Eito Yoshioka, Shigeru Kohtani and Hideto Miyabe *

School of Pharmacy, Hyogo University of Health Sciences, 1-3-6, Minatojima, Chuo-ku, Kobe, 650-8530, Japan; E-Mails: e.yoshioka@huhs.ac.jp (E.Y.); kohtani@huhs.ac.jp (S.K.)

* Author to whom correspondence should be addressed; E-Mail: miyabe@huhs.ac.jp; Tel.: +81-78-304-3094; Fax: +81-78-304-2794.

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Abstract: The title compound 2,3,4,9-tetrahydro-9-(3-hydroxy-1,4-dioxo-1H-dihydro-naphthalen-2-yl)-8-methoxy-3,3-dimethyl-1H-xanthen-1-one (5) was obtained by the nucleophilic addition of 2-hydroxy-1,4-naphthoquinone (4) to 2H-chromene derivative 3, which was prepared by the domino three-component coupling reaction of aryne precursor 1 with DMF and the active methylene compound dimedone (2). The one-pot synthesis of the title compound 5 from aryne precursor 1 was also achieved.

Keywords: multi-component reaction; domino reaction; arynes; heterocycles; synthesis

Arynes are highly reactive and kinetically unstable intermediates for constructing multisubstituted arenes with structural diversity and complexity [1,2]. In particular, the recent aryne-based chemistry has made great advances in synthetic chemistry [3–14]. Our laboratory is interested in developing domino reactions using arynes. We have recently developed the efficient insertion of arynes, generated in situ from ortho-(trimethylsilyl)aryl triflates and the fluoride ion, into the C=O π-bond of DMF [15–20].

Synthetic strategies involving domino processes offer the advantage of multiple carbon-carbon and/or carbon-heteroatom bond formations in a single operation [21,22]. In this paper, we report two synthetic methods for preparing the title compound 5 via a domino multicomponent coupling reaction starting from the generation of an aryne. Moreover, this molecule 5 has a pharmaceutically important structure, because a similar type of compound was studied as a neuropeptide Y Y5 receptor antagonist by Merck-Banyu researchers [23].
First, the 2H-chromene derivative 3 was prepared according to our reported method (Scheme 1) [17]. To suppress the competitive reaction of aryne A with dimedone (2), N,N-dimethylformamide (DMF) was employed as a solvent. In the presence of anhydrous TBAF (3 equiv.), treatment of triflate 1 with dimedone (2) in DMF at room temperature for 3 h gave the desired 2H-chromene 3 in 53% yield. This transformation proceeds via the insertion of aryne A, generated from ortho-(trimethylsilyl)aryl triflate 1, into the C=O of DMF and the nucleophilic addition of dimedone (2) to benzoxetene B or ortho-quinone methide C.

![Scheme 1. Preparation of 2H-chromene derivative 3.](image)

For the synthesis of the title compound 5, 2-hydroxy-1,4-naphthoquinone (4) was employed as a nucleophile (Scheme 2). In the presence of anhydrous TBAF (3 equiv.), we allowed 2H-chromene 3 to react with 1.1 equiv. of 2-hydroxy-1,4-naphthoquinone 4 in DMF. As expected, the title compound 5 was obtained in 67% yield. We were gratified to observe that 2-hydroxy-1,4-naphthoquinone 4 acts as a nucleophilic active methylene compound with the sufficient reactivity toward 2H-chromene 3.

![Scheme 2. Synthesis of title compound 5.](image)

As an alternative convenient approach to title compound 5, we next directed our attention to the direct one-pot synthesis of 5 from aryne precursor 1 (Scheme 3). The two-step preparation was successfully applied in the convenient one-pot synthesis. At first, triflate 1 in DMF was treated with dimedone (2) in the presence of anhydrous TBAF. After being stirred for 3 h, 2-hydroxy-1,4-
naphthoquinone (4, 2.1 equiv.) was added to the reaction mixture. After the purification, the desired title compound 5 was isolated in 40% yield.

![Scheme 3. One-pot synthesis of title compound 5.](image)

**Experimental**

**General Information**

Infrared spectra were measured on a FT/IR-4100 instrument (JASCO, Hachioji-city, Tokyo, Japan). $^1$H-NMR (400 MHz) and $^{13}$C-NMR (101 MHz) spectra were measured on a ECX-400 PSK (JEOL, Akishima-city, Tokyo, Japan) with CDCl$_3$ as an internal standard (77.0 ppm). Mass spectra (ESI-MS) were obtained by use of a Thermo Fisher Scientific Exactive LC/MS spectrometer (Bremen-city, Germany). For silica gel column chromatography, SiliCycle Inc. (Quebec-city, QC, Canada) SiliaFlash F60 was used.

2,3,4,4a-Tetrahydro-4a-hydroxy-8-methoxy-3,3-dimethyl-1H-xanthen-1-one (3)

To a solution of 3-methoxy-2-(trimethylsilyl)phenyl triflate (1, 105 µL, 0.40 mmol) and dimedone (2, 56 mg, 0.40 mmol) in DMF (3.4 mL) was added a solution of anhydrous TBAF (314 mg, 1.20 mmol) in DMF (0.60 mL) under argon atmosphere at room temperature. After being stirred at room temperature for 3 h, silica gel (1.0 g) was added to the reaction mixture, and then it was concentrated under reduced pressure. Purification of the residue by flash silica gel column chromatography (AcOEt:hexane = 1:8–1:0 with 2% CH$_2$Cl$_2$) afforded 2H-chromene 3 (58 mg, 53%). Colorless crystals. Sublimated decomposition 118–120 °C (CH$_2$Cl$_2$-iso-Pr$_2$O). IR (KBr) 3417 (br), 2957, 1671, 1603, 1566, 1467 cm$^{-1}$. $^1$H-NMR (C$_6$D$_6$) δ 8.21 (1H, s), 6.94 (1H, t, $J = 8.0$ Hz), 6.73 (1H, d, $J = 8.0$ Hz), 6.03 (1H, d, $J = 8.0$ Hz), 3.20 (3H, s), 2.39 (1H, br s), 2.32 (1H, dd, $J = 16.0, 1.5$ Hz), 2.13 (1H, dd, $J = 14.0, 1.0$ Hz), 2.03 (1H, br d, $J = 14.0$ Hz), 1.91 (1H, br d, $J = 16.0$ Hz), 0.94 (3H, s), 0.69 (3H, s). $^{13}$C-NMR (C$_6$D$_6$) δ 196.1, 158.2, 153.9, 132.2, 128.7, 124.7, 111.0, 110.3, 103.4, 96.7, 55.2, 52.6, 48.7, 31.4, 30.3, 27.8. HRMS (ESI+) calcd for C$_{16}$H$_{18}$O$_4$Na (M+Na$^+$): 297.1097, Found: 297.1095.

2,3,4,9-Tetrahydro-9-(3-hydroxy-1,4-dioxo-1H-dihydronaphthalen-2-yl)-8-methoxy-3,3-dimethyl-1H-xanthen-1-one (5)

To a solution of 2H-chromene 3 (16 mg, 0.060 mmol) and 2-hydroxy-1,4-naphthoquinone (4, 12 mg, 0.066 mmol) in DMF (600 µL) was added a solution of anhydrous TBAF (47 mg, 0.18 mmol) in DMF.
(90 µL) under argon atmosphere at room temperature. After being stirred at room temperature for 1 h, silica gel (0.1 g) was added to the reaction mixture, and then it was concentrated under reduced pressure. Purification of the residue by flash silica gel column chromatography (acetone/chloroform = 1:50–1:2) afforded compound 5 (17 mg, 67%). Dark red solid. $^1$H-NMR (CDCl$_3$) δ 8.07 (1H, br s), 8.01 (1H, dd, $J = 7.5, 1.2$ Hz), 7.68 (1H, br t, $J = 7.3$ Hz), 7.61 (1H, td, $J = 7.5, 1.2$ Hz), 7.15 (1H, t, $J = 8.2$ Hz), 6.70 (1H, d, $J = 8.2$ Hz), 6.53 (1H, d, $J = 8.2$ Hz), 5.44 (1H, br s), 3.67 (3H, s), 2.53 (2H, br s), 2.30 (1H, d, $J = 16.5$ Hz), 2.20 (1H, d, $J = 16.5$ Hz), 1.11 (3H, s), 1.01 (3H, s). $^{13}$C-NMR (CDCl$_3$) δ 197.4 (br), 182.0, 157.6, 153.0 (br), 151.2, 134.6, 132.8, 132.5, 129.5, 128.0, 126.9 (br), 125.8, 111.5, 110.3, 108.6, 106.2, 55.7, 50.7, 41.5, 32.1, 29.3, 27.2, 24.4; Three carbon peaks were missing due to overlapping. HRMS (ESI$^+$) calcd for C$_{26}$H$_{23}$O$_6$ (M+H$^+$): 431.1489, Found: 431.1473; Anal. calcd for C$_{26}$H$_{22}$O$_6$: C, 72.55; H, 5.15. Found: C, 71.77; H, 5.15.

**Procedure for One-Pot Synthesis**

To a solution of 3-methoxy-2-(trimethylsilyl)phenyl triflate (I, 158 µL, 0.60 mmol) and dimedone (2, 56 mg, 0.40 mmol) in DMF (5.1 mL) was added a solution of anhydrous TBAF (472 mg, 1.8 mmol) in DMF (0.90 mL) under argon atmosphere at room temperature. After being stirred at room temperature for 3 h, 2-hydroxy-1,4-naphthoquinone (4, 151 mg, 0.84 mmol) was added to the reaction mixture. After being stirred at room temperature for 1 h, silica gel (1.5 g) was added to the reaction mixture, and then it was concentrated under reduced pressure. Purification of the residue by flash silica gel column chromatography (acetone/chloroform = 1:50–1:2) afforded compound 5 (69 mg, 40%).

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**Author Contributions**

E. Yoshioka performed experiments and analyzed the data. S. Kohtani carried out part of the data analysis. H. Miyabe contributed to design of the study and manuscript writing.

**Conflicts of Interest**

The authors declare no conflict of interest.

**References**


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