displacement of one molecule of a trifluoroacetate anion in PIFA. The resulting adduct **A** undergoes a proton abstraction by the generated trifluoroacetate anion, providing an iodoenolate intermediate **B**. Then 1,3-iodo-migration[15a,16a] occurs in **B** to afford *C*-iodoniumenolate **C**. Next, intramolecular cyclization in **C** via bond formation between the carbonyl oxygen of the anilide and the sp^3 carbon connected

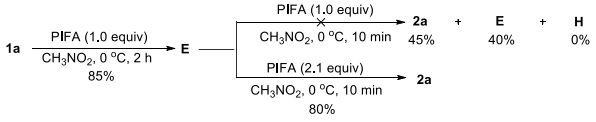


Scheme 2. Plausible mechanistic pathway for the formation of **2a**.

with the iodine gives **D**. Intermediate **E** is formed from **D** via the abstraction of a proton. The reaction of **E** with PIFA, following the same sequence of nucleophilic attack and 1,3-iodo-migration, gives the C−I intermediate **F**, which undergoes another sequence of three steps involving a reductive elimination, intramolecular cyclization and aromatization to generate **H**. Being a reactive intermediate containing an enamine moiety, **H** undergoes a third iodination reaction with PIFA leading to intermediate **I**. After the removal of one molecular of CF_3CO_2H, **I** is converted to the amphilic, iodonium **J** in coexistence with its conjugated iminium salt **K**.

In order to verify the mechanism we have proposed, we carried out control experiments to test the formation of intermediate **D** and **H**. When 1.0 equivalent of PIFA was used, substrate **1a** was

converted into intermediate **E** in 85% yield. However, the treatment of the isolated **E** with 1.0 equivalent of PIFA led to the formation of **2a** in 45% yield, the recovery of **E** in 40% yield and no formation of intermediate **H** at all. Treating intermediate **E** with 2.1 equivalent of PIFA enabled a complete reaction and the desired **2a** was obtained in 80% yield. The results indicated that the formation of **E** might be the rate-determining step.



Scheme 3. Control Experiments for Mechanistic Studies.

In summary, we have disclosed the synthesis of a novel class of spirooxindoles bearing an iodonium moiety via a PIFA-mediated cascade reaction. This process features the oxidative coupling of an enol oxygen atom and an sp^3 carbon, and an aryl carbon and an carbonyl carbon, followed by the formation of a C-I bond. The investigation on the application of these iodonium compounds in organic synthesis is being undertaken in our lab.[19]

Experimental Section

General procedure for preparation of spirooxindoles iodonium 2.

To a solution of substrate **1** (2 mmol) in CH_3NO_2 (20 mL) was slowly added PIFA (3.2 equiv) under stirring. The resulting mixture was immersed in ice-water of 0 °C, and the process of the reaction was monitored by TLC. Upon completion, the reaction mixture was evaporated to remove the solvent and the residue was purified by silica gel chromatography, using a mixture of 5% MeOH/DCM to afford the desired product **2**.

Acknowledgements

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[15] CCDC 1528484 (**2e**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Formula: $C_{55}H_{38}Cl_6F_6I_2N_4O_{10}$, unit cell parameters: a = 10.0271(18) b=11.878(2) c =12.522(2) P-1.

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[19] We appreciate the suggestion of further investigating the transformations of spirooxindole iodonium salt **2a** by one reviewer. Our preliminary study found that **2a** could be converted to 1-methylisatin upon treatment with $Cu(OTf)_2$ at 75 °C. See SI for details.

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COMMUNICATION

Formation of Spirooxindoles Iodonium from N-Substituted 3-Oxopentanediamides via PIFA-Mediated Oxidative Cascade Reactions

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