

# Metal-Free Benzannulation to Synthesis of 2,3-Disubstituted Naphthalenes: Reaction of 2-(Phenylethynyl)benzaldehyde and Alkynes by Brønsted Acid

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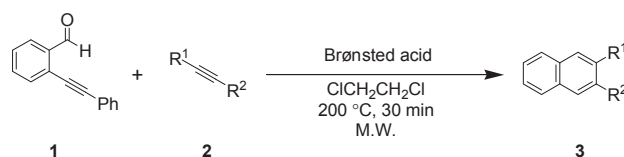
## Abstract

Metal-free benzannulation reaction of 2-(phenylethynyl)benzaldehyde and alkynes proceeded in the presence of Brønsted acid under microwave irradiation to give the 2,3-disubstituted naphthalenes.

Multiple substituted naphthalene derivatives are attractive from the viewpoint of biological, pharmaceutical, and material sciences. Numerous synthetic procedures have been reported for the preparation of multiple substituted naphthalenes. In general, to introduce various functional groups on naphthalene framework, transition-metal-catalyzed cross coupling reaction using organometallic or organohalogen compounds has been developed. An alternative approach to the preparation of them is benzannulation reaction, which can be remarkably tolerant of bulky substituents with high regioselectivity.<sup>1</sup> Recently, the Asao and Yamamoto group has reported Au or Cu-catalyzed benzannulation reaction of 2-(phenylethynyl)benzaldehyde and alkynes to afford multiple substituted naphthalenes.<sup>2a,3b</sup> Since the Asao and Yamamoto report, the synthesis of naphthalene derivatives by the transition-metal-catalyzed benzannulation reaction using 2-(phenylethynyl)benzaldehyde has been disclosed by various groups.<sup>2–8</sup>

In this paper, we report the metal-free benzannulation reaction of 2-(phenylethynyl)benzaldehyde and alkynes in the presence of Brønsted acid under microwave irradiation to afford 2,3-disubstituted naphthalenes (Scheme 1).

First, the effect of various Brønsted acids (0.45 mmol) on the benzannulation of 2-(phenylethynyl)benzaldehyde (**1**) (0.45 mmol) and diphenylacetylene (**2a**) (0.30 mmol) was investigated at 80 °C for 15 h (Table 1). In the cases of acetic,



Scheme 1.

Table 1. Effect of Brønsted acid

Entry	Brønsted acid	Yield (%) <sup>a)</sup>
1	CH <sub>3</sub> COOH	trace
2	CH <sub>2</sub> ClCOOH	trace
3	CHCl <sub>2</sub> COOH	1
4	CCl <sub>3</sub> COOH	19
5	CHF <sub>2</sub> COOH	4
6	CF <sub>3</sub> COOH	41
7	TfOH	18
8	10-Camphorsulfonic acid	4
9	TsOH·H <sub>2</sub> O	35

a) GC yield.

Table 2. Effect of Brønsted acid under microwave conditions

Entry	Brønsted acid	Yield (%) <sup>a)</sup>
1	CH <sub>3</sub> COOH	N.D.
2	CCl <sub>3</sub> COOH	N.D.
3	CF <sub>3</sub> COOH	28
4	CF <sub>3</sub> CF <sub>2</sub> COOH	39
5	CF <sub>3</sub> CF <sub>2</sub> CF <sub>2</sub> COOH	42
6	PhCOOH	N.D.
7	C <sub>6</sub> F <sub>5</sub> COOH	N.D.
8	TfOH	35
9	10-Camphorsulfonic acid	23
10	TsOH·H <sub>2</sub> O	64

a) <sup>1</sup>H NMR yield.

chloroacetic, dichloroacetic, trichloroacetic, difluoroacetic, trifluoromethanesulfonic, and 10-camphorsulfonic acids, only a small amount of 2,3-diphenylnaphthalene (**3a**) was formed (Entries 1–5 and 7, 8). On the other hand, the reaction using trifluoroacetic acid and *p*-toluenesulfonic acid monohydrate (TsOH·H<sub>2</sub>O), gave **3a** in moderate yields (Entries 6 and 9).<sup>9</sup>

To improve the yield of product, we investigated the effect of Brønsted acid on the reaction under microwave irradiation conditions. The benzannulation of **1** (0.45 mmol) and **2a** (0.30 mmol) in the presence of various Brønsted acids (0.45 mmol) was carried out at 200 °C for 30 min under microwave irradiation and these results are shown in Table 2. The treatment of

**Table 3.** Effects of reaction time and ratio of **1**, **2a** and TsOH·H<sub>2</sub>O under microwave conditions

Entry	Ar	<b>1</b> /mmol	TsOH·H <sub>2</sub> O/mmol	Yield (%) <sup>a)</sup>
1	Ph	0.45	0.45	64
2 <sup>b)</sup>	Ph	0.45	0.45	49
3	Ph	0.60	0.45	73
4	Ph	0.75	0.45	70
5 <sup>c)</sup>	Ph	0.30	0.45	60 <sup>d)</sup>
6	Ph	0.60	0.60	77
7	Ph	0.60	0.90	83 (49)
8	4-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	0.60	0.90	43
9	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	0.60	0.90	75
10	4-ClC <sub>6</sub> H <sub>4</sub>	0.60	0.90	84

a) <sup>1</sup>HNMR yield. The number in parenthesis shows isolated yield. b) The reaction was carried out for 60 min. c) **2a** (0.45 mmol) was used. d) The yield of **3a** was based on **1**.

acetic or trichloroacetic acids did not give **3a** at all (Entries 1–2). The use of fluoro-substituted carboxylic acids, such as trifluoroacetic, pentafluoropropionic, and heptafluorobutyric acids, led to the formation of **3a** in 28–42% yields (Entries 3–5). On the other hand, the reaction did not occur with benzoic or pentafluorobenzoic acids as Brønsted acids (Entries 6 and 7). When the reaction was carried out with sulfonic acids as Brønsted acid, the yield of **3a** was increased up to 64% (Entries 8–10).

Next, with TsOH·H<sub>2</sub>O as Brønsted acid, the effects of reaction time and the ratio of **1**, **2a** and TsOH·H<sub>2</sub>O on the benzannulation were investigated and these results are shown in Table 3. The reaction of **1** (0.45 mmol), **2a** (0.30 mmol) and TsOH·H<sub>2</sub>O (0.45 mmol) for a longer reaction time (60 min) afforded **3a** in lower yield (Entries 1 and 2). Although the yield of **3a** was improved by increasing of amount of **1** (0.60 mmol), further increase of the amount of **1** (0.75 mmol) led to no improvement of the yield of **3a** (Entries 3–4). In the case of the use of an excess amount of **2a** compared to **1**, the yield of **3a** was slightly reduced (Entry 5). The effect of the amount of Brønsted acid was studied (Entries 3 and 6–7). The use of 0.90 mmol of TsOH·H<sub>2</sub>O led to the best yield of **3a**.<sup>10–12</sup> Next, the effect of substituents on the aromatic ring (Ar) of **1** was investigated. In the case of **1** having 4-anisyl group, the yield of **3a** decreased due to the formation of unidentified products, which would be formed by the reaction of **1** (Ar = 4-CH<sub>3</sub>OC<sub>6</sub>H<sub>4</sub>) with itself (Entry 8). For both cases of **1** substituted 4-tolyl and 4-chlorophenyl groups, the benzannulation smoothly proceeded to give **3a** in good yields (Entries 9 and 10).

Finally, we investigated the effect of solvent on the reaction (Table 4). When aromatic solvents, toluene and chlorobenzene, and acetonitrile were used, **3a** was obtained in moderate yields (Entries 2–4). The use of DMF and DMSO showed no formation of **3a** (Entries 5 and 6). In the reaction, 1,2-dichloroethane solvent gave the best yield of **3a** (Entry 1).

The various alkynes **2** were allowed to react with **1** under the same reaction conditions as that of Entry 1 in Table 4 and these

**Table 4.** Effect of solvent under microwave conditions

Entry	Solvent	Yield (%) <sup>a)</sup>
1	ClCH <sub>2</sub> CH <sub>2</sub> Cl	83
2	Toluene	41
3	Chlorobenzene	48
4	CH <sub>3</sub> CN	49
5	DMF	N.D.
6	DMSO	N.D.

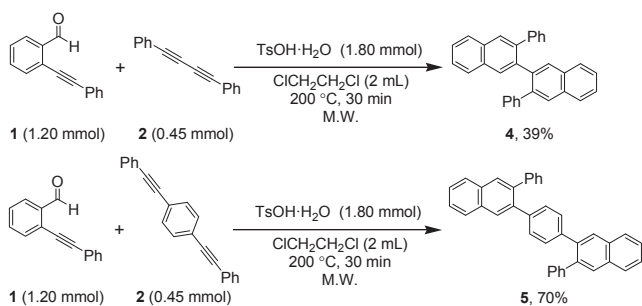
a) <sup>1</sup>HNMR yield.

**Table 5.** Benzannulation of **1** with various alkynes **2**

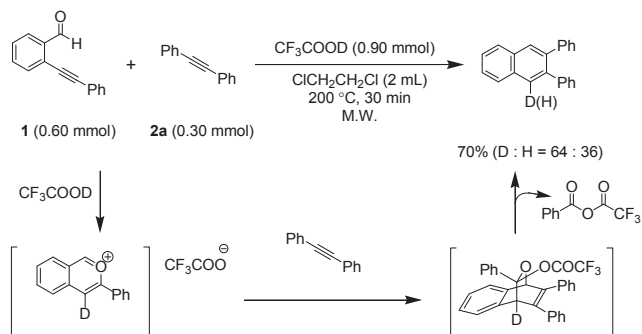
Entry	R <sup>1</sup>	R <sup>2</sup>	Yield (%) <sup>a)</sup>
1	Ph	CH <sub>3</sub>	<b>3b</b> , 63
2	Ph	C <sub>2</sub> H <sub>5</sub>	<b>3c</b> , 37 <sup>b)</sup>
3	Ph	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	<b>3d</b> , 59
4	Ph	4-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	<b>3e</b> , 40 <sup>c)</sup>
5	Ph	4-FC <sub>6</sub> H <sub>4</sub>	<b>3f</b> , 56
6	Ph	4-CNC <sub>6</sub> H <sub>4</sub>	<b>3g</b> , N.D.
7	Ph	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	<b>3h</b> , N.D.
8	<i>n</i> -C <sub>3</sub> H <sub>11</sub>	<i>n</i> -C <sub>5</sub> H <sub>11</sub>	<b>3i</b> , 61
9	Ph	H	<b>3j</b> , 28
10	<i>n</i> -C <sub>6</sub> H <sub>13</sub>	H	<b>3k</b> , 92

a) Isolated yield. b) 1-Phenylbutan-1-one (36%) was formed as by-product. c) 1-Phenyl-2-(4-methoxyphenyl)ethanone (42%) was formed as by-product.

results are shown in Table 5.<sup>13</sup> The reaction of **1** and 1-phenyl-1-alkynes, 1-phenyl-1-propyne and 1-phenyl-1-butyne, proceeded to form **3b** and **3c** in 63 and 37% yields, respectively (Entries 1 and 2). The yield of **3c** was low due to the formation of the hydration product, 1-phenylbutan-1-one (36%), as by-product (Entry 2). In the cases of the use of electron-rich aryl substituted ethynylbenzenes, such as 1-methyl-4-(phenylethynyl)benzene and 1-methoxy-4-(phenylethynyl)benzene, **3d** and **3e** were obtained in 59 and 40% yields, respectively (Entries 3 and 4). In the latter case, 1-phenyl-2-(4-methoxyphenyl)ethanone as by-product was also obtained in 42% yield. Next, the reaction of **2** having electron-withdrawing groups on the phenyl ring was examined. The benzannulation of 1-fluoro-4-(phenylethynyl)benzene took place to give **3f** in 56% yield (Entry 5). On the other hand, for the reaction of the diaryl-acetylenes substituted with strongly electron-withdrawing groups, such as cyano or nitro groups, on the phenyl moieties, the corresponding products **3g**, **3h** were not formed (Entries 6 and 7). These results agree with those of Re-catalyzed benzannulation.<sup>8a</sup> The reaction of dialkyl substituted alkyne, 6-dodecyne, with **1** gave **3i** in 61% yield (Entry 8). For the reac-



**Scheme 2.**



**Scheme 3.**

tion of aromatic terminal alkyne, phenylacetylene, the yield of **3j** was low (Entry 9). In contrast to that of aromatic terminal alkyne, the benzannulation of the alkyl substituted terminal alkyne, 1-octyne, proceeded efficiently to give **3k** in 92% yield (Entry 10).

It is important to note that the double benzannulation reaction of 1,4-diphenylbutadiyne and 1,4-bis(phenylethynyl)-benzene with **1** proceeded to afford **4** and **5**, in 39 and 70% yields, respectively (Scheme 2).

To investigate the reaction pathway, we carried out the reaction of 2-(phenylethynyl)benzaldehyde (**1**) with diphenylacetylene (**2a**) in the presence of trifluoroacetic acid-*d*, CF<sub>3</sub>COOD, as Brønsted acid at 200 °C for 30 min under microwave irradiation (Scheme 3). The deuterium incorporation at the 1-position on the product was confirmed by <sup>1</sup>H NMR.<sup>14</sup> From this result and the previous reaction pathway described by Asao and Yamamoto,<sup>3b</sup> one of the plausible reaction pathways is shown in Scheme 3. First, the deuteration or protonation to the carbon-carbon triple bond of **1** followed by the internal cyclization forms the benzopyrylium cation. Diels–Alder type cyclization of the benzopyrylium cation with **2a** gives the cyclic adduct. Finally, the elimination of acid anhydride from the cyclic adduct affords the 2,3-disubstituted naphthalene.

In conclusion, the metal-free benzannulation of 2-(phenylethynyl)benzaldehyde (**1**) with various alkynes **2** in the presence of TsOH·H<sub>2</sub>O as Brønsted acid under microwave irradiation for 30 min gave the corresponding 2,3-disubstituted naphthalene derivatives **3**. This protocol allowed the preparation of multiple and sterically hindered polycyclic aromatic hydrocarbons.

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- In all cases, the formation of 1-benzoylnaphthalene derivative, which could be formed by Au-catalyzed benzannulation reaction of **1** and alkyne, as by-product was not observed. See ref. 2a.
- Due to the difficult separation of a small amount of impurities, the isolated yield of **3a** was low.
- General procedure for the reaction of 2-(phenylethynyl)benzaldehyde (**1**) and alkynes **2**: A solution of 2-(phenylethynyl)benzaldehyde (**1**) (0.60 mmol, 124 mg), alkyne **2** (0.30 mmol), and TsOH·H<sub>2</sub>O (0.90 mmol, 171 mg) in ClCH<sub>2</sub>CH<sub>2</sub>Cl (2.0 mL) was treated at 200 °C for 30 min under microwave condition (Biotage INITIATOR); All reactions were carried out under temperature-constant operation). The reaction mixture was diluted with CHCl<sub>3</sub> and washed with saturated NaHCO<sub>3</sub> (aq) and brine. The organic layer was dried over MgSO<sub>4</sub>. After removal of the solvent under reduced pressure, the residue was purified by chromatography on SiO<sub>2</sub> to give the naphthalene derivatives. Further purification was carried out a recyclable preparative HPLC, if necessary. The structures of the products were assigned by their NMR spectra. The product was characterized by comparing its spectral data with previous report.<sup>8a</sup>
- The benzannulation of **1** (0.60 mmol) and **2a** (0.30 mmol) in the presence of TsOH·H<sub>2</sub>O (0.90 mmol) was carried out at 150 °C for 2 h without microwave irradiation to give **3a** in 53% yield.
- The 2-(phenylethynyl)benzaldehyde (**1**) and alkynes as the starting materials were completely consumed in all reactions in Table 5 and uncharacterized polymeric materials were formed on these reactions except for Entries 2 and 4.
- The ratio of 2,3-diphenylnaphthalene, which does not contain the deuterium, was slightly high. It seems that the H/D exchange between the CF<sub>3</sub>COOD and H<sub>2</sub>O contained in the solvent would be occurred.