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Synthesis and Structure of Conjugated Molecules with the Benzofulvene Core

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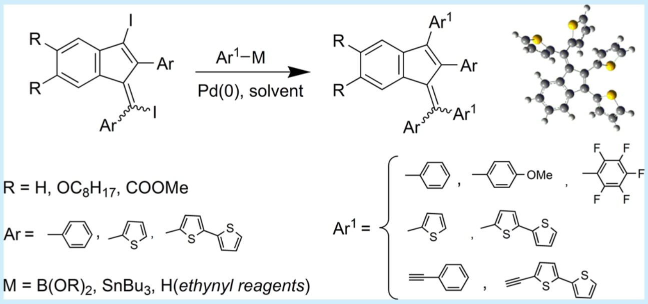
Ⓢ *Supporting Information*

ABSTRACT: A general method to synthesize conjugated molecules with a benzofulvene core is reported. Up to four conjugated substituents have been introduced via a three-step sequence including (1) synthesis of 1,2-bis(arylethynyl)-benzenes; (2) exo-dig electrophilic cyclization promoted by iodine; and (3) cross-coupling reaction of the resulting bis-iodobenzofulvenes with organoboron, organotin, or ethynyl derivatives under Pd catalysis. Structural aspects of the new compounds are discussed.



Benzofulvenes and related compounds have elicited extensive attention as biologically active molecules,[1] as precursors of functionalized indenes, which are interesting pharmaceutical agents,[2] and as molecular materials.[3] Despite their importance, a straightforward method for the synthesis of benzofulvene derivatives is still lacking. Different approaches to the synthesis of the fulvene skeleton have been reported, based on radical cyclization of enediynes,[4] thermal[5] and photochemical[6] cyclization of enyne-allenes, and transition-metal-catalyzed cyclization,[7] but most of them suffer from harsh reaction conditions, poor selectivity, or a limited scope. An interesting synthetic route is represented by a variation of the Bergman cyclization reaction[8] and consists of a 5-exo-dig cyclization of aryl enediynes promoted by electrophiles,[9] nucleophiles,[9c] or radicals.[4b−d] When bromine or iodine is used as the electrophile to promote the cyclization, the resulting bis-halogenated benzofulvenes appear to be very attractive intermediates for subsequent transformations,[9c] particularly via cross-coupling reactions. Despite the great synthetic potentiality of this approach, only one example has been reported so far, as a short end note, describing a Suzuki coupling reaction of the dibromo-diphenyl-benzofulvene with phenylboronic acid.[7k] Kovalenko et al.[4c] reported the synthesis of an organometallic benzofulvene derivative using an opposite approach: the treatment of aromatic enediynes with Bu_3SnH generates a 3-tributylstannyl-substituted benzofulvene, which is then used in a Stille cross-coupling reaction with aryl iodides under the Corey conditions. This method evidences the versatility of cross-coupling organometallic reactions for the functionalization of the benzofulvene core, but it is limited to the production of 3-substituted derivatives. More recently, Ye et al.[7i] reported a Suzuki coupling of 3-chlorobenzofulvene with various arylboronic acids, using $Pd(OAc)_2$ and S-Phos as the catalytic system. The fulvene unit possesses a cross-conjugated system which was exploited in cycloaddition reactions[10] and as a building block for the preparation of metallocene catalysts.[11]

In continuation of our studies on organometallic methods for the synthesis of conjugated molecules,[12] here we report a general route to obtain conjugated molecules containing the benzofulvene core. This method is based on the Pd-catalyzed cross-coupling reaction of the bis-iodo derivatives resulting from the iodine promoted 5-exo-dig cyclization of diaryl enediynes with conjugated organometallic reagents. The versatility of the method is given by the possibility of introducing up to four conjugated substituents on the benzofulvene (two in the synthesis of the bis-ethynylbenzene and two in the subsequent cross-coupling reactions of the resulting cyclized intermediates).

The 1,2-bis(arylethynyl)benzenes **7−12** were synthesized by the sequence reported in Scheme 1.

1,2-Diiodobenzene or its derivatives **1−3** were reacted with ethynyltrimethylsilane in the Cassar−Heck−Sonogashira reaction conditions, affording the corresponding bis-ethynyl intermediates. These were submitted without purification to a basic hydrolysis to remove the trimethylsilyl group. The

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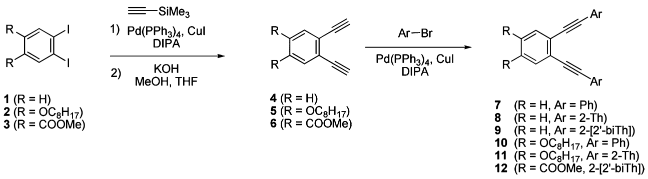
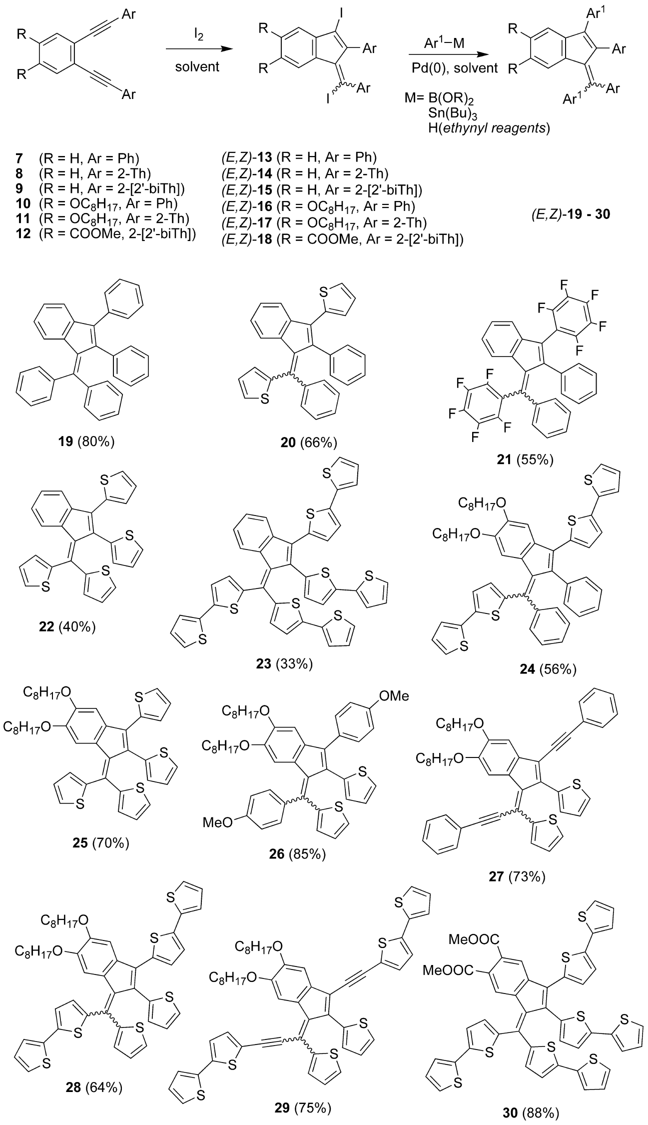
Scheme 1. Synthesis of 1,2-Bis(arylethynyl)benzenes 7−12



resulting 1,2-bis(ethynyl)benzenes **4−6** were finally converted into the 1,2-bis(arylethynyl)benzenes **7−12** by Cassar−Heck−Sonogashira reactions with three different aryl bromides, i.e. bromobenzene, 2-bromothiophene, and 5-bromo-2,2′-bithiophene.

The second step of the sequence consists of a nearly quantitative 5-exo-dig cyclization of the 1,2-bis(arylethynyl)benzenes **7−12**, promoted by iodine in chloroform or toluene affording derivatives **13−18**. These diiodobenzofulvenes are coupled with organoboronate, organostannane, or ethynyl reagents under Pd-catalysis, yielding compounds **19−30** (Scheme 2).

Scheme 2. Synthesis and Reactivity of Diiodobenzofulvenes



Diiodobenzofulvene **13** and the diiodobenzofulvene intermediates with R = OC_8H_{17} **16** and **17** were isolated and characterized prior to use in the subsequent cross-coupling reactions. In contrast, the diiodobenzofulvenes **14**, **15**, and **18** showed low stability and, after evaporation of the reaction solvent, yielded a black insoluble powder. Therefore, to prevent decomposition, they were not isolated after the cyclization step, but were reacted *in situ* with thiophen-2-ylboronic acid and 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,2′-bithiophene, yielding **22**, **23**, and **30**. All the benzofulvenes were obtained as two stereoisomers on the exocyclic double bond, with the exception of the compounds **19**, **22**, **23**, **25**, and **30**, which can exist as only one stereoisomer since Ar = Ar^1.

The structures of benzofulvenes **19** and **22** were studied by theoretical calculations. The structure of **19** was also investigated by X-ray analysis. All calculations were performed on the ground electronic state in vacuo at the DFT[13] level of approximation, using the functional B3PW91[14] with the 6-311+G(2d,p) basis set for all atoms. The GAUSSIAN 03[15] program was used. Molecular geometries were fully optimized starting from standard bond lengths and angles as input data. NBO (Natural Bond Orbital) analysis[16] was used to calculate atomic charges and provided preliminary information about the intramolecular interactions characterizing the compounds considered. Further computational details and tables with X-ray and computed data supporting the following discussion are reported in the Supporting Information (Tables SI1−SI11).

In the case of compound **19**, starting from geometries with different orientations of the phenyl rings with respect to the benzofulvene plane, the optimization process converged in all cases toward the same structure, reported in Figure 1. The calculated molecular geometry is in satisfying agreement with the experimental X-ray structure (Figure 2), thus suggesting the validity of the approximation used for calculations.

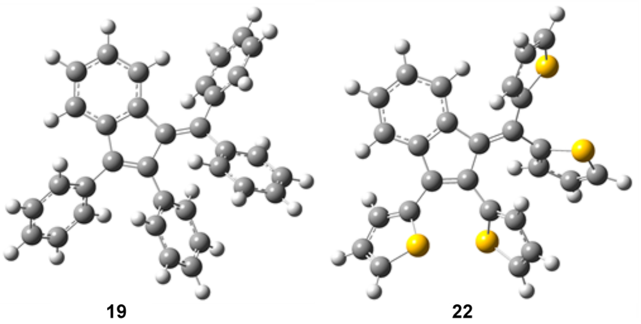


Figure 1. Most stable conformers of **19** and **22**, calculated in vacuo at the B3PW91/6-311+G(2d,p) level of approximation.

In the following discussion, the four aryl rings on the benzofulvene moiety have been numbered as 1 (ring C11−C16 in Figure 2), 2 (C17−C22), 3 (C23−C28), and 4 (C29−C34).

X-ray analysis revealed that **19** crystallizes in the *C*2/*c* space group with the phenyl rings significantly twisted with respect to the plane of the benzofulvene unit. The values of the dihedral angles between the planes through the benzofulvene core and the phenyl rings are ϕ_1 = 77.05(4)°, ϕ_2= 48.84(5)°, ϕ_3= 55.31(4)°, and ϕ_4= 55.38(4)° (the calculated values are 55°, 50°, 44°, and 54°, respectively). The inter-ring dihedral angle between the two central phenyls 2 and 3 is 33.98(5)° (the calculated value is 22°), and the distance between their centers is 3.822 Å (calculated value 3.9 Å). This nearly face-to-face

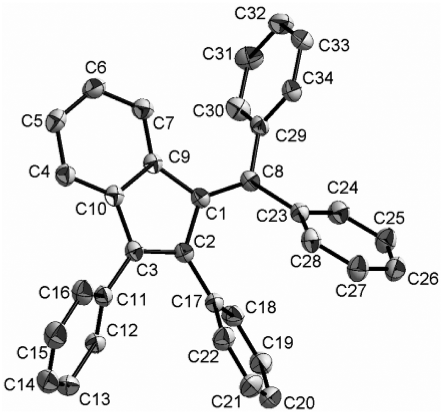


Figure 2. X-ray structure of compound **19**.

arrangement, together with the calculated atomic natural charges and the short inter-ring distance, suggests the existence of $\pi-\pi$ interactions[17] between the two aromatic rings.

Moreover, the values of the natural atomic charges and intramolecular C−H···C distances between adjacent phenyl rings suggest that the structure could be stabilized by weak intramolecular interactions of electrostatic nature and nonclassical C−H···π hydrogen bonds.

The structural study of benzofulvene **22** was more complicated. In principle, considering the relative positions of the sulfur atoms of the thiophene rings, at least 16 conformers should be taken into account. However, the conformational analysis of the benzofulvene moiety substituted with one and two thienyl units at the exocyclic double bond of benzofulvene indicated that the sulfur atom of the thienyl unit is preferentially in anti with respect to the benzene ring of the benzofulvene core. As a consequence, only eight conformational minima were considered. The energy difference between these minima is less that 2 kcal mol^{-1}, but **22** is not characterized by high conformational mobility, since the high rotational barrier does not allow an easy interconversion between different conformers. The thienyl units are significantly tilted with respect to the benzofulvene plane, with the inter-ring planes being in the range 40°−60° for all the conformers examined. In the most stable conformer, the thienyl units are twisted with sulfur atoms anti to each other (Figure 1) and the calculated dihedral angles are $\phi_1 = 48°$, $\phi_2 = 40°$, $\phi_3 = 54°$, and $\phi_4 = 49°$. This conformation significantly reduces the electrostatic repulsive interactions between the four positively charged sulfur atoms (the charges on the four sulfur atoms are in the range from 0.461 to 0.478) and the hydrogen atoms on the adjacent thienyl rings. As already determined for **19**, the two central thienyl rings tend to be nearly parallel, the inter-ring dihedral angle being 15° ca., and the calculated distance between their centers is 3.8 Å, thus suggesting, also in this case, the possible existence of stacked $\pi-\pi$ interactions. The arrangement of thienyl units does not allow the existence of C−H···π interactions between adjacent rings to be considered. However, a fundamental role could be played by attractive electrostatic interactions between positively charged sulfur atoms and negatively charged carbon atoms on adjacent thienyl rings (the distances between the sulfur atoms and ring carbon atoms are 3.2−4.9 Å).

By comparing the structure of the benzofulvene core calculated in compounds **19** and **22** with the molecular structure of the unsubstituted benzofulvene optimized at the same level of approximation in vacuo, some interesting observations are possible. The introduction of phenyl and thiophene rings on benzofulvene does not induce any significant change in the molecular geometry, with the exception of small variations of the C−C distances in the fulvene moiety. In contrast, significant variations of the atomic charges on the carbon atoms on the fulvene unit are calculated. The analysis of hyperconjugative $\pi \rightarrow \pi^*$ interactions involving the orbitals of the benzofulvene indicates that both tiophene and phenyl substituents induce a remarkable increase in the π-delocalization between the fused benzene and fulvene rings of the benzofulvene system, and within the fulvene unit, but have only a small influence on the delocalization within the benzene ring. In compound **19** the energy of delocalization (hyperconjugative interactions) increases about 7.2 kcal mol^{-1} with respect to the unsubstituted benzofulvene nucleus; in **22** the thienyl units exert a stronger effect, producing an increase of about 11.3 kcal mol^{-1}.

In summary, we have developed a general and straightforward method for the synthesis of substituted benzofulvenes. X-ray analysis and computational studies performed on structurally simple benzofulvenes **19** and **22**, for which only one stereoisomer exists, evidenced a molecular geometry in which all rings are twisted with respect to the benzofulvene plane.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Detailed experimental procedures, NMR spectra, X-ray analysis, and computational data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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