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Synthesis of indolequinones via a Sonogashira coupling/cyclization cascade reaction

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ABSTRACT

A mild strategy for constructing indolequinone motifs is described on the basis of the Sonogashira reaction and a copper-catalyzed intramolecular cyclization cascade reaction. The first step involves the palladium- and copper-catalyzed reaction between halogenated naphthoquinone and terminal acetylene to generate a coupling product, which then reacts in a copper-catalyzed intramolecular cyclization with the nitrogen functional group adjacent to the carbon–carbon triple bond.

Heterocycles, particularly indoles, are interesting and valuable because they are widely found in various biologically active natural and artificial compounds.[1] Therefore, development of efficient methods to synthesize these compounds continues to be an active research area. In particular, the intramolecular cyclization of *o*-alkynylanilines, which is typically prepared from *o*-haloanilines via the Sonogashira reaction, has been widely reported.[2,3] Despite the early successes using this method, there are limited applications for synthesizing indolequinones. These motifs are often found in antitumor agents such as mitomycin C[4] and EO9.[5] Recently, Shvartsberg group reported the stepwise synthesis of indolequinones from 3-acetylamino-2-bromo-1,4-naphthoquinone and terminal acetylenes by the Sonogashira reaction followed by the intramolecular cyclization of the isolated coupling products with K_2CO_3 in MeCN at 80 °C.[6] Some significant drawbacks of this method are the limitation of substituents on naphthoquinone substrates and the undesired elimination reactions during the cyclization step. In addition, we found that the dehalogenated compound of starting naphthoquinone 1a was gradually formed during the reaction with increasing temperature. Thus, development of one-pot synthesis of indolequinones under mild conditions is still challenging in organic synthesis (Scheme 1). Herein, we describe the development of a cascade reaction for constructing indolequinone motifs involving the Sonogashira reaction and intramolecular cyclization.

To screen the optimal reaction conditions, 2-bromo-3-(methylamino)naphthalene-1,4-dione (**1a**) having an electron-donating substituent on amino group was selected, because no coupling reaction was observed under the reported conditions.[6] The results are shown in Table 1. According to the procedure in the Castro–Stephens reaction,[7] the reaction of **1a** with **4a** (10 equiv with respect to **1a**) in the presence of Cu_2O (1 equiv with respect to **1a**) and pyridine (50 equiv with respect to **1a**, pyridine:copper = 25:1) in DMF at room temperature was examined. However, no conversion was observed. Alternatively, adding of 3 mol % $Pd(OAc)_2$ to the reaction mixture showed a mild conversion to the coupling product **2aa** and the cyclized product **3aa** in 3% and 6% yields, respectively (Table 1, entry 2). The use of 20 equiv of pyridine (pyridine:copper = 10:1) did not give the desired product, while 100 equiv of pyridine (pyridine:copper = 50:1) gave the desired product in moderate yield (41%) (Table 1, entry 3). Moreover, the use of 200 equiv of pyridine (pyridine:copper = 100:1) was not effective in increasing the yield further, which suggests that the optimum amount of pyridine is 100 equiv (pyridine:copper = 50:1). In addition, using 200 equiv of pyridine decreased the yield because of a slower cyclization process (Table 1, entry 4). The best result was obtained using 2.0 equiv of acetylene **4a** with respect to **1a** with a reaction time of 24 h (Table 1, entry 5). Regardless of the amount of acetylene, coupling reactions were completed within about 4 h (TLC monitoring). We speculate that the cyclization process starts from the ligation of the acetylene moiety of the coupling product **2aa** to the copper

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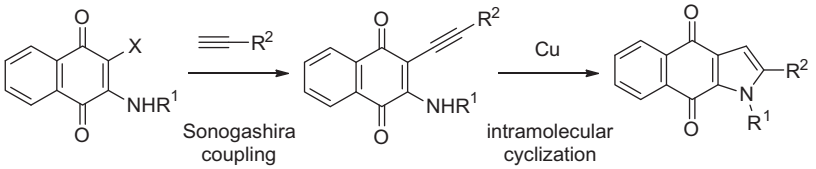
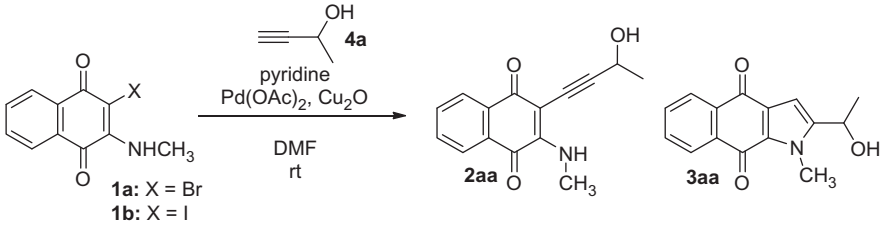


Scheme 1. Construction of indolequinone motifs.

Table 1
Reaction of 2-bromo-3-(methylamino)naphthalene-1,4-dione with but-3-yn-2-ol[a]



Entry	Time (h)	Alkyne **4a** (equiv)	Ratio of pyridine to Cu	**2aa** Yield (%)[b]	**3aa** Yield[b] (%)
1	48	10	10:1	trace	0
2	48	10	25:1	3	6
3	48	10	50:1	2	41
4	48	10	100:1	15	28
5	24	2	50:1	0	56
6[c]	48	2	500:1	10	0
7[d]	12	2	25:1	0	52
8[e]	12	2	50:1	0	51
9[f]	24	2	50:1	0	trace
10[g]	24	2	50:1	<13	trace
11[h]	24	2	50:1	0	47
12[i]	24	2	50:1	0	62

[a] Substrate **1** (0.5 mmol), $Pd(OAc)_2$ (3 mol %), Cu_2O (0.5 mmol), acetylene, and pyridine were stirred in DMF at rt.
[b] Isolated yield.
[c] Cu_2O (0.05 mmol) was used.
[d] Cu_2O (1.0 mmol) was used.
[e] $Pd(OAc)_2$ (10 mol %) was used.
[f] CuBr was used instead of Cu_2O.
[g] CuI was used instead of Cu_2O.
[h] DMF was omitted.
[i] **1b** was used as the substrate.

atom. Therefore, decreasing the amount of acetylene **4a** probably made the cyclization reaction faster. Decreasing the amount of Cu_2O caused no cyclized products to form after 48 h (Table 1, entry 6).[8] Meanwhile, increasing the amount of Cu_2O or $Pd(OAc)_2$ did not improve the yield either (Table 1, entries 7 and 8). The reaction with other copper(I) salts (CuBr, CuI)[9] yielded trace amounts of the cyclized product (Table 1, entries 9 and 10). Using DMF as a solvent is not essential, although the yield of **3aa** slightly decreased in the absence of DMF (Table 1, entry 11).[10] Iodide **1b** was also tested as a substrate in this reaction, and a slightly better yield was obtained compared to that obtained when using bromide **1a** as the substrate (Table 1, entry 12). Some palladium catalysts, such as $Pd(PPh_3)_2Cl_2$ and $Pd(PPh_3)_4$ were also used, but they gave a lower yield of **3aa** and formed byproducts such as the dehalogenated compound of **1a**.[11]

Further investigations were performed by varying the substituents on pyridine. The results are summarized in Table 2. Reaction of **1a** with 2,4-dimethylpyridine and 4-methylpyridine gave products **3aa** in 33% and 55% yields, respectively (Table 2, entries 2 and 3), while reaction with 2,6-dimethylpyridine, having a sterically hindered nitrogen atom, gave no cyclized product owing to the formation of unknown byproducts (Table 2, entry 1). Triethylamine was ineffective in promoting the coupling reaction of halogenated naphthoquinone **1a** with acetylene **4a**, although it is generally used as a base in the Sonogashira reaction (Table 2, entry 4). These results suggest that pyridine acts both as a base to deprotonate acetylene as well as a ligand for promoting the reaction. Similar results were reported as amine effects.[12] Coordination of pyridine to a dimeric or polymeric copper catalyst possibly produced an active monomeric catalyst (Scheme 2). Usually, bidentate or polydentate ligands are known to promote copper-mediated coupling reactions;[2a] our results showed that monodentate pyridine also promoted the coupling reaction.[13]

In order to determine which species play an important role in the final cyclization step, we isolated the coupling product **2aa** and tested it under various reaction conditions.[14] Following the optimized reaction conditions shown in Table 1, we obtained less than 5% of the cyclized product **3aa** (Table 3, entry 1). Meanwhile, almost no reaction occurred in the absence of Cu_2O even if **1a** was added to its reaction mixture (Table 3, entries 3 and 4). These