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Short Note

2,3,4,9-Tetrahydro-9-(3-hydroxy-1,4-dioxo-1*H*-dihydro-naphthalen-2-yl)-8-methoxy-3,3-dimethyl-1*H*-xanthen-1-one

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Abstract: The title compound 2,3,4,9-tetrahydro-9-(3-hydroxy-1,4-dioxo-1*H*-dihydro-naphthalen-2-yl)-8-methoxy-3,3-dimethyl-1*H*-xanthen-1-one (**5**) was obtained by the nucleophilic addition of 2-hydroxy-1,4-naphthoquinone (**4**) to 2*H*-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

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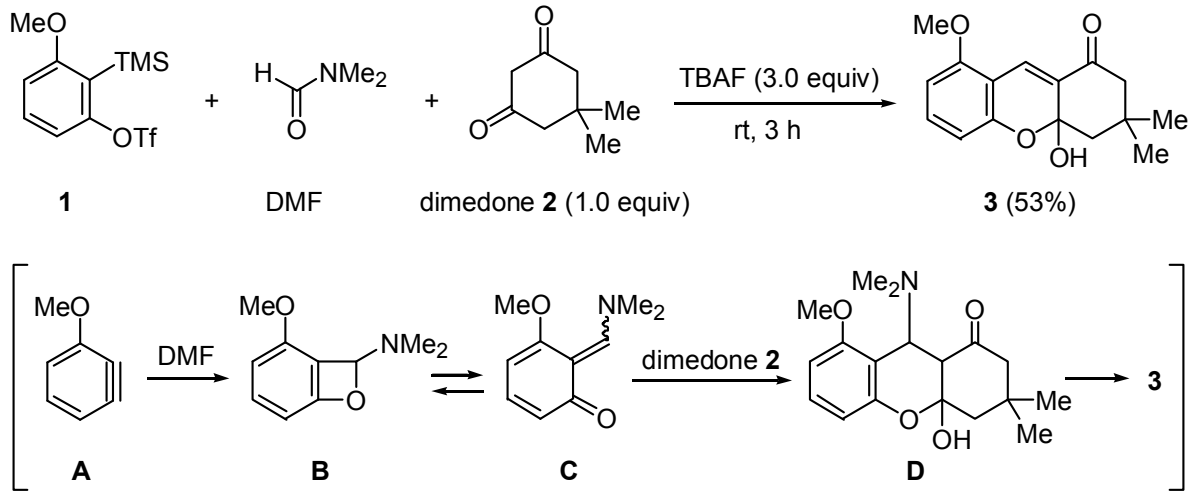
Arynes are highly reactive and kinetically unstable intermediates for constructing multisubstituted arenes with structural diversity and complexity [1,2]. In particular, the recent aryne-based chemistry has made great advances in synthetic chemistry [3–14]. Our laboratory is interested in developing 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].

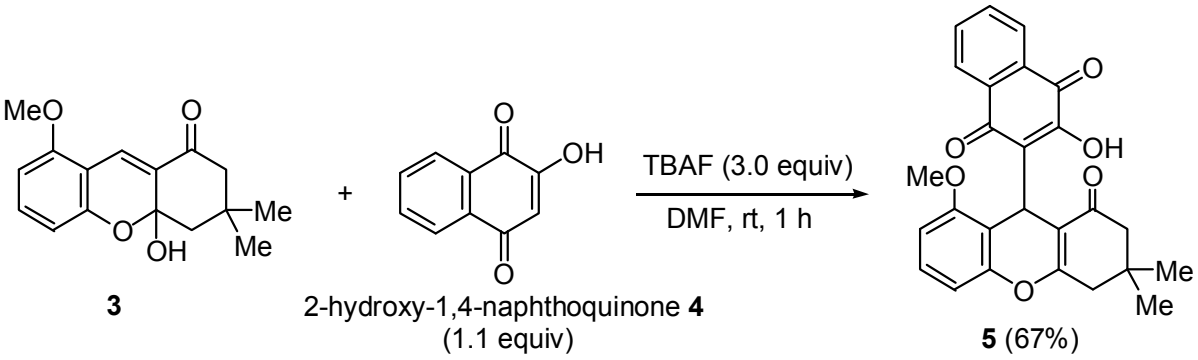
Synthetic strategies involving domino processes offer the advantage of multiple carbon-carbon and/or carbon-heteroatom bond formations in a single operation [21,22]. In this paper, we report two synthetic methods for preparing the title compound **5** via a domino multicomponent coupling reaction starting 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 2*H*-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 2*H*-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 2*H*-chromene derivative **3**.

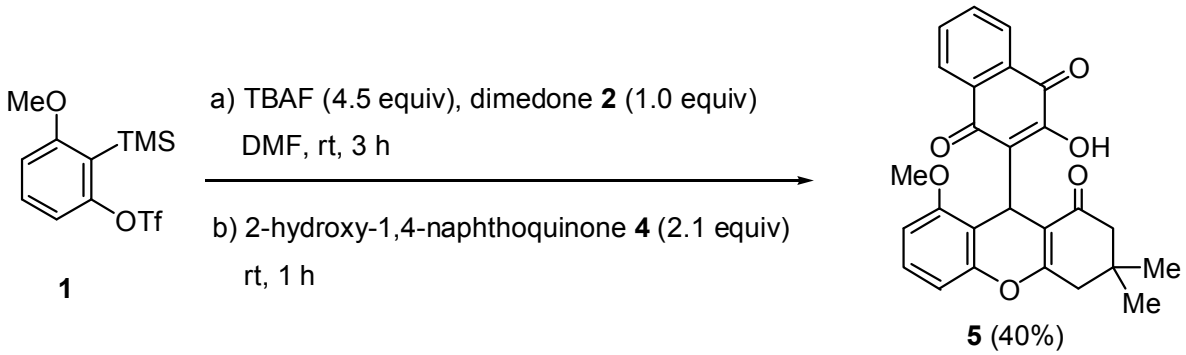
For the synthesis of the title compound **5**, 2-hydroxy-1,4-naphthoquinone (**4**) was employed as a nucleophile (Scheme 2). In the presence of anhydrous TBAF (3 equiv.), we allowed 2*H*-chromene **3** to react with 1.1 equiv. of 2-hydroxy-1,4-naphthoquinone **4** in DMF. As expected, the title compound **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 2*H*-chromene **3**.



Scheme 2. Synthesis of title compound **5**.

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**.

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_2Cl_2) afforded 2*H*-chromene **3** (58 mg, 53%). Colorless crystals. Sublimated decomposition 118–120 °C (CH_2Cl_2-iso-Pr_2O). IR (KBr) 3417 (br), 2957, 1671, 1603, 1566, 1467 cm^{-1}. ^{1}H-NMR (C_6D_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_6D_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 $C_{16}H_{18}O_4Na$ (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 2*H*-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 (**1**, 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

1. Peña, D.; Pérez, D.; Guitián, E. Insertion of arynes into δ-bonds. *Angew. Chem. Int. Ed.* **2006**, *45*, 3579–3581.
2. Yoshida, H.; Ohshita, J.; Kunai, A. Aryne, ortho-quinone methide, and ortho-quinodimethane: Synthesis of multisubstituted arenes using the aromatic reactive intermediates. *Bull. Chem. Soc. Jpn.* **2010**, *83*, 199–219.
3. Peña, D.; Escudero, S.; Pérez, D.; Guitián, E.; Castedo, L. Efficient palladium-catalyzed cyclotrimerization of arynes: Synthesis of triphenylenes. *Angew. Chem. Int. Ed.* **1998**, *37*, 2659–2661.

4. Yoshikawa, E.; Yamamoto, Y. Palladium-catalyzed intermolecular controlled insertion of benzyne-benzyne-alkene and benzyne-alkyne-alkene—Synthesis of phenanthrene and naphthalene derivatives. *Angew. Chem. Int. Ed.* **2000**, *39*, 173–175.
5. Liu, Z.; Larock, R.C. Palladium-catalyzed, sequential, three-component cross-coupling of aryl halides, alkynes, and arynes. *Angew. Chem. Int. Ed.* **2007**, *46*, 2535–2538.
6. Jayanth, T.T.; Cheng, C.-H. Nickel-catalyzed coupling of arynes, alkenes, and boronic acids: Dual role of the boronic acid. *Angew. Chem. Int. Ed.* **2007**, *46*, 5921–5924.
7. Saito, N.; Shiotani, K.; Kinbara, A.; Sato, Y. Nickel-catalyzed [2+2+2] cycloaddition of arynes and an unactivated alkene: Synthesis of 9,10-dihydrophenanthrene derivatives. *Chem. Commun.* **2009**, 4284–4286.
8. Zeng, Y.; Zhang, L.; Zhao, Y.; Ni, C.; Zhao, J.; Hu, J. Silver-mediated trifluoromethylation-iodination of arynes. *J. Am. Chem. Soc.* **2013**, *135*, 2955–2958.
9. Yoshida, H.; Fukushima, H.; Ohshita, J.; Kunai, A. CO_2 incorporation reaction using arynes: Straightforward access to benzoxazinone. *J. Am. Chem. Soc.* **2006**, *128*, 11040–11041.
10. Gilmore, C.D.; Allan, K.M.; Stoltz, B.M. Orthogonal synthesis of indolines and isoquinolines via aryne annulation. *J. Am. Chem. Soc.* **2008**, *130*, 1558–1559.
11. Sha, F.; Huang, X. A multicomponent reaction of arynes, isocyanides, and terminal alkynes: Highly chemo- and regioselective synthesis of polysubstituted pyridines and isoquinolines. *Angew. Chem. Int. Ed.* **2009**, *48*, 3458–3461.
12. Bhunia, A.; Porwal, D.; Gonnade, R.G.; Biju, A.T. Multicomponent reactions involving arynes, quinolines, and aldehydes. *Org. Lett.* **2013**, *15*, 4620–4623.
13. Bhunia, A.; Roy, T.; Pachfule, P.; Rajamohanan, P.R.; Biju, A.T. Transition-metal-free multicomponent reactions involving arynes, *N*-heterocycles, and isatins. *Angew. Chem. Int. Ed.* **2013**, *52*, 10040–10043.
14. Stephens, D.; Zhang, Y.; Cormier, M.; Chavez, G.; Arman, H.; Larionov, O.V. Three-component reaction of small-ring cyclic amine with arynes and acetonitrile. *Chem. Comm.* **2013**, *49*, 6558–6560.
15. Yoshioka, E.; Kohtani, S.; Miyabe, H. Sequential reaction of arynes via insertion into the π-bond of amides and trapping reaction with dialkylzincs. *Org. Lett.* **2010**, *12*, 1956–1959.
16. Yoshioka, E.; Miyabe, H. Insertion of arynes into the carbon-oxygen double bond of amides and its application into the sequential reactions. *Tetrahedron* **2012**, *68*, 179–189.
17. Yoshioka, E.; Kohtani, S.; Miyabe, H. A multicomponent coupling reaction induced by insertion of arynes into the C=O bond of formamide. *Angew. Chem. Int. Ed.* **2011**, *50*, 6638–6642.
18. Yoshioka, E.; Tanaka, H.; Kohtani, S.; Miyabe, H. Straightforward synthesis of dihydrobenzofurans and benzofurans from arynes. *Org. Lett.* **2013**, *15*, 3938–3941.
19. Yoshioka, E.; Kohtani, S.; Miyabe, H. Three-component coupling reactions of arynes for the synthesis of benzofurans and coumarins. *Molecules* **2014**, *19*, 863–880.
20. Yoshioka, E.; Tamenaga, H.; Miyabe, H. [4+2] Cycloaddition of intermediates generated from arynes and DMF. *Tetrahedron Lett.* **2014**, *55*, 1402–1405.
21. Ramachary, D.B.; Jain, S. Sequential one-pot combination of multi-component and multi-catalysis cascade reactions: An emerging technology in organic synthesis. *Org. Biomol. Chem.* **2011**, *9*, 1277–1300.

22. Dömling, A.; Wang, W.; Wang, K. Chemistry and biology of multicomponent reactions. *Chem. Rev.* **2012**, *112*, 3083–3135.
23. Sato, N.; Jitsuoka, M.; Shibata, T.; Hirohashi, T.; Nonoshita, K.; Moriya, M.; Haga, Y.; Sakuraba, A.; Ando, M.; Ohe, T.; *et al.* (9*S*)-9-(2-Hydroxy-4,4-dimethyl-6-oxo-1-cyclohexen-1-yl)-3,3-dimethyl-2,3,4,9-tetrahydro-1*H*-xanthen-1-one, a selective and orally active neuropeptide Y Y5 receptor antagonist. *J. Med. Chem.* **2008**, *51*, 4765–4770.