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# Aniline-Type Hypervalent Iodine(III) for Intramolecular Cyclization via C–H Bond Abstraction of Hydrocarbons Containing N- and O-Nucleophiles

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**Abstract:** We developed a method for the preparation of (diacetoxyiodo)-2-(*N*-alkylamido)benzene as an aniline-type hypervalent iodine(III). We also achieved direct cyclizations via C–H bond abstraction, such as the Hofmann-Löffler-Freytag reaction, a direct amination, and a direct lactonization, using the aniline-type hypervalent iodine(III) to obtain corresponding products in high yields.

**Keywords:** Aniline; C–H bond activation; Heterocycles; Hypervalent iodine; Intramolecular cyclization

Hypervalent iodine compounds have been utilized extensively in lieu of transition metals as environmentally friendly reagents for unique transformations in organic synthesis.[1] The design of hypervalent iodine compounds has been actively pursued to resolve such issues as chemoselectivity of oxidation and stability and solubility in organic solvent. Various alkyl- and alkoxy-substituted hypervalent iodine(III) compounds were developed for catalytic reactions, enantioselective reactions, reactions with recyclable iodoarene, and so forth.[2] Tether hypervalent iodines (III) bearing sulfonyl,[3] phosphinate,[4] boronate,[5] and nitro[6] groups were developed by Protasiewicz, Balthazor, Zhdankin, and Nikiforov groups, respectively (Figure 1A). A strategic motif that utilizes an aniline skeleton for the design of hypervalent iodine has allowed the installation of two different functional groups on the nitrogen center to construct a suitable reactive site. However, despite the successful synthesis of *N*-(2-iodylphenyl)acylamides[7] and benziodoxazoles[8] as aniline-type hypervalent iodines (V) by Zhdankin and co-workers (Figure 1B), no aniline-type hypervalent iodine(III) has been synthesized. On the other hand, the direct intramolecular cyclization via C–H bond abstraction of hydrocarbons containing nucleophiles has attracted considerable attention recently as an elegant and atom-economical approach.[9] As an example of a transition metal-free direct intramolecular cyclization, we cite the work of Muñiz and co-worker, who developed an iodine-catalyzed Hofmann-Löffler-Freytag reaction of *N*-alkyl sulfonamides via the effect of ligand (*m*-Cl–$C_6H_4CO_2$) on $\lambda^3$-iodane (PhI(*m*-Cl–$C_6H_4CO_2$)$_2$).[10] Kita and co-workers succeeded in a direct lactonization of carboxylic acids using *p*-anisiodine(III) diacetate in the presence of a stoichiometric amount of KBr.[11] In 2019, Nagib and co-workers developed an $I_2$-catalyzed direct intramolecular amination of imidates with PhI$(OAc)_2$ in polar solvent under thermal conditions, in which subsequent hydrolysis of resulting oxazolines with aq. HCl furnished the corresponding β-amino alcohols.[12]

We report herein a preparation of (diacetoxyiodo)-2-(*N*-alkylamido)benzene as a novel aniline-type hypervalent iodine(III) and a direct intramolecular cyclization with the compound.

(Diacetoxyiodo)-2-(*N*-alkylamido)benzenes (**1**) were prepared in three steps from commercially available 2-iodoaniline (Scheme 1). A precursor of hypervalent iodine(III) (**B**) was synthesized by acylation or sulfonylation of 2-iodoaniline and subsequent alkylation of amide (**A**). Oxidation of **B** with $NaBO_3 \cdot 4H_2O$ in AcOH provided desired (diacetoxyiodo)arenes (**1**).

The solid-state structure of (diacetoxyiodo)-2-(*N*-methylbenzamido)benzene (**1 h**) was obtained by sin-

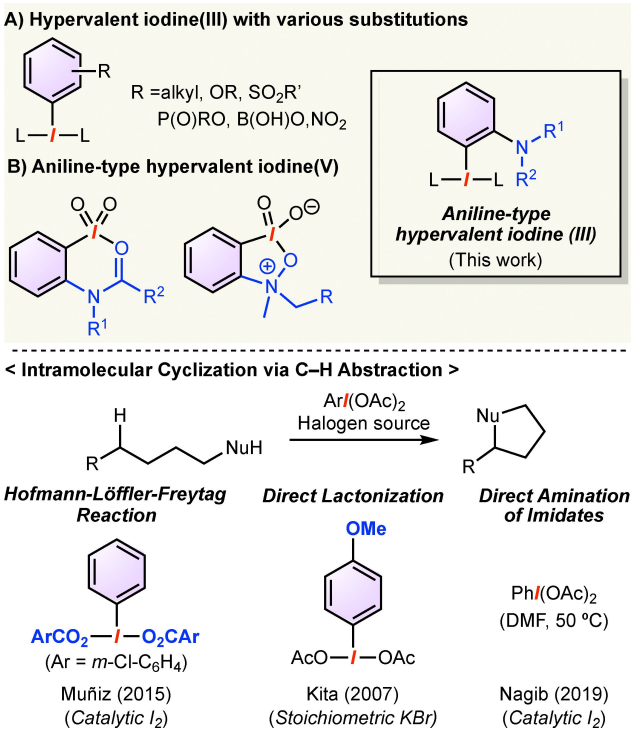
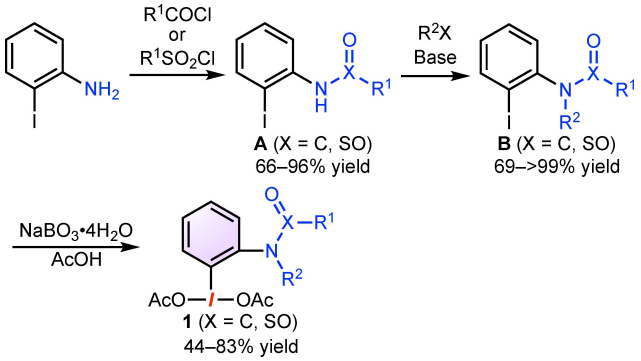



**Figure 1.** Designed hypervalent iodines and intramolecular cyclization with $ArI(OR)_2$.




**Scheme 1.** Preparation of (diacetoxyiodo)-2-(*N*-alkylamido) benzene (**1**).

gle-crystal X-ray crystallography.[13] Interestingly, the structure indicated that the diacetoxyiodanyl group and the amide group on **1 h** are perpendicular to the benzene ring on the iodoaniline skeleton (O2-I1-C1-C2 = 111.20°, C7-N1-C2-C1 = 65.43°, O4-I1-C1-C2 = 67.78°, C14-N1-C2-C1 = 109.71°) and parallel to each other (O2-I1-N1 = 101.76°, I1-N1-C8 = 73.48°, O4-I1-N1 = 66.64°, I1-N1-C14 = 118.62)(Figure 2).

To accomplish the $I_2$-catalyzed Hofmann-Löffler-Freytag reaction of *N*-alkyl sulfonamides (**2**), first, we screened for the optimum aniline-type (diacetoxyiodo) arenes(III) (**1**) in the reaction with **2 a** (Table 1). When (diacetoxyiodo)-2-(*N*-*n*-butyl-tosylamido)benzene (**1 a**)

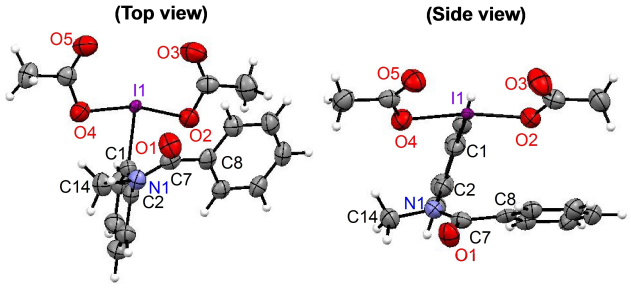
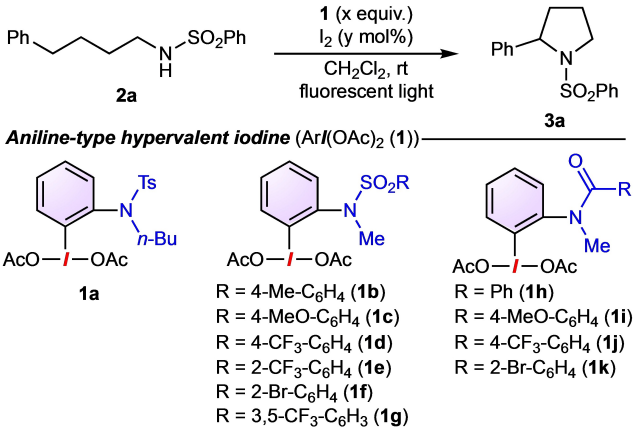



**Figure 2.** X-ray structures of **1 h**; ellipsoids at 50% probability. Selected lengths (Å), angles (°), and torsions (°).; I1-O2 2.140 Å, I1-O4 2.155 Å, C1-I1-O2 82.83°, C1-I1-O4 81.58°, C2-N1-C7 126.19°, C2-N1-C14 115.38°, O2-I1-C1-C2 111.20°, O4-I1-C1-C2 67.78°, C7-N1-C2-C1 65.43°, C14-N1-C2-C1 109.71°.

**Table 1.** Screening for optimum conditions for the Hofmann-Löffler-Freytag reaction of **2 a**.




| Entry | $ArI(OAc)_2$ (x equiv.) | y | Time (h) | Yield (%)[a] |
|---|---|---|---|---|
| 1 | **1 a** (1.0) | 2.5 | 15 | 31 [59] |
| 2 | **1 b** (1.0) | 2.5 | 15 | 63 [26] |
| 3 | **1 c** (1.0) | 2.5 | 15 | 63 [23] |
| 4 | **1 d** (1.0) | 2.5 | 15 | 69 [9] |
| 5 | **1 e** (1.0) | 2.5 | 15 | 59 [32] |
| 6 | **1 f** (1.0) | 2.5 | 15 | 70 [13] |
| 7 | **1 g** (1.0) | 2.5 | 15 | 59 [18] |
| 8 | **1 h** (1.0) | 2.5 | 15 | 78 [16] |
| 9 | **1 i** (1.0) | 2.5 | 15 | 81 [10] |
| 10 | **1 j** (1.0) | 2.5 | 15 | 69 [9] |
| 11 | **1 k** (1.0) | 2.5 | 15 | 69 [10] |
| 12 | **1 h** (1.2) | 5.0 | 15 | 97 |
| 13 | **1 i** (1.2) | 5.0 | 15 | 89 [8] |
| 14 | **1 h** (1.2) | 5.0 | 8 | 96 |

[a] Numbers in brackets indicate recovery of **2 a**.

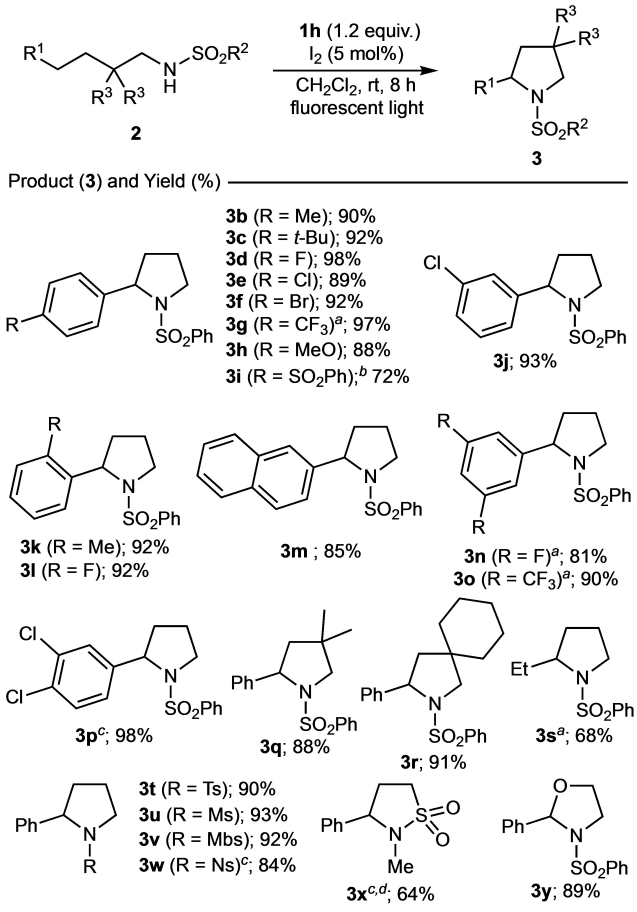
was used in the presence of catalytic $I_2$ (2.5 mol%) in $CH_2Cl_2$, 2-phenyl-pyrrolidine derivative (**3 a**) was obtained in 31% yield (Entry 1). Switching the alkyl group to a Me group instead of a *n*-Bu group of ArI

$(OAc)_2$ (**1b**–**1g**) improved the yield of **3a** to 59–70% (Entries 2–7). The use of (diacetoxyiodo)-2-(*N*-methylarylamido)benzenes **1h** and **1i** further increased the yield of **3a** to 78% and 81%, respectively (Entries 8 and 9), whereas the use of **1j** and **1k** did not improve the yield of **3a** (Entries 10 and 11). In the case of increased amounts of $ArI(OAc)_2$ (1.2 equiv.) and $I_2$ (5 mol%) in the reaction, the use of **1h** rather than **1i** generated **3a** in a higher yield (Entries 12 and 13). Shortening the reaction time to 8 h in the reaction using **1h** (1.2 equiv.) and $I_2$ (5 mol%) provided **3a** in 96% yield (Entry 14).

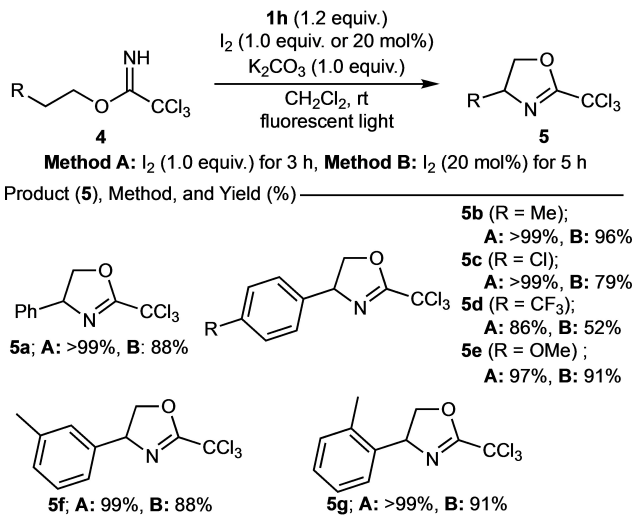
To explore the substrate scope of the Hofmann-Löffler-Freytag reaction, *N*-alkyl sulfonamides (**2**) were examined under the optimum reaction conditions (Table 1, Entry 14) (Scheme 2). Treatment of benzene sulfonamides bearing *p*-electron-donating group and *p*-electron-withdrawing group substituted arenes (**2b**–**2i**), *m*-substituted (**2j**) and *o*-substituted arenes (**2k** and **2l**), 2-naphthyl (**2m**), and disubstituted arenes (**2n**–**2p**) furnished corresponding products (**3b**–**3p**) in high yields (72–98%), respectively. The reaction of alkyl-substituted (**2q** and **2r**) and aliphatic (**2s**) benzene sulfonamides, as well as other sulfonyl groups, such as Ts (**2t**), Ms (**2u**), 4-methoxybenzenesulfonyl (Mbs) (**2v**), and Ns (**2w**) groups, also provided desired products (**3q**–**3w**) in high yields (68–93%). When inner sulfonamide (**2x**) and *O*-benzyl sulfonamide (**2y**) as variant sulfonamides were employed in the reaction, 3-substituted γ-sultam (**3x**) and 2-substituted oxazoline (**3y**) were obtained in 64% and 89% yields, respectively. It is noteworthy that the use of **1h** is extremely effective for the reaction of substrates bearing electron-withdrawing arenes (i.e., **2g**, **2i**, and **2o**).

We investigated a direct amination of trichloromethyl acetimidates (**4**) and a direct lactonization of carboxylic acids (**6**) to clarify the versatility of the direct intramolecular cyclization with aniline-type hypervalent iodine(III) (**1**). With regard to the direct amination of trichloromethyl acetimidates (**4**), the optimum reaction conditions were **4a**, $ArI(OAc)_2$ (**1h**) (1.2 equiv.), $I_2$ (1.0 equiv.), and $K_2CO_3$ (1.0 equiv.) in $CH_2Cl_2$ at room temperature (Method A), which gave 4,5-dihydro-4-phenyl-2-trichloromethyl oxazole (**5a**) in quantitative yield (Scheme 3). Various trichloroacetimidates bearing electron-donating group and electron-withdrawing group substituted arenes (**4b**–**4g**) also furnished corresponding products (**5b**–**5g**) in high yields (86–>99%). Additionally, we achieved an $I_2$-catalyzed direct amination of trichloroacetimidates (**4**) to obtain desired products (**5b**–**5g**) in 52–96% yields (Method B).

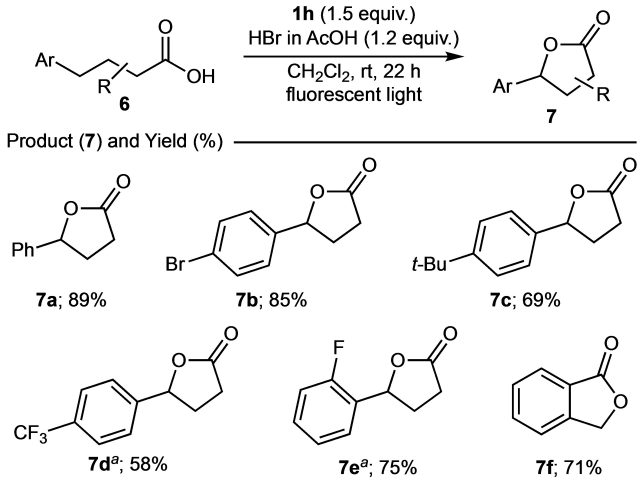
Furthermore, we developed a direct lactonization of carboxylic acid (**6**), which involves an intramolecular cyclization of an oxygen nucleophile with **1h** (Scheme 4). The optimum reaction conditions were **6a**, **1h** (1.5 equiv.), and HBr (in AcOH, 1.2 equiv.) in $CH_2Cl_2$ at room temperature, which afforded lactone




**Scheme 2.** Hofmann-Löffler-Freytag reaction of sulfonamides (**2**). a) $I_2$ (1.0 equiv.), b) $I_2$ (50 mol%), c) $I_2$ (20 mol%), and d) $K_2CO_3$ (1.2 equiv.).




**Scheme 3.** Direct amination of trichloromethyl acetimidates (**4**).

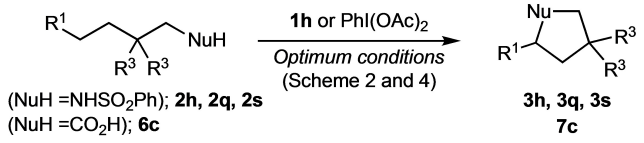



**Scheme 4.** Direct lactonization of carboxylic acids (**6**). a) **1h** (1.2 equiv.) and HBr in AcOH (1.0 equiv.).

(**7a**) in 89% yield. Use of carboxylic acids containing various substituted arenes (**6b**–**6e**) and *o*-alkyl benzoic acid (**6f**) in the reaction also furnished corresponding lactams (**7b**–**7f**) in 58–85% yields.

A comparative experiment between **1h** and PhI(OAc)$_2$ in these direct cyclization reactions indicated that the reactivity of **1h** is superior to that of PhI(OAc)$_2$ in terms of delivering high product yields (Scheme 5). In this regard, the reaction of **2h**, **2q**, **2s**, and **6c** with PhI(OAc)$_2$ under the same conditions as those with **1h** gave corresponding products **3h**, **3q**, **3s**, and **7c** in 78%, 64%, 55%, and 56% yields, respectively.

In conclusion, we developed a method for the preparation of (diacetoxyiodo)-2-(*N*-alkylamido) benzene (**1**) as a novel aniline-type hypervalent iodine (III) and identified the structure of **1h**, which is characterized by a parallel configuration between the diacetoxyiodanyl group and the amide group on **1h**. In addition, direct cyclization reactions via C–H bond abstraction, such as the Hofmann-Löffler-Freytag reaction, direct amination, and direct lactonization, using **1h** were achieved to obtain corresponding




| | Yield (%) | | | |
|---|---|---|---|---|
| ArI(OAc)$_2$ | **3h** | **3q** | **3s** | **7c** |
| **1h** | **88%** | **88%** | **68%** | **69%** |
| PhI(OAc)$_2$ | 78% | 64% | 55% | 56% |

**Scheme 5.** Comparison between **1h** and PhI(OAc)$_2$ in these direct cyclizations.

products in high yields. Aniline-type hypervalent iodine(III) can be utilized in various transformations including iodoarene-catalyzed reactions. The development of novel aniline-type hypervalent iodine(III) chemistry is underway in our laboratory.

## Experimental Section

### Procedure for Hofmann-Löffler-Freytag Reaction of Sulfonamides (2)

To a solution of **2a** (57.9 mg, 0.20 mmol) in $CH_2Cl_2$ (1.0 mL) was added **1h** (109.3 mg, 0.24 mmol) and iodine (2.5 mg, 0.01 mmol) at 0 °C, and the reaction mixture was stirred at room temperature for 8 h under fluorescent light (60 W fluorescent lamp; the distance between the fluorescent lamp and the reaction tube was 10 cm). Saturated $Na_2SO_3$ aqueous solution (5.0 mL) was added to the mixture, and the product was extracted with $CHCl_3$ (10 mL × 3). The organic phase was washed with Saturated $NaHCO_3$ aqueous solution (20 mL) and dried over $Na_2SO_4$. The organic phase concentrated under reduced pressure, and the crude products was purified by column chromatography (eluent: hexane/AcOEt = 4:1) to give the desired product **3a** (55.2 mg, 96% yield).

### Procedure for Direct Amination of Trichloromethyl Acetimidates (4)

To a solution of **4a** (53.3 mg, 0.20 mmol) in $CH_2Cl_2$ (1.0 mL) was added $K_2CO_3$ (27.6 mg, 0.20 mmol), **1h** (109.3 mg, 0.24 mmol) and iodine (50.8 mg, 0.20 mmol) at 0 °C, and the reaction mixture was stirred at room temperature for 3 h under fluorescent light (60 W fluorescent lamp; the distance between the fluorescent lamp and the reaction tube was 10 cm). Saturated $Na_2S_2O_3$ aqueous solution (5.0 mL) was added to the mixture, and the product was extracted with $CHCl_3$ (10 mL × 3). The organic phase was dried over $Na_2SO_4$. The organic phase concentrated under reduced pressure, and the crude products was purified by column chromatography (eluent: hexane/AcOEt = 20:1) to give the desired product **5a** (52.6 mg, > 99% yield).

### Procedure for Direct Lactonization of Carboxylic Acids (6)

To a solution of **6a** (32.8 mg, 0.20 mmol) in $CH_2Cl_2$ (2.0 mL) was added **1h** (136.6 mg, 0.30 mmol) and 25% HBr in AcOH solution (59.7 µl, 0.24 mmol) at 0 °C, and the reaction mixture was stirred at room temperature for 22 h under fluorescent light (60 W fluorescent lamp; the distance between the fluorescent lamp and the reaction tube was 10 cm). Saturated $NaHCO_3$ aqueous solution (5.0 mL) was added to the mixture at 0 °C, and the mixture was stirred at 0 °C for 5 min. The product was extracted with $CHCl_3$ (10 mL × 3). The organic phase was washed with saturated $NaHCO_3$ aqueous solution (10 mL) and dried over $Na_2SO_4$. The organic phase concentrated under reduced pressure, and the crude products was purified by column chromatography (eluent: hexane/AcOEt = 4:1) to give the desired product **7a** (28.8 mg, 89% yield).

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[13] CCDC-2062699 (**1 h**) 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.

## UPDATES

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