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Hypervalent Iodine(III)-Mediated Benzannulation of Enamines with Alkynes for the Synthesis of Polysubstituted Naphthalene Derivatives

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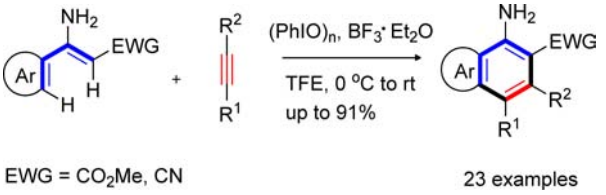
ABSTRACT



A series of functionalized 1-amino-2-naphthalenecarboxylic acid derivatives were synthesized from enamines and alkynes via a benzannulation strategy mediated by iodosylbenzene and $BF_3 \cdot Et_2O$. The advantages of this novel benzannulation process include broad substrate scope, good functional group tolerance, and mild reaction conditions without the use of heavy metals.

Hypervalent iodine(III) reagents were used extensively in organic synthesis as a result of their unique properties, such as readily availability, environmental benignity, and high reactivity.[1] Under metal-free conditions, the utilization of hypervalent iodine(III) reagents for C−N,[2] C−O,[3] or N−N[4] bond formation has been thoroughly investigated. In recent years, it was found that hypervalent iodine(III) reagents also showed remarkable reactivies for C−C bond formation. Following these strategies, biaryl compounds,[5] spirodienones,[6] or heterocycles[7] could be obtained successfully. Nevertheless, hypervalent iodine-(III)-mediated intermolecular cyclization procedures via C−C bond formation have been seldom reported, especially in the synthesis of carbocycles.[8]

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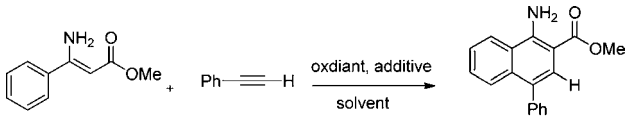
Polysubstituted naphthalenes are important raw materials both in medicinal chemistry and industrial chemistry not only because of their remarkable biological and pharmacological activities but also because of their electrochemical and photochemical properties.[9] Apart from these interesting activities, some naphthalene derivatives also find application in the design of chiral catalysts, ligands, and metal complexes.[10] Therefore, development of new methods for the synthesis of naphthalene derivatives, especially the polysubstituted ones, is of great importance. For the preparation of naphthalene derivatives, many efficient benzannulation strategies have been reported.[11] For example, Yamamoto and co-workers had developed a variety of benzannulations of enynals with alkynes or enols leading to naphthalenes with transition metals as catalyst.[11a−c] The benzannulation reaction of the Fischer carbene complexes, named the Wulff−Dötz reaction, was another important approach to naphthalene derivatives.[11d−g] However, most of these methodologies started from multistep-prepared materials and relied heavily on transition-metal catalysts. To develop simple methods for the preparation of naphthalene derivatives and in continuation of our efforts on the development of hypervalent iodine(III) mediated oxidative reactions,[12] herein we report a new benzannulation strategy for the synthesis of 1-amino-2-naphthalenecarboxylic acid derivatives from readily available enamines and alkynes mediated by $(PhIO)_n$ and $BF_3 \cdot Et_2O$.

Initial expieriments were carried out using enamine **1a** and phenylacetylene as the model substrates to test the feasibility of this transformation. As seen from Table 1, phenyliodine diacetate (PIDA), phenyliodine bis-trifluoroacetate (PIFA) or hydroxy(tosyloxy)iodobenzene (HTIB) showed low reactivity in this reaction. In the presence of these oxidants, **3aa** was obtained in low yield (entries 1−3). To our delight, by changing the oxidant to $(PhIO)_n$, yield of **3aa** was greatly improved to 85% (entry 4). Use of other additives, such as *p*-toluenesulfonic acid (PTSA), 60% HPF_6 water solution, or 40% HBF_4 water solution instead of $BF_3 \cdot Et_2O$ led to a decrease of the product yield (entries 5−7). There was no increase in yield of **3aa** when the dosage of $BF_3 \cdot Et_2O$ increased from 1.2 to 1.8 equiv. Decreasing the dosage of $BF_3 \cdot Et_2O$ to 0.6 equiv dramatically reduced the yield of product **3aa**, and only a trace amount of the product was detected (entries 8 and 9). Among the solvents tested, including 2,2,2-trifluoroethanol (TFE), CH_2Cl_2, CH_3CN, and EtOAc, TFE gave the best result (entries 10−12). Thus, the optimized procedure was chosen as follows: carried out the reaction in TFE in the presence of 1.1 equiv $(PhIO)_n$ and 1.2 equiv $BF_3 \cdot Et_2O$ at 0 °C to room temperature for 5 h (entry 4).

Table 1. Optimization of Iodine(III)-Mediated Benzannulation of Methyl 3-Amino-3-phenylacrylate and Phenylacetylene for the Synthesis of Methyl 1-Amino-4-phenyl-2-naphthoate[a]



1a 2a 3aa

entry	oxidant	solvent	additive (equiv)	yield[b] (%)
1	PIDA	TFE	$BF_3 \cdot OEt_2$ (1.2)	21
2	PIFA	TFE	$BF_3 \cdot OEt_2$ (1.2)	26
3	HTIB	TFE	$BF_3 \cdot OEt_2$ (1.2)	trace
4	$(PhIO)_n$	TFE	$BF_3 \cdot OEt_2$ (1.2)	85
5	$(PhIO)_n$	TFE	PTSA (1.2)	trace
6	$(PhIO)_n$	TFE	HPF_6 (1.2)[c]	76
7	$(PhIO)_n$	TFE	HBF_4 (1.2)[d]	68
8	$(PhIO)_n$	TFE	$BF_3 \cdot OEt_2$ (1.8)	84
9	$(PhIO)_n$	TFE	$BF_3 \cdot OEt_2$ (0.6)	trace
10	$(PhIO)_n$	CH_2Cl_2	$BF_3 \cdot OEt_2$ (1.2)	63
11	$(PhIO)_n$	CH_3CN	$BF_3 \cdot OEt_2$ (1.2)	trace
12	$(PhIO)_n$	EtOAc	$BF_3 \cdot OEt_2$ (1.2)	trace

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.5 mmol), oxidant (0.55 mmol), additive, in solvent (5 mL), 0 °C to rt, 5 h. [b] Isolated yield. [c] 60% HPF_6 water solution was used. [d] 40% HBF_4 water solution was used.

With the optimized conditions in hand, different substrates were tested for the synthesis of substituted 1-amino-2-naphthalenecarboxylic acid derivatives (Scheme 1). To our satisfaction, phenyl enamines bearing electron-donating or electron-withdrawing groups in the phenyl ring were all reacted well and the corresponding products were isolated with high yields (**3aa**−**ia**). To our surprise, when 3-amino-3-(2-methylphenyl)acrylic acid methyl ester (**1c**) was used as a substrate, benzannulation took place at the meta position of the methyl group of the aromatic ring to lead to product **3ca** in good yield and no steric effect of the *o*-methyl group was observed. Naphthyl enamine **1j** also reacted well, and the corresponding phenanthrene derivative **3ja** was obtained in good yield. However, when heterocyclic enamine **1k** was used as substrate, the reaction was complicated and only trace amount of the product **3ka** were detected. Reactions of the enamine **1l** bearing cyano as an electron-withdrawing group with phenylacetylene also proceeded smoothly and gave the desired product (**3la**) in moderate yield.

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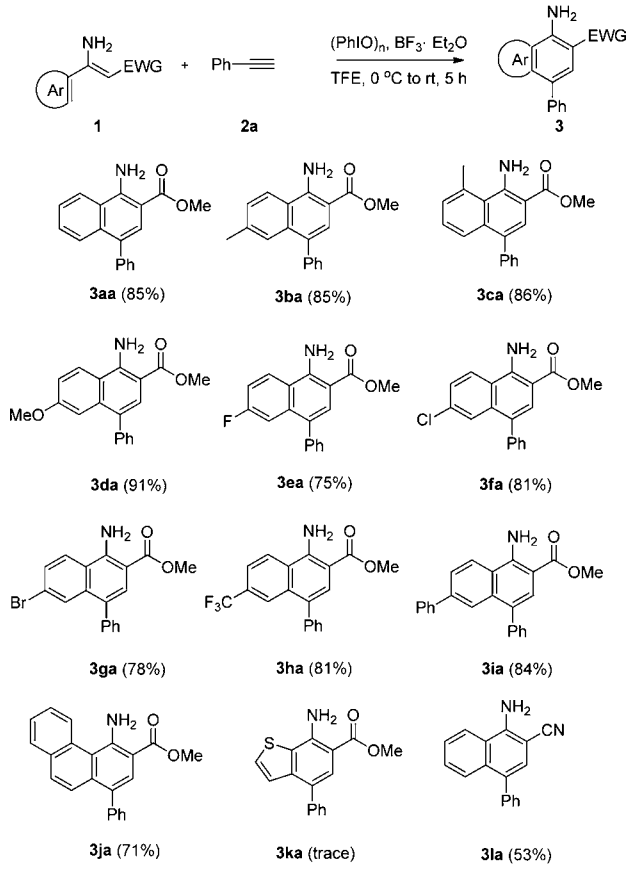
Scheme 1. Scope of Enamine Substrates for Iodine(III)-Mediated Benzannulation with Phenylacetylene[a]

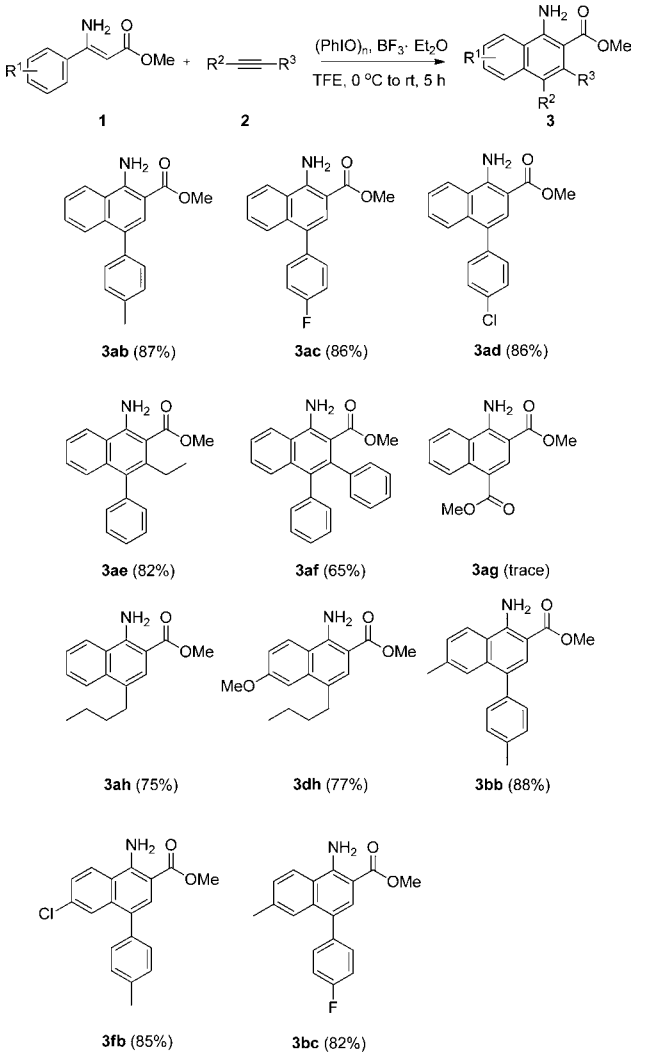


[a] Reaction conditions: **1** (0.5 mmol), **2a** (0.5 mmol), $(PhIO)_n$ (0.55 mmol), $BF_3 \cdot OEt_2$ (0.6 mmol), in TFE (5 mL), 0 °C to rt, 5 h, isolated yield.

In light of the above encouraging results, our further study was aimed at the scope of alkynes in this reaction. As seen from Scheme 2, substituted phenyl terminal alkynes all smoothly converted to the desired products in moderate to good yields (**3ab**–**ad**). Nonterminal alkynes, such as 1-(but-1-ynyl)benzene (**2e**) and 1,2-diphenylethyne (**2f**), also gave the corresponding products (**3ae**, **3af**) in moderate to good yields. The relatively lower yield of **3af** may be due to the decreased reactivity of the alkyne group or the steric effect of the two phenyl groups in 1,2-diphenylethyne. However, only a trace amount of product (**3ag**) was detected when methyl propiolate (**2g**) was used as the alkyne partner. The decreased reactivity of the alkyne by ester group maybe cause the failure to get product **3ag**. When 1-hexyne (**2h**), an aliphatic terminal alkyne, was used as substrate, the corresponding benzannulation products (**3ah**, **3dh**) were also obtained in good yields. Reaction of substituted phenylalkynes with various enamines also gave corresponding 1-amino-2-naphthalenecarboxylic acid derivatives **3bb**, **3fb**, and **3bc** in good to excellent yields.

All of the isolated products were identified by ^1H, ^{13}C NMR and HR-MS. The crystal structure of **3aa** was determined by X-ray crystallography (Figure 1).

Scheme 2. Synthesis of 1-Amino-2-naphthalenecarboxylic Acid Derivatives from Different Alkynes[a]



[a] Reaction conditions: **1** (0.5 mmol), **2a** (0.5 mmol), $(PhIO)_n$ (0.55 mmol), $BF_3 \cdot OEt_2$ (0.6 mmol), in TFE (5 mL), 0 °C to rt, 5 h, isolated yield.

On the basis of the properties of $(PhIO)_n$[13] and literature reports about the reaction of hypervalent iodine(III) reagents with enamine compounds,[7d,e,14] a possible mechanism is proposed in Scheme 3. First, depolymerization of $(PhIO)_n$ with $BF_3 \cdot OEt_2$ generates the iodine(III) reagent **A**. Reaction of **A** with enamine **1** gives the intermediate **B**. Nucleophilic attack of alkyne **2** on **B** generates **C**. The final benzannulation product **3** is then formed by intramolecular

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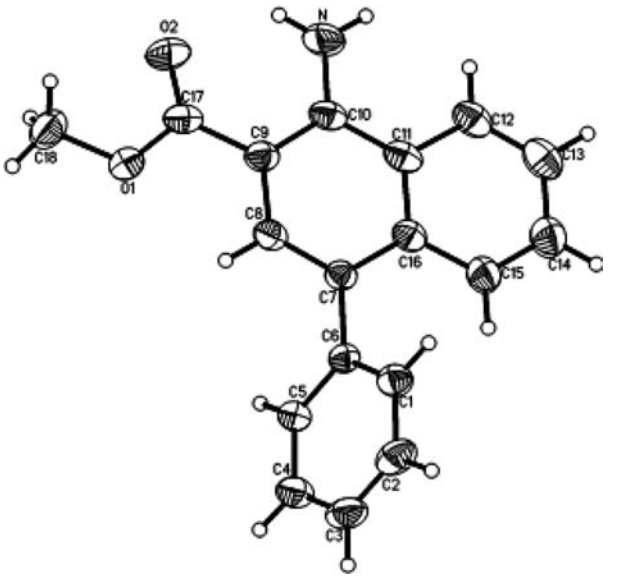
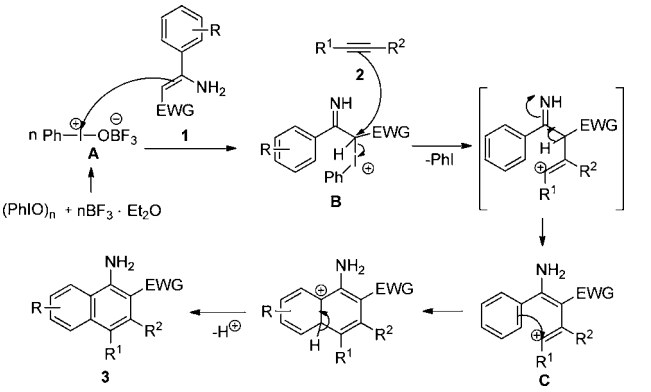


Figure 1. X-ray crystal structure of **3aa**.

electrophilic attack of the cationic carbon of **C** on the aromatic ring.

In summary, an efficient, direct oxidative benzannulation procedure was developed. This novel protocol afforded 1-amino-2-naphthalenecarboxylic acid derivatives in high yields from easily available enamines and alkynes in the presence of $(PhIO)_n$ and $BF_3 \cdot OEt_2$. Broad substrate scope, good functional group tolerance, and mild reaction conditions make the protocol a potential approach to the synthesis of useful naphthalene derivatives. Further studies to clearly understand the mechanism and extension of the scope of the protocol are currently under investigation in our laboratory.

Scheme 3. Possible Mechanism of the Hypervalent Iodine(III)-Mediated Benzannulation of Enamines with Alkynes



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Supporting Information Available. Experimental details and characterization data for products. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.