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A 2:1 Coupling Reaction of Arynes with Aldehydes via *o*-Quinone Methides: Straightforward Synthesis of 9-Arylxanthenes

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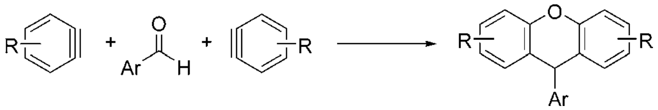
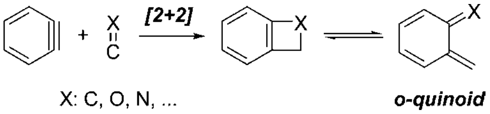
ABSTRACT



A novel coupling reaction, where an aldehyde and two molar amounts of an aryne are assembled selectively, has been demonstrated to afford diverse 9-arylxanthene derivatives in one step. *o*-Quinone methide arising from the [2 + 2] cycloaddition of an aldehyde with an aryne was postulated as a transient intermediate.

The [2 + 2] cycloadditions of arynes[1] with alkenes or carbon−heteroatom double bonds have attracted considerable attention as an efficient method for construction of benzocyclobutene skeletons, which are valence isomers of synthetically useful *o*-quinoid species (Scheme 1).[2,3] Although various electron-rich alkenes including vinyl ethers,[4] ketene acetals,[5] and enamines[6] readily undergo the [2 + 2] cycloaddition, few reports have been available on the reaction of carbonyl compounds with arynes. We have recently disclosed electrophilic coupling reactions of arynes, that is, synthesis of *N*-alkyl-*N*′-arylimidazolium salts via addition of imidazoles to arynes,[7a] insertion of arynes into an N−CO σ-bond of ureas,[7b] and three-component coupling of arynes with isocyanides and aldehydes,[7c] demonstrating that diverse heterocyclic skeletons were assembled straightforwardly from neutral neucleophiles and arynes. Based upon these results, we envisaged that a carbonyl oxygen atom may act as a nucleophilic site to arynes, leading to a new type of coupling reactions for the synthesis of heterocycles.[8−10] Herein we

Scheme 1



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(1) For reviews on arynes, see: (a) Kessar, S. V. In *Comprehensive Organic Synthesis*; Trost, B. M., Flemming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 4, p 483. (b) Pellissier, H.; Santelli, M. *Tetrahedron* **2003**, *59*, 701.

(2) For a review on the valence isomerization of cyclobutenes, see: Durst, T.; Breau, L. In *Comprehensive Organic Synthesis*; Trost, B. M., Flemming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 5, p 675.

(3) (a) For a review on *o*-quinone methides, see: Van De Water, R. W.; Pettus, T. R. R. *Tetrahedron* **2002**, *58*, 5367. (b) For a review on *o*-quinodimethanes, see: Segura, J. L.; Martin, N. *Chem. Rev.* **1999**, *99*, 3199.

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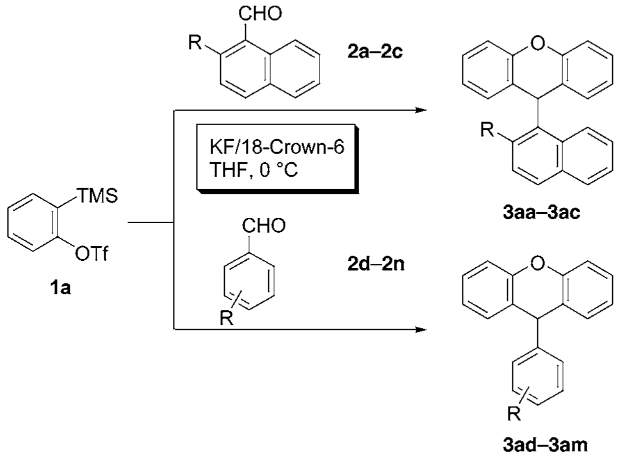
report that a 2:1 coupling reaction of arynes with aryl aldehydes via the [2 + 2] cycloaddition as a key step offers straightforwardly diverse xanthene derivatives,[11] which constitute such functionalized molecules as dyes and pharmaceuticals.[12]

We first examined the reaction of in situ-generated benzyne (from **1a** and KF/18-crown-6) with 2-benzyloxy-1-naphthaldehyde (**2a**) in THF at 0 °C and observed that two molar amounts of benzyne were coupled with **2a** to give 9-(2-bezyloxy-1-naphthyl)xanthene (**3aa**) in 70% yield (Table 1, entry 1). Treatment of 2-methoxy-1-naphthaldehyde (**2b**) with benzyne also produced 66% yield of **3ab** (entry 2), whereas the reaction of 1-naphthaldehyde (**2c**) resulted in a low yield (entry 3), indicating that the use of an electron-rich aldehyde is indispensable for the reaction to proceed smoothly. Similarly to the naphthaldehydes, the coupling reaction was applicable to a variety of benzaldehydes. Thus, when 2,6-dimethoxy- (**2d**) or 2,6-dibenzyloxybenzaldehyde (**2e**) was allowed to react with benzyne, the corresponding xanthene (**3ad** or **3ae**) was formed in 61% or 60% yield (entries 4 and 5). Furthermore, the reaction of a variously substituted methoxybenzaldehyde (**2f**−**i**) took place effectively, leading to the formation of the product (**3af**−**ai**) in a modest yield (entries 6−9). A methyl-substituted benzaldehyde (**2j**−**l**) could participate in the reaction as well to afford a reasonable to good yield of the respective xanthene (**3aj**−**al**), in contrast to the reaction of benzaldehyde (**2m**, 22% yield) or 4-trifluoromethylbenzaldehyde (**2n**, xanthene was not formed at all) (entries 10−14).

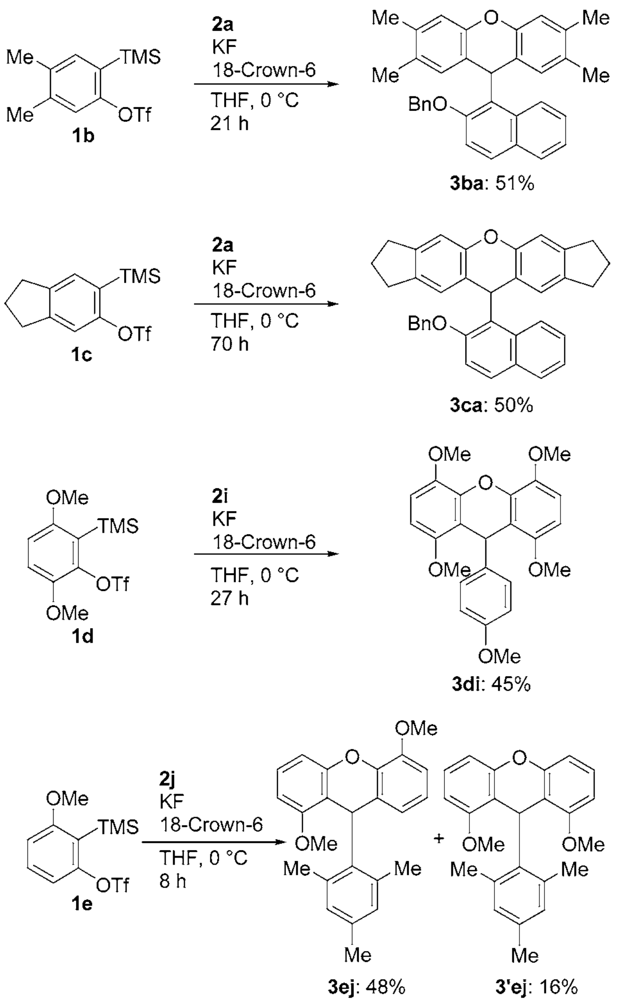
Table 1. 2:1 Coupling of Benzyne with an Aryl Aldehyde[a]



entry	R		time (h)	yield[b] (%)	product
1	BnO	**2a**	23	70	**3aa**
2	MeO	**2b**	24	66	**3ab**
3	H	**2c**	26	17	**3ac**
4	$2,6\text{-}(MeO)_2$	**2d**	20	61	**3ad**
5	$2,6\text{-}(BnO)_2$	**2e**	27	60	**3ae**
6	2-MeO	**2f**	7	54	**3af**
7	$2,4\text{-}(MeO)_2$	**2g**	5	53	**3ag**
8	$2,4,6\text{-}(MeO)_3$	**2h**	21	44	**3ah**
9	4-MeO	**2i**	18	42	**3ai**
10	$2,4,6\text{-}Me_3$	**2j**	4	58	**3aj**
11	$2,4\text{-}Me_2$	**2k**	8	41	**3ak**
12	$2,6\text{-}Me_2$	**2l**	5	38	**3al**
13	H	**2m**	20	22	**3am**
14	$4\text{-}CF_3$	**2n**	19	0	

[a] The reaction was carried out in THF at 0 °C using **1a** (0.45 mmol), **2** (0.15 mmol), KF (0.90 mmol) and 18-crown-6 (0.90 mmol). [b] Isolated yield based on **2**.

Scheme 2



We next investigated the 2:1 coupling reaction of a substituted aryne. As depicted in Scheme 2, a symmetrical aryne (from **1b**−**d**) efficiently underwent the coupling reaction, giving the polysubstituted xanthene (**3ba**, **3ca**, or **3di**) in 51%, 50%, or 45% yield, respectively. In addition, the reaction of 3-methoxybenzyne (from **1e**), an unsym-

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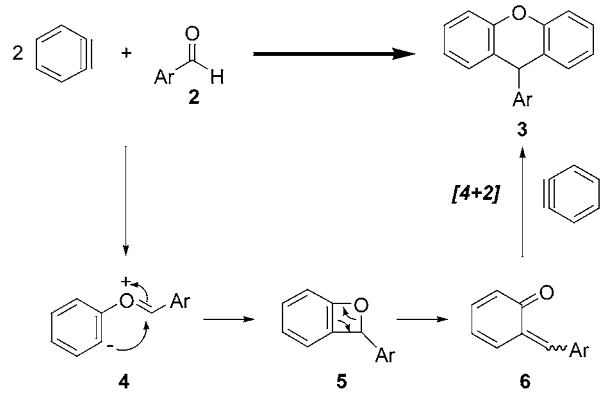
(8) Heaney and Nakayama reported independently on the synthesis of 1,3-benzodioxanes (ca. 20% yield) via a 1:2 coupling reaction of arynes with aryl aldehydes, where a large excess of aldehydes (ca. 40 equiv to aryne precursors) was used: (a) Heaney, H.; McCarty, C. T. *Chem. Commun.* **1970**, 123. (b) Nakayama, J.; Yoshida, M.; Simamura, O. *Chem. Lett.* **1973**, 451.

(9) Heaney also reported reactions of arynes with α,β-unsaturated aldehydes: Heaney, H.; Jablonski, J. M.; McCarty, C. T. *J. Chem. Soc., Perkin Trans. 1* **1972**, 2903.

metrical aryne, with **2j** provided 64% yield of two regioisomers (**3ej** and **3′ej**) in a 3:1 ratio.

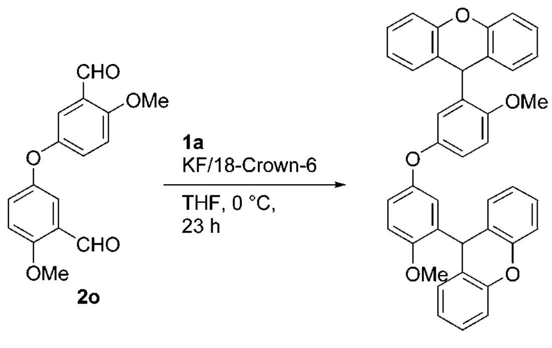
Scheme 3 describes a plausible reaction pathway of the 2:1 coupling. First, a nucleophilic attack of a carbonyl oxygen atom to an aryne gives a zwitterion (**4**), which then undergoes intramolecular cyclization to afford a benzoxete (**5**). Subsequent isomerization to an *o*-quinone methide (**6**), followed by [4 + 2] cycloaddition with a second aryne provides a xanthene. As was the case of the other electrophilic couplings of 3-methoxybenzyne, the carbonyl oxygen of **2j** would attack exclusively the aryne carbon at the meta position of the methoxy moiety.[1a,7] On the contrary, the following [4 + 2] cycloaddition between the resulting *o*-quinone methide and 3-methoxybenzyne may take place at each orientation, resulting in the formation of two regioisomers (**3ej** and **3′ej**).

Scheme 3



Finally, utility of the coupling reaction has been demonstrated by application to diformyldiphenyl ether **2o**. As shown in Scheme 4, each formyl group was coupled with two molar amounts of benzyne to provide bis(xanthylphenyl) ether **3ao** straightforwardly in 25% yield.

Scheme 4



3ao: 25%

In conclusion, a general and straightforward method for the synthesis of diverse xanthene derivatives has been accomplished based upon the novel 2:1 coupling reaction of arynes with aldehydes. Further studies on synthetic applications to other carbon−heteroatom double bonds are in progress.

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Supporting Information Available: Experimental procedures and characterization of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) For [2 + 2] cycloadditions of arynes with other carbon−heteroatom double bonds, see the following references. (a) Imines: Aly, A. A.; Mohamed, N. K.; Hassan, A. A.; Mourad, A.-F. E. *Tetrahedron* **1999**, *55*, 1111. (b) Thiones: Okuma, K.; Shiki, K.; Sonoda, S.; Koga, Y.; Shioji, K.; Kitamura, T.; Fujiwara, Y.; Yokomori, Y. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 155. (c) Selones: Okuma, K.; Okada, A.; Koga, Y.; Yokomori, Y. *J. Am. Chem. Soc.* **2001**, *123*, 7166.

(11) For synthesis of xanthenes by a nucleophilic coupling with arynes, see: (a) Vázquez, R.; de la Fuente, M. C.; Castedo, L.; Domínguez, D. *Synlett* **1994**, 433. (b) Knight, D. W.; Little, P. B. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1771.

(12) Hepworth, J. D. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon Press: Oxford, 1984; Vol. 3, p 874.