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Intramolecular [4 + 2] Cycloaddition Reactions of Diarylacetylenes: Synthesis of Benzo[*b*]fluorene Derivatives via Cyclic Allenes†

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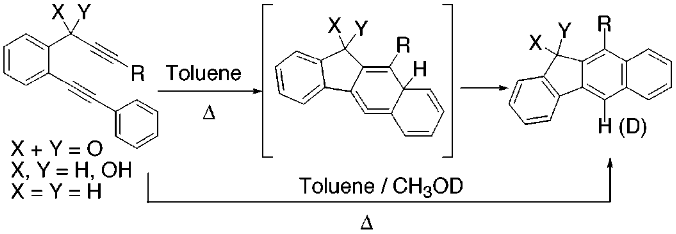
ABSTRACT



2-Propynyldiarylacetylenes undergo thermal intramolecular [4 + 2] cycloaddition to give benzo[*b*]fluorene derivatives in good yields. The hybridization of the tether connecting the reacting alkynes has a pronounced effect on the course of the reaction. Theoretical calculations and isotopic labeling studies support a mechanism which involves the generation of a cyclic allene intermediate that evolves to the final benzo[*b*]fluorene.

We recently reported[1] that the thermal cyclization of nonconjugated benzotriynes **1a** and **1b** (Table 1) and benzodiyne **2a** (Table 2)[2] leads directly to the benzo[*b*]fluorene skeleton (Scheme 1) which is a feature of a class of natural compounds that exhibit interesting biological activity.[3] Intramolecular [4 + 2] cycloadditions of alkynes with arenynes,[2,4] enynes,[5] diynes,[6] and arenenes[7] are known processes, some of them since the past century.

With a view to future synthetic applications, we investigated how the reaction is affected by the nature of the tether linking the diarylacetylene moiety to the other reacting acetylene. We found that the hybridization of the tether has a pronounced effect in terms of temperature requirements and yield. Our theoretical calculations and isotopic labeling

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† Dedicated to Prof. J. Barluenga on the occasion of his 60th birthday.

[1] Rodríguez, D.; Castedo, L.; Domínguez, D.; Saá, C. *Tetrahedron Lett.* **1999**, *40*, 7701−7704.

[2] Thermolysis of **2a** at 110 °C for 10 days to give the isomeric benzo[*b*]fluorenols **4a** (44%) and **5a** (13%) had been previously described: Schmittel, M.; Strittmatter, M.; Schenk, W. A.; Hagel, M. *Z. Naturforsch* **1998**, *53b*, 1015−1020.

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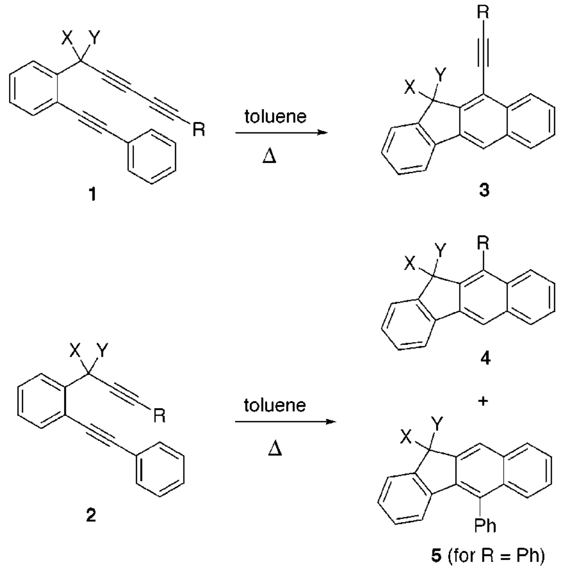
Scheme 1



studies support a mechanism which involves a cyclic allene[5a,b] intermediate that evolves to the final benzo[*b*]-fluorene.

We first studied the behavior of diarylacetylene **1c**, the silylated parent benzotriyne, which was prepared in 90% yield by reduction of **1a** with Et_3SiH and TFA at room temperature.[8] Not unexpectedly, **1c** was more recalcitrant than **1a** or **1b**, with complete consumption requiring 20 h of heating of a toluene solution in a sealed tube at 130 °C and affording only a moderate 40% yield of benzo[*b*]fluorene **3c** (Table 1). This result shows that the presence of an electron-withdrawing group on the tether makes the transition state more accessible, probably because of both conformational and electronic effects.[9]

Table 1. Thermal Cyclization of Benzotriynes **1**

	X, Y	R	reactn time (h)	*T* (°C)	product	yield (%)
1a	H, OH	TMS	10	100	**3a**	56
1b	H, OH	H	10	100	**3b**	60
1c	H, H	TMS	20	130	**3c**	40
1d	O	TMS	3	25	**3d**	98

Gratifyingly, while attempting to prepare diarylacetylene **1d** by Dess−Martin oxidation of **1a** in CH_3CN at rt, spontaneous cycloaddition took place, giving benzo[*b*]-fluorenone **3d** in 98% yield in only 3 h (Table 1). This dramatic improvement in kinetics and yield seems likely to be due to the carbonyl group favoring adoption of a conformation in which the π orbitals of the alkynes interact very easily in the transition state (see below).

We next examined whether the same effect occurred in the benzodiyne series **2**. When heated at 100 °C in toluene, benzodiynone **2b** (prepared in 90% yield by Dess−Martin oxidation of **2a**) gave a regioisomeric mixture of benzo[*b*]-fluorenones **4b** and **5b** in almost quantitative combined yield (Table 2).[10] Once again, the temperature required was significantly less than for X = H, Y = OH, that is, the energy of activation was reduced. Furthermore, heating solutions of benzodiynone **2c**[11] and its desilylated derivative **2d**[11] in a sealed tube at 150 °C smoothly produced the silylated benzo-[*b*]fluorenone **4c** and the parent benzo[*b*]fluoren-11-one **4d**,[12] whereas the corresponding alcohol derivatives (**2e** and **2f**) failed to cycloaromatize even under more severe conditions (Table 2).[1]

Table 2. Thermal Cyclization of Benzodiynes **2**

	X, Y	R	reactn time (h)	*T* (°C)	products (%)
2a	H, OH	Ph	11	170	**4a** (70%) + **5a** (26%)
2b	O	Ph	11	100	**4b** (72%) + **5b** (24%)
2c	O	TMS	13	150	**4c** (85%)
2d	O	H	13	150	**4d** (74%)
2e	H, OH	TMS	20	170	
2f	H, OH	H	20	170	

The above results are plausibly explained by either of the mechanisms depicted for the benzodiynes in Scheme 2. In the first, rate-limiting thermal cyclization of the benzodiyne affords the biradicals **6**, which must then undergo fast intramolecular radical coupling to furnish the strained cyclic allene **8**.[13] Alternatively, the two new σ bonds in **8** might arise in concert via transition state **7**.[5a] To decide between the two paths of Scheme 2, and to obtain energy data, we performed DFT[14] ab initio calculations[15] using the hybrid B3LYP,[16−18] functional with a 6-31G* basis set.[19] For triplet states or singlets with biradical character, an unrestricted formalism was used, allowing the α and β Kohn−Sham

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[9] Sammes, P. G.; Weller, D. J. *Synthesis* **1995**, 1205−1222.

[10] Benzo[*b*]fluorenones **4b** and **5b** had been obtained previously as byproducts when studying thermolysis of **2a** at 110 °C. See ref 2.

[11] See Supporting Information for experimental details.

[12] Streitwieser, A., Jr.; Brown, S. M. *J. Org. Chem.* **1988**, *53*, 904−906.

[13] For a theoretical study of 1,2,4-cyclohexatriene, a conjugated cyclic allene, see: Janoschek, R. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 476−478.

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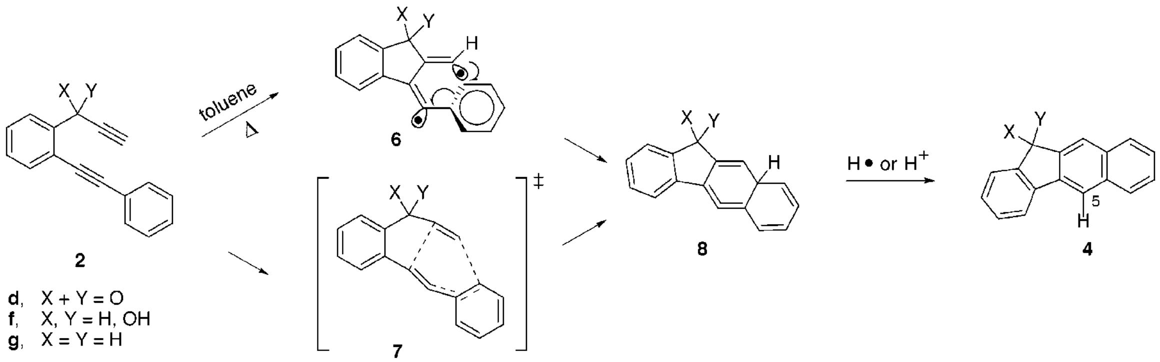
[15] All calculations were performed with the Gaussian 98 and Gaussian 94 program packages. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A. Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Baboul, A. G.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; González, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. Gaussian 98, Revision A.7, Gaussian, Inc., Pittsburgh, PA, 1998.

[16] Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648−5652.

[17] Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785.

Scheme 2



orbitals to break spin symmetry.[20] Geometrical optimization of **2d**, **2f**, and **2g** showed the alkynes to be much better placed for cyclization in the most reactive conformation of **2d** (1.7 kcal/mol above the minimum energy conformation) than in those of **2f** and **2g**. Whereas the tethering carbons in **2f** and **2g** are tetrahedral, with CCC angles of 111.7° and 113.9°, respectively, the sp^2 hybridization of the tethering carbon of **2d** imposes a CCC angle of 120.2° that not only places the alkyne carbons to be linked closer than in **2f** and **2g** (2.962 Å apart, vs 3.223 Å in **2f** and 3.347 Å in **2g**) but also makes the alkynes parallel, thereby facilitating π orbital interactions.

Biradicals **6d**,**f**,**g** adopt an angular geometry on the new vinyl moieties, placing the unpaired electrons in sp^2-like orbitals. The most stable configuration of biradical **6d** (Scheme 2) is 22.4 kcal/mol above diyne **2d**, whereas those of **6f** and **6g** are 28.8 and 29.4 kcal/mol above the corresponding diynes; this difference is attributable not only to the above-mentioned conformational advantage of **2d** over **2f** and **2g** but also to the carbonyl group of **2d** which extends the conjugation of the two new double bonds.[21] Since formation of the biradicals is endothermic, implying a late transition state, these relative stabilities should be similar to those of the transition states. The difference of 6.4 kcal/mol may explain the total lack of reactivity of **2f**.

To investigate the alternative concerted mechanism through transition states **7**, we performed B3LYP/6-31G* calculations for the models (Z)-1-phenyl-3-heptene-1,6-diyne and (*Z*)-7-phenyl-4-heptene-1,6-diyn-3-one. For the former, the concerted transition structure is very asynchronous, with NAO-based[22] Wiberg bond indexes[23] of 0.58 for the C2−C6 and 0.22 for C2′−C7, and for the latter all attempts to locate a concerted transition structure led to a saddle point for biradical formation.[24] These results suggest that biradicals **6** are involved in the formation of cyclic allenes **8**.

The most stable structures for intermediates **8d**, **8f**, and **8g** correspond to singlet states. However, the unrestricted Kohn−Sham MO determinant broke spin symmetry due to the biradicaloid character of the strained allenes (Table 3). The corresponding triplet states are higher in energy by about 3 kcal/mol. Note that formation of the allene is endothermic for **2f** and **2g** but slightly exothermic for **2d** (Table 3). All

Table 3. Energies Relative to Dibenzodiynes **2**, and Spin-Squared Expectation Values $\langle S^2 \rangle$, of Intermediates **6** and **8**

	biradical **6**		allene **8**	
	E (kcal/mol)	$\langle S^2 \rangle$	*E* (kcal/mol)	$\langle S^2 \rangle$
d	22.4	1.006	−0.3 (^{1}A)	0.527
			3.1 (^{3}A)	2.037
f	28.8	0.954	6.7 (^{1}A)	0.438
			10.4 (^{3}A)	2.038
g	29.4	0.958	6.0 (^{1}A)	0.548
			9.2 (^{3}A)	2.038

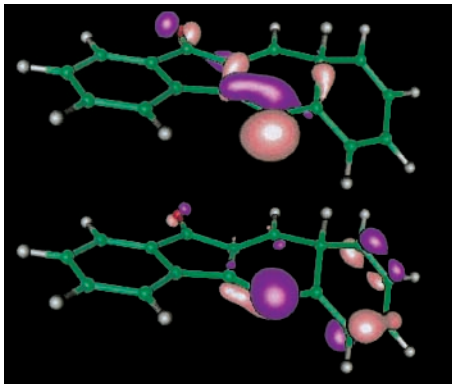


Figure 1. Highest occupied Kohn−Sham α molecular orbitals of **8d** (top, HOMO; bottom, HOMO − 1).

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[18] Although pure functionals have recently been used for description of species with biradical character, we achieved better results using hybrid functionals. Schreiner, P. R.; Prall, M. *J. Am. Chem. Soc.* **1999**, *121*, 8615−8627 and references therein.

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[21] The combination of these two factors was inferred using MCSCF and B3LYP calculations for the models (*Z*)-4-heptene-1,6-diyn-3-one and (*Z*)-3-heptene-1,6-diyne. Results to be published elsewhere.

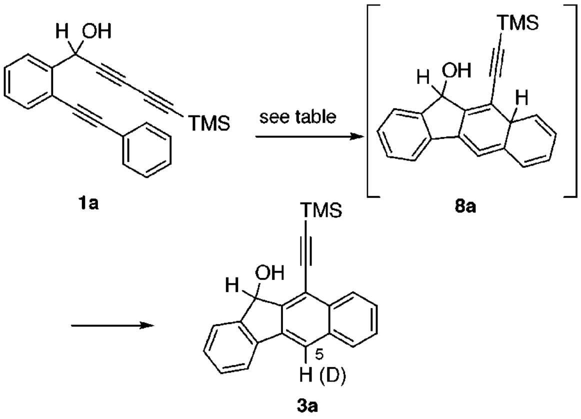
[22] Reed, A. E.; Curtiss, L. A.; Weinhold, F. *Chem. Rev.* **1988**, *88*, 899.

[23] Wiberg, K. A. *Tetrahedron* **1968**, *24*, 1083−1096.

the singlet forms can be described as strained cyclic allenes in which the π system is constructed of the p orbitals of all three carbons and an sp^2-like orbital placed on the central carbon (Figure 1).

Strained allenes **8** might evolve to aromatic products **4** by an intramolecular hydrogen shift or by abstraction of hydrogen from the solvent[25] or from another molecule of allene. To investigate the role of the solvent, we heated a solution of benzotriyne **1a** in toluene-d_8; the absence of deuterium in the final benzo[*b*]fluorene **3a** (Scheme 3) showed that H5 of **3a** came from allene **8a** itself. Involvement of the hydroxyl group of **1a** was ruled out by the finding that protected derivatives gave similar or even higher yields.[1]

Scheme 3



Deuteration experiments on the cycloaddition of **1a**

Solvent	T (°C)	Yield	% D at C-5
Toluene-d_8	100	56 %	——
Toluene + CD_3OD (4:1)	100	85 %	> 95 %
Toluene + CH_3OD (4:1)	100	84%	> 95 %
Toluene + CD_3OH (4:1)	100	81%	——

At this point we evaluated the influence of a proton source on the course of the reaction by running it in 80:20 (v/v) toluene/MeOH-d_4. Heating a solution of **1a** in this mixture for 10 h in a sealed tube at 100 °C gave **3a**-d_1 in 85% yield, an approximately 30% increase over the reaction in neat toluene;[26] more than 95% of the product was labeled at position 5. These results show the involvement of the added MeOH-d_4 in the evolution of the intermediate allene **8a**, whether by hydrogen abstraction (the radical path) or proton transfer (the ionic path). To distinguish between these alternatives, we heated benzotriyne **1a** in the presence of CH_3OD, which again gave a high yield of deuterated **3a**-d_1, and in the presence of CD_3OH, which led to no incorporation of deuterium (Scheme 3). Since the methyl hydrogens of methanol are much more susceptible to homolytic abstraction than the hydroxyl hydrogen, we conclude that the ionic mechanism is in operation here.

In conclusion, we have found that two types of diarylacetylene, benzotriynes **1** and benzodiynes **2**, undergo intramolecular [4 + 2] cycloaddition to give benzo[*b*]fluorene derivatives in good yields. The hybridization of the tether connecting the reacting alkynes has a pronounced effect on the course of the reaction. Theoretical calculations and isotopic labeling studies support a mechanism that involves initial formation of a 1,4-vinyl biradical which then undergoes fast intramolecular coupling to a strained cyclic allene intermediate that evolves to the benzo[*b*]fluorene derivatives. Application of this methodology to the synthesis of natural benzo[*b*]fluorene antibiotics is in progress.

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Supporting Information Available: Experimental procedures and characterization of compounds **1**−**4c**,**d** and details of deuteration experiments on **1a**; Cartesian coordinates of **2**, **6**, and **8d**,**f**,**g**; ^{1}H and ^{13}C NMR spectra for **1a**, **2c**, and **4c**; and ^{1}H NMR for **3a** and **3a**−d_1. This material is available via the Internet at http://pubs.acs.org.

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(24) Results to be published elsewhere.

(25) This hypothesis had been suggested previously by Danheiser et al. See ref 5a.

(26) Increased yield in the presence of a proton source (ArOH) has been observed previously in intramolecular [4 + 2] cycloadditions. See ref 5a.