Organic LETTERS

Letter

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

pubs.acs.org/OrgLett

Oxidative Rearrangement of Secondary Amines Using Hypervalent Iodine(III) Reagent

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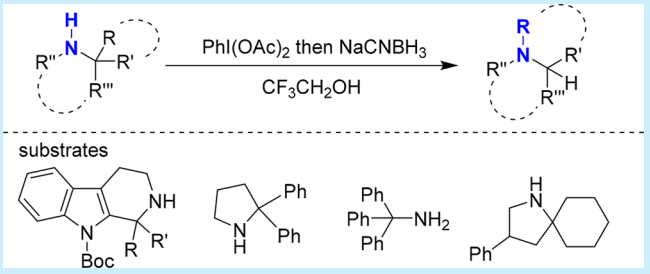
Supporting Information

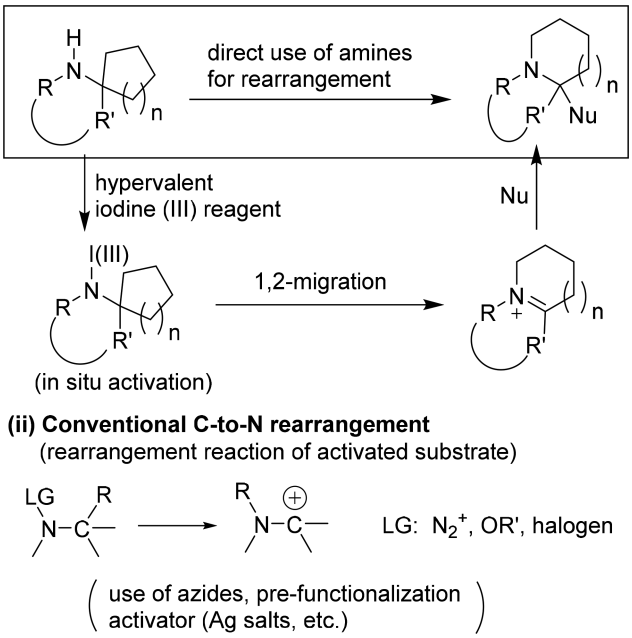
ABSTRACT: A hypervalent iodine(III) reagent mediated oxidative skeletal rearrangement reaction of secondary amines is reported. The transformation, which uses $PhI(OAc)_2$ in CF_3CH_2OH, was found to be highly efficient at inducing the direct 1,2-C-to-N migration of secondary amines. This method offers facile and divergent access to polycyclic and macrocyclic indole-fused compounds. The synthetic potential of the method is also demonstrated through its application to several substrates, including secondary as well as primary amines.



Due to the significance of 1,2-rearrangement reactions in organic chemistry,[1] the development of new methodologies remains an important challenge. Recently, hypervalent iodine reagents have been employed in various oxidative rearrangement reactions,[2] owing to their electrophilic properties and leaving group capabilities.[3] C-to-C and C-to-N (amide nitrogen) migration reactions are particularly common. For C-to-C migrations, various alkenes have been employed for 1,2-aryl group migrations, ring expansions, and ring contractions.[4,5] For C-to-N (amide nitrogen) migrations, the Hofmann rearrangement is an important synthetic approach for converting amides into the corresponding amines and their derivatives.[6] In contrast to these established transformations, migration reactions to heteroatoms other than the amide nitrogen have been under-explored. Among these reactions, a C-to-O migration using hypervalent iodine reagents was only reported for the first time by Wengryniuk in 2016, who demonstrated the facile synthesis of medium-sized cyclic ethers by the oxidative rearrangement of benzylic tertiary alcohols using a poly(cationic) hypervalent iodine reagent.[7] However, to our knowledge, C-to-N migration using amines has yet to be reported.

We envisioned that the treatment of secondary amines with a hypervalent iodine(III) reagent could result in in situ generation of a N−I (III) active species (Scheme 1, (i)) that could undergo 1,2-C-to-N migration. The incipient iminium intermediate could be trapped by the appropriate nucleophiles to afford tertiary amines with significantly different skeletons compared to the starting materials. The 1,2-rearrangement reactions of nitrogen atoms bearing leaving groups, such as azides, hydroxylamine derivatives, and *N*-chloroamines, are well-known transformations (Scheme 1, (ii)).[8−10] In these transformations, the use of azides or the prior introduction of leaving groups on the nitrogen atoms is necessary. Furthermore, a stoichiometric amount of a silver salt is generally required to induce rearrangement reactions of *N*-chloroamines.[10] In contrast, the direct use of secondary amines as substrates in 1,2-C-to-N migration reactions has been much less explored,[11,12] despite the potential of these transformations in offering an efficient and straightforward strategy for the synthesis of saturated nitrogen heterocycles, which are ubiquitous structural motifs in bioactive molecules, including alkaloid natural products and pharmaceuticals.

Scheme 1. 1,2-C-to-N Rearrangements



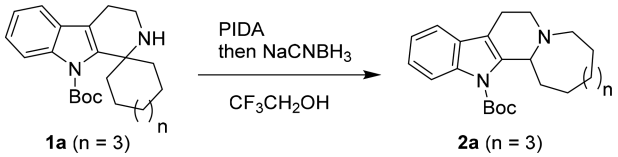
Received: February 26, 2018

DOI: 10.1021/acs.orglett.8b00675
Org. Lett. XXXX, XXX, XXX−XXX

Herein, we describe the oxidative skeletal rearrangement of secondary amines mediated by hypervalent iodine reagents. We found that the reaction system, which utilizes phenyliodine(III) diacetate ($PhI(OAc)_2$) in CF_3CH_2OH, enables the direct 1,2-C-to-N migration of secondary amines. This metal-free method provides facile and divergent access to polycyclic or macrocyclic indole-fused compounds via a one-pot transformation. The use of different types of secondary, as well as primary amines demonstrate the versatility of this method for the synthesis of a wide range of amine compounds. A radical pathway is suggested to be involved in these transformations based on mechanistic investigation using radical scavengers.

The rearrangement reaction of spiro-indole compound **1a**[13] was initially investigated because of the biologically importance of indole-fused compounds[14] and our continued interest in heterocycle synthesis[12c] (Table 1). After optimizing various reaction conditions, we found that 1,2-C-to-N migration occurred smoothly using hypervalent iodine reagents, such as $PhI(OAc)_2$ in CF_3CH_2OH, and that subsequent treatment with $NaCNBH_3$ led to the formation of rearranged product **2a** in high yield (89%, entry 1). $NaCNBH_3$ showed better efficiency as a reductant in CF_3CH_2OH, compared to $NaBH_4$ and $NaBH(OAc)_3$ (see the Supporting Information (SI)). Interestingly, possible side reactions, such as imine formation via secondary amine oxidation, were not observed under these conditions. Examination of other commercially available iodine(III) reagents showed that $PhI(OAc)_2$ was optimal for this transformation, while iodosobenzene and Koser's reagent, hydroxy(tosyloxy)iodobenzene,[15] gave decreased yields (entries 2 and 3). Interestingly, phenyliodine bis(trifluoroacetate) (PIFA) also showed lower efficiency (entry 4). The lower conversion was probably due to the strong acidity of trifluoroacetic acid generated in situ, which likely inhibits the reaction between the amine and iodine reagent. *N*-Iodosuccinimide (NIS) or *o*-iodoxybenzoic acid (IBX) also failed to promote the rearrangement reaction (entries 5 and 6). Furthermore, the effect of solvent proved to be crucial in these transformations. In contrast to CF_3CH_2OH, very poor results were obtained when reactions were conducted in MeOH, CH_3CN, or $(CF_3)_2CHOH$ (entries 7–9).[16] As a result, the conditions shown in entry 1 have been identified as optimal.[17]

Table 1. Study of Reaction Conditions[a]



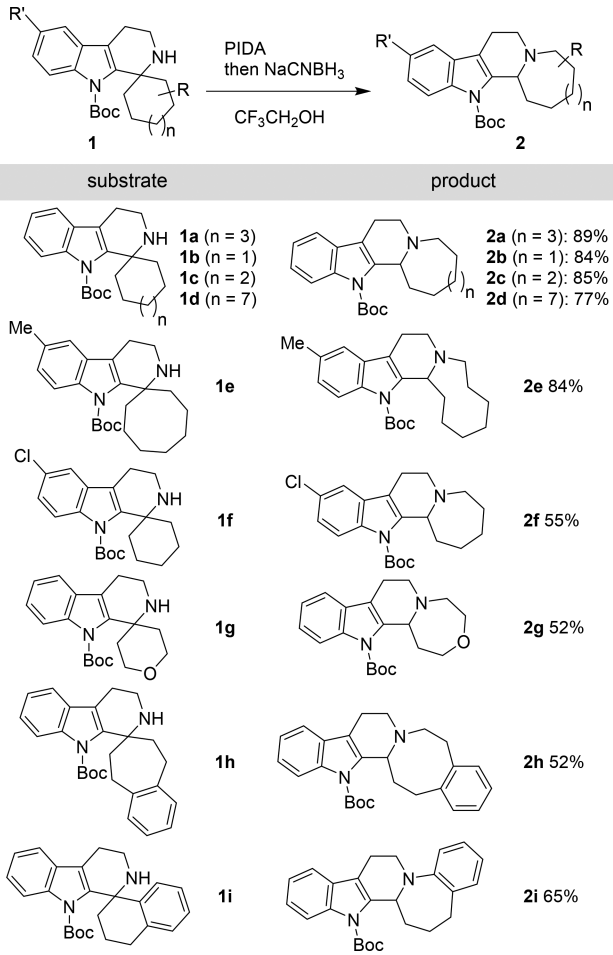
1a (n = 3) **2a** (n = 3)

entry	reagent	solvent	yield (%)
1	PIDA	CF_3CH_2OH	89
2	PhI=O	CF_3CH_2OH	31
3	PhI(OH)OTs	CF_3CH_2OH	7
4	PIFA	CF_3CH_2OH	54
5	NIS	CF_3CH_2OH	ND[b]
6	IBX	CF_3CH_2OH	ND[b]
7	PIDA	MeOH	12
8[c]	PIDA	CH_3CN	ND[b]
9	PIDA	$(CF_3)_2CHOH$	12

[a]Reaction conditions: reagent (1.3 equiv) in solvent (0.05 M) at 0 °C to rt then $NaCNBH_3$ (5.0 equiv) at 0 °C to rt. [b]Not detected on TLC. [c]Reaction conditions: reagent (1.3 equiv) in solvent (0.05 M) at 0 °C to rt; evaporation; $NaBH_4$ (5.0 equiv) in MeOH at 0 °C to rt.

With the optimized conditions in hand, the substrate scope of this transformation was explored (Table 2). The effect of ring size on the rearrangement was first investigated. Compounds **1b–d** bearing cyclohexane, cycloheptane, and cyclododecane rings, respectively, gave the corresponding 7-, 8-, and 13-membered fused ring products (**2b–d**), respectively, in good yields. Pleasingly, substrate **1b** bearing a cyclohexane ring, which has the smallest ring strain among cycloalkanes, smoothly underwent rearrangement, showing the efficiency of $PhI(OAc)_2$ as an activator of an oxidative rearrangement reaction of amines.[18] Substrates **1e** and **1f** bearing methyl and chloride substituents at the indole 5-position, respectively, were well tolerated under the reaction conditions. Furthermore, 1,4-oxazepine-fused compound **2g** was obtained from substrate **1g**. Benzo-fused substrates **1h** and **1i** also gave satisfactory results. Notably, aromatic-ring-migration product **2i** was selectively obtained from substrate **1i**. The observed migratory tendency (aryl group over alkyl group) was consistent with that observed in the standard rearrangement reactions. To our knowledge, these results are the first examples of the 1,2-C-to-N migration of secondary amines using hypervalent iodine reagents.

Table 2. Generality of Rearrangement Reaction[a]



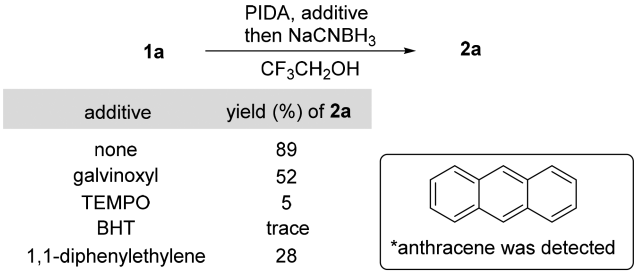
[a]Reaction conditions: PIDA (1.3 equiv) in CF_3CH_2OH (0.05 M) at 0 °C to rt then $NaCNBH_3$ (5.0 equiv) at 0 °C to rt.

Although mechanistic details remain unclear, the following features are noteworthy. First, to confirm generation of an

DOI: 10.1021/acs.orglett.8b00675
Org. Lett. XXXX, XXX, XXX–XXX

iminium ion intermediate, we obtained ^{1}H and ^{13}C NMR spectra (in $CDCl_3$) of the reaction mixture prepared from the reaction of **1a** with $PhI(OAc)_2$ in CF_3CH_2OH after solvent removal. The iminium ion was observed in the spectra, while formation of the *N*,*O*-acetal was not (see the SI). Second, we conducted the reaction of **1a** in the presence of various radical scavengers, including galvinoxyl, TEMPO (2,2,6,6-tetramethylpiperidine 1-oxyl), BHT (2,6-di-*tert*-butyl-*p*-cresol), 1,1-diphenylethylene, and 9,10-dihydroanthracene (Scheme 2). This

Scheme 2. Reactions with Radical Scavengers

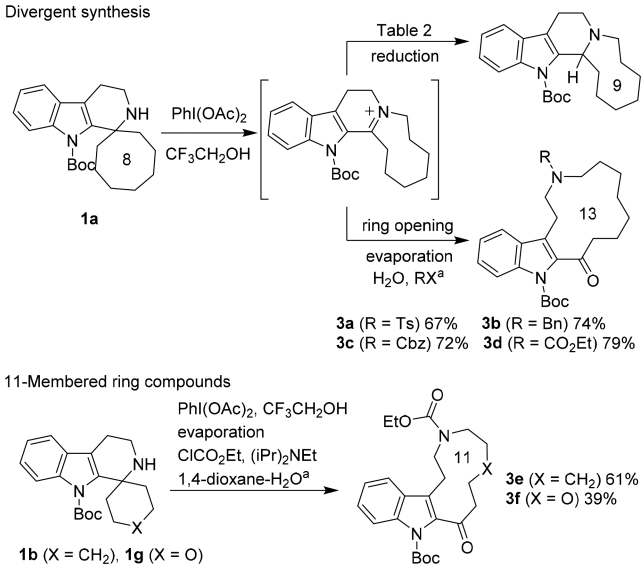


additive	yield (%) of **2a**
none	89
galvinoxyl	52
TEMPO	5
BHT	trace
1,1-diphenylethylene	28
9,10-dihydroanthracene	19*

resulted in a moderate to significant decrease in the yield of compound **2a** in all cases. It should be noted that in the reaction with 9,10-dihydroanthracene[19] we detected the generation of anthracene by ^{1}H NMR analysis (see the SI). On the basis of these observations, a radical pathway, such as the generation of a nitrogen-centered radical, might be involved in these transformations.[20,21]

Having demonstrated the generality of the $PhI(OAc)_2$-mediated rearrangement reaction for the synthesis of polycyclic compounds, we turned our attention to its application in the synthesis of macrocyclic and medium-sized ring compounds by using an iminium ion as the common intermediate (Scheme 3).

Scheme 3. Synthesis of Macrocyclic and Medium-Sized Ring Compounds

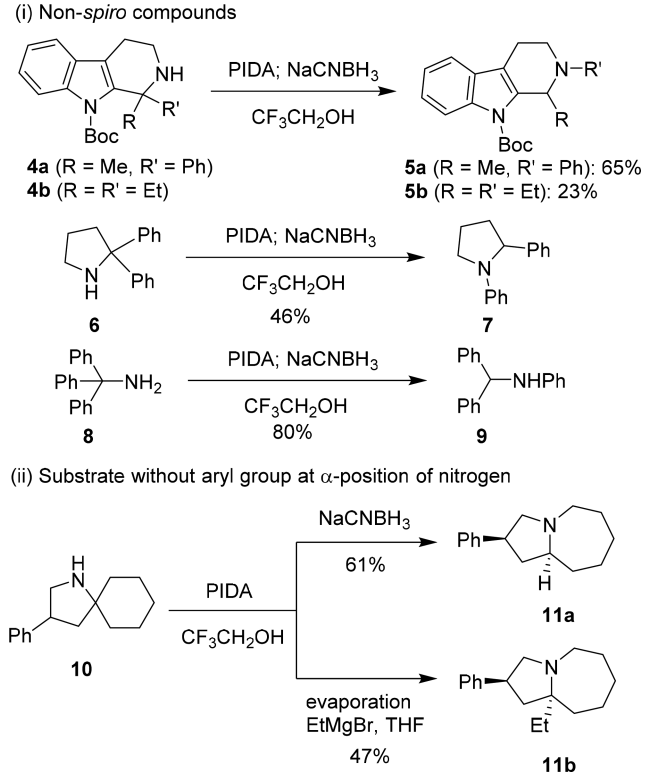


[a]Reaction conditions, for **3a**: TsCl (1.2 equiv), Na_2CO_3 aq, CH_2Cl_2. For **3b**: BnBr (1.1 equiv), Na_2CO_3 aq, CH_2Cl_2, reflux. For **3c**, CbzCl (1.2 equiv), Na_2CO_3 aq, toluene, 0 °C to rt. For **3d**–**f**: ethyl chloroformate (4.4 equiv), $(iPr)_2NEt$ (10 equiv), 1,4-dioxane–H_2O.

The development of new methods for the synthesis of macrocyclic and medium-sized ring compounds is important because of the significant increase in interest in the medicinal applications of larger ring compounds.[22] After investigating reaction conditions for transformation of the iminium ion intermediate, we found that ring-expanded compounds were obtained via hydrolysis under basic conditions and subsequent trapping of the generated secondary amine with appropriate electrophiles in a one-pot operation. As shown in Scheme 3, 13-membered macrocycles **3a**–**d** bearing various substituents, such as tosyl, benzyl, benzyloxycarbonyl, and ethoxycarbonyl groups, respectively, on the secondary amino nitrogen were obtained from **1a** and the corresponding electrophiles. The ketone functionality of these compounds could be useful as a functional handle for further derivatization. Synthetically challenging medium-sized ring compounds **3e** and **3f** were also obtained from **1b** and **1g**, respectively, though in lower yields, compared to the reaction of **1a**. As described above, the rearrangement reaction of indole **1** provided divergent access to indole-fused compounds with polycyclic or macrocyclic structures.

Finally, we conducted several experiments to assess whether the $PhI(OAc)_2$-mediated oxidative rearrangement was compatible with different types of substrates (Scheme 4). First, we

Scheme 4. Reaction of Different Types of Amines



examined the reaction of non-spiro indole compounds **4a** and **4b** (Scheme 4, (i). The rearrangement reaction of **4a** proceeded smoothly to give phenyl-migrated product **5a** in good yield. However, a lower yield was observed for diethyl substrate **4b**, showing that further improvement is necessary for substrates with substituents that have relatively poor migratory aptitude. Next, the reaction of nonindole substrate 2,2-diphenyl pyrrolidine (**6**) was investigated. 1,2-Diphenylpyrrolidine (**7**) was obtained in 46% yield via migration of the phenyl group,

DOI: 10.1021/acs.orglett.8b00675
Org. Lett. XXXX, XXX, XXX–XXX

showing the feasibility of this method for the synthesis of aryl-substituted amines. In addition to secondary amines, primary amine tritylamine (**8**) also gave a satisfactory result. Finally, we examined substrate **10** bearing no indolyl amine or benzyl amine structure (Scheme 4, (ii). Pleasingly, spiro-compound **10** gave a satisfactory result, affording fused compound **11a** bearing a 1-azabicyclo[5.3.0]decane structure, which is found in biologically active natural products.[23] Notably, a carbon nucleophile was successfully introduced into the iminium ion intermediate by reacting with Grignard reagent EtMgBr to afford **11b** bearing a quaternary-substituted carbon center. The above results suggest that a broad array of substrates are compatible with these hypervalent iodine mediated oxidative rearrangement reactions.

In summary, we present the first hypervalent iodine mediated oxidative rearrangement reaction of secondary amines. The transformation, which employs $PhI(OAc)_2$ in CF_3CH_2OH, allows the direct use of secondary amines as substrates for 1,2-C-to-N migration reactions. The versatility of this method for the synthesis of a wide range of amines was demonstrated by its application to the divergent synthesis of polycyclic and macrocyclic indole-fused compounds and the reaction of compounds **4**, **6**, **8**, and **10**, including a primary amine, as shown in Scheme 4. This protocol is also attractive because it can be readily carried out using a commercially available hypervalent iodine reagent. Further investigations of these transformations, including mechanistic studies, are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00675.

Full experimental details and characterization data (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was financially supported by the Japan Society for the Promotion of Science (JSPS) KAKENHI Grant Nos. T17K082100 (K.M.) and A15H046320 (H.F.) and the Platform for Drug Discovery, Informatics, and Structural Life Science from MEXT. K.M. acknowledges the research fund from the Society of Iodine Science (SIS). We are grateful to Prof. Richmond Sarpong (University of California, Berkeley) for useful discussions.

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(13) 8-Membered ring compound **1a** was used instead of 6-membered ring compound **1b** because the purification of **2a** by SiO_2 column chromatography was easier than that of **2b**.

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(16) Higher acidity of $(CF_3)_2CHOH$ (pK_a of 9.3) might reduce the electron donating ability of amines.

(17) The reaction of the nonprotected spiro indole did not give the rearranged product.

DOI: 10.1021/acs.orglett.8b00675
Org. Lett. XXXX, XXX, XXX−XXX

(18) Compounds **1a** and **1b** did not undergo the rearrangement reaction with NCS.
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