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# Synthesis of 6*H*-Dibenzo[*b*,*d*]pyran-6-ones from Aryl 3-Bromopropenoates via a Sequential One-Pot Procedure Using the Sonogashira Coupling−Benzannulation Reaction

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Various kinds of 6*H*-dibenzo[*b*,*d*]pyran-6-ones **4** were synthesized via a sequential one-pot procedure using the Sonogashira coupling−benzannulation reaction of aryl 3-bromopropenoates **1**, in which the *ortho*-position of aryl group is substituted with enynes or iodine, with acetylenes **2** in the presence of palladium and copper catalysts. The Sonogashira coupling between the aryl 3-bromopropenoates **1a** and **1b**, bearing enynes at the *ortho*-position of aryl group, and alkynes **2a**−**g** gave the enyne intermediates **3** in situ, which subsequently underwent the palladium-catalyzed benzannulation reaction to afford the 6*H*-dibenzo[*b*,*d*]pyran-6-ones **5a**−**g** and **6**. The Sonogashira coupling between the aryl 3-bromopropenoate **1c**, bearing iodine at the *ortho*-position of aryl group, and diynes **2f** and **2h** produced the diyne intermediates **13**, which underwent the benzannulation reaction to afford the 6*H*-dibenzo[*b*,*d*]pyran-6-ones **14f** and **14h**.

## Introduction

6*H*-Dibenzo[*b*,*d*]pyran-6-ones are widespread in nature[1] and exhibit biological activities.[2] They have also been used as intermediates for the synthesis of more complicated structural units and naturally occurring substances.[3] Although various methods have been reported for the synthesis of 6*H*-dibenzo[*b*,*d*]pyran-6-ones, few methods are known for the construction of 6*H*-dibenzo[*b*,*d*]pyran-6-one skeletons accompanied by aromatization in a one-step procedure.[4−9] For example, cycloaddition−elimination sequences of coumarins[4] or 3-nitrochromone,[5] rearrangements of spiro compounds,[6] biomimetic synthesis of alternariol derivatives,[7] the coupling reaction of an active quinone with phenols,[8] and cycloaromatization of endiynes[9] are known. Recently, we reported efficient methods for the construction of benzene rings using palladium-catalyzed benzannulation reactions, and we succeeded in synthesizing multifunctionalized and polysubstituted benzenes.[10] These methodolo-

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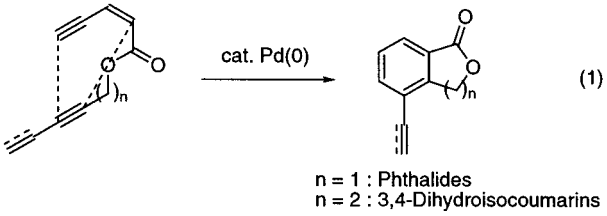
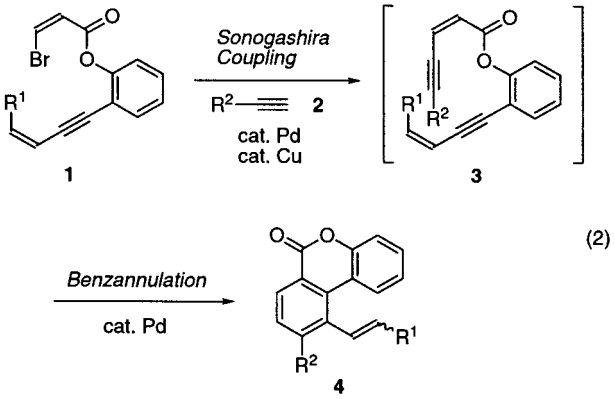
gies were further extended to an *intramolecular* benzannulation reaction of bis-enynes or enyne-diynes.[10c,d] More recently we have developed a new synthetic method for phthalides and 3,4-dihydroisocoumarins from 2-penten-4-ynoates bearing 4-penten-2-ynyl and 5-hexen-3-ynyl as the ester group (eq 1).[11] It is noteworthy that the *intramolecular* [4 + 2] benzannulation proceeded in highly regio- and chemoselective manner.




(1)

As a further extension of this *intramolecular* benzannulation reaction, we attempted to carry out the palladium-catalyzed reaction of 2-(3-buten-1-ynyl)phenyl (*Z*)-2-penten-4-ynoate **3**, in which the *ortho*-position of aryl group is substituted with 3-buten-1-ynyl. It was expected that **3** would give 6*H*-dibenzo[*b*,*d*]pyran-6-ones **4** through the benzannulation reaction. To synthesize **3**, the Sonogashira coupling reaction[12] between 2-(3-buten-1-ynyl)-phenyl (*Z*)-3-bromopropenoate **1** and alkynes **2** was performed. However, unexpectedly, the reaction between **1** and **2** gave the benzannulation product **4**; the Sonogashira coupling and subsequent benzannulation took place all at once under the Sonogashira conditions (eq 2).

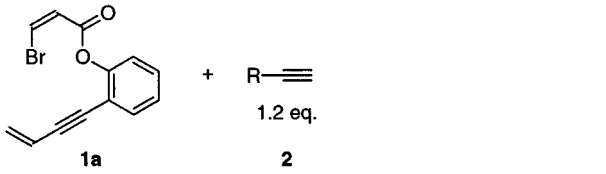



(2)

## Results and Discussion

**Synthesis of 6*H*-Dibenzo[*b*,*d*]pyran-6-ones.** First, the reaction of **1a** with 1-pentyne **2a** was carried out in the presence of catalytic amounts of $Pd(PPh_3)_4$ (1.3 mol %) and CuI (2.6 mol %) at room temperature. 9-Propyl-10-vinyl-6*H*-dibenzo[*b*,*d*]pyran-6-one **5a** was isolated in 33% yield. After many trials, we could synthesize **5a** in 69% yield under the optimized conditions; $Pd(PPh_3)_4$ (5 mol %), CuI (10 mol %) in $Et_3N$−THF (1:1) solution at 80 °C (Table 1, entry 1). When the reaction of **1a** was carried out at lower temperatures, such as room temperature or 50 °C, the reaction stopped at a significantly early stage, and a small amount of bis-enyne (the Sonogashira coupling product) was accompanied along with the desired **5a**. In addition, the selection of solvents was important. $Et_3N$−THF (1:1) solvent was the most effective for the sequential reaction; other solvents such as $Et_3N$−toluene[13] diminished the yield of **5a** to 31%. The reaction of **1a** with phenylacetylene **2b** and methyl propargyl ether **2c** gave the corresponding 6*H*-dibenzo-[*b*,*d*]pyran-6-ones **5b**[14] and **5c**, respectively, in moderate to high yields under the optimized conditions (entries 2 and 3). The 6*H*-dibenzo[*b*,*d*]pyran-6-one **5d** substituted by a hydroxy group was also synthesized by the reaction of **1a** with propargyl alcohol **2d** (entry 4). Not only simple alkynes, but also conjugated alkynes, such as the conjugated enyne **2e** and the conjugated diyne **2f**, were good coupling partners to **1a**. Furthermore, the propargylacetylene containing an enyne group **2g** underwent the

**TABLE 1. Synthesis of 6*H*-Dibenzo[*b*,*d*]pyran-6-ones**




**1a** **2** **5**

| entry | | alkynes | product | isolated yield (%) |
|---|---|---|---|---|
| 1 | **2a** | *n*-$C_3H_7$— | **5a** | 69 |
| 2 | **2b** | Ph— | **5b** | 51 |
| 3 | **2c** | —O— | **5c** | 92 |
| 4 | **2d** | HO— | **5d** | 37 |
| 5 | **2e** | | **5e** | 54 |
| 6 | **2f** | *n*-$C_6H_{13}$— | **5f** | 69 |
| 7 | **2g** | | **5g** | 23 |

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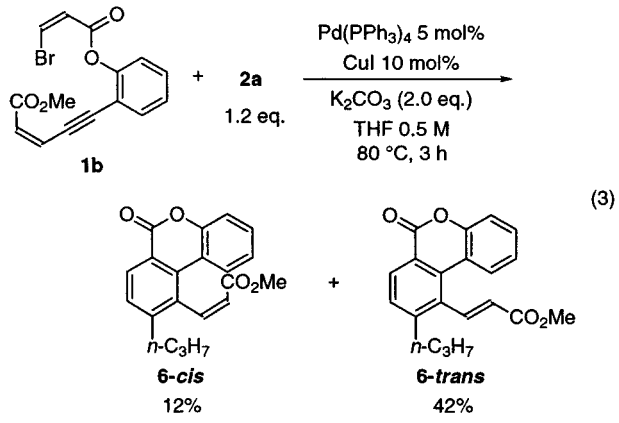
(13) Toluene is the best solvent for the precedent palladium-catalyzed benzannulation reactions.

(14) The structure of **5b** was confirmed by an X-ray crystallographic analysis. See Supporting Information.

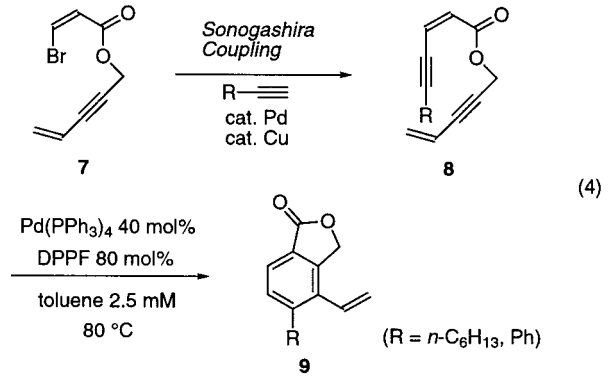
sequential reaction in a manner similar to give **5g** in 23% yield (entry 7).

To synthesize a functionalized 6*H*-dibenzo[*b*,*d*]pyran-6-one, we carried out the reaction of aryl 3-bromopropenoate **1b**, in which the *ortho*-position of aryl group is substituted with methoxycarbonyl-enyne functionality, with 1-pentyne **2a** (eq 3). Though the reaction in $Et_3N$−THF solvent did not give a satisfactory result, the use of THF−$K_2CO_3$ system gave a mixture of the corresponding 6*H*-dibenzo[*b*,*d*]pyran-6-one **6-*cis*** (12%) and **6-*trans*** (42%). It should be noted that the *cis*−*trans* isomerization did not occur in the previous benzannulation reactions.[10] The steric hindrance between an ester group and aromatic ring, together with the use of basic reaction conditions, might cause the isomerization.



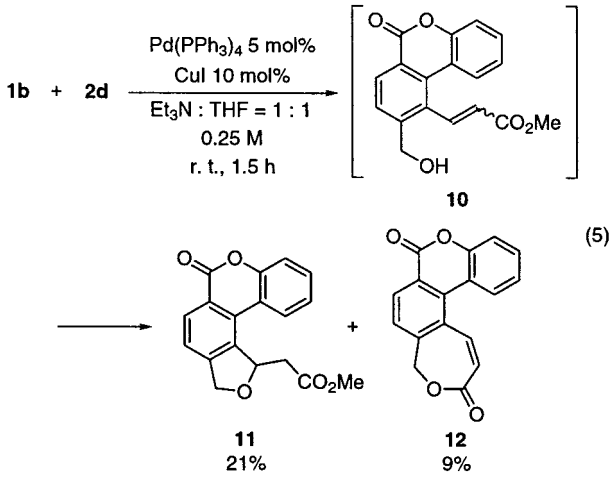

(3)

It is noteworthy that the palladium- and copper-catalyzed sequential reaction did not occur in the initially reported palladium-catalyzed benzannulation,[10] even in the reaction of *intramolecular* bis-enyne substrates (eq 4).[11] Under the Sonogashira conditions, **8** was isolated and the in situ benzannulation of **8** did not take place. The benzannulation of **8** needed the use of the standard catalytic systems.



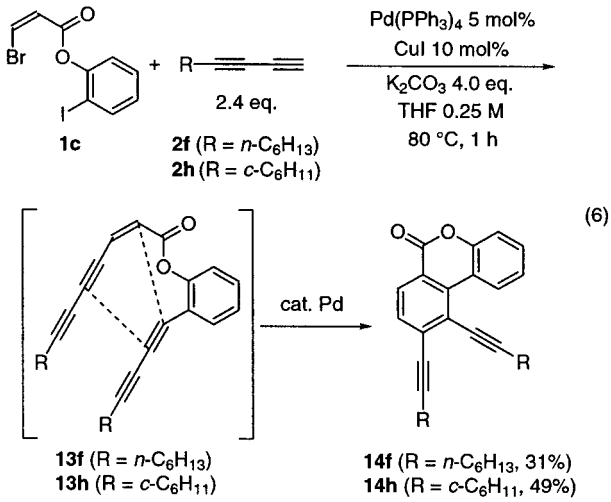

(4)

**Synthesis of Tetracyclic Compounds.** Since it is interesting and important to construct polycyclic skeletons in a short step, we next attempted to synthesize tetracyclic compounds. The reaction of **1b** with propargyl alcohol **2d** was carried out under similar conditions: Pd($PPh_3$)$_4$ (5 mol %) and CuI (10 mol %) in $Et_3N$−THF solvent. As expected, the benzannulation product **10** which would be formed through the Sonogashira coupling underwent in situ cyclization to give a mixture of **11** (21%) and **12** (9%) (eq 5).




(5)

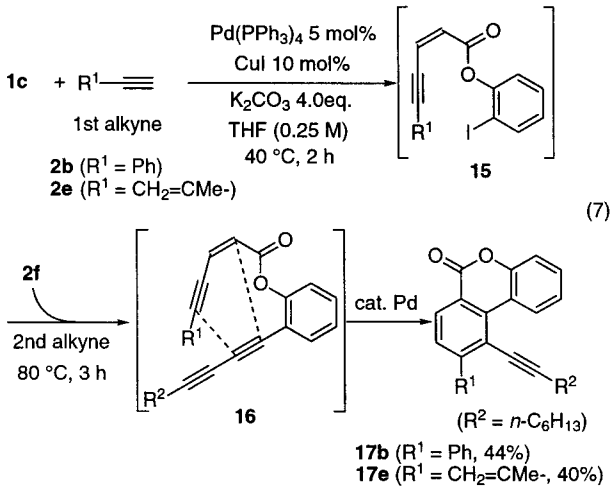
**Three-Component Coupling Reactions.** Multicomponent coupling reactions that directly yield the desired products via sequential reactions offer significant advantage over a stepwise procedure. We investigated three-component coupling reactions of the Sonogashira coupling−benzannulation reaction protocol (eq 6). The dihalide




(6)

compound **1c** reacted with 2 equiv of 1,3-decadiyne **2f** to give the corresponding 6*H*-dibenzo[*b*,*d*]pyran-6-one **14f** in 31% yield. This reaction most probably proceeds via the Sonogashira coupling adduct **13f** that has an endiyne moiety and a diyne moiety. Cyclohexyldiyne **2h** also reacted with **1c**, and the three-component coupling product **14h** was obtained in 49% yield. Accordingly, it is clear that *two* different types of the Sonogashira coupling and *one* benzannulation takes place in a single operation.

We next attempted to incorporate two different kinds of alkynes in the three-component coupling reaction. In the reaction of **1c** with 2-methylenyne **2e** (2.5 equiv) (eq 7), the Sonogashira coupling reaction was observed only at the bromopropenoate moiety, and the aryl iodide moiety remained unreacted. This observation indicates that the bromopropenoate moiety is more reactive than the aryl iodide moiety under the sequential reaction conditions, suggesting that the use of less reactive alkynes gives the alkynylated aryl iodides **15**, and the subsequent addition of more reactive alkynes produces




the benzannulation precursors **16**. The experimental procedure for the reaction of **1c** with two different alkynes **2b** and **2f** is shown in eq 7. First, phenylacetylene **2b** (1.5 equiv) was used under the standard conditions, and the reaction progress was monitored by GC. After 2 h at 40 °C, **1c** was consumed completely. Then, the second alkyne, 1,3-decadiyne **2f**, was added, and the mixture was stirred at 80 °C for 3 h. The desired product **17b** was obtained in 44% yield. 2-Methylenyne **2e** was also used as the first alkyne, and the expected product **17e** was obtained in 40% yield.

## Conclusions

We have developed a new synthetic procedure for the construction of 6*H*-dibenzo[*b*,*d*]pyran-6-ones via the sequential Sonogashira coupling−benzannulation reaction. The use of a 1,2-disubstituted aromatic ring as a spacer between O atom and alkyne, most probably, brings an alkyne near an enyne moiety to facilitate the benzannulation reaction. Starting from 2-iodophenyl 3-bromopropenoate **1c**, *two sequential* Sonogashira couplings followed by benzannulation protocol were accomplished.

## Experimental Section

**The Sequential Sonogashira Coupling−Benzannulation of Aryl Bromopropenoate 1a. A Representative Procedure.** To a mixture of $Pd(PPh_3)_4$ (29 mg, 0.025 mmol) and CuI (9.6 mg, 0.050 mmol) were added $Et_3N$ (1.0 mL), a THF (1.0 mL) solution of **1a** (139 mg, 0.50 mmol), and methyl propargyl ether **2c** (51 $\mu$L, 0.60 mmol) under an argon atmosphere at room temperature, and the mixture was stirred for 1 h at 80 °C. The mixture was passed through a short silica gel column chromatography (hexane and ether), and the solvent was evaporated. The residue was further purified by silica gel column chromatography (hexane:AcOEt = 10:1) to give **5c** (122 mg, 92%).

**The Sequential Sonogashira Coupling−Benzannulation of Aryl Bromopropenoate 1b.** To a mixture of $Pd(PPh_3)_4$ (29 mg, 0.025 mmol), CuI (9.6 mg, 0.050 mmol), $K_2CO_3$ (138 mg, 1.0 mmol), and **1b** (168 mg, 0.50 mmol) were added THF (1.0 mL) and 1-pentyne **2a** (59 $\mu$L, 0.60 mmol) under an argon atmosphere at room temperature, and the mixture was stirred for 3 h at 80 °C. The mixture was passed through a short silica gel column chromatography (hexane and ether), and the solvent was evaporated. The residue was further purified by silica gel column chromatography (hexane:AcOEt = 10:1) to give **6-*cis*** (20 mg, 12%) and **6-*trans*** (68 mg, 42%).

**The Three-Component Coupling Reaction of 1c with Diynes. A Representative Procedure.** To a mixture of $Pd(PPh_3)_4$ (17 mg, 0.015 mmol), CuI (5.8 mg, 0.030 mmol), and $K_2CO_3$ (166 mg, 1.2 mmol) was added a THF (1.2 mL) solution of **1c** (106 mg, 0.30 mmol) and **2f** (96 mg, 0.72 mmol) under an argon atmosphere at room temperature, and the mixture was stirred for 1 h at 80 °C. The mixture was passed through a short silica gel column chromatography (hexane and ether), and the solvent was evaporated. The residue was further purified by silica gel column chromatography (hexane:AcOEt = 50:1) to give **14f** (39 mg, 31%).

**The Three-Component Coupling Reaction of 1c with Two Different Alkynes. A Representative Procedure.** To a mixture of $Pd(PPh_3)_4$ (17 mg, 0.015 mmol), CuI (5.8 mg, 0.030 mmol), and $K_2CO_3$ (166 mg, 1.2 mmol) was added a THF (1.2 mL) solution of **1c** (106 mg, 0.30 mmol) and **2b** (first alkyne, 49 mL, 0.45 mmol) under an argon atmosphere at room temperature, and the mixture was stirred for 2 h at 40 °C. Then, **2f** (second alkyne, 48 mg, 0.36 mmol) was added, and the reaction mixture was stirred for 3 h at 80 °C. The mixture was passed through a short silica gel column chromatography (hexane and ether), and the solvent was evaporated. The residue was further purified by GPC (THF) to give **17b** (50 mg, 44%).

**Acknowledgment.** We thank Dr. Chizuko Kabuto at the Instrumental Analysis Center of this department for the measurement of the X-ray crystallographic data of **5b**.

**Supporting Information Available:** Details for the preparation and spectroscopic data for compounds **1a**−**c**, **2h**, **5**, **6**, **9**, **11**, **12**, **14**, **17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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