Benzynes

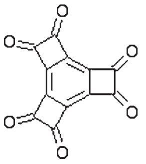
DOI: 10.1002/anie.200700926

A New Oxocarbon $C_{12}O_6$ via Highly Strained Benzyne Intermediates

*Holger Butenschön**

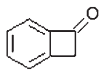
Keywords:
arynes · carbocycles · heterocumulenes · oxocarbons · strained molecules

Electroneutral carbon oxide compounds, with CO and CO_2 being the most common representatives, are a rather unusual class of compounds.[1] Higher heterocumulenes, which consist exclusively of carbon and oxygen atoms, are less stable and were often observed only by matrix isolation spectroscopy[2] or by mass spectrometric methods. Schwarz and co-workers reported that C_2O_2 rapidly decomposes with formation of CO.[3] The oxocarbon compounds $C_{24}O_6$ and $C_{32}O_8$ were prepared by Diederich and co-workers in the context of the synthesis of the cyclocarbon compounds C_{18} and C_{24}.[4] Recently Suzuki and co-workers added a new member to the oxocarbon family: $C_{12}O_6$ (**1**).[5]

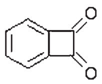


1

Since their first syntheses by Cava and Muth more than 40 years ago, benzocyclobutenone (**2**)[6] and benzocyclobutenedione (**3**)[7] have frequently been used for the construction of polycyclic natural as well as unnatural products by ring-expansion reactions.[8] An important example is the photochemical ring opening of **3** and some of its derivatives to the reactive diketene, followed by a cycloaddition with a quinone to reach finally enantiomerically pure derivatives of daunomycinone.[9] The addition of lithiated carbon nucleophiles to tricarbonylchromium complexes of **2** and of **3** leads to oxyanion-driven ring-expansion reactions such as dianionic oxy-Cope rearrangements at temperatures as low as −78 °C.[10,11]



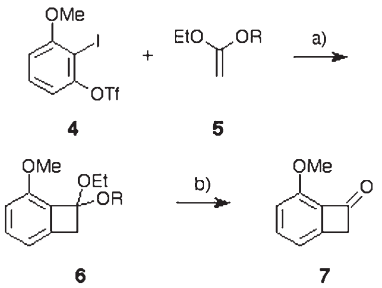
2



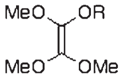
3

The currently most widely used synthesis of **2** is based on a diazotation of anthranilic acid, elimination of N_2 and CO_2 with intermediate benzyne formation, and an in situ [2+2] cyclization with 1,1-dichloroethene. The cycloadduct is hydrolyzed to form **2**, which can be dibrominated at C-2 with *N*-bromosuccinimide to give **3** after hydrolysis.[12,13] Alternatively, **3** can be obtained by photodecarbonylation of 1,3-bis(ethylenedioxy)indan-2-one followed by hydrolysis of the acetal groups.[14]

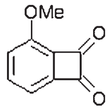
Suzuki and co-workers significantly improved the access to a variety of benzocyclobutene derivatives by making use of an iodine–lithium exchange reaction of *ortho*-iodoaryltriflates such as **4**. Elimination of triflate causes formation of the respective benzyne.[15] A subsequent [2+2] cycloaddition with silyl ketene acetal **5** and acetal cleavage of **6** with aqueous HF affords the benzocyclobutenone **7** in high yield under very mild reaction conditions (Scheme 1). The method was particularly efficient for *ortho*-iodoaryltriflates with an alkoxy or benzyloxy substituent next to the iodo substituent. The overall regioselectivity is explained by the inductive electron-withdrawing effect of the alkoxy or benzyloxy group and is consistent with frontier orbital considerations.[16] When **5** was replaced by the fully oxygenated silyl acetal **8** (R = Si*t*BuMe₂), the synthesis was successfully extended to the more highly strained benzocyclobutenediones such as **9**.[17] As in the case of compound **5**, the *tert*-butyldimethylsilyl derivative was most commonly used.



Scheme 1. a) BuLi, THF, −78 °C, 10 min, 89%; b) aq HF, MeCN, 0 °C, 30 min, 99%. R = $SitBuMe_2$.



8



9

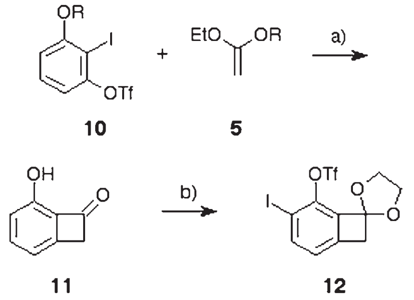
Cyclobutano-annulated arenes should, particularly in the case of functionalized annulated rings,[18,19] allow the synthesis of more complex polycycles and deserve attention with respect to molecular strain and the possible bond-length alternation according to the Mills–Nixon effect.[8] A synthetic sequence, which corresponds to that leading to **7** or **9**, would involve a highly strained, angular cyclobutano-annulated benzyne as a reactive intermediate.

In an elegant repetitive reaction sequence, Suzuki and co-workers indeed

---

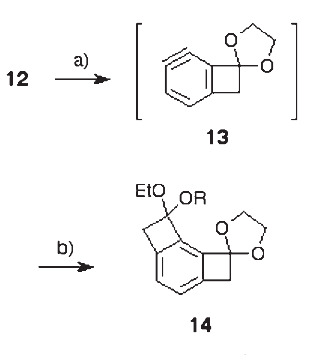
[*] Prof. Dr. H. Butenschön
Institut für Organische Chemie
Leibniz Universität Hannover
Schneiderberg 1B
30167 Hannover (Germany)
Fax: (+49) 511-762-4661
E-mail: holger.butenschoen@mbox.oci.uni-hannover.de
Homepage: http://www.oci.uni-hannover.de/AK_Butenschoen/startseite.htm

showed this to be possible (Scheme 2): elimination of triflate from metalated **10**, and an in situ [2+2] cycloaddition with **5** followed by hydrolysis with aqueous HF in acetonitrile afforded 6-hydroxybenzocyclobutenone (**11**). The iodide and triflate groups were introduced and the acetal was formed to give **12**. Now the stage was set for the formation of the cyclobutano-annulated benzyne intermediate **13**, which after [2+2] cycloaddition with **5**, afforded **14** in high yield, in addition to a very small amount of the other regioisomer (Scheme 3). The corresponding acetals were obtained using **8**.[20]



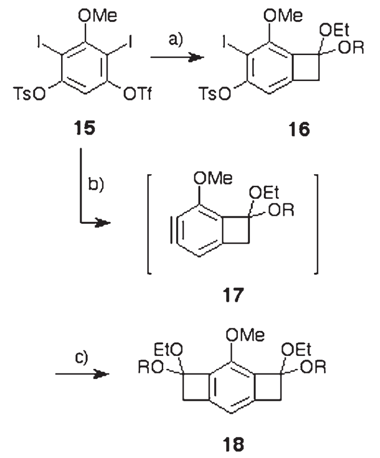
Scheme 2. a) 1. BuLi, THF, −78 °C; 2. aq HF, MeCN, 81 %; b) 1. I_2, $Hg(OAc)_2$, CH_2Cl_2; 2. TfO_2, $i Pr_2NEt$, CH_2Cl_2; 3. $HOCH_2CH_2OH$, TsOH, C_6H_6, 64 %. R = Si*t*BuMe$_2$, Tf = trifluoromethanesulfonyl, Ts = toluene-4-sulfonyl.

The excellent regioselectivity of this remarkable cycloaddition is *not* due to presence of the acetal moiety in **13**, as evidenced by a similarly high regioselectivity observed in the absence of this functional group. Instead, Suzuki and co-workers invoke the four-membered ring itself as the crucial factor, as indicated by a dramatic decrease in regioselectivity for the corresponding indane derivative. According to Streitwieser et al. and also Finnegan, the orbitals of the bridgehead carbon atoms that are used for the single bonds to the strained annulated ring have an increased p character.[21,22] Consequently the sp-hybridized carbon atom next to the strained annulated ring is bound to an orbital of higher electronegativity because of the increased s character. This causes the other sp carbon atom to be more electron deficient. The polarity of the triple bond in angular cyclobutano-annulated benzynes such as **13** was confirmed by theoretical calculations and is in accord with the regioselectivities observed for the reactions with nucleophiles (piperidine) or dienes (2-methoxyfuran).[20]



Scheme 3. a) BuLi, THF, −78 °C; b) **5**, 71 % (regioisomer 2.3 %). R = Si*t*BuMe$_2$.

After the existence of angular cyclobutano-annulated benzynes had been shown, Suzuki and co-workers investigated the possibility of linear analogues. When the unsymmetrically substituted arene **15** was treated with **5** in the presence of BuLi, not only was the monoannulation product **16** formed, but also the diannulation product **18**, and this observation was independent of the number of equivalents of BuLi and the reaction temperature. In addition, they obtained varying amounts of the deiodination product of **16** (Scheme 4). These results clearly show the intermediacy of the strained benzyne **17**. The observation that the second annulation step requires an elevated temperature of −78 °C in contrast to −95 °C for the first annulation step was exploited by developing a reaction sequence that used two equal or different arynophiles in a one-pot diannulation procedure to afford the respective tri-, tetra- or pentacycles in 41–81 % yield.[23] These results clearly establish the method of Suzuki and co-workers as a powerful tool in the synthesis of polycyclic compounds.

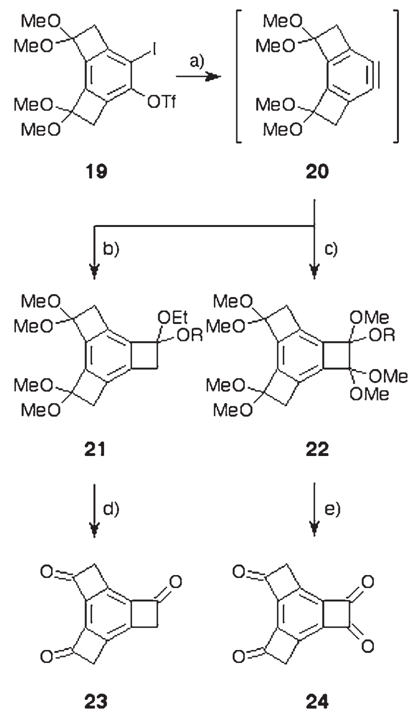


Scheme 4. a) **5**, 1.05 equiv BuLi, 72 % (along with 4 % of deiodiation product from **16**, 8 % of **18**); b) **5**, 2.3 equiv BuLi, −95→−78 °C; c) **5**, 72 % as a 1:1 mixture of diastereomers (along with 8 % of deiodination product of **16**). R = Si*t*BuMe$_2$.

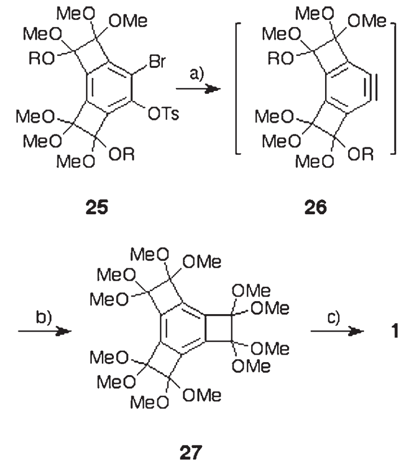
After the intermediacy of cyclobutano-annulated benzynes such as **13** and **17** had been established, the even more demanding challenge of whether the formation of higher homologues such as bis(cyclobutano)-annulated benzynes might be feasible, was tackled. To achieve this, iodotriflate **19** was prepared with key steps that involved [2+2] cycloaddition reactions of the respective (cyclobutano-annulated) benzyne derivatives. Compound **19** was subjected to the usual conditions with **5** or **8** as the arynophile to afford the cycloadducts **21** or **22**, which were hydrolyzed to triketone **23** or tetraketone **24**, respectively (Scheme 5). The reaction sequences confirm beyond any doubt that the highly strained bis(cyclobutano)-annulated benzyne **20** is the key intermediate. Remarkably, a significant alternation in the bond length of the arene ring was not seen in the structure of **24**. However, the C−C bond length (sp^2–sp^2) of the 1,2-diketone moiety is unusually large [160.0(3) pm].[24]

The formation of tris(cyclobutano)-annulated arenes is not limited to **23** or **24**. In a recent study, Suzuki and co-workers extended this chemistry to the use of tetrasubstituted ketene acetals such as **8**.[5] In this way, the fully substituted tricycle **25** (R = Si*t*BuMe$_2$) was prepared and treated with BuLi in diethyl ether, thus generating the benzyne **26** (R = Si*t*BuMe$_2$), which was trapped with **8** (R = SiMe$_3$) to afford the respective tricyclobutabenzene as a 6:1 mixture of diastereomers. Substitution of the silyloxy groups by using trimethyl orthoformate afforded dodecamethoxytricyclobutabenzene (**27**), which, like compound **24**, did not show a significant bond length alternation in the arene ring. The bond lengths between the *sp*^{3}-hybridized dimethoxy-substituted carbon atoms in the annulated rings is 161.4(2) pm.

The hydrolysis of the acetal groups in **27** was achieved with concentrated D_2SO_4[4] and resulted in a complete



Scheme 5. a) BuLi, −78 °C, 5 min; b) **5**, 79 %; c) **8**, 61 %; d) aq HF, MeCN, −10→25 °C, 2 h; e) 1. aq HF, MeCN, −16 °C, 20 min; 2. $BF_3 \cdot Et_2O$, H_2O, THF, −20→25 °C, 2 h, 49 %. R = Si*t*BuMe$_2$.



Scheme 6. a) BuLi, Et_2O, 0 °C; b) 1. **8** (R = $SiMe_3$); 2. $(MeO)_3CH$, TsOH, MeOH, 60 °C, 51–56 %; c) conc. D_2SO_4.

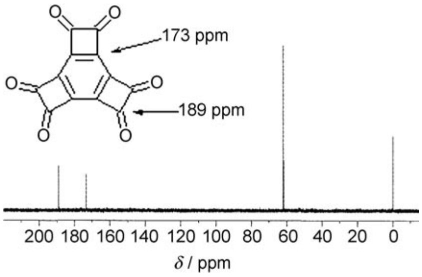
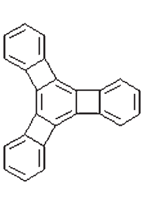


Figure 1. ^{13}C NMR spectrum of **1** (125 MHz, D_2SO_4, trimethylsilane as standard). Reprinted with permission from Ref. [5]. Copyright 2006 American Chemical Society.

removal of all 12 methoxy groups and formation of the new oxocarbon $C_{12}O_6$ (**1**; Scheme 6), the structure of which was unequivocally confirmed by the observation of only 2 signals in the ^{13}C NMR spectrum at $\delta = 173$ and 189 ppm, in addition to that of the methanol formed (Figure 1). Although no structure analysis of **1** is available to date, theoretical calculations predict a planar structure with almost no alternation in bond length for the benzene ring.[5] This inference clearly contrasts with the geometry of the central benzene ring in the triangular [4]phenylene (**28**), which was prepared by Diercks and Vollhardt some time ago.[25]


28

Although tricyclobutabenzene has been known for some time,[26] the synthesis of the hexaketone **1** is remarkable because all of the carbon atoms in **1** are sp^2 hybridized without the stabilization of annulated aromatic rings as in [4]phenylene. Therefore, a significantly increased reactivity of the keto groups in **1** compared to those in the already strained and reactive benzocyclobutenedione (**3**) would be expected. A particularly intriguing idea in this context is the possibility of a multiple photodecarbonylation of **1** that would finally lead to the cyclocarbon C_6.[27]

The syntheses of bis- and tris(cyclobutano)-annulated arenes with acetal or keto functionalities on the annulated rings are a very promising basis for their application in multidirectional ring-expansion reactions.

---

[1] G. Seitz, P. Imming, *Chem. Rev.* **1992**, *92*, 1227–1260.
[2] G. Maier, *Pure Appl. Chem.* **1991**, *63*, 275–282.
[3] D. Schröder, C. Heinemann, H. Schwarz, J. N. Harvey, S. Dua, S. J. Blanksby, J. H. Bowie, *Chem. Eur. J.* **1998**, *4*, 2550–2557.
[4] Y. Rubin, C. B. Knobler, F. Diederich, *J. Am. Chem. Soc.* **1990**, *112*, 1607–1617.
[5] T. Hamura, Y. Ibusuki, H. Uekusa, T. Matsumoto, J. S. Siegel, K. K. Baldridge, K. Suzuki, *J. Am. Chem. Soc.* **2006**, *128*, 10032–10033.
[6] M. P. Cava, K. Muth, *J. Am. Chem. Soc.* **1960**, *82*, 652–654.
[7] M. P. Cava, D. R. Napier, R. J. Pohl, *J. Am. Chem. Soc.* **1963**, *85*, 2076–2080.
[8] A. K. Sadana, R. K. Saini, W. E. Billups, *Chem. Rev.* **2003**, *103*, 1539–1602.
[9] K. Krohn, H. Rieger, E. Broser, P. Schiess, S. Chen, T. Strubin, *Liebigs Ann. Chem.* **1988**, 943–948.
[10] M. Brands, H. G. Wey, J. Bruckmann, C. Krüger, H. Butenschön, *Chem. Eur. J.* **1996**, *2*, 182–190.
[11] H. Butenschön, *Pure Appl. Chem.* **2002**, *74*, 57–62.
[12] H. Dürr, H. Nickels, L. A. Pacala, M. Jones, Jr., *J. Org. Chem.* **1980**, *45*, 973–980.
[13] M. S. South, L. S. Liebeskind, *J. Org. Chem.* **1982**, *47*, 3815–3821.
[14] D. Leinweber, H. Butenschön, *Tetrahedron Lett.* **1997**, *38*, 6385–6386.
[15] A. M. Dyke, A. J. Hester, G. C. Lloyd-Jones, *Synthesis* **2006**, 4093–4112.
[16] T. Hosoya, T. Hasegawa, Y. Kuriyama, T. Matsumoto, K. Suzuki, *Synlett* **1995**, 177–179.
[17] T. Hosoya, T. Hamura, Y. Kuriyama, M. Miyamoto, T. Matsumoto, K. Suzuki, *Synlett* **2000**, 520–522.
[18] L. S. Liebeskind, L. J. Lescosky, C. M. McSwain, Jr., *J. Org. Chem.* **1989**, *54*, 1435–1439.
[19] P. Maurin, M. Ibrahim-Ouali, M. Santelli, *Tetrahedron Lett.* **2001**, *42*, 8147–8149.
[20] T. Hamura, Y. Ibusuki, K. Sato, T. Matsumoto, Y. Osamura, K. Suzuki, *Org. Lett.* **2003**, *5*, 3551–3554.
[21] A. Streitwieser, Jr., G. R. Ziegler, P. C. Mowery, A. Lewis, R. G. Lawler, *J. Am. Chem. Soc.* **1968**, *90*, 1357–1358.
[22] R. A. Finnegan, *J. Org. Chem.* **1965**, *30*, 1333–1335.
[23] T. Hamura, T. Arisawa, T. Matsumoto, K. Suzuki, *Angew. Chem.* **2006**, *118*, 6996–6998; *Angew. Chem. Int. Ed.* **2006**, *45*, 6842–6844.
[24] T. Hamura, Y. Ibusuki, H. Uekusa, T. Matsumoto, K. Suzuki, *J. Am. Chem. Soc.* **2006**, *128*, 3534–3535.
[25] R. Diercks, K. P. C. Vollhardt, *J. Am. Chem. Soc.* **1986**, *108*, 3150–3152.
[26] E. Heilbronner, B. Kovac, W. Nutakul, A. D. Taggart, R. P. Thummel, *J. Org. Chem.* **1981**, *46*, 5279–5284.
[27] F. Diederich, personal communication (March 9, **2007**).