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Communication

Synthesis and reactivity of carbazole-containing hypervalent iodine(III) reagents

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ABSTRACT

A range of bench-stable carbazole-containing hypervalent iodine(III) reagents were synthesized by I – N bond formation in good yields. This kind of benziodoxolone reagents was used for a C—N coupling reaction to introduce a carbazole group to aromatic heterocycle compounds.

N-Substituted carbazoles are privileged scaffolds in various natural products and functional materials [1]. For instance, carbazoles have many important biological activities, such as anti-cancer, anti-viral and anti-inflammatory [2]. And in the field of materials science, carbazole derivatives have been widely studied as organic light-emitting devices (OLEDs) and solar cells materials for their unique optical and electrochemical properties [3]. *N*-Arylated carbazoles, such as 4,4′-*N*,*N*′-dicarbazol-biphenyl (CBP), are a kind of small molecule OLED materials, which are generally prepared by C—N coupling reactions [4]. Ullmann condensation and Buchwald-Hartwig coupling reaction are general and effective strategies for construction of *N*-substituted carbazoles via forming C—N bonds [5]. However, due to the steric hindrance and low nucleophilicity of N-atom in the aromatic system, traditional methods often require a high reaction temperature, strong base and pre-activated starting materials. Hence, the development of alternative way to *N*-substituted carbazoles is highly demanded.

Hypervalent iodine reagents, especially benziodoxole derivatives, have become a class of significant group-transfer reagents in organic synthesis [6]. In the past decades, several studies of the benziodoxolone-based hypervalent iodine reagents containing I—N bonds have been reported, that makes it possible to construct C—N bonds by using hypervalent iodine reagents (Scheme 1A). In 1994, Zhdankin and co-workers first reported a thermally stable azidobenziodoxolone compound, which was an efficient reagent for direct C—H azidation reactions [7]. Afterwards, in 1997, Zhdankin's group reported benziodoxolone derivatives containing amido moiety, and these compounds could be used for amidation of C—H bonds [8]. In 2015, Kiyokawa and co-workers developed a protocol for preparing the hypervalent iodine reagents including a phthalimidate group, which provided a new approach for oxidative amination reactions [9]. Recently, Bolm's group demonstrated a range of sulfoximidoyl-containing hypervalent iodine reagents, and these reagents could be utilized to add to styrenes by a photocatalytic process [10]. Moreover, in 2017, Waser's group reported a series of indole- and pyrrole-containing benziodoxolone reagents [11]. The PyrroleBX and IndoleBX were used for C–H functionalization of arenes to give C2 and C3 substituted pyrroles and indoles. In this context, we would like to develop a method to synthesize carbazole-containing benziodoxolone derivatives, aiming at expanding the synthetic methods of *N*-arylated carbazole derivatives. Herein, we reported a protocol to synthesize carbazole-containing hypervalent iodine(III) reagents in good to excellent yields from *N*-TMS-carbazoles and acetoxybenziodoxolone. These new reagents are bench-stable and can be used for the

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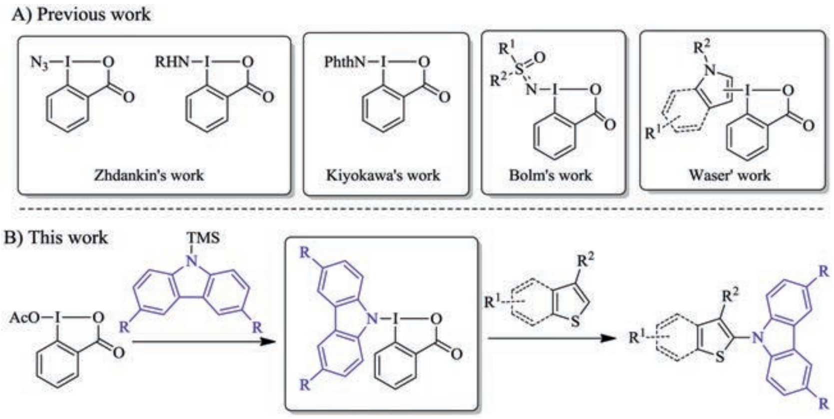
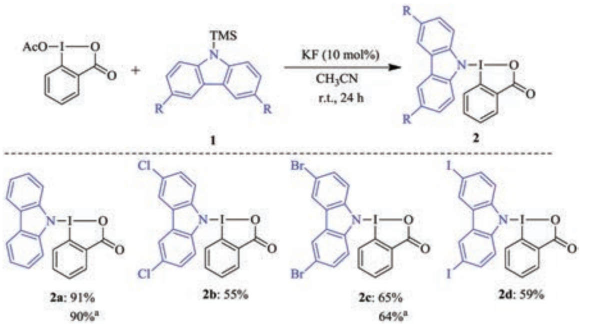


Scheme 1. Nitrogen-containing benziodoxolone derivatives.



Scheme 2. Scope of carbazole-containing hypervalent iodine reagents. Reaction conditions: KF (10 mol%), **1** (4.0 mmol), acetoxybenziodoxolone (4.0 mmol), in dry CH_3CN (10 mL) at room temperature. Isolated yields. ^{a}10 mmol scale.

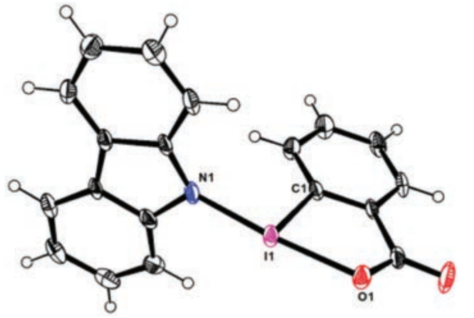


Fig. 1. Single-crystal X-ray diffraction structure of **2a**. The thermal ellipsoids are set at 35% probability (CCDC: 1909836).

Cu-catalyzed C—N coupling reaction of carbazole and aromatic heterocyclic substrates (Scheme 1B).

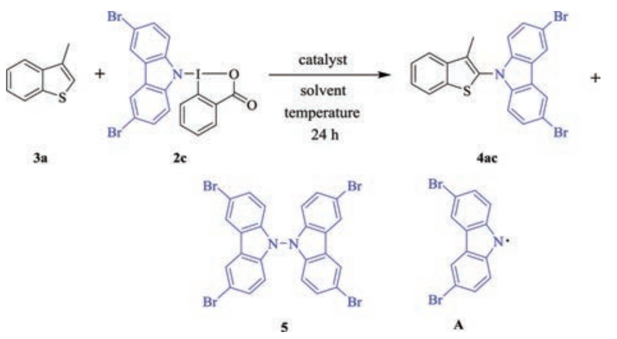
We first focused on the synthesis of carbazole-containing hypervalent iodine reagents. We chose *N*-TMS-carbazoles as the carbazole source to react with acetoxybenziodoxolone for synthesizing the desired compounds. To our delight, with 10 mol% KF as an additive, acetoxybenziodoxolone and **1a** were mixed in dry CH_3CN and stirred for 24 h at room temperature, the desired hypervalent iodine product **2a** was obtained in 91% yield (Scheme 2). When non-dry CH_3CN was used as the solvent, the yield of product **2a** decreased obviously, to only 32%. Furthermore, hypervalent iodine reagents containing 3,6-dichloro-, dibromo-, and diiodine-substituted carbazole groups all went smoothly to afford the desired products in good yield. In addition, the synthesis of hypervalent iodine product **2a** and **2c** could be easily scaled up to the 10 mmol scale without yield decreased. All the carbazole-containing hypervalent iodine reagents are stable under ambient condition, and soluble in DCM, $CHCl_3$ and DMSO, but almost insoluble in CH_3CN at room temperature. When *N*-TMS-carbazoles were replaced by carbazoles (N—H) or metal carbazolide (metal = Li, Na or K) to react with acetoxybenziodoxolone in a variety of reaction conditions, no desired products **2** were obtained.

The structure of **2a** was further confirmed by XRD. As shown in Fig. 1, the N1-I1-O1 angle of 170.74(15)° and the N1-I1-C1 angle of 92.9(2)° show the molecule has a distorted T-shape, in accord with the typical structure of benziodoxolone derivatives. The I1-N1 bond length of 2.069(4) Å is shorter than the one in Zhdankin's reagents or Kiyokawa's reagents, presumably due to the steric hindrance.

To highlight the potential utility of these novel reagents, we attempted to investigate their intrinsic reactivity in organic synthesis. We treated 3-methylbenzo[*b*]thiophene **3a** and 1.0 equiv. of carbazole-containing hypervalent iodine reagent **2c** as the model substrates, and the reaction was performed in the presence of 10 mol% CuCl as a catalyst, with dry acetonitrile as solvent at 80 °C for 24 h. The desired C—N coupling product **4ac** could be obtained in 18% yield (determined by NMR analysis), meanwhile, N—N coupling bicarbazole by-product **5** could be obtained in 52% yield (Table 1, entry 1), presumably via the dimerization of carbazole radical **A**. Subsequently, the effects of other copper catalysts were examined for the reaction. CuBr or CuTc was found to give bicarbazole product **5** beyond 65% yield and no product **4ac** was detected (Table 1, entries 2 and 3). Surprisingly, using $Cu(OTf)_2$ or $(CuOTf)_2C_6H_6$ as the catalyst, **4ac** was obtained in good yields with trace amount of byproduct **5** (Table 1, entries 4 and 5). And when $Cu(CH_3CN)_4PF_6$ was used (Table 1, entry 6), product **4ac** was formed in a higher yield of 63% (isolated in 58%). Then, a solvent screening showed that switching the solvent from CH_3CN to DCM, DCE, THF or DMSO resulted in lower yield of product **4ac** (Table 1, entries 7–10). Additionally, the change of the reaction temperature could not improve the yield of **4ac** (Table 1, entries 11 and 12). In particular, the reaction only afforded byproduct **5** in absence of the copper catalyst (Table 1, entry 13).

With the optimal reaction conditions in hand, the scope of this C—N coupling reaction was explored. As shown in Table 2, diverse carbazole-containing hypervalent iodine reagents were first employed to react with substrate **3a**. The products bearing electron-withdrawing groups such as Cl, Br or I at 3,6-position

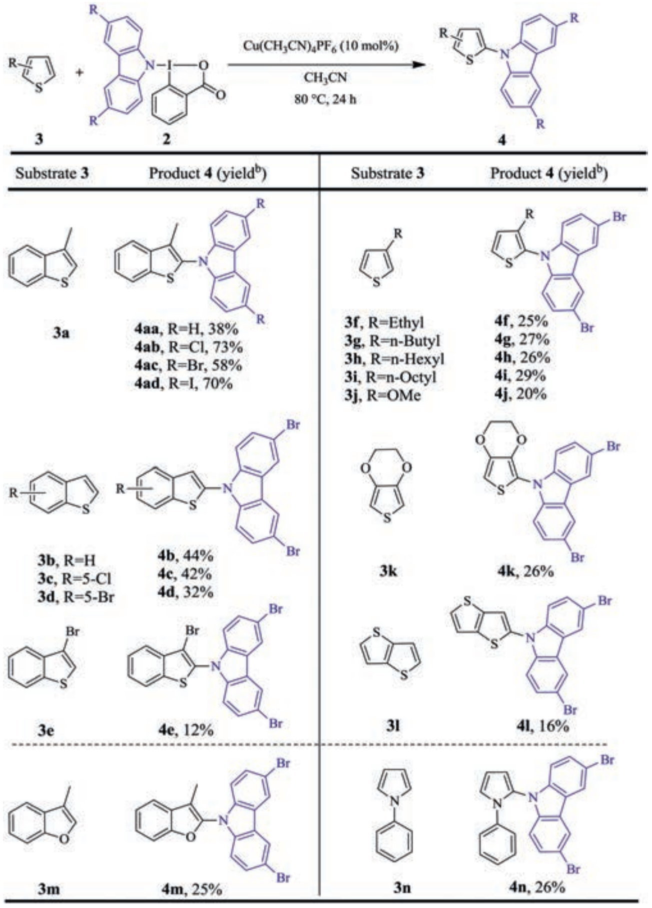
Table 1
Optimization of reaction conditions of **3a** and **2c**.[a]



Entry	Cat. (10 mol%.)	Solvent	Temp. (°C)	Yield (%)[b] **4ac/5**
1	CuCl	CH_3CN	80	18/52
2	CuBr	CH_3CN	80	0/67
3	CuTc	CH_3CN	80	0/65
4	$Cu(OTf)_2$	CH_3CN	80	47/trace
5	$(CuOTf)_2C_6H_6$	CH_3CN	80	55/trace
6	$Cu(CH_3CN)_4PF_6$	CH_3CN	80	63 (58[c])/trace
7	$Cu(CH_3CN)_4PF_6$	DCM	80	25/trace
8	$Cu(CH_3CN)_4PF_6$	DCE	80	37/trace
9	$Cu(CH_3CN)_4PF_6$	THF	80	20/25
10	$Cu(CH_3CN)_4PF_6$	DMSO	80	0/60
11	$Cu(CH_3CN)_4PF_6$	CH_3CN	60	44/trace
12	$Cu(CH_3CN)_4PF_6$	CH_3CN	100	38/trace
13	–	CH_3CN	80	0/72

[a] Reaction conditions: **3a** (0.3 mmol), **2c** (0.2 mmol), 10 mol% catalyst, in solvent (4.0 mL) at the temperature described.
[b] NMR yields with 1,3,5-trimethoxybenzene as internal standard.
[c] Isolated yield.

Table 2
Scope of the products **4** from **3** and **2**.[a]



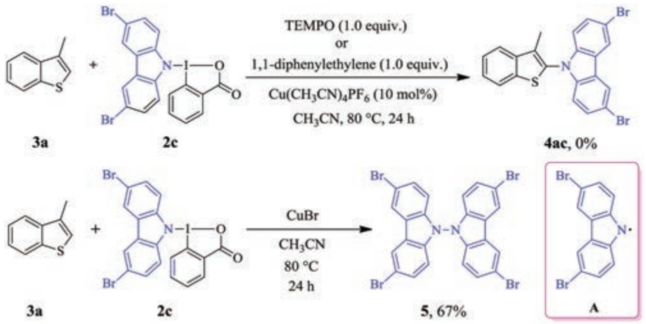
Substrate 3	Product 4 (yield[b])	Substrate 3	Product 4 (yield[b])
3a	**4aa**, R=H, 38% **4ab**, R=Cl, 73% **4ac**, R=Br, 58% **4ad**, R=I, 70%	**3f**, R=Ethyl **3g**, R=n-Butyl **3h**, R=n-Hexyl **3i**, R=n-Octyl **3j**, R=OMe	**4f**, 25% **4g**, 27% **4h**, 26% **4i**, 29% **4j**, 20%
3b, R=H **3c**, R=5-Cl **3d**, R=5-Br	**4b**, 44% **4c**, 42% **4d**, 32%	**3k**	**4k**, 26%
3e	**4e**, 12%	**3l**	**4l**, 16%
3m	**4m**, 25%	**3n**	**4n**, 26%

[a]Reaction conditions: **3** (0.3 mmol), **2** (0.2 mmol), $Cu(CH_3CN)_4PF_6$ (10 mol%), in CH_3CN (4 mL) at 80 °C for 24 h.
[b]Isolated yield.

of carbazole group were obtained in good yields. But the yield of product containing an unsubstituted carbazole group was reduced to 38%, presumably attributed to the less stability of the non-substituted carbazole radical. Next, a variety of benzo[*b*]thiophene derivatives were treated with hypervalent iodine reagent **2c** to give C2 substituted benzo[*b*]thiophene derivates in moderate yields, except **4e** in a comparatively lower yield. In addition, thiophene substrates bearing electron-donating groups were also suitable for the reaction to give corresponding C2 carbazole-substituted products. The regio-selectivity presumably results from the denser electron at position 2 than position 3. To further investigate the scope of heterocyclic substrates, **3m** and **3n** could be respectively transformed to the desired products **4m** and **4n** in 25% and 26% yield under the standard reaction. Unfortunately, strong electron-withdrawing groups (-CF_3 and $-CO_2Et$) were not tolerated in the reaction.

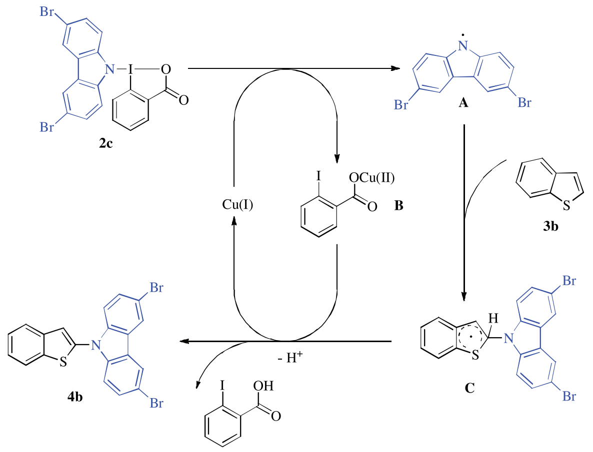
A preliminary study to investigate the mechanism of aforementioned reactions was conducted. Two control experiments were carried out under optimal reaction conditions. When adding 1,1-diphenylethylene and 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) separately as radical inhibitors into the reaction mixture of **3a** and **2c**, no desired product **4ac** were detected by NMR analysis (Scheme 3). These experimental results and the formation of compound **5** suggested that this reaction might involve a radical process.

On the basis of our experiment results and the previous reports [12], a plausible reaction mechanism was proposed. As shown in Scheme 4, substrate **3b** and reagent **2c** were chosen as the model to describe the mechanism. First, the reagent **2c** produced a *N*-centered carbazole radical **A** by a Cu(I)-mediated single electron transfer (SET) process, simultaneously released a Cu(II) species **B**. Next, the carbazole radical **A** reacted with **3b** generated the radical intermediate **C**. Finally, the radical intermediate **C** was oxidized by the Cu(II) species **B** and deprotonated to give desired product **4b**, and regenerated a Cu(I) species.



Scheme 3. Control experiments.

In conclusion, we developed an efficient strategy for the preparation of novel carbazole-containing hypervalent iodine reagents involving N—I bond. These reagents are stable under ambient conditions, and can be used for a direct C—N coupling reaction of aromatic heterocycles and carbazole group. Particularly, a variety of carbazole derivates containing multiple halogen atoms of high interest for organic photoelectric materials can be obtained in one-pot by this method. We believe that these reagents have broad applications in organic synthesis and materials science.



Scheme 4. Proposed mechanism.

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