Strained Intermediates in Intramolecular Dehydro Diels−Alder Reactions: Rearrangement of Cyclic Allenes via 1,2-Dehydro[10]annulenes

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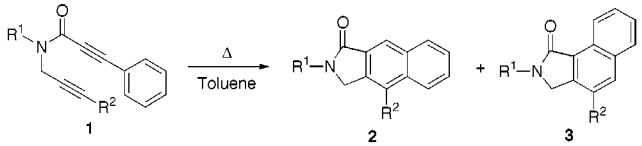
Received May 8, 2001
Revised Manuscript Received July 23, 2001

Intramolecular dehydro Diels−Alder reactions between acetylenes and phenylacetylenes have been known since the 19th century[1] and are well-documented.[2] The intermediates in these reactions are 1,2,4-cyclohexatrienes, strained cyclic allenes[3] which are also observed in [4 + 2] enyne−alkyne dehydro Diels−Alder reactions[4] and the [1,6] electrocyclization of 1,3-hexadien-5-ynes.[5] These intermediates normally evolve to aromatic products by cyclohexatriene isomerization, which in the presence of proton donors occurs preferentially by an intermolecular ionic pathway,[6] but numerous mechanistic questions remain unanswered. In this contribution we report a novel electrocyclic rearrangement of cyclic allenes (isonaphthalenes) that involves 1,2-dehydro[10]-annulenes[7] as intermediates.

Continuing our investigations on the intramolecular dehydro Diels−Alder reactions of aryldiacetylenes,[8] we heated toluene solutions of *N*-propargyl phenylpropiolamides **1a**−**c** at 160 °C in a sealed tube. This gave not only the expected benzo[*f*]isoindol-1-ones **2a**−**c**, but also, as the major isolated products, the isomeric benzo[*e*]isoindol-1-ones **3a**−**c** (Table 1).[9]

These results are compatible with the mechanism indicated in the scheme shown below, which was analyzed by means of DFT B3LYP/6-31G* calculations on **1d** (R^1= Me, R^2= H).[10] The cyclohexatriene **4d**, formed by initial [4 + 2] cyclization,[11] can undergo either isomerization to **2d** or an allowed six-electron electrocyclic ring-opening process affording (5*E*,7*Z*)-1,2-dehydro-[10]annulene **5d**.[12] The barrier to the intramolecular isomerization process is ca. 17 kcal/mol,[13] whereas the ring-opening process has a very low activation enthalpy (6.8 kcal/mol)[14] and is mildly exothermic ($\Delta H^{0K} = -16.7$ kcal/mol) as befits the formation of a product whose aromatic character is shown by its equalized bond lengths. Simultaneous rotation of the C5−C6 and C7−C8 bonds of **5d** results in its isomerization to the (5*E*,7*Z*)-annulene **6d** (1.2 kcal/mol more stable) via a transition state 18.5 kcal/mol higher in energy, and [1,6]-electrocyclization of **6d** then leads to cyclic allene **7d** (1.4 kcal/mol more stable than **4d**), which upon aromatization yields the rearranged benzo[*e*]isoindolone **3d** (Figure 1).

Table 1. Dehydro Diels−Alder Reactions of Phenylpropiolamides **1**



entry		R^1	R^2	benzo[*f*] isoindole **2** (%)	benzo[*e*] isoindole **3** (%)	ratio **2**:**3**
1	**1a**	^{t}Bu	H	8	63	1:7.9
2	**1b**	Et	H	13	56	1:4.3
3	**1c**	Cy	H	18	58	1:3.2
4	**1c**	Cy	H	85	−	1:0[a]
5	**1e**	Cy	Me	−	−	−
6	**1f**	Cy	Ph	60[b]	17	3.5:1
7	**1g**	Cy	TMS	−	88	0:1
8	**1g**	Cy	TMS	92	−	1:0[a]

[a] In the presence of added PhOH (10 equiv). [b] Mixture of isomers.

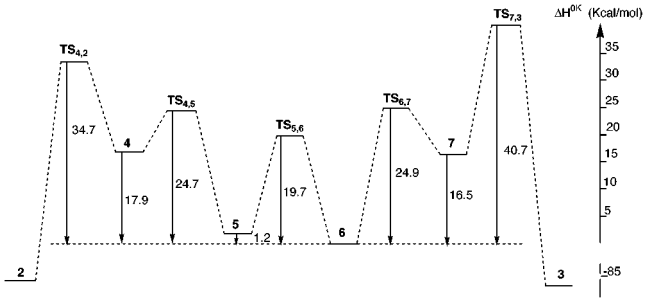


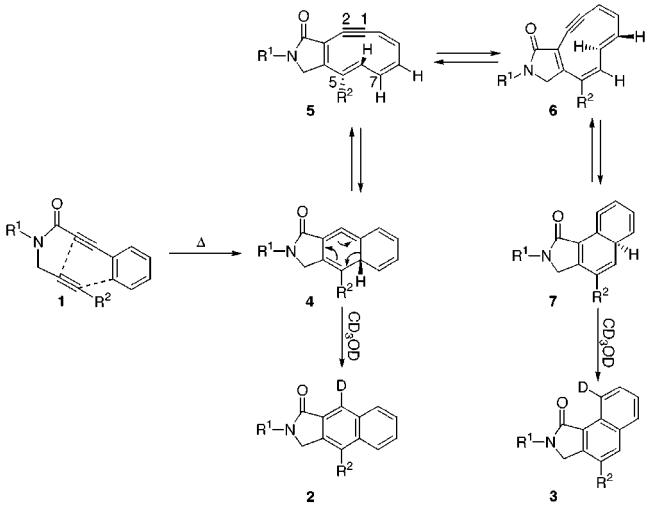
Figure 1. Energy profile for phenylpropiolamide **1d**.

Labeling studies of the reaction of **1c** support the above mechanistic hypothesis: in the presence of CD_3OD (10−20 equiv), deuterium was incorporated in both **2** and **3** in the positions shown in the scheme. Further, no **3c** was formed when the intermolecular protonation process **4c** → **2c** was favored by

(1) Michael, A.; Bucher, J. E. *Chem. Ber.* **1895**, *28*, 2511.
(2) (a) Dykstra, H. B. *J. Am. Chem. Soc.* **1934**, *56*, 1625. (b) Butz, L. W.; Joshel, L. M. *J. Org. Chem.* **1941**, *6*, 3344; *J. Org. Chem.* **1942**, *7*, 1311.
(3) (a) For a review of the reactivity and structure of cyclic allenes, see: Johnson, R. P. *Chem. Rev.* **1989**, *89*, 1111. (b) For a theoretical study of 1,2,4-cyclohexatriene, see: Janoscheck, R. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 476−478.
(4) (a) Danheiser, R. L.; Gould, A. E.; Fernández de la Pradilla, R.; Helgason, A. L. *J. Org. Chem.* **1994**, *59*, 5514−5515. (b) Burrell, R. C.; Daoust, K. J.; Bradley, A. Z.; DiRico, K. J.; Johnson, R. P. *J. Am. Chem. Soc.* **1996**, *118*, 4218−4219. (c) Schmittel, M.; Strittmatter, M.; Schenk, W. A.; Hagel, M. *Z. Naturforsch.* **1998**, *53b*, 1015−1020.
(5) (a) Roth, W. R.; Hopf, H.; Horn, C. *Chem. Ber.* **1994**, *127*, 1765−1779. (b) Hopf, H.; Berger, H.; Zimmermann, G.; Nüchter, U.; Jones, P. G.; Dix, I. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1187−1190. (c) Fernández-Zertuche, M.; Hernández-Lamoneda, R.; Ramírez-Solís, A. J. *J. Org. Chem.* **2000**, *65*, 5207−5211.
(6) Rodríguez, D.; Navarro, A.; Castedo, L.; Domínguez, D.; Saá, C. *Org. Lett.* **2000**, *2*, 1497−1500.
(7) Cyclization of 1,6-didehydro[10]annulene intermediates to 1,5-dehydronaphthalenes was reported by Myers, A. G.; Dragovich, P. S. *J. Am. Chem. Soc.* **1993**, *115*, 7021−7022 (see also references therein).
(8) Rodríguez, D.; Castedo, L.; Domínguez, D.; Saá, C. *Tetrahedron Lett.* **1999**, *40*, 7701−7704.
(9) The structures of compounds **2** and **3** were established by spectroscopic data and by an X-ray analysis of **3a.** See Supporting Information for details.
(10) All calculations were performed using the Gaussian98 program package: 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.
(11) B3LYP/6-31G* studies indicate that the initial [4 + 2] cyclization takes place through a biradical stepwise pathway with an activation enthalpy $\Delta H^{\ddagger}(0K) = 28.0$ kcal/mol. See also ref 6.
(12) In recent related studies (5*Z*,7*Z*)-1,2-dehydro[10]annulenes had been suggested as a fascinating route for interconversion of cyclic allenes: Atienza, C.; Mateo, C.; de Frutos, O.; Echavarren, A. M. *Org. Lett.* **2001**, *3*, 153−155.
(13) The isomerization probably involves two consecutive 1,2 hydrogen shifts (see ref 4b).
(14) The activation enthalpy from **4d** to the planar isomer (5*Z*,7*Z*)-1,2-dehydro[10]annulene is much higher (29.6 kcal/mol).

10.1021/ja016157o CCC: $20.00
Published on Web 08/24/2001

carrying out the cyclization of **1c** in the presence of the proton donor PhOH (10 equiv) or in 5:1 toluene/MeOH (Table 1, entry 4).[15] Finally, the proposed mechanism is compatible with the observed dependence of the isomer ratio **3**:**2** on the temperature (Table 2), since the rapid increase in the **3c**:**2c** ratio between 160 and 215 °C is in keeping with the process leading to **2c** being entropically disfavored with respect to the one leading to **3c**, which suggests that the aromatization of **4c** preferentially occurs by an intermolecular pathway. The fall in the **3c**:**2c** ratio from 8:1 to 3:1 at 245 °C may be due to the equilibria of the reversible subsequence **4c** ↔ **5c** ↔ **6c** ↔ **7c** shifting toward **4c** as the temperature rises.



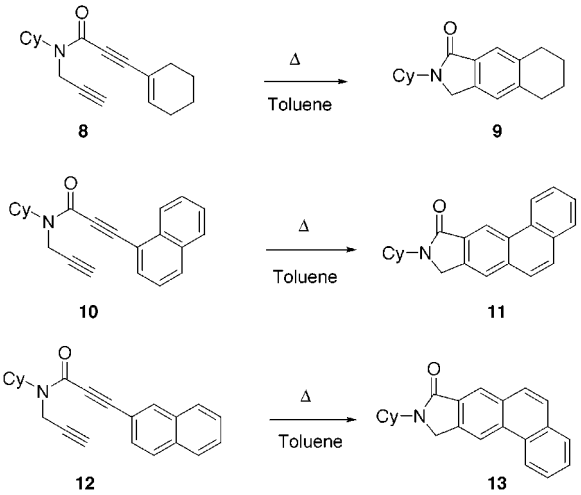
The intramolecular Diels−Alder reactions of the propargyl propiolamides **8**, **10** and **12** gave only unrearranged aromatic products corresponding to **2**. The nonaromatic cyclohexenyl derivative **8** uneventfully gave the corresponding annelated isoindole **9** (62% yield), and the naphthalenyl derivatives **10** and **12** exclusively afforded naphthoisoindolones **11** and **13**, in 75 and 58% yield, respectively (**13** arises from regioselective cyclization at C1 of the naphthalenyl system of **12**). In these latter two cases the corresponding rearranged allenes **7** would have completely lost all aromaticity and would therefore be much less stable than the corresponding initial allenes **4**. In fact, B3LYP/6-31G* calculations show the **7**-type allene corresponding to **10** to be 10.1 kcal/mol (ΔE) less stable than the initial **4**-type allene.

Table 2. Variation of the Isomer Ratio **3c**:**2c** with Temperature

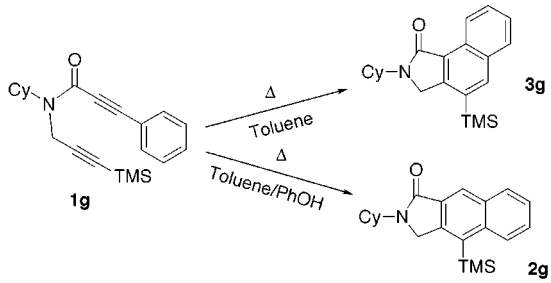
temperature (°C)	160	180	215	245
ratio **3c**:**2c** [a]	3.2:1	4:1	8:1	3:1

[a] Ratio determined by integration of the ^{1}H NMR signals of the reaction mixture.

When propargyl phenylpropiolamides with $R^2 \neq$ H were tried, the methyl derivative **1e** gave a complex mixture, probably because of side reactions due to the allylic nature of the methyl hydrogens of the intermediate allene **4e**. In the case of **1f**, three products were isolated: 4-phenylbenzo[*f*]isoindolone **2f** and its isomer 9-phenylbenzo[*f*]isoindolone (not shown), in 60% combined yield; and the benzo[*e*]isoindolone **3f** in 17% yield (Table



1, entry 6).[16] More interesting as regards potential applications in synthesis was the case of the TMS derivative **1g**, which when heated in toluene at 160 °C gave exclusively the rearranged product **3g** (in 88% yield), and when heated in the presence of a good hydrogen donor (phenol) gave exclusively the unrearranged product **2g** (in 92% yield). Although **7g** is lower in energy than allene **4g** (ΔE = 2.7 kcal/mol),[17] addition of phenol favors the intermolecular protonation path.



To sum up, a novel rearrangement of cyclic allenes during dehydro Diels−Alder reactions has been observed. A mechanism involving dehydro[10]annulene intermediates formed by ring opening nicely accounts for isotopic labeling and temperature dependence. Appropriate choice of conditions (temperature, solvent, substrate substituents) allows the reaction to be directed toward rearranged or unrearranged products. Further work is in progress.

Acknowledgment. This paper is dedicated to Professor Michael P. Cava on the occasion of his 75th birthday. We thank the Dirección General de Enseñanza Superior (Spain) for financial support under Project PB98-0606, the Centro de Supercomputación de Galicia (CESGA) for allocation of computer time, and the Ministerio de Educación y Ciencia for a predoctoral grant to D. Rodríguez. We also thank Prof. Echavarren for helpful discussions.

Supporting Information Available: Experimental procedures for and characteristics of compounds **1a**, **2a**, **2g**, **3a**, **3g**, **9**, **11**, and **13**; the X-ray diffractometric crystal structure of **3a**; B3LYP/6-31G* Cartesian coordinates of all species and full computational details. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) It is worth noting that addition of radical hydrogen donors such as 1,4-cyclohexadiene or γ-terpinene had no effect although radical paths for cyclic allenes had been observed (see ref 4a). It seems that cyclic allenes much prefer ionic proton abstraction. See ref 6.

(16) In a similar system, no benzo[*e*]isoindolones were detected: Klemm, L. H.; McGuire, T. M.; Gopinath, K. W. *J. Org. Chem.* **1976**, *41*, 2571−2579.

(17) Calculations were performed on the *N*-methyl analogue of **1g**.