

CHEMISTRY A European Journal



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Accepted Article Title: Didehydroisobenzofuran: a new reactive intermediate for construction of isoacenofuran Authors: Toshiyuki Hamura, Suguru Matsuoka, Sunna Jung, Kaoru Miyakawa, Yu Chuda, and Ryo Sugimoto This manuscript has been accepted after peer review and appears as an Accepted Article online prior to editing, proofing, and formal publication of the final Version of Record (VoR). This work is currently citable by using the Digital Object Identifier (DOI) given below. The VoR will be published online in Early View as soon as possible and may be different to this Accepted Article as a result of editing. Readers should obtain the VoR from the journal website shown below when it is published to ensure accuracy of information. The authors are responsible for the content of this Accepted Article. To be cited as: Chem. Eur. J. 10.1002/chem.201804655 Link to VoR: http://dx.doi.org/10.1002/chem.201804655 **Supported by** ACES

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Didehydroisobenzofuran: a new reactive intermediate for construction of isoacenofuran

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Dedication ((optional))

Abstract: An efficient generation method of didehydroisobenzofuran, a new heteroaryne species, was developed by bromine–lithium exchange of the dibromoisobenzofuran. The reactive intermediate, thus generated, was trapped by appropriate arynophile to give the [2+2], [2+3], and [2+4] cycloadducts, respectively. Moreover, the reaction could be applied to the syntheses of isoanthracenofurans (anthra[2,3-*c*]furans), a novel class of heteroacenes, with isoelectoronic structure to the corresponding acenoheteroles (anthra[2,3-*b*]furans).

Design and generation of a reactive intermediate is an important subject in organic chemistry, because discovery of a novel reactivity inherent in its unique structure would lead to develop a new reaction, which opens a way to access to various functionalized organic molecules.^[1]



Scheme 1. Didehydroisobenzofuran, a new reactive intermediate for construction of polycyclic structure.

In this context, we previously reported a *formal* synthetic use of didehydroisobenzofuran **1**, possessing a highly strained 1,2-didehydroarene structure at the C_5-C_6 position, enabling rapid construction of polycyclic structures through the successive cycloadditions (Eqs. 1 and 2).^[2] In this process,

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dibromoisobenzofuran **2** served as a synthetic equivalent to **1**, allowing expeditious assembly of polycycle **5** by two directional [2+4] cycloadditions.^[3–5] Further study on developing the synthetic utility of dibromoisobenzofuran **2** revealed that the *direct* generation of didehydroisobenzofuran **1** was feasible by two-step protocol including the bromine–lithium exchange of dibromoisobenzofuran **2** (Eq. 3). This new heteroaryne, thus generated, was trapped with arynophile to give functionalized isobenzofuran with various synthetic potential.^[6,7] Moreover, the [2+4] cycloadduct was converted to isoanthracenofuran, a novel class of heteroacenes with isoelectoronic structure to the corresponding anthra[2,3-*b*]furans, which is described in this communication.

Table 1 shows the initial study for the generation of didehydroisobenzofuran, which was trapped with arynophile.^[8,9] Upon treatment of dibromodiphenyisobenzofuran **8**, a model substrate, with *n*-BuLi (2.0 equiv) in the presence of diphenylisobenzofuran **9** (1.5 equiv, THF, 0 °C \rightarrow r.t., 3 h), [2+4] cycloaddition occurred to give the cycloadduct **10** in 40% yield (entry 1). The structure of **10** was determined by NMR analysis. Screening of the reaction conditions revealed that toluene was a choice of solvent to produce the desired product in better yield (entry 3). Moreover, *s*-BuLi and PhLi were also available for the generation of didehydroisobenzofuran, giving the cycloadduct **10** in moderate yield (entries 4 and 5). These results were contrary to the poor results using *t*-BuLi, *i*-PrMgBr, and *i*-PrMgCI+LiCI (entries 6–8).

Table 1. Generation and trapping of didehydroisobenzofuran.

Ph O Ph Br Br Br Br	Ph + O Ph 9	$\begin{array}{c} \text{conditions}^{1} \\ 0 \ ^{\circ}\text{C} \rightarrow \text{r.t.} \end{array} \begin{array}{c} \text{Ph} \\ \text{O} \\ \text{Ph} \\ 10 \end{array}$	Ph O Ph
Entry	R-Met	Solvent	Yield (%)
1	<i>n</i> -BuLi	THF	40
2	<i>n</i> -BuLi	Et ₂ O	42
3	<i>n</i> -BuLi	toluene	57
4	<i>s</i> -BuLi	THF	38
5	PhLi	THF	41
6	<i>t</i> -BuLi	THF	_2)
7	<i>i</i> -PrMgBr	THF	_3)
8	<i>i</i> -PrMgBr•LiCl	THF	19

¹⁾ R-Met (2.0 equiv) and diphenylisobenzofuran **9** (1.5 equiv) were used.
 ²⁾ The reduced 5-bromo-1,3-diphenylisobenzofuran was produced in 14% yield. ³⁾ The starting materials were recovered.

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In these reactions, one plausible structure of byproducts was the dual-cycloadduct (structure not shown) by further reaction with the initially formed cycloadduct **10**, which was detected by MALDI-TOF mass spectrometry (Figure S1).^[10] This competing reaction with didehydroisobenzofuran was due to the similar reactivity of the furan moiety in **10** compared with that of diphenylisobenzofuran **9**.

To suppress the formation of the above-mentioned **11**^[11] multiple-cycloadducts, dibromoisobenzofuran possessing sterically crowded 2,6-xylyl groups in the furan precursor moiety was tested another as of didehydroisobenzofuran. In addition, to gain the precise two-step behavior regarding the generation of didehydroisobenzofuran, the reaction was conducted at lower temperature: upon treatment of 11 with 1.2 equiv of n-BuLi (1.60 M in hexane) in the presence of dimethyl furan 12 (6.0 equiv, THF, $-95 \rightarrow -78$ °C, 5 min), the [2+4] cycloadduct 14 was obtained only in 4% yield, and the major product was bromoisobenzofuran 13 lacking one bromine atom (88%). This result implies that aryllithium species A generated by the Br/Li exchange of 11 has a finite lifetime at -78 °C.[12,13]

On the other hand, if the same reaction was performed initially at -78 °C followed by warming to -50 °C, [2+4] cycloadduct **14** was obtained as a major product in 53% yield. At -50 °C, lithio species **A** undergoes 1,2-elimination of LiBr to generate the didehydroisobenzofuran **B**. These behaviors provided us with the handle to control generation of the two reactive species **A** and **B**.



Scheme 2. [2+4] Cycloaddition of sterically congested didehydroisobenzofuran.

By using various arynophiles, functionalized isobenzofurans were accessible via the [2+4], [2+3], and [2+2] cycloadditions (Scheme 3). Typical experimental procedure is represented by furan cycloaddition: To a mixture of dibromide **11** and furan **15** (5.0 equiv) in THF was slowly added *n*-BuLi (1.5 equiv in hexane) at -40 °C. After 5 h, the reaction was stopped by adding water. Extractive workup followed by purification by silica-gel column chromatography gave the cycloadduct **16** in 81% yield. Similarly, diphenylisobenzofuran **9a** and dialkynylisobenzofuran **9b** prove to be applicable for the [2+4] cycloaddition, affording pentacycles **17a** and **17b** in 94% yield and 86% yield, respectively. Moreover, ketene silyl acetal **18**

worked well as a trapping agent to give the [2+2] cycloadduct **19** in 79% yield. In addition, the [2+3] cycloaddition was realized by reaction of didehydroisobenzofuran **B** and nitrone **20** to produce the cycloadduct **21**, albeit in low yield.^[14]



Scheme 3. [2+4], [2+3], and [2+2] cycloadditions of didehydroisobenzofuran. 1) Ar: 2,6-dimethylphenyl. 2) Arynophile (1.2~5.0 equiv) and R-Li (1.5~2.5 equiv) were used. 3) *n*-BuLi, toluene, $-78 \text{ }^{\circ}\text{C} \rightarrow \text{rt}$. 4) *n*-BuLi, toluene, $-40 \text{ }^{\circ}\text{C}$.

As one of the synthetic application, the high-ordered polyacene framework could be efficiently synthesized by two-directional annulation of didehydroisobenzofuran (Scheme 4).^[15]



Scheme 4. Efficient synthetic access to high-ordered polyacene framework via two-directional annulations of didehydroisobenzofuran C.

In the first step, the [2+4] cycloaddition of didehydroisobenzofuran **C** and diphenylisobenzofuran **9** described in Table 1 (entry 3) was conducted to give the mono-cycloadduct **10**, which was directly used as an arynophile by reaction with dibromobenzyne **D**, selectively generated from tetrabromobenzene (**22**)^[16] (*n*-BuLi, toluene, $-40 \rightarrow 0$ °C),

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affording the diepoxypentacene **23**. Subsequent third cycloaddition of heptacyclic aryne **E**, generated from **23**, and isobenzofuran **9** occurred cleanly to produce the highly condensed polycycle **24** as a mixture of stereoisomers.

Scheme 5 shows the conversion of the [2+4] cycloadduct 17a to the isoanthracenofuran 26a by two-step sequences including the reductive aromatization of the ring opened diol derivative. Interestingly, the first ring opening of the substrate 17a with 4 M H_2SO_4 (THF, 50 °C) proceeded in S_N2' manner to give the diol 25a in high yield without producing the isomeric diol 25a'. Subsequent reductive aromatization of 25a occurred cleanly by treatment with 3.0 equiv of SnCl₂ (toluene, 25 °C). Evaporation of the solvent, followed by washing the crude product with MeOH gave essentially pure isoanthracenofuran 26a as a blue solid. Importantly, the product 26a is a novel class of heteroacene in that an o-quinoidal structure is only drawn in the closed-shell resonance form, and therefore, it would show unique physyical properties as well as high reactivities compared to the corresponding isoelectronic acene analogues (e.g. diphenyltetracene).^[17] Indeed, NMR analysis showed that isoanthracenofuran 26a dissolved in CDCl3 was readily oxidized to the endoperoxide 27a (Figure S2), although 26a was relatively stable in the solid-state and could be stored under Ar atomospher for several months.

In a similar two-step sequence, the isobenzofuran **17b** could also be converted to the dialkynylated isoanthracenofuran **26b**, which was more stable than diaryl derivative **26a**. In this case, the formation of endoperoxide **27b** occurred gradually after 1 h (Figure S4).



Scheme 5. Syntheses of isoanthracenofurans 26a and 26b.

The absorption spectra of **26a** and **26b** in CH₂Cl₂ are shown in Figure 1, together with that of 1,3-diarylisobenzofuran **17a** for comparison. Isoanthracenofuran **26a** has its absorption maximum at 647 nm, which is largely red-shifted compared to isobenzofuran **17a** (λ_{abs} = 358 nm). This result clearly shows the significant effect by introducing butadiene units on to the isobenzofuran core, which makes the structure more quinoidal. In addition, the introduction of phenylethynyl groups into the accene core significantly affects the photophysical property: the alkynyl derivative **26b** exhibits an absorption in the near-infrared (NIR) region with the maximum at 720 nm, which is red-shifted about 73 nm in comparison with that of **26a**, revealing its quite narrow bandgap electronic structure.



Figure 1. UV-vis absorption spectra of isobenzofuran 17a, and isoanthracenofurans 26a and 26b (in CH₂Cl₂).

In summary, an efficient generation method of didehydroisobenzofurans, a new heteroaryne species, was developed by bromine-metal exchange of the dibromoisobenzofurans. The reactive intermediates, thus generated, were efficiently trapped by appropriate arynophiles to give the various cycloadducts, and some of them could be converted to anthra[2,3-c]furans, а novel class of structure heteroacenes, with isoelectoronic to the Further corresponding (anthra[2,3-b]furans). synthetic applications are under active investigation in our laboratory.

Acknowledgements

This work was supported by JSPS KAKENHI Grant Number JP15H05840 in Middle Molecular Strategy and JST ACT-C Grant Number JPMJCR12YY, Japan.

Keywords: reactive intermediate • didehydroisobenzofuran • isoacenofuran • polycycle • *π*-conjugated molecule

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