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COMMUNICATION

Three-component coupling using arynes and DMF: straightforward access to coumarins *via ortho*-quinone methides†

Hiroto Yoshida,* Yu Ito and Joji Ohshita

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***ortho*-Quinone methides, arising from a formal [2 + 2] cycloaddition between arynes and DMF, were found to facilely undergo a [4 + 2] cycloaddition with ester enolates or ketenimine anions to produce diverse coumarins in a straightforward manner.**

ortho-Quinone methides (*o*-QMs)[1] are labile and transient intermediates, which have been widely utilized as defensive chemicals in nature. Their structural motifs also play vital roles in vitamin E chemistry and metabolism,[2] and anti-cancer properties of anthracyclines.[3] Despite the universal knowledge about *o*-QMs as biologically active components, there should be a number of unexploited reactions of potential synthetic value, which would be feasible by suitable combination of *o*-QMs and designed reagents.[1b] In this regard, we have previously disclosed that a 2 : 1 coupling reaction of arynes with aldehydes offered straightforwardly xanthene derivatives of structural diversity,[4] where *o*-QMs, arising from a formal [2 + 2] cycloaddition between arynes and aldehydes, act as key intermediates.[5] The six-membered oxygen-containing heterocyclic frameworks of the xanthenes are assembled by a [4 + 2] cycloaddition between the *exo* enone moieties of *o*-QMs and arynes, and thus we envisaged that the use of other combinations of carbonyl compounds and 2π components in the reaction with arynes should result in a new type of coupling reactions for the synthesis of benzo-annulated *O*-heterocycles. We report herein that the novel three-component coupling using arynes and DMF provides direct access to coumarins,[6] which constitute an important class of such biologically active compounds as carbochromen (coronary heart disease treatment),[7] pachyrrhizine (mosquitocidal activity),[8] warfarin (anticoagulant)[9] and AP2238 (anti-Alzheimer drug candidate)[10] (Fig. 1).

We first conducted the reaction of *in situ*-generated benzyne (from **1a**[11] and KF) with diethyl malonate (**2a**) in DMF at 80 °C, and observed that 3-(ethoxycarbonyl)coumarin (**3a**) was produced in 79% yield (entry 1, Table 1). It should be noted that the same reaction in THF led to the C–C bond cleavage of **2a** as we reported before,[12,13] showing that the solvents distinctly switch the course of the reaction. As depicted in Scheme 1, nucleophilic attack of a carbonyl oxygen of DMF to benzyne would trigger the reaction.[14] The resulting zwitterion (**4**) undergoes intramolecular cyclization to give benzoxete **5**, which then isomerizes to an *o*-QM (**6**) *via* electrocyclic ring-opening. Subsequent [4 + 2] cycloaddition between **6** and an enolate of **2a**,[15,16] followed by elimination of an ethoxide and dimethylamine, furnishes **3a**. Other malonates (**2b–2d**) were also smoothly coupled with benzyne and DMF to afford the respective coumarins (**3b–3d**) in high yields (entries 2–4), and furthermore the three-component coupling was applicable to β-ketoester (**2e**) and malononitrile (**2f**)[17] (entries 5 and 6), albeit in moderate yields. The functional

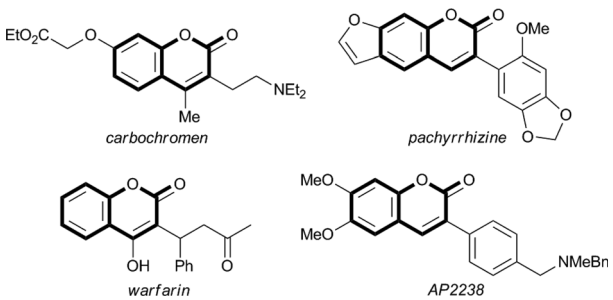

Fig. 1 Biologically active coumarins.

Table 1 Three-component coupling of benzyne, DMF and active methylene compounds[a]

1a 2 3

Entry	Z^1	Z^2	Time/h	Yield[b] (%)	3
1	CO_2Et	CO_2Et (**2a**)	5	79	**3a**
2	CO_2n-Bu	CO_2n-Bu (**2b**)	4	87	**3b**
3	CO_2i-Pr	CO_2i-Pr (**2c**)	10	79	**3c**
4	CO_2t-Bu	CO_2t-Bu (**2d**)	17	72	**3d**
5	C(O)Me	CO_2Me (**2e**)	5	55	**3e**
6	CN	CN (**2f**)	1.5	39	**3f**
7	$P(O)(OEt)_2$	CO_2Et (**2g**)	5	74	**3g**
8	$SO_2(p$-tol)	CN (**2h**)	6	53	**3h**
9	SO_2Ph	CO_2Et (**2i**)	8	44	**3i**

[a] The reaction was carried out in DMF (4 mL) at 80 °C using **1a** (0.40 mmol), **2** (0.20 mmol) and KF (0.80 mmol). [b] Isolated yield based on **2**.

Department of Applied Chemistry, Graduate School of Engineering, Hiroshima University, Higashi-Hiroshima 739-8527, Japan. E-mail: yhiroto@hiroshima-u.ac.jp; Fax: +81-82-424-5494; Tel: +81-82-424-7724

† Electronic supplementary information (ESI) available: Experimental procedure including spectroscopic and analytical data. See DOI: 10.1039/c1cc11955a

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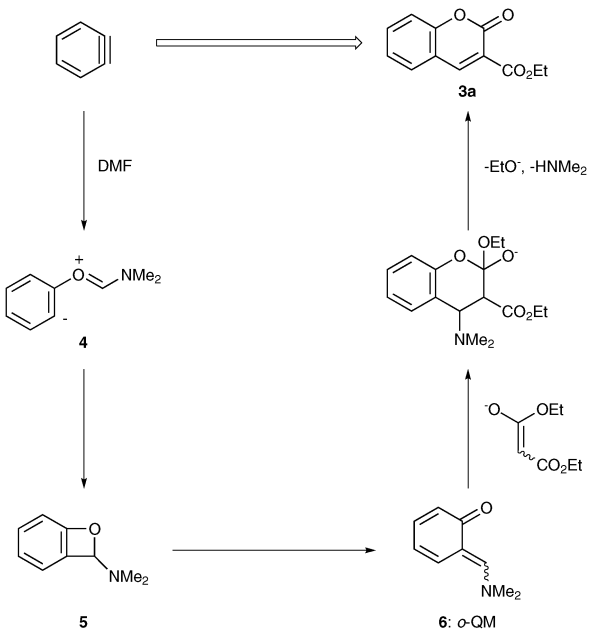


Scheme 1 A reaction pathway for the formation of **3a**.

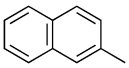
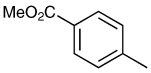
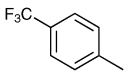
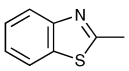
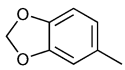
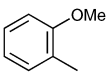
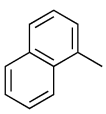
group compatibility of the present reaction was high enough, and thus active methylene compounds bearing a diethylphosphoryl (**2g**) or an arylsulfonyl group (**2h** and **2i**) were convertible into the coumarins (**3g–3i**) with these functional groups remaining intact throughout the reaction (entries 7–9).

Besides active methylene compounds, arylacetic acid esters and arylacetonitriles proved to serve efficaciously as third components in the reaction. As described in Table 2, ethyl 2-pyridylacetate (**2j**) and ethyl 4-pyridylacetate (**2k**) smoothly participate in the reaction to afford **3j** and **3k** in 95% and 70% yield (entries 1 and 2), whereas the reaction of ethyl 3-pyridylacetate (**2l**) resulted in a lower yield (entry 3), suggesting that facile deprotonation of the methylene moieties, being attributable to the stable resonance structures of the corresponding enolates, would be crucial for the efficient coupling. Treatment of phenylacetonitrile (**2m**) or 2-naphthylacetonitrile (**2n**) with benzyne and DMF also provided good yields of the coumarins (**3m** and **3n**) (entries 4 and 5), and furthermore the reaction of arylacetonitriles (**2o** and **2p**) having an electron-withdrawing group at the *para* position readily took place (entries 6 and 7). Substituted coumarins containing a benzothiazole (**3q**) or a benzodioxole (**3r**) moiety could be fabricated based on the three-component coupling (entries 8 and 9), however, the reaction of sterically demanding nitriles became sluggish (entries 10–12).

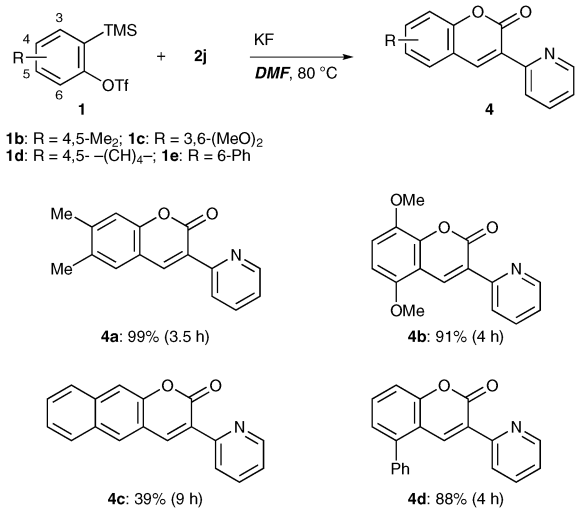
The scope of the reaction was further examined by using substituted arynes (Scheme 2). Similarly to the case of simple benzyne, 4,5-dimethylbenzyne (from **1b**) and 3,6-dimethoxybenzyne (from **1c**) smoothly reacted with **2j** and DMF to produce high yields of the multisubstituted coumarins (**4a** and **4b**), while the reaction of 2,3-naphthalyne (from **1d**) led to the formation of **4c** in 39% yield. Perfect regioselectivity was observed in the reaction of 3-phenylbenzyne (from **1e**), in which the oxygen atom derived from DMF was attached at the *meta* position of the phenyl group.[18]

On the supposition that salicylaldehyde might be an intermediate species in the present coupling,[19,20] we carried out the

Table 2 Three-component coupling of benzyne, DMF and arylacetic acid esters/arylacetonitriles[a]

Entry	Ar	Z	Time/h	Yield[b] (%)	3
1		CO_2Et (**2j**)	2.5	95	**3j**
2		CO_2Et (**2k**)	3	70	**3k**
3		CO_2Et (**2l**)	8.5	28	**3l**
4	Ph	CN (**2m**)	6.5	60	**3m**
5		CN (**2n**)	19	66	**3n**
6		CN (**2o**)	5.5	99	**3o**
7		CN (**2p**)	6	68	**3p**
8		CN (**2q**)	8.5	64	**3q**
9		CN (**2r**)	3	40	**3r**
10		CN (**2s**)	5.5	39	**3s**
11		CN (**2t**)	6	31	**3t**
12		CN (**2u**)	10.5	30	**3u**

[a] The reaction was carried out in DMF (4 mL) at 80 °C using **1a** (0.40 mmol), **2** (0.20 mmol) and KF (0.80 mmol). [b] Isolated yield based on **2**.



Scheme 2 Synthesis of coumarins using substituted arynes.

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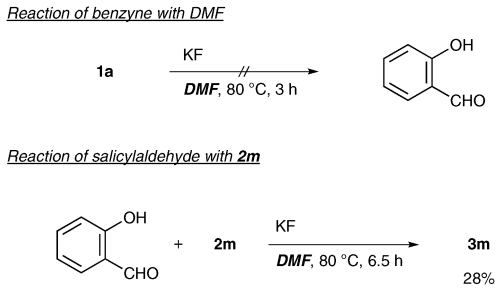

Scheme 3 Mechanistic investigation of the three-component coupling.

reaction of benzyne with DMF (Scheme 3), however, no trace of salicylaldehyde was formed under our conditions, which rules out its intermediacy in the three-component coupling.[21] Although the reaction of salicylaldehyde with **2m** actually provided **3m**, the efficiency is considerably lower than that of the present reaction.

In conclusion, we have demonstrated that *o*-QMs, generated from arynes and DMF, are efficaciously coupled with active methylene compounds, arylacetic acid esters or arylacetonitriles to offer the direct access to diverse coumarins, which comprise integral parts of biologically active compounds and pharmaceuticals. Further studies on novel coupling reactions using *o*-QMs as well as on extension of the reaction scope are in progress.

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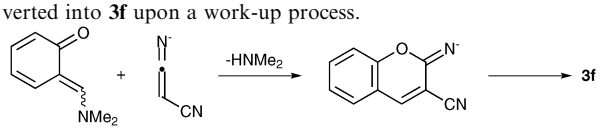
15 At present, we have no decisive evidence for whether the [4+2] cycloaddition proceeds concertedly or stepwise.

16 A fluoride acts as a base for the formation of an enolate. See ref. 13*d*.

17 In this case, the [4+2] cycloadditon between an *o*-QM and a ketenimine anion provides an iminocoumarin, which is then converted into **3f** upon a work-up process.



18 This regioselectivity can be ascribed to avoidance of the unfavourable steric repulsion between the phenyl moiety and the incoming DMF in the nucleophilic attack.

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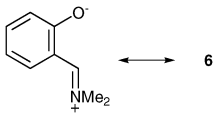
21 As a referee commented, the following betaine, being the resonance structure of *o*-QM **6**, may also serve as the key intermediate in the present reaction.



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