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Highly Regioselective Synthesis of 1,3-Diiodonaphthalene Derivatives via a Sequential Cascade Iodocyclization

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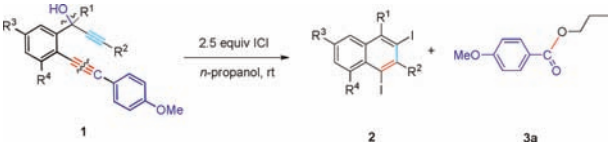
ABSTRACT



A novel and flexible sequentially cascade iodocyclization for the synthesis of highly substituted 1,3-diiodinated naphthalene derivatives in up to 99% yield under mild conditions is reported. The dihalogenated moiety can be readily introduced into the naphthalenes in a position that is usually not easily functionalized.

Electrophilic cyclization of nucleophiles with alkyne or allene bound substrates has proven to be an effective method for the synthesis of functionalized heterocyclic and carbocyclic compounds.[1−12] Many important heterocycles and carbocycles, such as furans,[2] benzo[*b*]furans,[3] pyrroles,[4] indoles,[5] isoquinolines,[6] quinolines,[7] benzo[*b*]thiophenes,[8] isocoumarins,[9] α-pyrones,[9] naphthols,[10] naphthalenes,[11] and indenes,[12] have been accessed based on this strategy. However, only limited reports concerning sequential cascade iodocyclization have been presented in the literature. Cascade iodocyclization shows the undeniable benefits, including metal-free and mild conditions, as well as economies of time, labor, and waste generation. Quite recently, Wu and co-workers have reported an interesting iodine-mediated cascade cyclization of enediynes, which produces iodinated benzo[*a*]carbazoles.[13] In the context of our ongoing interest in iodocyclization chemistry,[14] and our efforts to develop efficient synthetic methods of carbocyclic compounds,[15] we report a sequential cascade iodocyclization for the synthesis of naphthalene derivatives with high regioselectivity.

Our initial study began with 1-[2-(4-methoxyphenylethynyl)phenyl]-3-phenylprop-2-yn-1-ol (**1a**) (0.2 mmol)

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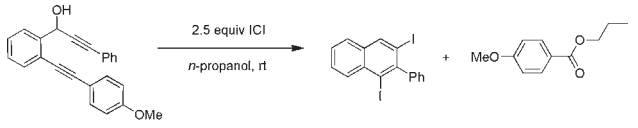
and 2 equiv of ICl in *n*-propanol at room temperature. Gratifyingly, the desired 1,3-diiodo-2-phenylnaphthalene (**2a**) was isolated in good yield (77%), along with 4-methoxybenzoic acid propyl ester in 80% after 1 h (Table 1, entry 1). The structure of compound **2a** was identified unambiguously by X-ray diffraction (Figure 1). With other solvents such as methanol, ethanol, 2-propanol, and *n*-butanol, no superior results were obtained (Table 1, entries 2−5). On increasing the amount of ICl to 2.5 equiv, a 90% yield of **2a** was obtained (Table 1, entry 6). Surprisingly, on further increasing the amount of ICl to 4.0 equiv gave the decreased yield of 84% (Table 1, entrie 7). The reaction was also tested in different temperatures, but no better results were observed (Table1, entries 8 and 9). The study of other electrophiles such as I_2, NIS, and IBr showed that lower yields of the desired products were obtained (Table 1, entries 10−12). The reaction was also carried out in dry *n*-propanol but with almost no differences (Table 1, entry 13).

Table 1. Optimization of Cascade Iodocyclization of **1a**[a]



1a 2a 3a

entry	electrophile (equiv)	solvent	products/yield[b] (%)	
1	ICl (2)	*n*-propanol	**2a**/77	**3a**/80
2	ICl (2)	C_2H_5OH	**2a**/74	**3b**/77
3	ICl (2)	CH_3OH	**2a**/72	**3c**/70
4	ICl (2)	2-propanol	**2a**/68	**3d**/54
5	ICl (2)	*n*-butanol	**2a**/74	**3e**/93
6	ICl (2.5)	*n*-propanol	**2a**/90	**3a**/85
7	ICl (4)	*n*-propanol	**2a**/82	**3a**/94
8[d]	ICl (2.5)	*n*-propanol	**2a**/86	**3a**/87
9[e]	ICl (2.5)	*n*-propanol	**2a**/82	**3a**/90
10	I_2(2.5)	*n*-propanol	**2a**/24	**3a**/30
11	NIS(2.5)	*n*-propanol	nr[c]	nr[c]
12	IBr(2.5)	*n*-propanol	**2a**/48	**3a**/53
13	ICl(2.5)	dried *n*-propanol	**2a**/88	**3a**/89

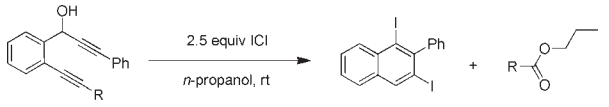
[a] All reactions were run under the following conditions, unless otherwise indicated: 0.2 mmol of **1a** with 2.5 equiv of ICl in 4 mL of *n*-propanol at room temperature. [b] Isolated yield. [c] nr = no reaction. [d] The reaction was run at 0 °C. [e] The reaction was run at 40 °C.

With an attempt to optimize the yield of the product **2a**, we further studied the influences of the leaving group in the substrate. Table 2 shows a screening of the influence. We observed that electron-rich R groups showed moderate to good results (Table 2, entries 1−4 and 7), while electron-poor R groups went against the cascade iodocyclization (Table 2, entries 5 and 6). This may be because the alkynes with tethered electron-rich R groups are conducive to the coordination to the iodide cation and then undergo the cascade cyclization process. Therefore, substrates with 4-methoxyphenyl R group were in favor of the reaction.

With a series of detailed investigations mentioned above, the reaction conditions were eventually optimized as (Table 1 entry 6) follows: 1.0 equiv of **1a** and 2.5 equiv of ICl in *n*-propanol at room temperature.

To investigate the generality and the scope of this cyclization, various representative 1,6-diyn-4-en-3-ols **1a**−**w** were then submitted to the above conditions, as depicted in Table 3.

Table 2. Study of the Influence of the Leaving Group in the Substrate[a]



1 2a 3

entry	substrate	R	products/yield[b] (%)	
1	**1a**	*p*-OMe-C_6H_4	**2a**/90	**3a**/85
2	**1ab**	*p*-Me-C_6H_4	**2a**/63	**3ab**/42
3	**1ac**	*n*-propyl	**2a**/33	
4	**1ad**	Ph	**2a**/41	trace
5	**1ae**	1- naphthyl	**2a**/50	**3ae**/23
6	**1af**	TMS	nr[c]	nr[c]
7	**1ag**	*p*-NO_2-C_6H_4	dec[d]	dec[d]

[a] All reactions were run under the following conditions, unless otherwise indicated: 0.2 mmol of **1** with 2.5 equiv of ICl in 4 mL *n*-propyl alcohol at room temperature. [b] Isolated yield. [c] nr = no reaction. [d] dec = decomposed.

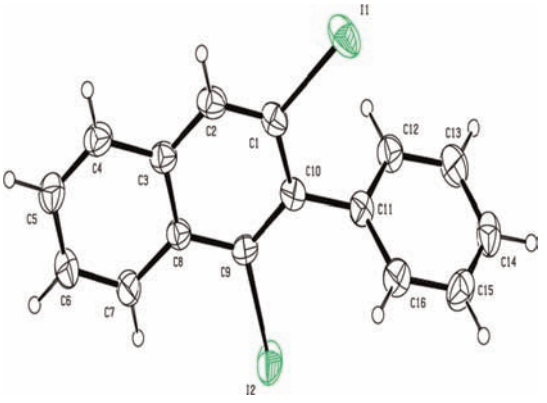


Figure 1. Structure of **2a**.

The reactions of substrates **1b**−**j** bearing an electron-donating or an electron-withdrawing aromatic R^2 group produced the corresponding 1,3-diiodinated naphthalene derivatives **2b**−**j** in good to excellent yields. However,

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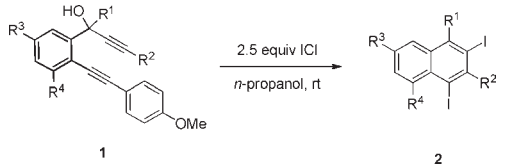
Table 3. Cascade Iodocyclization to1,3-Diiodinated Naphthalene Derivatives[a]



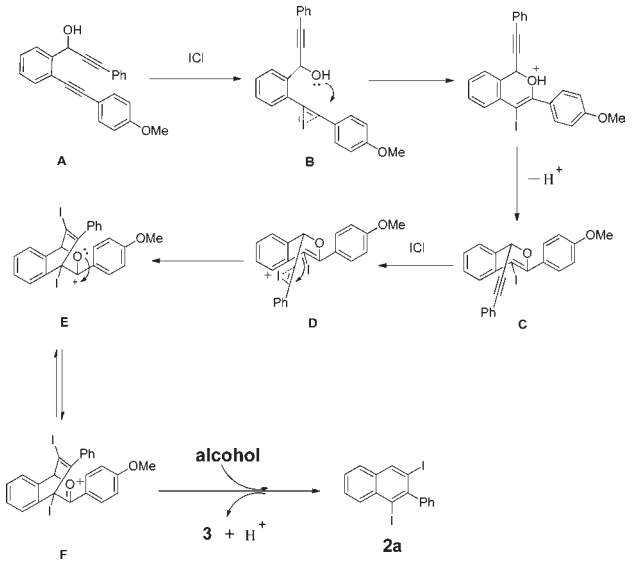
1 2

entry	substrate	products/ yield[b] (%)
1	R^1 = H, R^2 = Ph, R^3 = H, R^4 = H	**2a**/90
2	R^1 = H, R^2 = *p*-Me-C_6H_4, R^3 = H, R^4 = H	**2b**/72
3	R^1 = H, R^2 = *o*-Me-C_6H_4, R^3 = H, R^4 = H	**2c**/74
4	R^1 = H, R^2 = 3,4-dimethylphenyl, R^3 = H, R^4 = H	**2d**/58
5	R^1 = H, R^2 = *o*-Cl-C_6H_4, R^3 = H, R^4 = H	**2e**/88
6	R^1 = H, R^2 = *m*-Cl-C_6H_4, R^3 = H,R^4 = H	**2f**/87
7	R^1 = H, R^2 = *p*-Cl-C_6H_4, R^3 = H, R^4 = H	**2g**/95
8	R^1 = H, R^2 = *o*-Br-C_6H_4, R^3 = H, R^4 = H	**2h**/80
9	R^1 = H, R^2 = *m*-Br-C_6H, R^3 = H, R^4 = H	**2i**/88
10	R^1 = H, R^2 = *p*-Br-C_6H_4, R^3 = H, R^4 = H	**2j**/99
11	R^1 = H, R^2 = *p*-OMe-C_6H_4, R^3 = H, R^4 = H	dec[d]
12	R^1 = H, R^2 = 1-naphthyl, R^3 = H, R^4 = H	**2l**/83
13	R^1 = H, R^2 = *n*-propyl, R^3 = H, R^4 = H	**2m**/72
14	R^1 = H, R^2 = TMS, R^3 = H, R^4 = H	nr[c]
15	R^1 = H, R^2 = Ph, R^3 = F, R^4 = H	**2o**/85
16	R^1 = H, R^2 = Ph, R^3 = OMe, R^4 = H	**2p**/74
17	R^1 = H, R^2 = Ph, R^3 = H, R^4 = Me	**2q**/7
18	R^1 = H, R^2 = Ph, R^3 = H, R^4 = Cl	**2r**/4
19	R^1 = ethyl, R^2 = Ph, R^3 = H, R^4 = H	**2s**/70
20	R^1 = isopropyl, R^2 = Ph, R^3 = H, R^4 = H	**2t**/68
21	R^1 = Ph, R^2 = Ph, R^3 = H, R^4 = H	**2u**/42
22	R^1 = *m*-Me-C_6H_4, R^2 = Ph, R^3 = H, R^4 = H	**2v**/43
23	R^1 = H, R^2 = cyclohexenyl, R^3 = H, R^4 = H	**2w**/30

[a] All reactions were run under the following conditions, unless otherwise indicated: 0.2 mmol of **1** with 2.5 equiv of ICl in 4 mL of *n*-propanol at room temperature. [b] Isolated yield. [c] nr = starting **1** was recovered in 40%. [d] dec = decomposed.

electron-withdrawing aryl groups got better results than those with an electron-donating group in this reaction (entries 2−4 vs 5−10). We envisioned that an electron-withdrawing aromatic R^2 group led to the decline of the density of the electron of the alkynyl moiety, which was unfavorable for coordination with the iodide cation, while the other alkynyl moiety with an electron-rich group was more easy to react. This was conducive to the first cyclization step (Scheme 1). Subsequently, we designed compound **1k** and discovered that it even failed to obtain the corresponding product, which was in accord with the above presumption (entry 11). The reactions also worked

Scheme 1



well with the compounds **1l** and **1m** having a naphthyl or an aliphatic group at R^2, which proceeded to give the desired 1,3-diiodinated products **2l** and **2m** in good yields (entries 12 and 13), while compound **1n** with a TMS R^2 group gave no desired product **2n** and was recovered in 40% yield (entry 14). We have also investigated the effect of substituent at R^3 and R^4. To our delight, **1o** and **1p** gave the corresponding products in good yield (entry 15−16), but **1q** and **1r** only gave the desired product in yields of 7% and 4%, respectively (entries 17 and 18). We considered that the failure to get a good yield of **1q** and **1r** may be the result of the steric effect of the substituent at R^4 to prevent the second cyclization step (Scheme 1). We further tested the effect of substituent at R^1. Similarly, the substrates **1s**−**v** underwent the cyclization smoothly to give the corresponding 1,3-diiodinated naphthalenes (entries 19−22). However, compounds with more steric effects gave a lower yield. Furthermore, to expand the scope of this reaction, we also investigated **1w** with a vinyl group. It was found that compound **1w** was smoothly converted into the corresponding 1,3-diiodinated naphthalene **2w**, which, however, only was obtained in a low yield of 30% (entry 23).

On the basis of the above observations, we propose the following plausible mechanisms for this sequential cascade iodocyclization (Scheme 1). We envisioned the following. (i) Coordination of the alkynyl moiety of **A** to an iodide cation gave the complex **B**. (ii) The hydroxyl group

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of the propargylic alcohol moiety, which acts as the nucleophile, attacked the halogenated alkyne group intermediate (via 6-endo-trig cyclization) and then released the hydrogen cation to afford the intermediate **C**. (iii) Intermediate **C** coordinated with the excess iodide cation to give the complex **D**. (iv) This cationic charge induced a 6-endo-trig attack of the vinyl group to generate intermediate **E**. (v) Intermediate **E** was in resonance with oxonium ion **F**, which occurred with domino bond cleavage and then was captured by alcohol to form 1,3-diiodinated naphthalene **2a** and ester **3**.

In summary, a novel and flexible method for the synthesis of highly substituted 1,3-diiodinated naphthalene derivatives in up to 99% yield from simple 1,6-diyne-4-en-3-ols under mild reaction conditions has been developed. The dihalogenated moiety can be readily introduced into the naphthalenes in a position usually not easy to functionalize. The resulting diiodinated products can be used to prepare more complex compounds by using known organopalladium chemistry. Further studies on the sequential cascade iodocyclizations are in progress in our laboratory.

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Supporting Information Available. Detailed experimental procedure and copies of ^{1}H NMR and ^{13}C NMR spectra of all compounds and X-ray data of **2a** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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