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

Hiroshi Haneda,[†] Shohei Eda,[†] Masato Aratani,[†] and Toshiyuki Hamura*[,†,‡]

[†]Department of Chemistry, School of Science and Technology, Kwansei Gakuin University, 2-1 Gakuen, Sanda, Hyogo 669-1337, Japan

[‡]Japan Science and Technology Agency, ACT-C, 4-1-8 Honcho, Kawaguchi, Saitama 332-0012, Japan

Ⓢ *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.
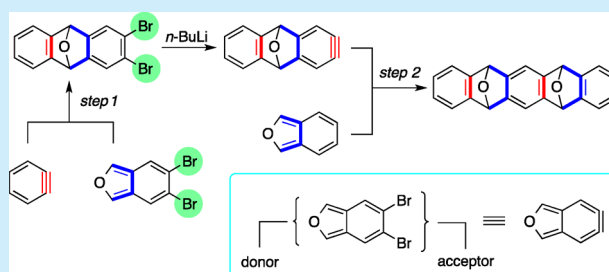
Isobenzofurans are 10π electron systems with quinoid structures, which makes them useful intermediates for various natural/unnatural product syntheses.[1] Among various possibilities, [4 + 2] cycloaddition with dienophiles is a reliable method for the construction of a polycyclic structure.[2] However, 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

Scheme 1. Two-Directional Annulations of Didehydroisobenzofuran II
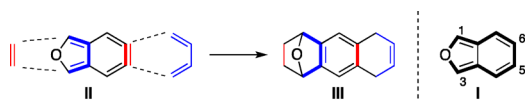
Scheme 2. Formal Use of Didehydroisobenzofuran by Dual [2 + 4] Cycloadditions of Benzyne and Isobenzofuran
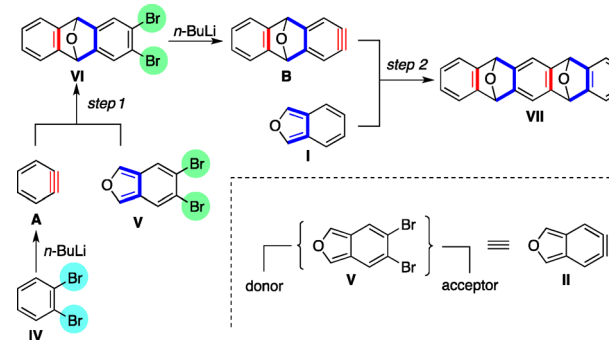
different arynophiles (step 1 and step 2). The first [4 + 2] cycloaddition of dibromoisobenzofuran **V** and benzyne **A**, selectively generated from dibromobenzene **IV**, gives tetracyclic compound **VI**, which, in turn, serves as a benzyne donor, leading to the selective generation of benzyne **B**. Second [2 + 4] cycloaddition of benzyne **B** and isobenzofuran **I** gives polycyclic compound **VII**.

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

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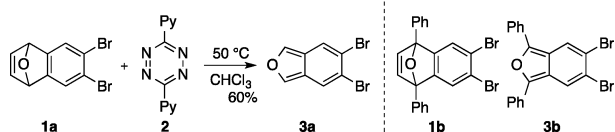
material was cleanly consumed. Purification by silica-gel column chromatography under Ar atmosphere gave **3a** in 60% yield as white solids,[9] which can be stored under Ar atmosphere in a refrigerator for several months. Similarly, 5,6-dibromo-1,3-diphenylisobenzofuran (**3b**) was prepared from epoxynaphthalene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

Scheme 4 shows the initial model study for the first [4 + 2] cycloaddition. When dibromobenzene **4** was treated with 1.0

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

| 4: 1 equiv, 3a: 1 equiv | 18% | 25% |
| 4: 5 equiv, 3a: 1 equiv | 42% | 4% |
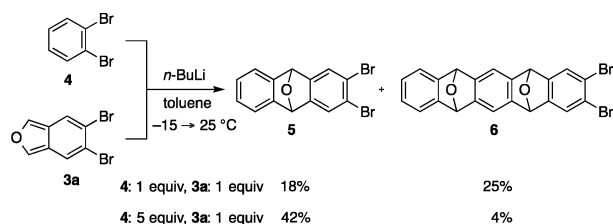
equiv of *n*-BuLi in the presence of dibromoisobenzofuran **3a** (1.0 equiv, toluene, −15 → 25 °C), cycloadduct **5** was obtained in 18% yield. A sizable amount of bis-cycloadduct **6** (25%) was also produced. Although the difference in reactivity is not easily expected, this result indicates the order 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%).

Further investigation revealed that introduction of the electron-deficient fluoro group on the aromatic ring achieved selective benzyne generation (Scheme 5). Upon treatment of
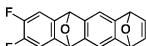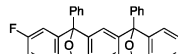
Scheme 5. Successive [2 + 4] Cycloadditions of Benzyne and Isobenzofuran
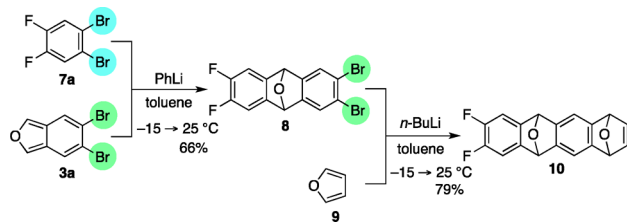
1,2-dibromo-4,5-difluorobenzene (**7a**) with 1.1 equiv of PhLi in the presence of **3a** (1.2 equiv, toluene, −15 → 25 °C), 4,5-difluorobenzyne was selectively generated to give monocycloadduct **10** as almost the exclusive product in 66% yield. In this case, PhLi was effective as a benzyne initiator 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.

This successive process can be performed in one pot by sequential addition of the arynophiles (Table 1). When the

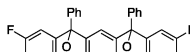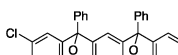**Table 1. One-Pot Dual [4 + 2] Cycloadditions**

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.

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).

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
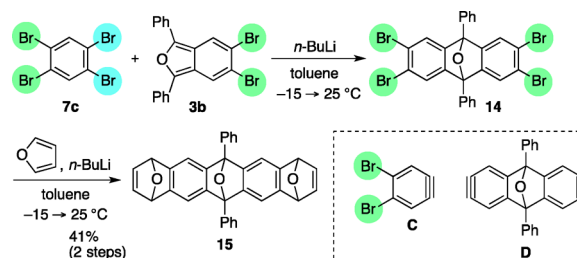
intercepted by **3b** to afford the cycloadduct **14**.[11] The tetrabromoarene **14**, produced by the first cycloaddition, can be viewed as a bis-aryne equivalent. Indeed, dual [2 + 4] cycloadditions of bis-aryne **D** by treatment of **14** with *n*-BuLi in the presence of furan gave bis-cycloadduct **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

Scheme 7. Dual [4 + 2] Cycloaddition of Bis-isobenzofuran into the Substituted Pentacene
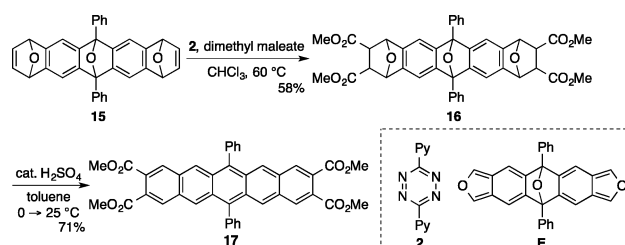
15 was heated in chloroform at 60 °C with tetrazine **2** and dimethyl maleate, the dual [4 + 2] cycloadditions of bis-isobenzofuran **E**[12] occurred cleanly to give bis-cycloadduct **16** in 58% yield. Bis-isobenzofuran **E** is synthetically useful in that the rapid introduction of the fused rings 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]

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.

AUTHOR INFORMATION

Corresponding Author

*E-mail: thamura@kwansei.ac.jp.

Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) Patil, A. O.; Heeger, A. J.; Wudl, F. *Chem. Rev.* **1988**, *88*, 183. (b) Roncali, J. *Chem. Rev.* **1997**, *97*, 173. (c) Friedrichsen, W. *Adv. Heterocyl. Chem.* **1980**, *26*, 135. (d) Friedrichsen, W. *Adv. Heterocyl. Chem.* **1999**, *73*, 1.

(2) For selective examples, see: (a) Binger, P.; Wedemann, P.; Goddard, R.; Brinker, U. H. *J. Org. Chem.* **1996**, *61*, 6462. (b) Rodrigo, R. *Tetrahedron* **1988**, *44*, 2093. (c) Wong, H. N. C. *Acc. Chem. Res.* **1989**, *22*, 145. (d) Man, Y.-M.; Mak, T. C. W.; Wong, H. N. C. *J. Org. Chem.* **1990**, *55*, 3214. (e) Chan, S.-H.; Yick, C.-Y.; Wong, H. N. C. *Tetrahedron* **2002**, *58*, 9413. (f) Rainbolt, J. E.; Miller, G. P. *J. Org. Chem.* **2007**, *72*, 3020.

(3) (a) Warrener, R. N. *J. Am. Chem. Soc.* **1971**, *93*, 2346. (b) Warrener, R. N.; Shang, M.; Butler, D. N. *Chem. Commun.* **2001**, 1550. (c) Sygula, A.; Sygula, R.; Rabideau, P. W. *Org. Lett.* **2006**, *8*, 5909. (d) Pei, B. J.; Chan, W. H.; Lee, A. W. M. *Org. Lett.* **2011**, *13*, 1774.

(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.

(5) Hamura, T.; Chuda, Y.; Nakatsuji, Y.; Suzuki, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 3368.

(6) For selected reviews on arynes, see: (a) Hoffmann, R. W. *Dehydrobenzene and Cycloalkynes*; Academic Press: New York, 1967. (b) Kessar, S. V. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, U.K., 1991; Vol. 4, pp 483−515. (c) Pellissier, H.; Santelli, M. *Tetrahedron* **2003**, *59*, 701. (d) Wenk, H. H.; Winkler, M.; Sander, W. *Angew. Chem., Int. Ed.* **2003**, *42*, 502. (e) Yoshida, H.; Takaki, K. *Synlett* **2012**, *23*, 1725. (f) Bhunia, A.; Yetra, S.; Biju, R. A. T. *Chem. Soc. Rev.* **2012**, *41*, 3140. (g) Dubrovskiy, A. V.; Markina, N. A.; Larock, R. C. *Org. Biomol. Chem.* **2013**, *11*, 191.

(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**.

(12) (a) Christopfel, W. C.; Miller, L. L. *J. Org. Chem.* **1986**, *51*, 4169. (b) Chiba, T.; Kenny, P. W.; Miller, L. L. *J. Org. Chem.* **1987**, *52*, 4327.

(13) For selected reports on synthesis of 6,13-disubstituted pentacenes, see: (a) Anthony, J. E.; Brooks, J. S.; Eaton, D. L.; Parkin, S. R. *J. Am. Chem. Soc.* **2001**, *123*, 9482. (b) Payne, M. M.; Delcamp, J. H.; Parkin, S. R.; Anthony, J. E. *Org. Lett.* **2004**, *6*, 1609. (c) Swartz, C. R.; Parkin, S. R.; Bullock, J. E.; Anthony, J. E.; Mayer, A. C.; Malliaras, G. G. *Org. Lett.* **2005**, *7*, 3163. (d) Miao, Q.; Chi, X.; Xiao, S.; Zeis, R.; Lefenfeld, M.; Siegrist, T.; Steigerwald, M. L.;

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.

(14) For selected reviews on pentacenes, see: (a) Bendikov, M.; Wudl, F.; Perepichka, D. F. *Chem. Rev.* **2004**, *104*, 4891. (b) Anthony, J. E. *Chem. Rev.* **2006**, *106*, 5028. (c) Anthony, J. E. *Angew. Chem.* **2008**, *120*, 460; *Angew. Chem., Int. Ed.* **2008**, *47*, 452. (d) Bettinger, H. F. *Pure Appl. Chem.* **2010**, *82*, 905.

(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.