

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

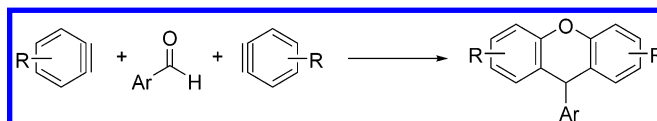
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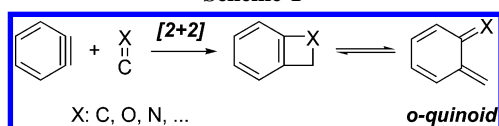
ABSTRACT



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 arynes¹ with alkenes or carbon–heteroatom double bonds have attracted considerable attention as an efficient method for construction of benzo-cyclobutene skeletons, which are valence isomers of synthetically useful *o*-quinoid species (Scheme 1).^{2,3} Although

Scheme 1



various electron-rich alkenes including vinyl ethers,⁴ ketene acetals,⁵ and enamines⁶ 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 nucleophiles 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

(1) For reviews on arynes, see: (a) Kessar, S. V. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, 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., Fleming, 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.

(4) Wasserman, H. H.; Solodar, J. *J. Am. Chem. Soc.* **1965**, 87, 4002.

(5) (a) Hosoya, T.; Hamura, T.; Kuriyama, Y.; Suzuki, K. *Synlett* **2000**, 520. (b) Hamura, T.; Ibusuki, Y.; Sato, K.; Matsumoto, T.; Osamura, Y.; Suzuki, K. *Org. Lett.* **2003**, 5, 3551.

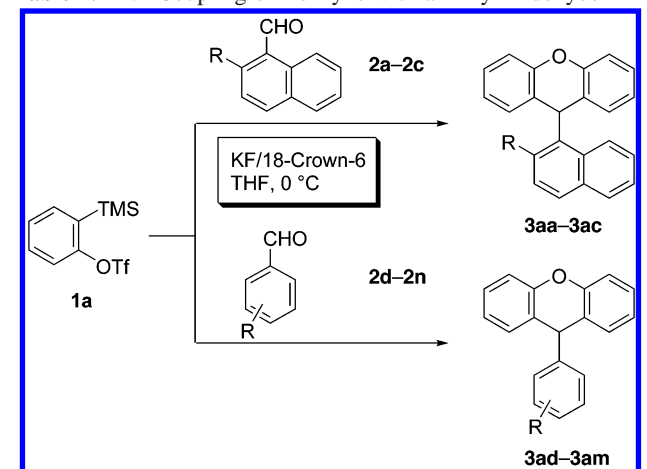
(6) (a) Kametani, T.; Kigasawa, K.; Hiiragi, M.; Hayasaka, T.; Kusama, O. *J. Chem. Soc. C* **1971**, 1051. (b) Gingrich, H. L.; Huang, Q.; Morales, A. L.; Jones, M., Jr. *J. Org. Chem.* **1992**, 57, 3803.

(7) (a) Yoshida, H.; Sugiura, S.; Kunai, A. *Org. Lett.* **2002**, 4, 2767. (b) Yoshida, H.; Shirakawa, E.; Honda, Y.; Hiyama, T. *Angew. Chem., Int. Ed.* **2002**, 41, 3247. (c) Yoshida, H.; Fukushima, H.; Ohshita, J.; Kunai, A. *Angew. Chem., Int. Ed.* **2004**, 43, 3935.

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-benzyloxy-1-naphthyl)xanthene (**3aa**) in 70% yield (Table 1, entry 1). Treatment of 2-methoxy-1-naphthaldehyde (**2b**)

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-(MeO) ₂	2d	20	61	3ad
5	2,6-(BnO) ₂	2e	27	60	3ae
6	2-MeO	2f	7	54	3af
7	2,4-(MeO) ₂	2g	5	53	3ag
8	2,4,6-(MeO) ₃	2h	21	44	3ah
9	4-MeO	2i	18	42	3ai
10	2,4,6-Me ₃	2j	4	58	3aj
11	2,4-Me ₂	2k	8	41	3ak
12	2,6-Me ₂	2l	5	38	3al
13	H	2m	20	22	3am
14	4-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**.

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-

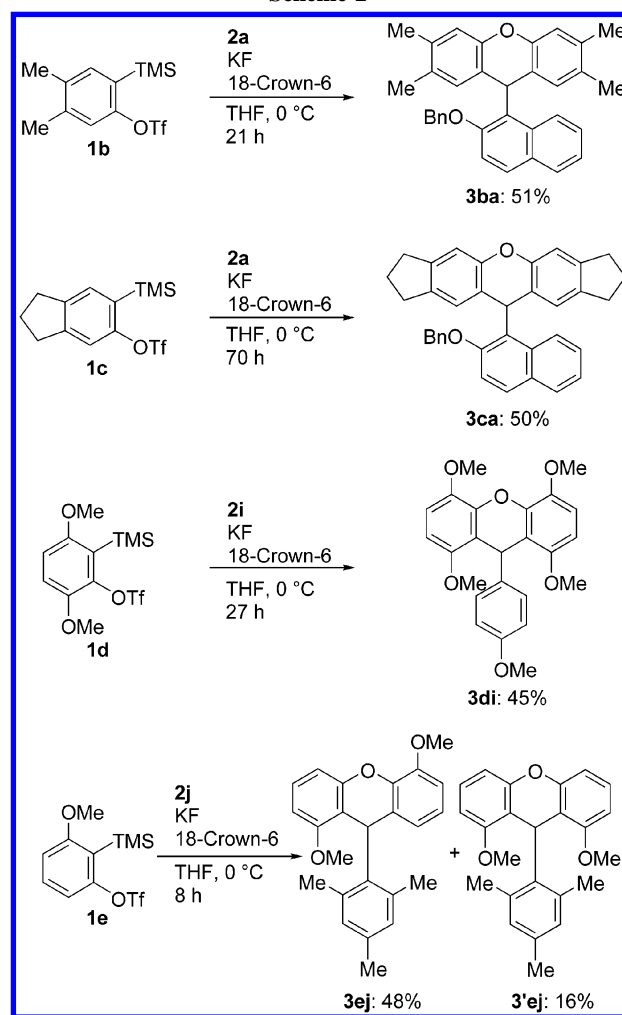
(8) Heaney and Nakayama reported independently on the synthesis of 1,3-benzodioxanes (ca. 20% yield) via a 1:2 coupling reaction of arynes with aryl aldehydes, where a large excess of aldehydes (ca. 40 equiv to aryne precursors) was used: (a) Heaney, H.; McCarty, C. T. *Chem. Commun.* **1970**, 123.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

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).

We next investigated the 2:1 coupling reaction of a substituted aryne. As depicted in Scheme 2, a symmetrical

Scheme 2

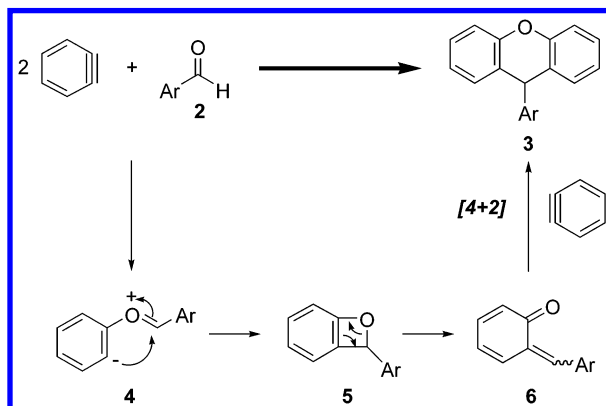


aryne (from **1b-d**) efficiently underwent the coupling reaction, giving the polysubstituted xanthene (**3ba**, **3ca**, or **3di**) in 51%, 50%, or 45% yield, respectively. In addition, the reaction of 3-methoxybenzyne (from **1e**), an unsym-

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

Scheme 3



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 +

(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.

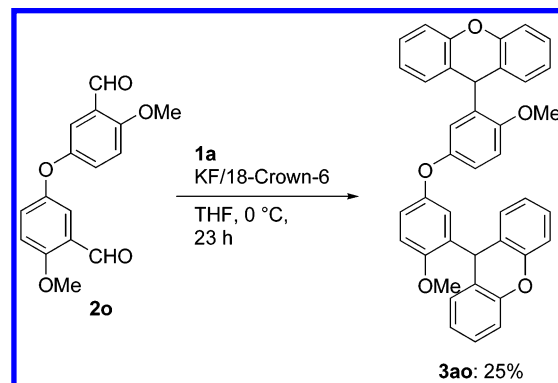
(11) For synthesis of xanthenes by a nucleophilic coupling with arynes, see: (a) Vázquez, R.; de la Fuente, M. C.; Castedo, L.; Domínguez, D. *Synlett* **1994**, 433. (b) Knight, D. W.; Little, P. B. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1771.

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

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**).

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

Scheme 4



amounts of benzyne to provide bis(xanthylphenyl) ether **3ao** straightforwardly in 25% yield.

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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