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An Effective Synthetic Entry to Fused Benzimidazoles *via* Iodocyclization

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Abstract: A protocol for the synthesis of the fused heterocyclic polycyclic compounds pyrrole[1,2-*a*]benzimidazoles, piperidine[1,2-*a*]benzimidazoles and oxa-fused benzimidazoles using iodine and silver nitrate by an *exo-dig* or *endo-dig* cyclization pathway at room temperature has been developed. Silver nitrate is a key additive for improving the yield, and the improvement is a result of this additive eliminating the influence of iodine ions (I^-), which would otherwise lead to the formation of bis-iodine by-products. Cyclizations involving terminal and substituted alkynes were performed. Further functionalizations demonstrated that the iodo derivatives obtained are potential synthetic intermediates that can increase the molecular complexity.

Keywords: cyclization; fused benzimidazoles; iodine; silver nitrate

Fused benzimidazoles constitute an important class of heterocyclic scaffolds used in drug discovery and dye chemistry.[1] Harb et al. prepared a molecule (**1**) with antibacterial activity, which showed marked activity against Gram-positive and Gram-negative bacteria.[1e] Additionally, fused benzimidazole moieties have been found in other bioactive molecules such as lipid peroxidation inhibitor (**2**) that potently inhibit NADPH-induced lipid peroxidation and Fe^{2+}-induced lipid peroxidation.[1d] Fused benzimidazole moieties are also used in dye chemistry, as reported by Libeer et al., and in quaternary ammonium salts (**3**), and their analogues are used for sensitizing photographic silver halide emulsions.[2] (Figure 1)

Although fused benzimidazoles are important building block in synthetic chemistry, available strategies for the synthesis of these compounds are limited. Oxygen- or nitrogen-containing fused benzimidazoles have been synthesized by C–H bond activation,[3] rhodium-catalyzed cyclization,[4] solid-phase synthesis,[5] radical cyclization,[6a] CuI/I_2-promoted electrophilic tandem cyclization.[6b] Most of the methods used for the synthesis of fused benzimidazoles require harsh reaction conditions. Therefore, it is imperative to develop a novel and convenient method requiring mild reaction conditions for the synthesis of fused benzimidazoles.

Recently, electrophilic cyclizations of functionally substituted alkynes have attracted considerable attention because they can help in the preparation of various heterocyclic and carbocyclic compounds that are

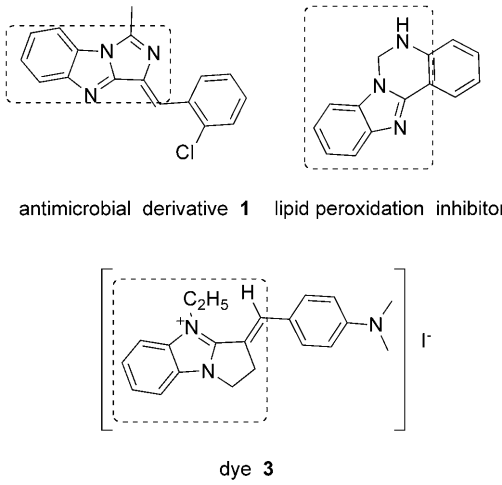
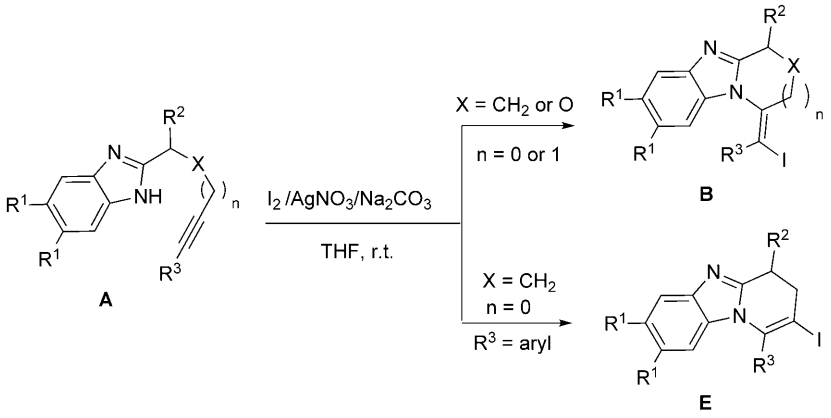


Figure 1. The related structures of fused benzimidazoles.



Scheme 1. Synthesis of fused tricyclic benzimidazoles.

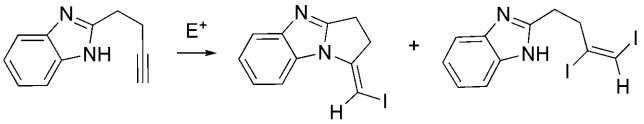
useful intermediates in the synthesis of natural products and pharmaceuticals.[7] In electrophilic cyclization, iodine has been found to be an important and versatile element for the synthesis of functionalized heterocycles such as isoquinolines,[7g,h] indoles,[7d] chromones,[7c] and other heterocycles.[7a,8] Although iodocyclization-based protocols can be successfully used for the preparation of iodinated alkenes, there are some inherent disadvantages such as the formation of bis-iodine by-products.[7g,h,i]

In view of the valuable uses of iodinated alkenes in the production of asymmetrically substituted olefins, it is very important to develop more effective protocols to prepare single-isomer iodinated products. In this paper, we present our recent findings on the regio- and stereo-controlled synthesis of fused iodobenzimidazoles in the presence of $AgNO_3$, which is an important additive for improving the yield of products.[9] It is thought that this improvement is a result of $AgNO_3$ preventing the formation of bis-iodine by-products (Scheme 1).

The requisite cyclization precursors benzimidazoles (**A**) were readily synthesized by previously reported methods from *o*-phenylenediamines and various acetylenic acids through a condensation reaction and subsequent cyclization reaction involving acetic acid.[10]

Initially, 2-(but-3-ynyl)-1*H*-benzo[*d*]imidazole (**A1**) was chosen as the model substrate for investigating the optimum reaction conditions, including solvents, reaction temperatures, reaction times, and amounts of $AgNO_3$. As shown in Table 1, we first studied the reactions of **A1** with I_2 (3.0 equiv.) in THF at room temperature in the presence of a variety of bases (3.0 equiv.) for 2 h (Table 1, entries 1–6). Under base-free conditions, this protocol gave the desired fused benzimidazole product **B1** in 44% yield and the bis-iodine by-product **C1** in 43% yield (Table 1, entry 1). The addition of inorganic bases could increase the yields of **B1**, for example, $NaHCO_3$ and Na_2CO_3 increased the yield to 66% and 78%, respectively (Table 1, entries 2 and 3); however, the by-product **C1** was also formed with 13–22% yields. Besides, we also

Table 1. Iodine-mediated cyclization: optimiazion of the reaction conditions.[a]



A1 B1 C1

Entry	Electrophile (equiv.)	Solvent	Base	Yield [%]	
				B1	**C1**
1	I_2 (3.0)	THF	–	44	44
2	I_2 (3.0)	THF	$NaHCO_3$	66	22
3	I_2 (3.0)	THF	Na_2CO_3	78	13
4	I_2 (3.0)	THF	NaOH	trace	trace
5	I_2 (3.0)	THF	Et_3N	0	0
6	I_2 (3.0)	THF	AcONa	58	29
7	NBS(3.0)	THF	Na_2CO_3	trace	trace
8	NIS(3.0)	THF	Na_2CO_3	trace	trace
9	I_2 (1.5)	THF	Na_2CO_3	79	13
10	I_2 (1.0)	THF	Na_2CO_3	71	12
11	I_2 (0.5)	THF	Na_2CO_3	45	0
12	I_2 (1.5)	CH_2Cl_2	Na_2CO_3	71	14
13	I_2 (1.5)	MeCN	Na_2CO_3	74	15
14	I_2 (1.5)	MeOH	Na_2CO_3	trace	trace
15[b]	I_2 (1.5)	THF	Na_2CO_3	21	4
16[b,c]	I_2 (1.5)	THF	Na_2CO_3	64	11
17[d]	I_2 (1.5)	THF	Na_2CO_3	75	13
18	**I_2 (1.5)/$AgNO_3$ (1.0)**	**THF**	**Na_2CO_3**	**93**	**0**
19	I_2 (1.5)/$AgNO_3$ (0.5)	THF	Na_2CO_3	80	11
20	I_2 (1.5)/$AgNO_3$ (1.5)	THF	Na_2CO_3	88	0
21	$AgNO_3$ (1.0)	THF	Na_2CO_3	0	0

[a] **A1** (0.3 mmol), electrophile, base 0.9 mmol, room temperature, 2 h.
[b] The reaction temperature was 0 °C.
[c] The reaction time was prolonged to 16 h.
[d] The reaction time was prolonged to 4 h.

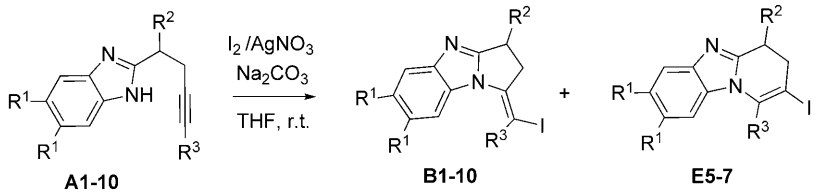
investigated the use of other inorganic and organic bases such as NaOH, Et_3N, and AcONa, but some of them dramatically decreased the yields of the products and even inhibited the reaction or substrate conversion (Table 1, entries 4–6). Other electrophiles, including NBS and NIS, were screened in THF at room temperature for 2 h. The results showed that iodine was the most effective electrophile (Table 1, entries 1–8). In addition, when the amount of iodine was decreased from 3.0 to 1.5 equiv., the yield and selectivity of the target compound were found to have been improved (79% yield, Table 1, entry 9). However, any further decrease in the amount of iodine did not lead to better yields (Table 1, entries 10 and 11). Subsequently, we screened different solvents, and the results showed that THF is the most suitable for this reaction (Table 1, entries 9, 12–14). Decreasing the temperature or prolonging the reaction time did not improve the yield and selectivity of the products (Table 1, entries 15–17). The formation of the by-product **C1** resulted in a decrease in the yield of the desired product, and therefore, we tried to improve the yield and selectivity of this transformation by adding an additive. To our surprise, when $AgNO_3$ (1.0 equiv.) was employed, we obtained good yield and selectivity; and the target product **B1** was obtained in 93% yield and **C1** was not detected (Table 1, entry 18). However, further investigations showed that increasing or decreasing the amount of $AgNO_3$ did not give better yields (Table 1, entries 19 and 20). Additionally, no product was detected in the absence of silver nitrate (Table 1, entry 21). Briefly, the optimum results were obtained when **A1** (0.30 mmol) was treated with 1.5 equiv. of iodine, 3.0 equiv. of Na_2CO_3, and 1.0 equiv. of $AgNO_3$ and THF was used as the solvent at room temperature for 2 h.

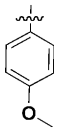
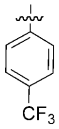
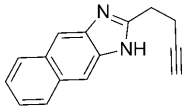
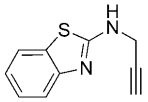
To evaluate the scope of the proposed methods, we attempted to investigate the cyclization of a variety of substituted benzimidazoles (**A**) under the above-mentioned optimum conditions. As shown in Table 2, the protocol was tolerant to the substituents at the position of the R^1 group, including H, methyl and chloro groups (Table 2, entries 1–3). Good yield was also obtained when an alkyl group was introduced at the R^2 position (Table 2, entry 4). Additionally, the introduction of some substituents at the terminal position of the alkynyl groups of various benzimidazoles was also investigated (Table 2, entries 5–8). When R^3 was a phenyl or substituted phenyl group with an electron-donating group, the transformation proceeded well to form intriguing target products; however, a longer time (12 h) was needed to complete the substrate conversion (Table 2, entries 5–7). Introducing a substituted phenyl group with an electron-withdrawing group (4-CF_3Ph) at the R^3 position resulted in a dramatic decrease in the yield of the product, presumably due to electronic effects (Table 2, entry 8). To our surprise, when R^3 was hydrogen, five membered ring-closure products were obtained, however, when R^3 was a phenyl or substituted phenyl group, six-membered products were received, perhaps due to electronic effects. In addition, replacement of the benzimidazole ring with a naphthoimidazole ring also gave a good yield (Table 2, entry 9). However, when we interchanged the benzimidazole ring with a benzothiazole heterocycle, the transformation did not occur under the above-mentioned optimum conditions (Table 2, entry 10).

To further explore the scope of this cyclization, we used it to synthesize piperidine[1,2-*a*]benzimidazoles and oxa-fused benzimidazoles (**B11–B30**) by using the compounds **A11–A30** as the starting materials. As shown in Table 3, the tolerance of the cyclization system was remarkable, and moderate to excellent yields of the desired products were obtained (Table 3, entries 1–18). First, various piperidine[1,2-*a*]benzimidazoles were prepared and excellent yields were obtained when R^1 was hydrogen or methyl, chloro and methoxycarbonyl groups (Table 3, entries 1–4). When R^3 was a phenyl group, substituted phenyl group, or 3-pyridyl group, the reaction proceeded well to form intriguing cyclized products. However, the transformation needed a longer time to complete the substrate conversion (60 h) (Table 3, entries 5–12). Furthermore, various substituted oxa-fused benzimidazoles were obtained in good yields (Table 3, entries 13–17). When R^1 was hydrogen or a chloro group, and R^3 was hydrogen (Table 3, entries 13 and 14), good yields were obtained, but a duration of 4 h was needed to complete the substrate conversion. When R^3 was a methyl group, although the reactions proceeded well to form oxa-cyclized products, the transformation needed a much longer time (36 h) (Table 3, entries 15–17). 2-(Pent-4-ynyl)-1*H*-naphtho-[2,3-*d*]imidazole (**A28**) was tolerated in the reaction, and a good yield was obtained (Table 3, entry 18). However, introducing several substituents at the R^3 position of the annelated substrates led to a drastic decrease in the yields of the desired products under the optimum reaction conditions, presumably due to the steric effects (Table 3, entries 19 and 20).

In principle, the cyclization of alkynes possessing a nucleophile group in proximity to the triple bond can yield various heterocycles *via* different ring-closing pathways. As shown in Scheme 2, there are two possible mechanisms for this transformation, which give three possible products: pathway A, the *exo-dig* cyclization process yields products **B** or **D**; pathway B, the *endo-dig* cyclization process leads to the formation of a product **E**. However, with our strategies, only **E5–E7** – *via* the *endo-dig* cyclization pathway – were obtained, and others were performed *via* the *exo-dig* cyclization pathway. All the fused benzimidazoles synthesized were characterized by ^{1}H NMR, ^{13}C NMR

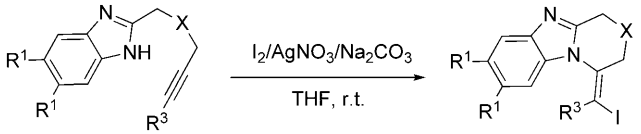
Table 2. Iodine-mediated synthesis of pyrrole[1,2-*a*]benzimidazoles.[a]



Entry	R^1	R^2	R^3	Product **B**	Yield [%]
1	H	H	H	**B1**	94
2	CH_3	H	H	**B2**	90
3	Cl	H	H	**B3**	94
4	H	hexyl	H	**B4**	92
5[b]	H	H		**E5**	90
6[b]	Cl	H		**E6**	82
7[b]	H	H		**E7**	90
8[b]	H	H		**E8**	trace
	Substrate **A**			Product **B**	
9				**B9**	92
10				**B10**	trace

[a] The reaction was carried out in the presence of 1.5 equiv. of I_2, 3.0 equiv. of Na_2CO_3, 1.0 equiv. of $AgNO_3$ and THF as the solvent at room temperature for 2 h.
[b] The reaction time was prolonged to 12 h.

Table 3. Iodine-mediated synthesis of piperidine[1,2-*a*]benzimidazoles and oxa-fused benzimidazoles.[a]



A11-A30 **B11-30**

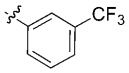
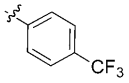
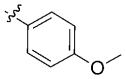
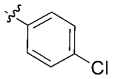
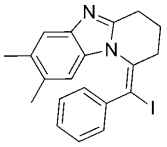
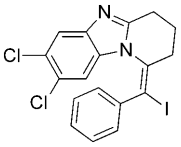
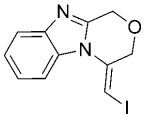
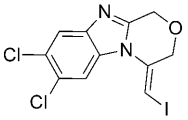
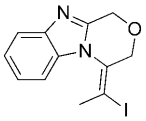
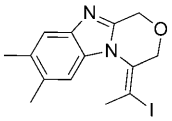
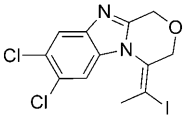
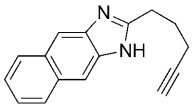
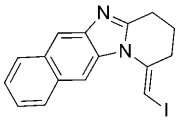
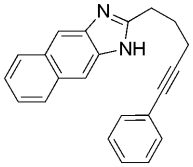
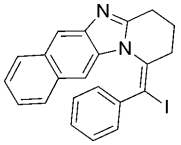
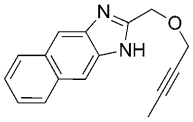
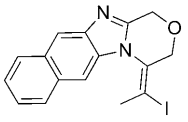
Entry	R^1	R^3	X	Time [h]	Product **B**	Yield [%]
1	H	H	CH_2	2	**B11**	93
2	CH_3	H	CH_2	2	**B12**	91
3	Cl	H	CH_2	2	**B13**	90
4	$COOCH_3$	H	CH_2	2	**B14**	93
5	H		CH_2	60	**B15**	81
6	H		CH_2	60	**B16**	84
7	H		CH_2	60	**B17**	55
8	H		CH_2	60	**B18**	71
9	H		CH_2	60	**B19**	70
10	H		CH_2	60	**B20**	85

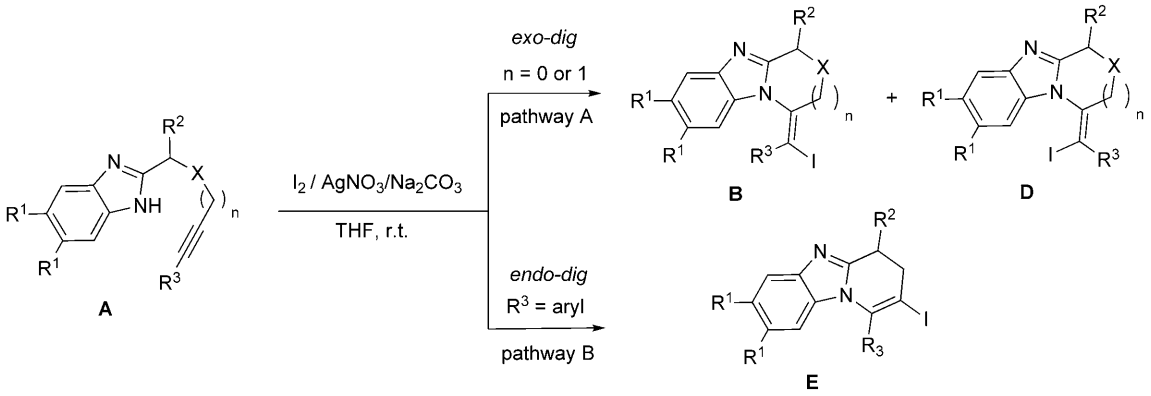
Table 3. (Continued)

Entry	R^1	R^3	X	Time [h]	Product **B**	Yield [%]
11	CH_3		CH_2	60	**B21**	 71
12	Cl		CH_2	60	**B22**	 84
13	H	H	O	4	**B23**	 62
14	Cl	H	O	4	**B24**	 76
15	H	CH_3	O	36	**B25**	 88
16	CH_3	CH_3	O	36	**B26**	 82
17	Cl	CH_3	O	36	**B27**	 81
	Substance **A**				Product **B**	
18				2	**B28**	 88
19				60	**B29**	 trace
20				36	**B30**	 trace

[a] The reaction was carried out in the presence of 1.5 equiv. of I_2, 3.0 equiv. of Na_2CO_3, 1.0 equiv. of $AgNO_3$ and the use of THF as the solvent at room temperature in 2 h.

and MS data. Besides, the structures of **B1**, **E5** and **B17** were determined by X-ray diffraction (XRD) studies (Figure 2, see the Supporting Information for details).[11]

A plausible mechanism for the formation of fused benzimidazoles *via* iodocyclization is depicted in Scheme 3. First, the carbon-carbon triple bonds of the substrate **A** are activated by coordination with iodine to form the I-alkyne π-complex **F**; subsequently, attack of the nitrogen atom at the electron-deficient triple bonds leads to intermediates **G** or **G′** *via* the *exo- dig* or *endo-dig* ring-closing pathway, which is followed by proton transfer to produce the target products **B** or **E**. We hypothesize that iodocyclization to form fused benzimidazoles goes by an ionic mechanism.[12] Adding silver nitrate would assist an ionic re-



Scheme 2. Intramolecular cyclization of **A1.**

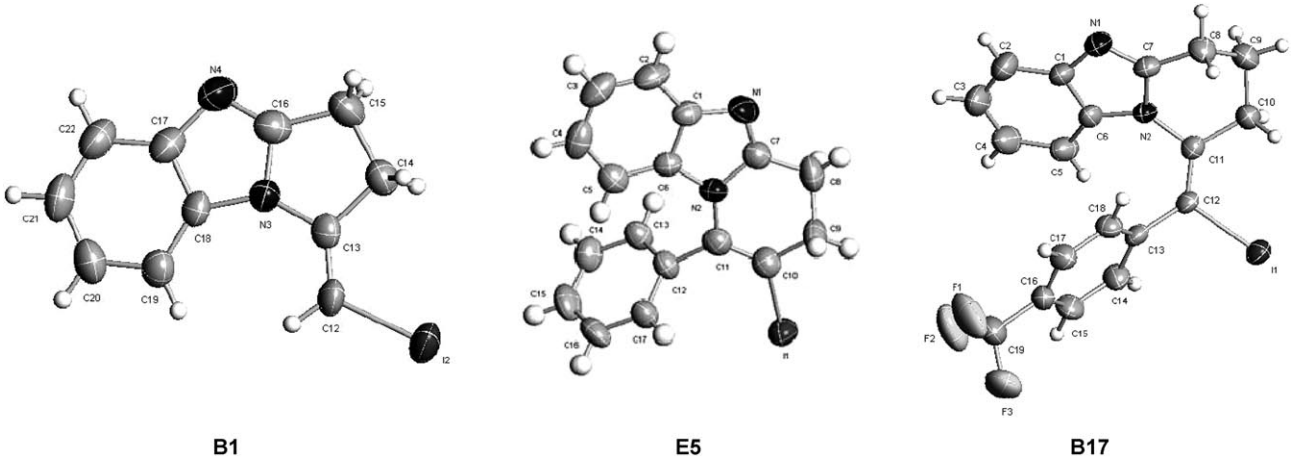


Figure 2. X-ray crystal structures of **B1**, **E5** and **B17**.

action and eliminate iodide ion in the reaction solution to prevent iodide ion attacking intermediate **F** forming bis-iodine by-products in the form of silver iodide.

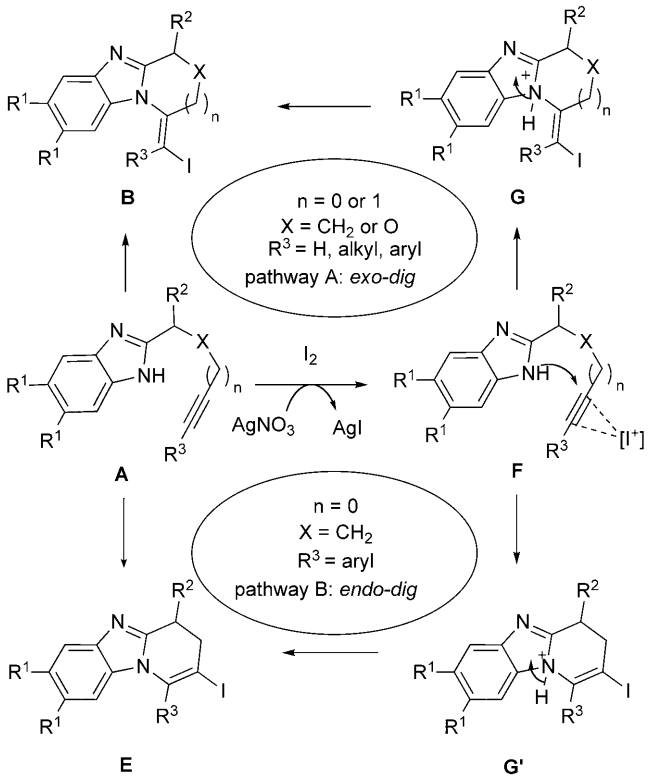
The synthesis of iodo-benzimidazoles has attracted much attention because they are generally considered as important building blocks for several drug molecules and natural products (Scheme 4). For example, the Suzuki coupling of **B1** with phenylboronic acid can easily afford **H** in 94% yield. Compound **B1** undergoes a Sonogashira coupling reaction with 1-ethynyl-4-methylbenzene to give the corresponding **I** in 88% yield. Further studies involving the application of these intriguing iodo-benzimidazoles are under investigation in our laboratory, and the results will be reported in due course.

In summary, we have developed an approach to synthesize various fused benzimidazoles *via* iodine-induced cyclization. These reactions are run under mild conditions, are tolerant to various substituted substrates, and can generally provide fused benzimidazole products in good to excellent yields. In addition, the presence of the halogen functionality, especially the iodo group, in the heterocyclic products renders the products useful as substrates for both the efficient preparation of interesting bioactive molecules and the construction of a compound library for drug screening.

Experimental Section

Typical Procedure for Synthesis of the Substrates (A1 as an Example)

To a solution of substituted or unsubstituted 1,2-phenylenediamine[13a] (2.0 mmol) in methanol (20 mL) was added 4-pentynoic acid[13b] (1.0 equiv.) and EDCI (1.1 equiv.). The reaction mixture was stirred at room temperature for 4–5 h while being monitored by TLC. The solvent was concentrated under vacuum and the amide intermediate derivatives were precipitated by the addition of water. After filtration, the solid was dried. Then the solid was dissolved in neat acetic acid, and stirred at 90 °C under N_2 for 5 h. The acetic acid was distilled off; the residue was dissolved in ethyl ace-



Scheme 3. A plausible mechanism for the iodocyclization.

tate (EtOAc), and washed by saturated $NaHCO_3$, brine, dried over anhydrous Na_2SO_4. Evaporation of the solvent followed by chromatography on a silica gel column with Petro Ether (PE)/EtOAc (4/1, v/v) as eluent to give the desired *2-(but-3-ynyl)-1H-benzo[d]imidazole* **(A1):** ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.13–2.15$ (m, 1H, CH), 2.73–2.79 (m, 2H, CH_2), 3.18 (t, $J = 6.9$ Hz, 2H, CH_2), 7.24–7.28 (m, 2H, ArH), 7.57–7.60 (m, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 17.3$, 28.3, 70,3, 83.2, 122.5, 152.8; ESI-MS: $m/z = 171$ $[M + H]^+$; HR-MS (ESI): $m/z = 171.0920$, calcd. for $C_{11}H_{11}N_2$ $[M+H]^+$: 171.0922.

General Procedure for Synthesis of B1–B28, E5–E7 (B1 as an Example)

To a solution of 0.3 mmol of **A1** in 10 mL of THF were added 0.45 mmol of iodine, 0.9 mmol of Na_2CO_3 and 0.3 mmol $AgNO_3$. The mixture was stirred at room temperature, after the starting materials had been completely consumed as monitored by TLC, the solvent was removed under reduced pressure, and the residue was taken up in EtOAc and washed with saturated $Na_2S_2O_3$, brine, dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by a flash column chromatography to provide **B1**.

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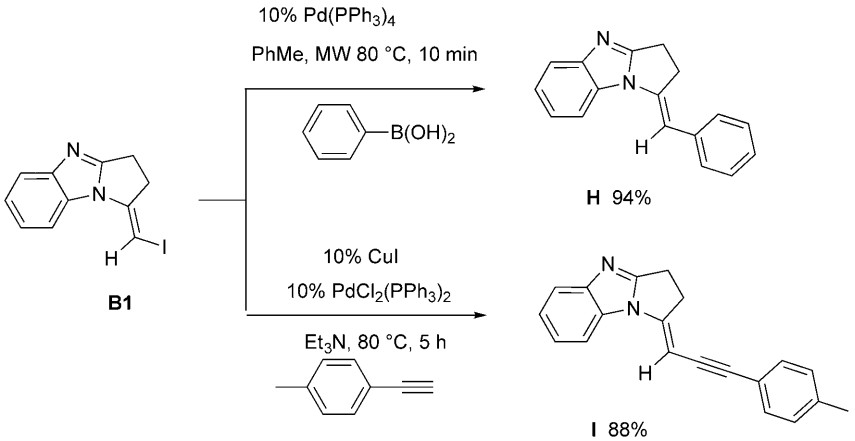

Scheme 4. Diversification of fused indo-benzimidazoles.

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