

Scheme 1. Possible dienes prepared from 1,6-enynes.

Fullerenes

DOI: 10.1002/ange.200502404

Thermal [2+2] Intramolecular Cycloadditions of Fuller-1,6-enynes**

Nazario Martín,* Margarita Altable,
Salvatore Filippone, Angel Martín-Domenech,
Mireia Güell, and Miquel Solà

The transition-metal-catalyzed cyclization of enynes (mostly 1,6-enynes) **1** has been extensively studied as it provides a powerful method for the construction of carbo- and heterocyclic systems (**2–5**) in a simple manner (Scheme 1).^[1] Cycloisomerization of enynes to form novel diene structures is currently a major challenge both synthetically and mechanistically. Among the different cyclic products obtained, meta-thesis-type product **5** is a useful building block whose formation involves an interesting mechanism in which the carbon–carbon double bond of the enyne is completely cleaved.^[2] In this chemical transformation, cyclobutene species **6** were suggested as precursors of dienes **5**.^[3] Cyclobutenes **6** have been considered to be highly strained species

as they are the equivalent of a *trans*-cycloheptene, a species not known to exist at ambient temperature.^[4] However, the cyclobutene isomer **7** is an olefin that is stable at 118 °C.^[5] Furthermore, cyclobutene **8** has recently been isolated as a stable and well-characterized silane derivative.^[6]

Recently, we reported that 1,6-enynes in which fullerene C₆₀ was used as the alkene component (fuller-1,6-enynes) undergo a highly efficient and regioselective [2+2+1] intramolecular Pauson–Khand reaction with [Co(CO)₈] to form a new type of fullerene derivative with an unprecedented three or five fused pentagonal rings on the fullerene surface.^[7] Herein, we report that the thermal treatment of fuller-1,6-enynes leads very efficiently and in a totally regioselective manner to the formation of stable cyclobutene adducts without the need of any catalyst. To the best of our knowledge, this is the first example of a thermal [2+2] cyclization that involves a fullerene double bond as the alkene unit of the reactive 1,6-enyne to form novel organofullerenes endowed with the rather unusual cyclobutene moiety **6**. These findings confirm that species of type **6** are stable at room temperature and can be easily obtained from the appropriate strained 1,6-enynes by thermal treatment. The reaction, which has proven to be generally applicable, takes place through a concerted [2+2] mechanism according to ONIOM (UB3LYP/6-31G*:AM1) theoretical calculations.

Although [2+2] cycloadditions of fullerenes are not common, several examples in which mostly photochemical methods were employed are known. Hoke et al. first reported that benzene reacted with C₆₀ to give a series of [2+2] cycloadducts, from which the monoadduct was isolated and characterized.^[8] Since then, other photochemical [2+2] cycloadditions of fullerenes have been reported.^[9]

The synthesis of the starting fuller-1,6-enynes **10a–e** was carried out by 1,3-dipolar cycloaddition reaction of the azomethine ylides, which were generated in situ from propargyl-containing glycine derivatives^[10] **9a–e** and formaldehyde, to [60]fullerene in refluxing chlorobenzene for 1 h following Prato's procedure.^[11] The novel fulleropyrrolidines **10a–c** and previously reported compounds **10d–e**^[7a–b] were obtained as stable brown solids in moderate yields (30–49 %; 55–65 % based on recovered C₆₀; Scheme 2). Fuller-1,6-enynes **10a–e** are suitable precursors for further chemical transformations: They undergo thermal intramolecular cyclization upon heating in refluxing chlorobenzene for 3 h,

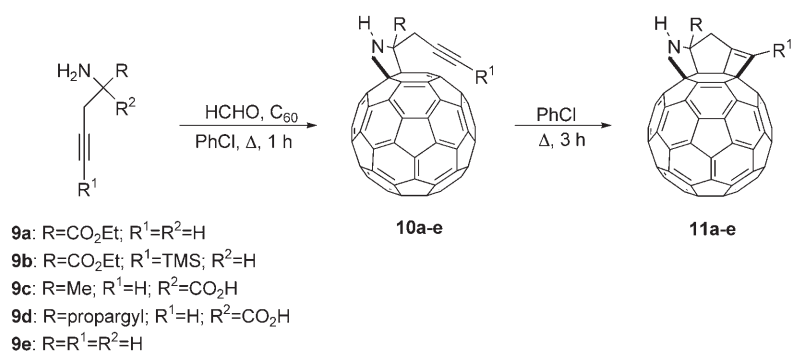
[*] Prof. Dr. N. Martín, M. Altable, Dr. S. Filippone,
Dr. A. Martín-Domenech
Departamento de Química Orgánica I
Facultad de Ciencias Químicas
Universidad Complutense de Madrid
Ciudad Universitaria s/n, 28040 Madrid (Spain)
Fax: (+34) 91-394-4103
E-mail: nazmar@quim.ucm.es

M. Güell, Prof. Dr. M. Solà
Institut de Química Computacional y Dpto de Química
Universidad de Girona
17071 Girona, Catalonia (Spain)

[**] These investigations were financially supported by the MEC of Spain (Projects BQU2002-00855 and BQU2002-0412-C02-02). S.F. thanks the CAM for a postdoctoral contract. M.A. and M.G. thank the MEC for research grants.



Supporting information for this article is available on the WWW under <http://www.angewandte.org> or from the author.



Scheme 2. [2+2] cycloaddition reaction of fuller-1,6-enynes **10a–e**. TMS = trimethylsilyl.

leading to the novel fullerocyclobutenes **11** in excellent yields (75–95 %).

Note that substitution on the pyrrolidine ring in compounds **10** plays an important role on the outcome of the reaction. Thus, *gem*-disubstituted fuller-1,6-enynes **10a–d** afforded the respective cyclobutenes **11a–d** as stable solids in very high yields. In contrast, cyclobutene **11e** (R = R¹ = H) was obtained in low yield (15 %) and found to be unstable. These findings clearly indicate that the reactivity of fuller-1,6-enynes is controlled by the rigid geometry between the reactive ene and yne groups, which in turn depends on the substitution pattern at atom C2 of the pyrrolidine ring.^[12] Fuller-1,6-enyne **10d** is suitably functionalized with two propargyl groups that are able to undergo a twofold thermal cyclization reaction. However, only compound **11d**, resulting from a single thermal cyclization, was obtained, probably as a result of the high strain of the expected bis(cyclobutene).

The structures of the novel compounds **10** and **11** were unambiguously established by UV/Vis, FTIR, and ¹H and ¹³C NMR spectroscopic techniques, as well as by mass spectrometry. As diagnostic signals in the ¹H NMR spectra, the alkynyl proton of fuller-1,6-enynes **10** appears at around δ = 2.3 ppm whereas the olefinic protons of cyclobutenes **11** appear around δ = 7.0 ppm. In the ¹³C NMR spectra of compounds **11**, the bridgehead olefinic carbon atom appears at δ ≈ 150–161 ppm. However, compound **11b** presents a deshielded signal at δ ≈ 169.4 ppm owing to the presence of the TMS group on the adjacent olefinic carbon, in agreement with previous reports for compound **8**.^[6]

The heteronuclear multiple-bond connectivity (HMBC) NMR spectrum of representative compound **11d** is shown in Figure 1, and it clearly shows that the protons of the three methylene groups present in the molecule are coupled to the quaternary carbon atoms of the pyrrolidine ring (C^a: δ = 76.8 ppm; C^b: δ = 84.1 ppm). Moreover, the methylene group of the cyclopentane ring (δ = 3.34, 3.58 ppm) and the olefinic proton (δ = 7.56 ppm) are coupled (²J_{CH}) to the bridgehead olefinic carbon (C^c) at δ = 161.0 ppm, thus supporting the structural assignment (see Supporting Information). The structures of all new compounds were further confirmed by HMQC and HMBC experiments, through comparison with UV/Vis spectra, which exhibit the typical signatures for the *cis*-1-bis-adducts,^[13] and by mass spectroscopy.

To further support the structural assignments, we carried out a cyclic voltammetry study of compounds **10a–c** and **11a–c** in *o*-dichlorobenzene/MeCN (4:1) as solvent and with tetra-*n*-butylammonium perchlorate as the supporting electrolyte at room temperature (see Supporting Information). Precursor fulleropyrrolidines **10a–c** showed four reversible reduction waves, whereas only three reversible reduction waves were observed for compounds **11a–c** under the same experimental conditions. A remarkable negative shift in the redox potentials (34–65 mV) relative to the values for pristine C₆₀ (*E*_{red}^{1/2} = −0.800, −1.209, −1.673, −2.127 V) was observed for **10a–c** which is attributed to the saturation of one double bond in the fullerene, thus raising the

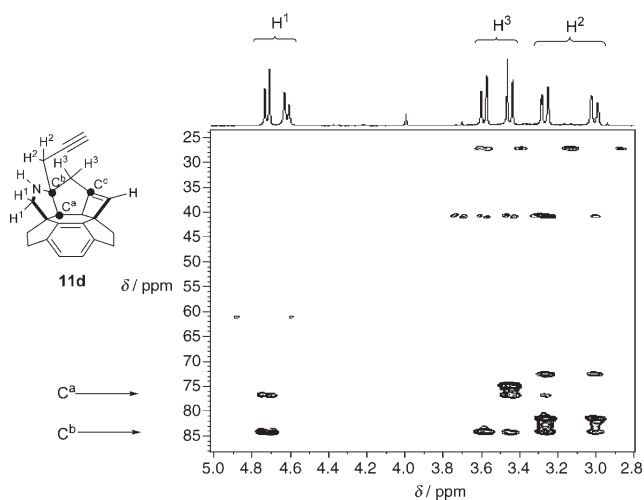


Figure 1. Part of the ¹H–¹³C multiple-bond shift-correlation spectrum of compound **11d**.

energy of the LUMO. *Cis*-1-biscycloadducts **11a–c** resulting from the [2+2] cycloaddition exhibit half-wave reduction potentials that are shifted to more-negative values (80–130 mV) relative to those for the parent C₆₀, and a significant shift (46–67 mV) compared with their respective precursors. These findings are in full agreement with the results of previous electrochemical studies of related fullerene derivatives containing one or two saturated double bonds and confirm the cathodic shift of biscycloadducts relative to related monocycloadducts.^[14]

Together, these data support the unambiguous structure of the novel C₆₀-based cyclobutene derivatives and thus remove the possibility of other structures stemming from thermal rearrangements.

The intramolecular thermal reaction of compounds **10** leads regioselectively to the formation of the respective *cis*-1 regioisomers, which are also obtained as a mixture of enantiomers provided that the thermal cyclization yields, besides the stereogenic center on the pyrrolidine ring, two new stereogenic carbon atoms on the fullerene surface with well-defined stereochemistry. To the best of our knowledge, this is the first example of three fused rings on the same hexagonal ring of the fullerene containing a cyclo-

butene moiety. Furthermore, these results confirm that cyclobutene structures **6** are stable and that their thermal formation is possible from strained 1,6-enynes.

To determine the reaction mechanism, a theoretical analysis of three different possible reaction paths was carried out.^[15] First, we studied the mechanism proposed by Gilbert and co-workers that involves a [2+1] cycloaddition to give a cyclopropylcarbene intermediate, which in a subsequent step evolves through a 1,2-carbon shift to the final product.^[16] We were able to locate the two possible cyclopropylcarbene intermediates. However, the energy barriers involved in the paths from reactants to products through these cyclopropylcarbene intermediates were found to be larger than 50 kcal mol⁻¹ and, for this reason, this mechanism was rejected. Second, we analyzed another mechanism that involves a diradical intermediate that already comprises one of the two C–C bonds to be formed. This radical mechanism was also considered by Bachrach and Gilbert for the reaction between cyclopentyne and ethene.^[16b] A systematic search for the two possible diradical intermediates always reverted to the final product. Finally, we investigated the possibility of a concerted pathway. In this case, we located the transition state (TS) depicted in Figure 2 which has an energy barrier of 27.5 kcal

mol⁻¹. The structure of this TS points to a concerted but very asynchronous addition, as suggested in previous work on similar chemical processes.^[17,18] The energy barrier and the structure of this TS bear some resemblance to those found for the addition of ethylene to ketene and isocyanate^[17] and also for the addition of ethylene to ethyne. In this latter case, the energy barrier computed at the UB3LYP/6-31G* level is about 7 kcal mol⁻¹ higher than that of the corresponding **10a**→**11a** reaction, as expected from the fact that the double bond in C₆₀ is more activated toward cycloaddition reactions than that of ethylene.^[19] The TS has some diradical character with the carbon atom of the CH terminus of the 1,6-enyne structure containing a localized α electron, while the unpaired

β electron is delocalized mainly around the darkened pyraclyene unit of C₆₀ in Figure 2. This transition state also has a molecular structure that denotes productlike (late) character. The process is found to be exothermic by 14.9 kcal mol⁻¹. In summary, we have discovered novel reactivity of suitable functionalized fullerene-1,6-enynes **10**, which efficiently undergo regioselective *cis*-1 thermal intramolecular [2+2] cyclization to afford a new type of fullerene derivative that contains elusive fused cyclobutenes, thus confirming the stability and synthetic availability of important intermediates of type **6**. Theoretical calculations reveal that the cyclization proceeds through an unusual concerted reaction mechanism which is favored by the strain of the enyne moiety. These results shed some light on the controversial stability of fused cyclobutenes and show that they can be thermally generated from strained 1,6-enynes, thus paving the way to an interesting scenario for further chemical transformations.

Received: July 11, 2005

Revised: November 18, 2005

Published online: January 20, 2006

Keywords: cycloaddition · enynes · fullerenes · fused-ring systems · regioselectivity

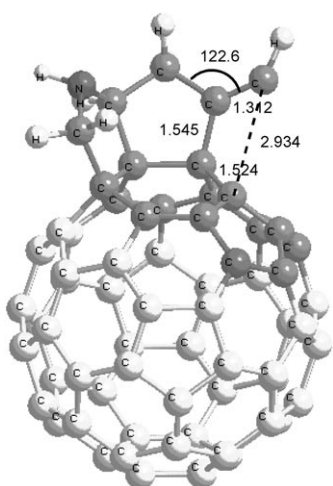


Figure 2. Optimized transition-state structure (ONIOM(UB3LYP/6-31G*:UAM1)) with the most relevant bond lengths [Å] and angles [°]. Darkened atoms constitute the model system treated at high level in the ONIOM approach.

mol⁻¹. The structure of this TS points to a concerted but very asynchronous addition, as suggested in previous work on similar chemical processes.^[17,18] The energy barrier and the structure of this TS bear some resemblance to those found for the addition of ethylene to ketene and isocyanate^[17] and also for the addition of ethylene to ethyne. In this latter case, the energy barrier computed at the UB3LYP/6-31G* level is about 7 kcal mol⁻¹ higher than that of the corresponding **10a**→**11a** reaction, as expected from the fact that the double bond in C₆₀ is more activated toward cycloaddition reactions than that of ethylene.^[19] The TS has some diradical character with the carbon atom of the CH terminus of the 1,6-enyne structure containing a localized α electron, while the unpaired

- [1] Reviews: a) G. C. Lloyd-Jones, *Org. Biomol. Chem.* **2003**, *1*, 215–236; b) C. Aubert, O. Buisine, M. Malacria, *Chem. Rev.* **2002**, *102*, 813–834; c) S. T. Diver, A. Giessert, *Chem. Rev.* **2004**, *104*, 1317–1382; d) A. M. Echavarren, C. Nevado, *Chem. Soc. Rev.* **2004**, *33*, 431–436.
- [2] Reviews: a) M. Mori, *Top. Organomet. Chem.* **1998**, *1*, 133–154; b) C. S. Poulsen, R. Madsen, *Synthesis* **2003**, 1–18.
- [3] a) R. J. Madhushaw, Ch.-Y. Lo, Ch.-W. Hwang, M.-D. Su, H.-C. Shen, S. Pal, I. R. Shaikh, R.-S. Liu, *J. Am. Chem. Soc.* **2004**, *126*, 15560–15565; b) N. Chatani, H. Inoue, T. Kotsuma, S. Murai, *J. Am. Chem. Soc.* **2002**, *124*, 10294–10295; c) C. Nieto-Oberhuber, S. López, A. M. Echavarren, *J. Am. Chem. Soc.* **2005**, *127*, 6178–6179.
- [4] a) B. M. Trost, M. Yanai, K. Hoogsteen, *J. Am. Chem. Soc.* **1993**, *115*, 5294–5295; b) E. J. Corey, F. A. Carey, R. A. E. Winter, *J. Am. Chem. Soc.* **1965**, *87*, 934–935; c) For a review, see: J. F. Liebman, A. Greenberg, *Chem. Rev.* **1976**, *76*, 311–365.
- [5] W. F. Maier, P. v. R. Schleyer, *J. Am. Chem. Soc.* **1981**, *103*, 1891–1900.
- [6] G. Oba, G. Moreira, G. Manuel, M. Koenig, *J. Organomet. Chem.* **2002**, *643–644*, 324–330.
- [7] a) N. Martín, M. Altable, S. Filippone, A. Martín-Domech, *Chem. Commun.* **2004**, 1338–1339; b) N. Martín, M. Altable, S. Filippone, A. Martín-Domech, A. Poater, M. Solà, *Chem. Eur. J.* **2005**, *11*, 2716–2729; c) G. Schick, T. Jarrosson, Y. Rubin, *Angew. Chem.* **1999**, *111*, 2508–2512; *Angew. Chem. Int. Ed.* **1999**, *38*, 2360–2363; d) W. Qian, S.-C. Chuang, R. B. Amador, T. Jarrosson, M. Sander, S. Pieniazek, S. I. Khan, Y. Rubin, *J. Am. Chem. Soc.* **2003**, *125*, 2066–2067.
- [8] S. H. Hoke, J. Molstad, D. Dilettato, M. J. Jay, D. Carlson, B. Kahr, R. G. Cooks, *J. Org. Chem.* **1992**, *57*, 5069–5071.
- [9] a) S. R. Wilson, N. Kaprinidis, Y. Wu, D. I. Schuster, *J. Am. Chem. Soc.* **1993**, *115*, 8495–8496; b) G. Vassilikogiannakis, M. Orfanopoulos, *J. Am. Chem. Soc.* **1997**, *119*, 7394–7395; c) B. Bildstein, M. Schweiger, H. Angleitner, H. Kopacka, K. Wurst, K.-H. Ongania, M. Fontani, P. Zanello, *Organometallics* **1999**, *18*, 4286–4295; d) T.-Y. Hsiao, S. K. Chidambareswaran, Ch.-H. Cheng, *J. Org. Chem.* **1998**, *63*, 6119–6122.

- [10] A. López, R. Pleixats, *Tetrahedron: Asymmetry* **1998**, *9*, 1967–1977.
- [11] a) M. Prato, M. Maggini, *Acc. Chem. Res.* **1998**, *31*, 519–526; b) N. Tagmatarchis, M. Prato, *Synlett* **2003**, 768–779.
- [12] This geometrical effect has also been observed in the Pauson–Khand reaction of related fullerenynes (see reference [7]).
- [13] a) K. Kordatos, S. Bosi, T. Da Ros, A. Zambon, V. Lucchini, M. Prato, *J. Org. Chem.* **2001**, *66*, 2802–2808; b) Y. Nakamura, N. Takano, T. Nishimura, E. Yashima, M. Sato, T. Kudo, J. Nishimura, *Org. Lett.* **2001**, *3*, 1193–1196.
- [14] a) L. Echegoyen, L. E. Echegoyen, *Acc. Chem. Res.* **1998**, *31*, 593–601; b) N. Martín, L. Sánchez, B. Illescas, I. Pérez, *Chem. Rev.* **1998**, *98*, 2527–2547; c) M. Carano, T. Da Ros, M. Fanti, K. Kordatos, M. Paolucci, M. Prato, S. Bofia, F. Zerbetto, *J. Am. Chem. Soc.* **2003**, *125*, 7139–7144.
- [15] Calculations were performed with a two-layered ONIOM-(B3LYP/6-31G*:AM1) approach using the Gaussian 03 program (Gaussian03 (Revision B.02), M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery, Jr., T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, J. A. Pople, Gaussian, Inc., Pittsburgh, PA, **2003**). For open-shell species the geometry optimizations were performed within the unrestricted methodology, while the closed-shell singlet molecules were optimized using the restricted formalism. Single-point ONIOM(UB3LYP/6-31G*:UAM1) energies were computed for all species using the unrestricted method to obtain the reported energy barriers and reaction energies. To ensure that the TS connects reactants and products, full optimizations were performed by slightly shifting the geometry of the TS in either sense.
- [16] a) D. W. Laird, J. C. Gilbert, *J. Am. Chem. Soc.* **2001**, *123*, 6704–6705; b) S. M. Bachrach, J. C. Gilbert, *J. Org. Chem.* **2004**, *69*, 6357–6364.
- [17] a) F. P. Cossío, G. Roa, B. Lecea, J. M. Ugalde, *J. Am. Chem. Soc.* **1995**, *117*, 12306–12313; b) S. Yamabe, K. Kuwata, T. Minao, *Theor. Chem. Acc.* **1999**, *102*, 139–146; c) D. Freitag, M. Drees, S. Goutal, T. Strassner, P. Metz, *Tetrahedron* **2005**, *61*, 5616–5621.
- [18] H. Cao, S. G. Van Ornum, J. Deschamps, J. Flippen-Anderson, F. Laib, J. M. Cook, *J. Am. Chem. Soc.* **2005**, *127*, 933–943.
- [19] M. Solà, J. Mestres, J. Martí, M. Duran, *Chem. Phys. Lett.* **1994**, *231*, 325–330.