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Site-Specific Preparation of 2-Carboalkoxy-4-substituted Naphthalenes and 9-Alkylphenanthrenes and Evidence for an Allene Intermediate in the Novel Base-Catalyzed Cyclization of 2-Alkynylbiphenyls

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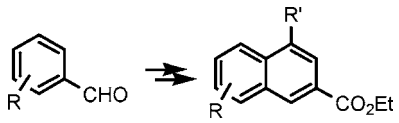
ABSTRACT



A site-specific preparation of 2-carboalkoxy-4-substituted naphthalenes and 9-alkylphenanthrenes is described. The successful cyclization of an allene intermediate provides supportive evidence for the previously proposed mechanism.

Polysubstituted naphthalene derivatives are important building blocks for the synthesis of pharmaceuticals[1] and polycyclic aromatic electronic materials.[2] A variety of methods have been developed for their preparation including electrophilic substitution of naphthalenes,[3] coupling of halonaphthalenes with organolithium or Grignard reagents,[4] annulations via Fischer carbenes,[5] palladium-catalyzed cyclization of alkynes with benzynes[6] and cyclization of alkynes,[7] [3+3] benzannulation of benzenoid ring systems,[8] reaction of 1-methoxybenzocyclobutene and alkynes,[9] $TiCl_4$-mediated annulations of α-aryl-substituted carbonyl compounds with alkynes,[10] and benzotriazole-assisted aromatic ring annulation.[11] However, these methods involve expensive catalysts or multistep synthesis. In some cases, regioselectivity was difficult to achieve. Therefore, a new and efficient methodology for the site-specific synthesis of polysubstituted naphthalenes was of interest to us. Herein, we wish to report a novel base-catalyzed cyclization to prepare polysubstituted naphthalene derivatives.

In our previous reported work in the base-catalyzed cyclization of fluorinated enynes, we found that the presence of a vinylic fluorine in the enyne successfully promoted cyclization (with a DABCO or DBU base system) and provided a site-specific synthesis of 1-alkyl-3-fluoronaphthalenes.[12] In contrast, (*Z*)-non-1-en-3-yn-1-ylbenzene gave no reaction with DABCO or DBU.[12] We proposed that the

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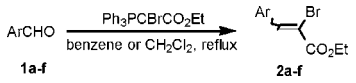
vinylic fluorine increased the acidity of the propargylic hydrogens and facilitated the formation of an allene intermediate which reacted with the π aryl ring system to form the cyclized product. However, in the fluorine-containing enyne system, we were not able to observe the proposed allene intermediate nor were we successful in independently synthesizing the allene intermediate. Thus, two key questions remained: first, was the cyclization specific to fluorine-containing enynes or would other electron-withdrawing groups also facilitate cyclization and truly broaden the overall scope of this novel site-specific approach; and second, could unequivocal evidence be obtained to support the proposed allene intermediate in the mechanistic interpretation of this cyclization process?

First, we investigated the effect of a carboalkoxy group in the enyne to facilitate cyclization. The requisite carboalkoxy-substituted enynes were prepared by the Sonogashira reaction[13] of terminal alkynes with α-bromocinnamates, which could be readily prepared from the Wittig reaction of aromatic aldehydes with $Ph_3PCBrCO_2Et$.[14] The *Z*/*E* ratio in the products **2a**−**d** was determined by the chemical shifts of the vinyl protons in the proton NMR spectra of the *Z*/*E* mixtures. The vinyl protons in the *Z* isomers appeared at a lower field due to the deshielding effect from the ester groups.[15] These results are summarized in Table 1.

Table 1. Preparation of α-Bromocinnamates

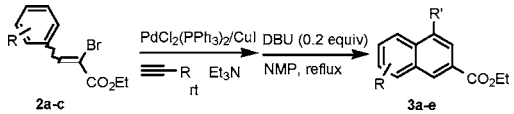


entry	ArCHO	ratio[a] (*Z*/*E*) of product	product	isolated yield[b] (%)
1[c]	C_6H_5	83:17	**2a**	67
2[c]	4-$O_2NC_6H_4$	96:4	**2b**	95
3[c]	4-$MeOC_6H_4$	78:22	**2c**	82
4[d]	2-naphthaldehyde	79:21	**2d**	94

[a] Determined by ^{1}H NMR. [b] Based on aldehyde. [c] Benzene was the solvent. [d] CH_2Cl_2 was the solvent.

The resultant α-bromocinnamates **2a**−**c** were obtained as a mixture of *Z* and *E* isomers, where the *Z* isomers were the major products (these mixtures were utilized in the following cyclization step). Sonogashira reaction[13] of the α-bromocinnamates **2a**−**c** with terminal alkynes gave the corresponding enynes. Because it was difficult to separate the *Z*/*E* mixtures from each other and only the (*E*)-enynes could cyclize with our base system, the mixtures were used directly for the next step without characterization. When DBU (0.2 equiv) was employed as the base, the polysubstituted naphthalene derivatives **3a**−**e** were obtained in moderate to good yields for the two steps. The results of these reactions indicated that the presence of either an electron-donating or an electron-withdrawing group on the aromatic ring had little effect on the outcome of the cyclization step. However, when R is the 4-nitro group (entry 2), the temperature required for the cyclization step is somewhat lower (170 °C vs 200 °C in other cases). These results are summarized in Table 2.

Table 2. Formation of Polysubstituted Ethyl 2-Naphthoates

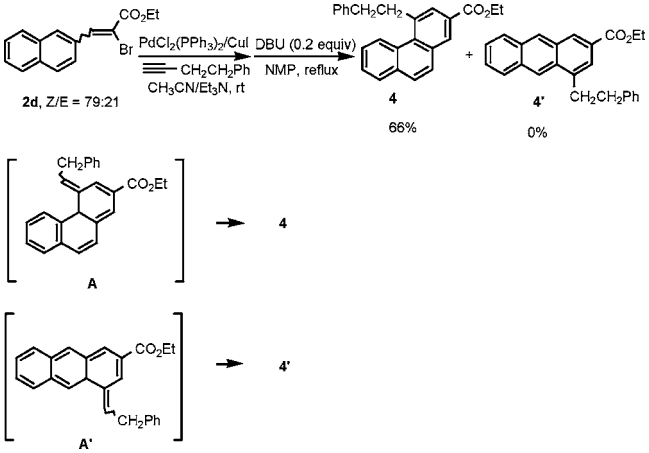


entry	R	R′	product	time (h)	isolated yield[a] (%)
1	H	CH_2CH_2Ph	**3a**	3	64
2	4-O_2N	*n*-C_4H_9	**3b**	2.5	46
3	4-MeO	*n*-C_4H_9	**3c**	5	73
4	4-MeO	*n*-$C_{10}H_{21}$	**3d**	5	59
5	4-MeO	CH_2CH_2Ph	**3e**	5	58

[a] Two steps, based on the corresponding α-bromocinnamates **2a**−**c**.

When 2-naphthaldehyde was employed as the substrate, theoretically, there could be two possible products from two different cyclization directions of the corresponding enyne. However, phenanthrene derivative **4** was isolated as the sole product and no anthracene **4′** was observed (Scheme 1). The

Scheme 1. Sole Formation of **4**



phenanthrene structure **4** was confirmed by its single X-ray crystallographic structure determination.[16] This selectivity could be explained by computational work previously reported in which the total molecular energy of phenanthrene

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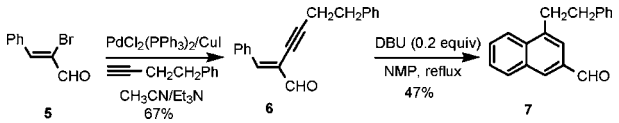
(16) CCDC 617807 (**4**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif or by e-mailing data_request@ccdc.cam.ac.uk or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax +44 1223 336033. Also see the Supporting Information.

is lower than that of anthracene.[17] Another possible explanation is that, when both structures of the intermediates (prior to two possible final products) are drawn, it is clear that the formation of intermediate **A** is more favorable than **A′** because the aromaticity of one benzene ring is retained whereas in the case of **A′** the aromaticity of both benzene rings is destroyed.[18]

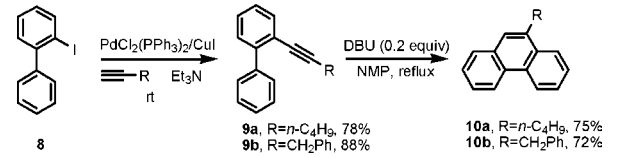
The presence of an aldehyde group on the double bond of enynes could also facilitate the base-catalyzed cyclization as well. For example, when α-bromocinnamaldehyde **5** was employed as the substrate, the enyne **6** could be prepared from its reaction with 4-phenyl-1-butyne under cocatalysis of $PdCl_2(PPh_3)_2$ and CuI in CH_3CN/Et_3N. 4-Phenethyl-2-naphthaldehyde **7** was prepared in moderate yield (Scheme 2).

Scheme 2. Formation of **7**



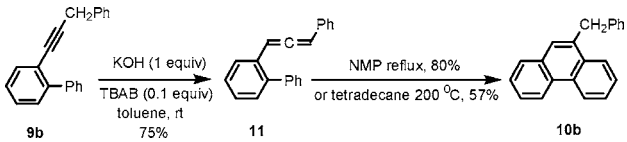
When the double bond of the enyne was part of an aromatic ring, the cyclization occurred smoothly under our conditions as well to afford phenanthrene derivatives. 2-Iodo biphenyl **8** was reacted with a terminal alkyne under Sonogashira conditions. The resultant 2-alkynyl-substituted biphenyls **9a** and **9b**, when treated with DBU (0.2 equiv) in refluxing NMP, gave 9-alkyl phenanthrenes **10a** and **10b**[6b] in good yields, respectively (Scheme 3).

Scheme 3. Preparation of Phenanthrenes **10a** and **10b**



In our previous report,[12] an allene intermediate was proposed in the mechanistic interpretation of the overall cyclization process. To provide support for this proposed mechanistic intermediate, the following experiment was performed. When **9b** was stirred with KOH (1.0 equiv) and tetra-*n*-butylammonium bromide (TBAB) (0.1 equiv) as the phase-transfer catalyst in toluene at room temperature,[19] the resultant allene **11** was isolated. Subsequently, when **11** was heated in refluxing NMP, **10b** was formed (it was identical to the product **10b** formed from **8** in Scheme 3). To rule out the possibility of a trace amount of base formed from NMP at high temperature (200 °C), tetradecane was used as the solvent for the cyclization of **11** and **10b** was obtained in 57% yield (Scheme 4). Thus, these experiments provided

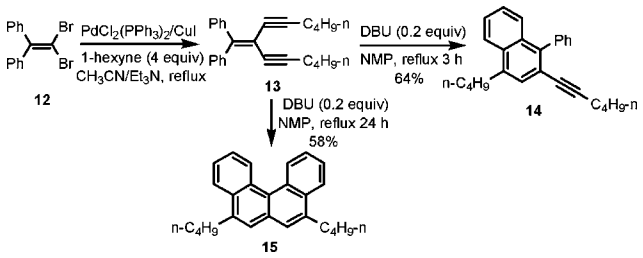
Scheme 4. Formation of **10b** from Allene **11** without Base



supportive evidence for the allene intermediate in the mechanism of the cyclization reaction under base-catalyzed conditions.

Interestingly, when 1,1-dibromo-2,2-diphenylethene **12**[20] was employed as the substrate, its Sonogashira reaction with excess 1-hexyne gave the endiyne **13**, which could undergo cyclization to give naphthalene derivative **14** or benzo[c]-phenanthrene derivative **15** as a function of reaction conditions (Scheme 5). Presumably, **15** was formed from two

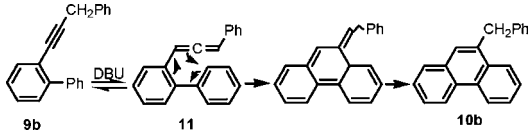
Scheme 5. Formation of **14** and **15**



consecutive cyclizations. The first cyclization seemed to occur very smoothly (3 h). However, much more time (21 h) was required for the subsequent cyclization to form **15**.

Accordingly, on the basis of these experiments and the deuterium experiment reported in the previous communication, the following mechanism is proposed (Scheme 6).[12]

Scheme 6. Mechanism for the Formation of Phenanthrenes



First, the base catalyzes the isomerization of **9b** to the allene **11**,[21] which undergoes a 6π cycloaddition to form a three-ring system followed by isomerization to form the final product **10b**.

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In this communication, we have demonstrated that this novel base-catalyzed cyclization is not restricted to fluorinated substrates. Esters and aldehyde-substituted enynes, as well as 2-alkynylbiphenyls, could also participate in this reaction. The previously proposed mechanism was further strengthened by successful cyclization of an isolated allene intermediate. Considering the importance of naphthalene and phenanthrene derivatives, this method should find wide application in the synthesis of polycyclic aromatic hydrocarbons.

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Supporting Information Available: Experimental procedure for the synthesis of **2a**−**d**, **3a**−**e**, **4**, **6**, **7**, **9a**,**b**, **10a**,**b**, **11**, and **13**−**15** and their characterization by ^{1}H NMR, ^{13}C NMR, and HRMS; copies of ^{1}H and ^{13}C NMR of compounds **2d**, **3a**−**e**, **4**, **6**, **7**, **9a**,**b**, **10a**, **11**, and **13**−**15**; ORTEP plot of **4**; and complete X-ray crystallographic data of compound **4** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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