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Dibromoisobenzofuran as a Formal Equivalent of Didehydroisobenzofuran: Reactive Platform for Expeditious Assembly of Polycycles

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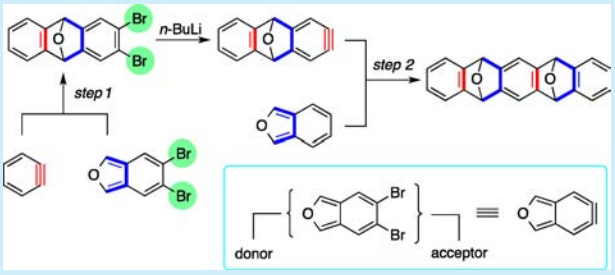
Ⓢ *Supporting Information*

ABSTRACT: Two-directional annulation of dibromoisobenzofuran, a formal equivalent to didehydroisobenzofuran, was developed. Importantly, selective bromine−lithium exchange allows the tandem generation of benzynes and dual cycloadditions with two different arynophiles. Also described is the application to the synthesis of a substituted pentacene.

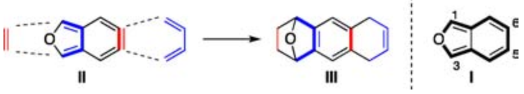


Isobenzofurans are 10π electron systems with quinoid structures, which makes them useful intermediates for various natural/unnatural product syntheses.[1] Among various possibilities, [4 + 2] cycloaddition with dienophiles is a reliable method for the construction of a polycyclic structure.[2] However, isobenzofuran **I** having no substituent at the C_1 and C_3 positions is unstable and regarded as a transient intermediate with a few exceptions, which has limited the availability of this attractive molecule.[3,4]

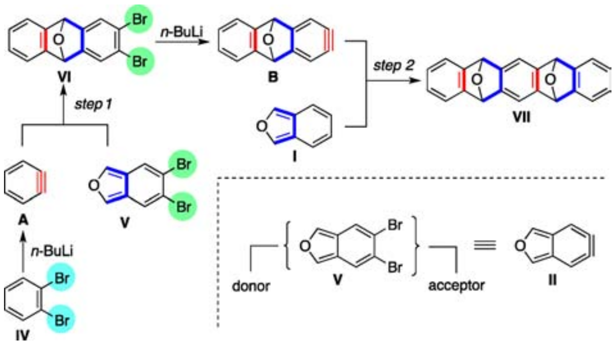
In our ongoing study on developing the synthetic utility of the reactive molecules,[5] we came up with an idea to use a *donor−acceptor molecule*, having electron-donating and electron-withdrawing moieties in one molecule, enabling the rapid introduction of the fused rings onto the central core ring. In particular, we are intrigued by the use of a formal equivalent to didehydroisobenzofuran **II**, possessing a highly strained 1,2-didehydroarene structure at the C_5−C_6 position in **I**, as it could serve as a reactive platform for expeditious assembly of polycycles by two directional annulations (Scheme 1).

Herein, we disclose dual annulations of dibromoisobenzofuran **V**, a formal equivalent of didehydroisobenzofuran **II**, via successive [2 + 4] cycloadditions of benzyne[6] and isobenzofuran (Scheme 2). Importantly, selective bromine−lithium exchange from two dibromides **IV** and **V** enables the tandem generation of benzynes and dual cycloadditions with two different arynophiles (step 1 and step 2). The first [4 + 2] cycloaddition of dibromoisobenzofuran **V** and benzyne **A**, selectively generated from dibromobenzene **IV**, gives tetracyclic compound **VI**, which, in turn, serves as a benzyne donor, leading to the selective generation of benzyne **B**. Second [2 + 4] cycloaddition of benzyne **B** and isobenzofuran **I** gives polycyclic compound **VII**.

Scheme 1. Two-Directional Annulations of Didehydroisobenzofuran II



Scheme 2. Formal Use of Didehydroisobenzofuran by Dual [2 + 4] Cycloadditions of Benzyne and Isobenzofuran



The essential point of this integrated synthesis[7] is *isolability of dibromoisobenzofuran* **V**, which would provide great opportunities to use these potentially attractive molecules under various reaction conditions.

Scheme 3 shows the preparation of dibromoisobenzofuran. Upon heating of epoxynaphthalene **1a**[8] with 3,6-di(2-pyridyl)-1,2,4,5-tetrazine (**2**) in chloroform at 50 °C,[3a] the starting

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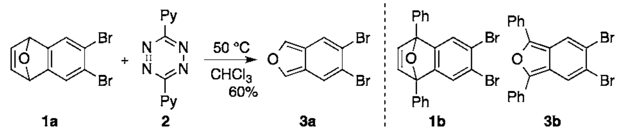
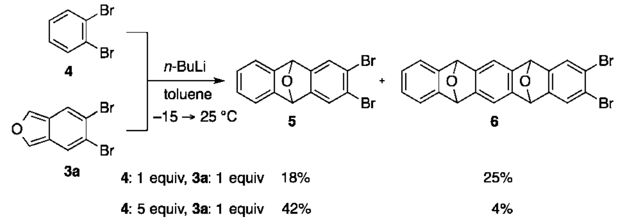
Scheme 3. Preparation of Dibromoisobenzofuran



material was cleanly consumed. Purification by silica-gel column chromatography under Ar atmosphere gave **3a** in 60% yield as white solids,[9] which can be stored under Ar atmosphere in a refrigerator for several months. Similarly, 5,6-dibromo-1,3-diphenylisobenzofuran (**3b**) was prepared from epoxynaphthalene **1b**.

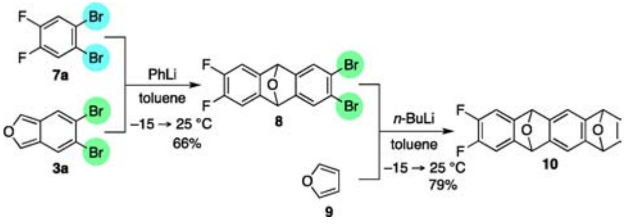
Scheme 4 shows the initial model study for the first [4 + 2] cycloaddition. When dibromobenzene **4** was treated with 1.0 equiv of *n*-BuLi in the presence of dibromoisobenzofuran **3a** (1.0 equiv, toluene, −15 → 25 °C), cycloadduct **5** was obtained in 18% yield. A sizable amount of bis-cycloadduct **6** (25%) was also produced. Although the difference in reactivity is not easily expected, this result indicates the order of the reactivity among the three dibromides, **4** ≈ **5** > **3a**, which caused the competitive second benzyne generation from monocycloadduct **5**. In this case, however, excess amounts of the starting material **4** (5.0 equiv) improved the yields of the monocycloadduct **5** (42%).

Scheme 4. Initial Model Study on the Selective Generation of Benzyne



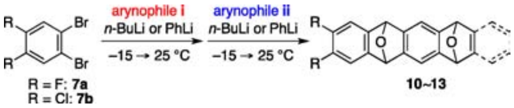
Further investigation revealed that introduction of the electron-deficient fluoro group on the aromatic ring achieved selective benzyne generation (Scheme 5). Upon treatment of 1,2-dibromo-4,5-difluorobenzene (**7a**) with 1.1 equiv of PhLi in the presence of **3a** (1.2 equiv, toluene, −15 → 25 °C), 4,5-difluorobenzyne was selectively generated to give monocycloadduct **10** as almost the exclusive product in 66% yield. In this case, PhLi was effective as a benzyne initiator in comparison with *n*-BuLi (**8**: 49% yield). The cycloadduct **8**, thus obtained, can be used for the second cycloaddition: treatment of **8** with 1.1 equiv of *n*-BuLi in the presence of furan (2.7 equiv, toluene, −15 → 25 °C) gave the bis-cycloadduct **10** in 79% yield as a mixture of stereoisomers.

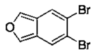
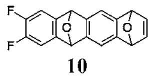
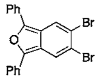
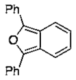
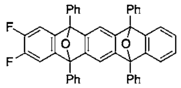
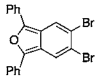
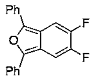
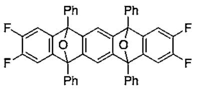
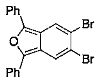
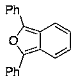
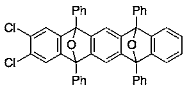
Scheme 5. Successive [2 + 4] Cycloadditions of Benzyne and Isobenzofuran



This successive process can be performed in one pot by sequential addition of the arynophiles (Table 1). When the above-mentioned first cycloaddition was conducted under the same reaction conditions, the formation of the monocycloadduct **8** was observed by TLC. The second arynophile, furan in toluene, was added to the reaction mixture at −15 °C, to which was slowly added *n*-BuLi and the temperature raised to 25 °C, giving hexacycle **10** in 44% yield (entry 1). The dual reactions with isobenzofuran **3b** (the first arynophile) and isobenzofuran **3c** (the second arynophile) also gave cycloadduct **11** (entry 2). Similarly, the successive [2 + 4] cycloadditions with isobenzofurans **3b** and **3d** gave the highly fluorinated cycloadduct **12** in 62% yield (entry 3). The successive processes also proved to be applicable to 1,2-dibromo-4,5-dichlorobenzene (**7b**), selectively affording heptacycle **13** in 44% yield (entry 4).

Table 1. One-Pot Dual [4 + 2] Cycloadditions

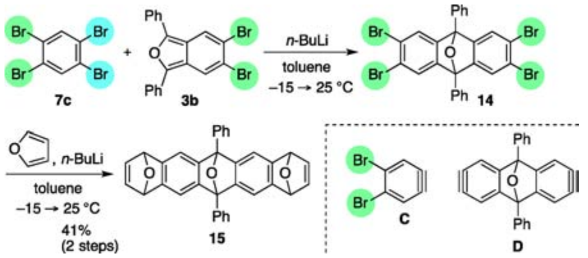


entry	R	i	ii	product[c]	yield (%)
1[a,d,e]	F	 **3a**	 **9**	 **10**	44
2[b,c,e]	F	 **3b**	 **3c**	 **11**	52
3[a,c,f]	F	 **3b**	 **3d**	 **12**	62
4[a,c,f]	Cl	 **3b**	 **3c**	 **13**	44

[a] In toluene. [b] In chlorobenzene. [c] *n*-BuLi was used for the first cycloaddition. [d] PhLi was used for the first cycloaddition. [e] *n*-BuLi was used for the second cycloaddition. [f] PhLi was used for the second cycloaddition.

It is worth mentioning that 1,2,4,5-tetrabromobenzene (**7c**) nicely worked as a reactive platform,[10] allowing the 3-fold cycloaditions *in one pot* (Scheme 6). The key of this process is the selective bromine−lithium exchange of tetrabromobenzene **7c**, cleanly generating the dibromobenzyne **C**, which was

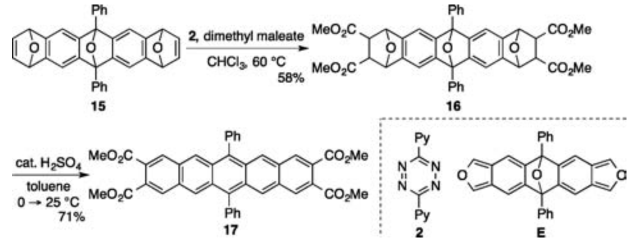
Scheme 6. Two-Directional 3-Fold [4 + 2] Cycloadditions



intercepted by **3b** to afford the cycloadduct **14**.[11] The tetrabromoarene **14**, produced by the first cycloaddition, can be viewed as a bis-aryne equivalent. Indeed, dual [2 + 4] cycloadditions of bis-aryne **D** by treatment of **14** with *n*-BuLi in the presence of furan gave bis-cycloadduct **15** as a mixture of diastereomers. The stereochemistry of the bis-cycloadducts was not determined. More importantly, the successive three ring constructions could be carried out in one pot, affording the 3-fold cycloadduct **15** with high synthetic utility.

Scheme 7 shows one of the synthetic transformations of the cycloadduct **15** into a substituted pentacene. When cycloadduct **15** was heated in chloroform at 60 °C with tetrazine **2** and dimethyl maleate, the dual [4 + 2] cycloadditions of bis-isobenzofuran **E**[12] occurred cleanly to give bis-cycloadduct **16** in 58% yield. Bis-isobenzofuran **E** is synthetically useful in that the rapid introduction of the fused rings and/or functionalization onto the isobenzofuran nucleus would be possible through the dual cycloadditions. Subsequent acid catalyzed aromatization cleanly occurred by treatment of **16** with H_2SO_4 in toluene at 25 °C. Purification of the crude products by silica gel column chromatography gave substituted pentacene **17** in 71% yield as blue solids.[13−15] The structure of **17**[13m] was determined by X-ray analysis.[16]

Scheme 7. Dual [4 + 2] Cycloaddition of Bis-isobenzofuran into the Substituted Pentacene



In summary, dual cycloadditions of didehydroisobenzofuran equivalent with various arynophiles allowed rapid construction of highly functionalized bis-cycloadducts, which were amenable to selective transformation en route to substituted pentacene derivatives. Further synthetic applications are under active investigation in our laboratories.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and compound characterization 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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(4) Recently, we developed one-pot synthetic method of 1,3-diarylisobenzofurans by sequential reaction of methyl 2-formylbenzoate with two identical or different aryl metal species; see: Hamura, T.; Nakayama, R. *Chem. Lett.* **2013**, *42*, 1013.

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(7) For integration of reactions, see: Suga, S.; Yamada, D.; Yoshida, J.-i. *Chem. Lett.* **2010**, *39*, 404.

(8) For preparation, see the Supporting Information.

(9) It is important to protect isobenzofuran from oxygen. If not, isobenzofuran **3a** was gradually oxidized in solution to give 4,5-dibromophthalaldehyde. Moreover, the parent isobenzofuran **I** was purified by silica gel column chromatography under Ar atmosphere, and a deoxygenated solution of **I** could be stored in a refrigerator for a several hours. Stability and reactivity of 5,6-disubstituted isobenzofurans are now in progress, which will be reported in a full paper.

(10) Tetrabromobenzene **7c** can serve as a 1,4-benzdiyne equivalent. For pioneering studies by Hart on the generation and trapping of 1,4-benzdiyne equivalents, see: (a) Hart, H.; Ok, D. *J. Org. Chem.* **1986**, *51*, 979. (b) Hart, H.; Lai, C.-Y.; Nwokogu, G.; Shamouilian, S.; Teuerstein, A.; Zlotogorski, C. *J. Am. Chem. Soc.* **1980**, *102*, 6649. For other examples, see: (c) Chen, Y.-L.; Sun, J.-Q.; Wei, X.; Wong, W.-W.; Lee, A. W. M. *J. Org. Chem.* **2004**, *69*, 7190. (d) Morton, G. E.; Barrett, A. G. M. *J. Org. Chem.* **2005**, *70*, 3525. (e) Schuster, I. I.; Cracium, L.; Ho, D. M.; Pascal, R. A., Jr. *Tetrahedron* **2002**, *58*, 8875. (f) Duong, H. M.; Bendikov, M.; Steiger, D.; Zhang, Q.; Sonmez, G.; Yamada, J.; Wudl, F. *Org. Lett.* **2003**, *5*, 4433. (g) Hamura, T.; Arisawa, T.; Matsumoto, T.; Suzuki, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 6842.

(11) This site selectivity in the bromine−lithium exchange is due to the electron withdrawal of the four bromo atoms in **7c**, which leads to the selective generation of tribromophenyllithium. Subsequent elimination of lithium bromide from this intermediate produced dibromobenzyne **C**.

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Nuckolls, C. *J. Am. Chem. Soc.* **2006**, *128*, 1340. (e) Ono, K.; Totani, H.; Hiei, T.; Yoshino, A.; Saito, K.; Eguchi, K.; Tomura, M.; Nishida, J.; Yamashita, Y. *Tetrahedron* **2007**, *63*, 9699. (f) Palayangoda, S. S.; Mondal, R.; Shah, B. K.; Neckers, D. C. *J. Org. Chem.* **2007**, *72*, 6584. (g) Wang, Y.; Fu, N.; Chan, S.; Lee, H.; Wong, H. N. C. *Tetrahedron* **2007**, *63*, 8586. (h) Lehnherr, D.; McDonald, R.; Tykwinski, R. R. *Org. Lett.* **2008**, *10*, 4163. (i) Lehnherr, D.; Murray, A. H.; McDonald, R.; Ferguson, M. J.; Tykwinski, R. R. *Chem.—Eur. J.* **2009**, *15*, 12580. (j) Kaur, I.; Jia, W.; Kopreski, R. P.; Selvarasah, S.; Dokmeci, M. R.; Pramanik, C.; McGruer, N. E.; Miller, G. P. *J. Am. Chem. Soc.* **2008**, *130*, 16274. (k) Wang, J.; Liu, K.; Liu, Y.; Song, C.; Shi, Z.; Peng, J.; Zhang, H.; Cao, X. *Org. Lett.* **2009**, *11*, 2563. (l) Tang, M. L.; Oh, J. H.; Reichardt, A. D.; Bao, Z. *J. Am. Chem. Soc.* **2009**, *131*, 3733. (m) Li, S.; Zhou, L.; Nakajima, K.; Kanno, K.; Takahashi, T. *Chem.—Asian J.* **2010**, *5*, 1620.

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(15) Cycloadducts **11–13** could also be converted to the corresponding 5,7,12,14-tetraphenylpentacene derivatives under the suitable conditions. Experimental details and physical properties of these compounds will be reported in due course.

(16) For details, see the Supporting Information.