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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. 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. 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.

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, chloroacetic, dichloroacetic, trichloroacetic, difluorooacetic, 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·H2O), gave 3a in moderate yields (Entries 6 and 9).

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...
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 Bromsted acids (Entries 6 and 7). When the reaction was carried out with sulfonic acids as Bremsted acid, the yield of 3a was increased up to 64% (Entries 8–10).

Next, with TsOH·H₂O as Bremsted acid, the effects of reaction time and the ratio of 1, 2a and TsOH·H₂O 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·H₂O (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 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 Bremsted acid was studied (Entries 3 and 7). The use of 0.90 mmol of TsOH·H₂O led to the best yield of 3a.10,12 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-CH₃OC₆H₄) 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 results are shown in Table 5.13 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-methoxyphenylethynyl)ethane 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 diarylacetylenes 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.14 The reaction of dialkyl substituted alkyne, 6-dodecynyl, with 1 gave 3i in 61% yield (Entry 8). For the reac-
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-diphenylbutadiene 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, CF₃COOD, 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 ¹H NMR.¹⁴ From this result and the previous reaction pathway described by Asao and Yamamoto,¹⁰ 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 benzopropylenecation. Diels–Alder type cyclization of the benzopropylenecation 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·H₂O 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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References
1 For a review on benzannulation, see: S. Kotha, S. Misra, S. Halder. Tetrahedron 2008, 64, 10775.
9 In all cases, the formation of 1-benzoylnaphthalene derivative, which could be formed by Au-catalyzed benzannulation reaction of 1 and alkynyl, as by-product was not observed. See ref. 2a.
10 Due to the difficult separation of a small amount of impurities, the isolated yield of 3a was low.
11 General procedure for the reaction of 2-(phenylethynyl)benzaldehyde (I) and alkynes 2: A solution of 2-(phenylethynyl)benzaldehyde (1) (0.60 mmol, 124 mg), alkylene 2 (0.30 mmol), and TsOH·H₂O (0.90 mmol, 171 mg) in CHCl₃/CH₃Cl (2.0 mL) was treated at 200 °C for 30 min under microwave condition (Biogate INITIATOR; All reactions were carried out under temperature-constant operation). The reaction mixture was diluted with CHCl₃ and washed with saturated NaHCO₃ (aq) and brine. The organic layer was dried over MgSO₄. After removal of the solvent under reduced pressure, the residue was purified by chromatography on SiO₂ 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.¹⁶
12 The benzannulation of 1 (0.60 mmol) and 2a (0.30 mmol) in the presence of TsOH·H₂O (0.90 mmol) was carried out at 150 °C for 2 h without microwave irradiation to give 3a in 53% yield.
13 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.
14 The ratio of 2,3-diphenylnaphthalene, which does not contain the deuterium, was slightly high. It seems that the H/D exchange between the CF₃COOD and H₂O contained in the solvent would be occurred.