ORGANIC
LETTERS

2005
Vol. 7, No. 26
5849−5851

A New Method for the Functionalization of [60] Fullerene: An Unusual 1,3-Dipolar Cycloaddition Pathway Leading to a C_{60} Housane Derivative

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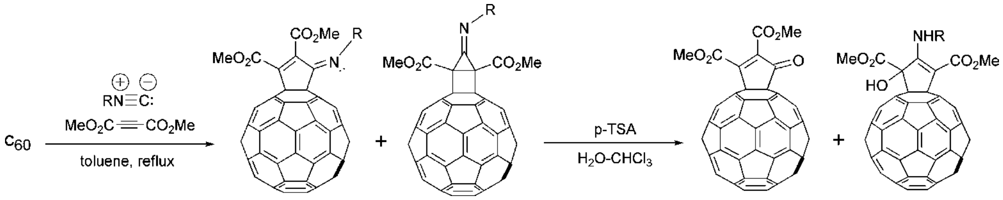
Received October 3, 2005

ABSTRACT



A variant of the Huisgen 1,3-dipolar cycloaddition reaction provides a new and convenient functionalization of fullerenes. This method complements the widely used Prato and Bingel–Hirsch reactions. The derived, highly functionalized cyclopentenone and cyclopentenamine fullerene compounds upon hydrolysis are suitable for further functionalization and may serve well in the synthesis of new C_{60} derivatives possessing uncommon and interesting properties.

Derivatives of various fullerene compounds, particularly C_{60}, have found both useful and interesting applications in many different fields such as material[1] and biomedical sciences.[2] For instance, the physical properies of C_{60} derivatives render these molecules interesting from the point of view of nonlinear optical materials.[3] Furthermore, Wudl and coworkers have shown that C_{60} can fit the active site of the HIV-1 protease, inhibiting this enzyme,[4] and paving the way to investigations of the biological properties of fullerenes.[2,5] Therefore, the development of new methods for the synthesis of C_{60} derivatives represents an increasingly important target.

Given that the reactivity of C_{60} is typical of an electron-deficient olefin, namely that it reacts with nucleophiles and is a reactive 2π component in cycloadditions,[6] it is surprising that only few reactions are employed for the funcionalization of fullerenes, including the Prato[7] and the Bingel−Hirsch[8] reactions. Regarding the Huisgen 1,3-dipolar cycloaddition,[9] we were attracted to the extremely convenient generation of the requisite zwitterionic species (1,3-dipoles) by the addition of various nucleophiles to activated acetylenes.[10] Particularly,

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(1) Reviews: (a) Diederich, F.; Kessinger, R. *Acc. Chem. Res.* **1999**, *32*, 537−545. (b) Wilson, S. R.; Schuster, D. I.; Meier, M. S.; Maggini, M.; Prato, M.; Taylor, R. In *Fullerenes: Chemistry, Physics, and Technology*; Kadish, K. M., Ruoff, R. S., Eds.; Wiley-Interscience: New York, 2000; pp 91−176. (c) See the special issue on "Funcionalized Fullerene Materials" in: *J. Mater. Chem.* **2002**, *12* (7), 1931−2159. Prato, M., Martin, N., Eds. (d) Zhou, Z.; Wilson, S. R. *Curr. Org. Chem.* **2005**, *9*, 789−811.

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(5) (a) Nakamoura, E.; Tokuyama, H.; Yamago, S.; Shiraki, T.; Sugiura, Y. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 2143-2151. (b) Cassel, A. M.; Scrivens, W. A.; Tour, J. M. *Angew. Chem., Int. Ed.* **1998**, *37*, 1528−1531.

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(7) (a) Maggini, M.; Scorrano, G.; Prato, M. *J. Am. Chem. Soc.* **1993**, *115*, 9798−9799. (b) Prato, M.; Maggini, M. *Acc. Chem. Res.* **1998**, *31*, 519−526. (c) Tat, F. T.; Zhou, Z.; MacMahon, S.; Song, F.; Rheingold, A.; Echegoyen, L.; Schuster, D. I.; Wilson, S. R. *J. Org. Chem.* **2004**, *69*, 4602−4606.

(8) (a) Bingel, C. *Chem. Ber.* **1993**, *126*, 1957−1959. (b) Hirsch, A.; Lamparth, I.; Karfunkel, H. R. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 437−438. (c) Zhou, Z.; Schuster, D. I.; Wilson, S. R. *J. Org. Chem.* **2003**, *68*, 7612−7617.

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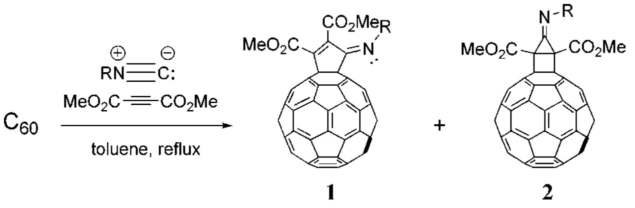
10.1021/ol052393i CCC: $30.25

the zwitterion derived from an isocyanide and dimethyl acetylene dicarboxylate (DMAD) has been recently shown to undergo cycloaddition to various dipolarophiles, thus establishing a synthesis of pyrrole, furan, and highly substituted cyclopentadienoid systems.[11] Recognizing the convenience and efficiency of this three-component Nair methodology,[11] we decided to examine its potential in the context of addition reaction with C_{60} as the dipolarophile. In practice, when *tert*-butyl isocyanide, DMAD, and C_{60} were refluxed in toluene for 24 h, two products were isolated in 74% total yield. The identical M^+ peaks of their mass spectra and the dissimilar ^{13}C NMR spectra of these products indicated that they are the imine structural isomers **1** and **2** shown in Table 1. The isolation of C_{60} housane derivative **2** represents a synthesis of a fully substituted bicyclo[2.1.0]-pentane (housane).[12]

Table 1. 1,3-Dipolar Cycloaddition of the Adduct Derived from Isonitriles and DMAD to C_{60}



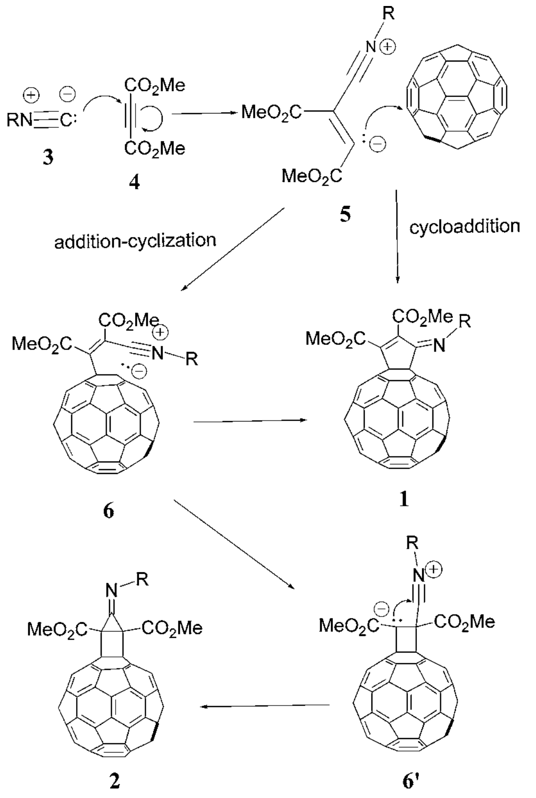
R	yield (%)	ratio **1**:**2**
a, *tert*-butyl	74	60:40
b, cyclohexyl	65	80:20
c, 4-methoxyphenyl	55	75:25

As evident from Table 1, this reaction proved to be general with respect to the isocyanide component. In fact, the ready availability of isocyanides[13] imparts an additional element of practicality to this methodology.

The presumed mechanistic details of this cycloaddition are shown in Scheme 1.

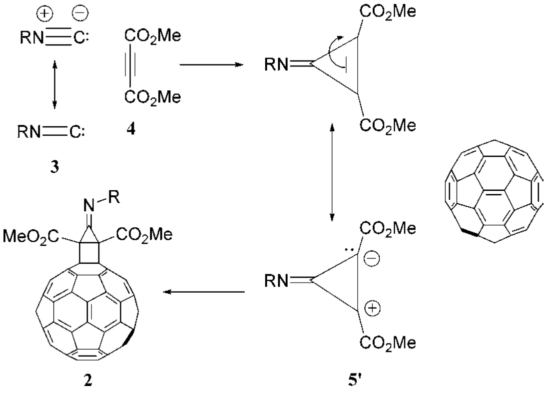
The initial event is the formation of zwitterion **5** from isocyanide **3** and DMAD (**4**). Zwitterion **5** can add to the electrophilic carbon−carbon double bond of C_{60} giving rise to putative intermediate **6**, which then undergoes cyclization to deliver the observed products **1** directly, and **2** via intermediate **6′**. Alternatively, concerted 1,3-dipolar cycloaddition of **5** to C_{60} can also produce **1** (Scheme 1).

Scheme 1. Mechanistic Details of the Reaction of C_{60} with **3** and **4**



Since relatively difficult 4-*endo-trig* and 3-*exo-dig* ring closures[14] are invoked for the formation of **2** through **6** and **6′** respectively, an alternative and more likely mechanistic pathway for forming **2** via addition of 1,3-dipolarophile **5′** to C_{60} is shown in Scheme 2. In turn, **5′** may be formed through a carbenoid addition of isonitrile **3** to DMAD (**4**).

Scheme 2. Alternative Mechanistic Pathway for the Formation of **2**



Isomer **1** was assigned the *anti* structure shown in Table 1 since it was found to be significantly more stable than the *syn* (R group on the same side with the bulk of the fullerene)-isomer (for both **a** and **b**),[15] which apparently does not form at all.

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(10) Winterfeldt, E. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 423−434.

(11) (a) Nair, V.; Vinod, A. U.; Ramesh, C. *J. Org. Chem.* **2001**, *66*, 4427−4429. (b) Nair, V.; Vinod, A. U.; Abhilash, N.; Menon, R. S.; Santhi, V.; Varma, R. L.; Viji, S.; Mathew, S.; Srinivas, R. *Tetrahedron* **2003**, *59*, 10279−10286. (c) Nair, V.; Menon, R. S.; Beneesh,. B.; Sreekumar, V.; Bindu, S. *Org. Lett.* **2004**, *6*, 767−769.

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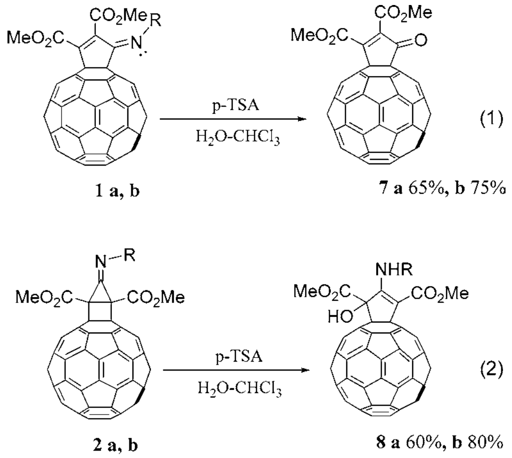
(14) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734−736. Nevertheless, there have been reactions reported which seemingly contradict Baldwin’s rules.

On the other hand, **2**, was shown to be more polar on TLC as expected on the basis of the more exposed nature of the imine N lone pair relative to **1**. Although **1** and **2** could be easily separated by column chromatography in the case of **a** and **b**, **1c** and **2c** were inseparable.

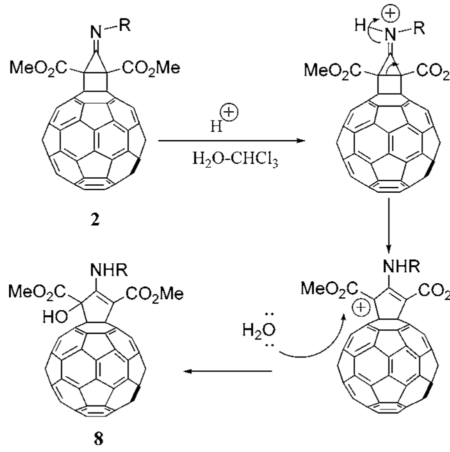
As anticipated, attempted acid-catalyzed hydrolysis of **1** and **2** led to two different products, namely the cyclopentenone derivative **7** (Scheme 3, eq 1) from **1** and the cyclopentenamine derivative **8** from **2** (Scheme 3, eq 2).[16]

Scheme 3. Hydrolysis Products of **1** and **2**



The mechanism for the formation of **8** comprises protonation of the imine **2** followed by opening of the cyclopropane ring and almost simultaneous attack of water at the developing carbocation (Scheme 4).

Scheme 4. Mechanism of Hydrolysis of **2**



Consistently, acid-catalyzed hydrolysis of the 3:1 inseparable mixture of **1c**:**2c** (Table 1), led to an approximately 3:1 separable mixture of **7**:**8c**.

In summary, a variant of the Huisgen 1,3-dipolar cycloaddition reaction, provides a new method for the functionalization of [60] fullerene as its cyclopentenone derivative **7**,[20] obtained most efficiently by the hydrolysis of cyclohexylimine **1b** (Table 1 and Scheme 3). The construction of C_{60} housane derivative **2** via the novel cycloaddition pathway described is noteworthy.[11,12,21]

Acknowledgment. We thank Professors Stephen R. Wilson (NYU, presently at Luna nanoWorks) and James W. Canary (NYU) for generous donations of both laboratory space and expendable supplies. Very helpful discussions with Professors William R. Moore (West Virginia University) and Kathlyn A. Parker (SUNY at Stony Brook) are also gratefully acknowledged.

Supporting Information Available: Experimental procedures and spectral data for products **1**, **2**, **7**, and **8** as well as MM2 energy calculations for **1** and its geometrical isomer **1′**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[15] (a) See the Supporting Information for the MM2 energy calculation of **1** and its *syn* geometrical isomer **1′** using the Spartan 04 for windows software by Wavefunction. (b) Given the endothermicity of the present reaction, this thermodynamic argument can be readily transformed into a kinetic one by virtue of the Hammond postulate.

[16] This structural assignment for **8a** is fully consistent with the mass spectrum (M^+, 963) and the ^{13}C NMR spectrum: δ 171 and 167.5 ppm, two ester carbonyls; δ 163.5 and 74.5 ppm, enamine carbons;[11c,17] δ 149−137 ppm C_{60} sp^2carbons;[18] δ 73.5 ppm hydroxy-substituted carbon α to ester;[19] δ 52 and 50 ppm C_{60} sp^3 carbons;[18] δ 53−54 ppm two methyl carbons of the esters; δ 45.5 ppm quaternary *tert*-butyl carbon; δ 29 ppm *tert*-butyl methyl groups. See the Supporting Information. Numerous attempts to obtain crystals of **8a**, suitable for X-ray crystallographic analysis, failed.

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[21] For the first synthesis of a highly strained and a bridgehead substituted bicyclo[2.1.0]pentane (housane) derivative, see: (a) Moore, W. R.; Ward, H. R.; Merritt, R. F. *J. Am. Chem. Soc.* **1961**, *83*, 2019−2020, and (b) Gassman, P. G.; Mansfield, K. T. *J. Org. Chem.* **1967**, *32*, 915−920, respectively.