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An efficient synthetic route to 1,3-bis(arylethynyl)-isobenzofuran by using alkoxybenzocyclobutenone as a reactive platform

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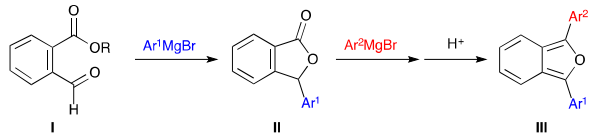
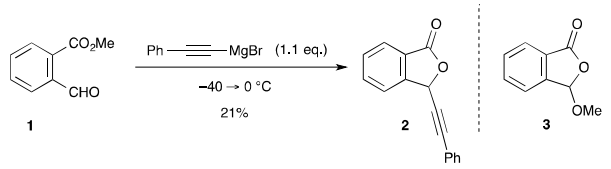
An efficient synthetic method of 1,3-bis(arylethynyl)-isobenzofurans has been developed. Nucleophilic addition of alkynyllithium to benzocyclobutenone and subsequent oxidative ring cleavage of the four-membered ring gave keto-aldehyde, which, in turn, accepted the second nucleophile to produce isobenzofurans after acid treatment.

Isobenzofurans are 10π electron systems with quinoid structures, which makes them useful building blocks for natural/unnatural product syntheses.[1,2] Among various possibilities, [4+2] cycloaddition with dienophiles is a reliable method for the rapid construction of polycyclic structure.[3,4] However, the progress in this area is limited presumably due to the lack of general synthetic access to π-extended derivatives. In this context, we recently reported an efficient synthetic method of functionalized 1,3-diarylisobenzofurans via sequential nucleophilic additions to 2-formylbenzoate (**I** → **II** →□□□□).[5] By using two identical or different aryl Grignard reagents, symmetrical and unsymmetrical isobenzofurans **III** could be selectively prepared in one-pot (Scheme 1).



Scheme 1 One-pot preparation of 1,3-diarylisobenzofuran via sequential nucleophilic additions to 2-formylbenzoate.

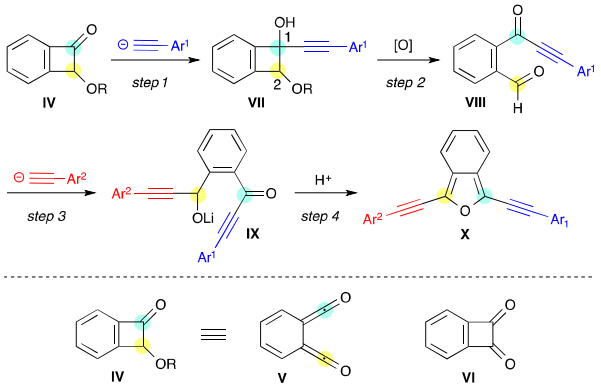
However, further attempts to prepare dialkynyl-isobenzofurans, a new class of π-extended isobenzofurans, have failed, due to the difficulty in the introduction of two alkynyl groups by the double nucleophilic additions to formyl benzoate. In fact, when methyl 2-formylbenzoate (**1**) was treated with 1.1 equiv. of (phenylethynyl)magnesium bromide (–40 → 0 °C), the desired 3-alkynylphthalide **2** was obtained only in 21% yield, accompanied by a sizable amount of phthalide **3**.[6,7] Moreover, second nucleophilic addition of alkynyl metal species to the phthalide **2** resulted in the formation of a complex mixture of products (Scheme 2).



Scheme 2 Initial attempt to prepare dialkynylisobenzofuran by double nucleophilic additions.

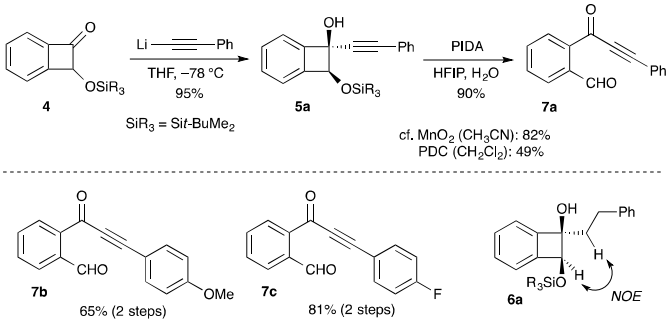
With these unsuccessful results, we designed an alternative synthetic route to dialkynylisobenzofurans. Our idea is to use of small ring compounds with potentially attractive reactivities, since they can serve as a reactive platform for introducing various functionalities onto the reactive core ring. More importantly, they can easily undergo ring cleavage by releasing the high strain.[8] Along these lines, we selected alkoxybenzocyclobutenone **IV**, which can be viewed as a *masked form* of a synthetic equivalent of intriguing species **V**.[9] Although oxidation level of alkoxyketone **IV** is different from that of diketone **VI**, isomeric form of **V**, it can sequentially accept two alkynyl metal species at each carbon on the four-membered ring through the oxidative ring cleavage of cyclobutane (Scheme 3).[10] Thus, the first nucleophilic addition of alkynyl anion to **IV** gives alcohol **VII** (step 1), which undergoes oxidative ring cleavage of the four-membered ring to give keto-aldehyde **VIII** (step 2). The latter process would be facilitated by the presence of electron donating alkoxy group at

C_2 position (*vide infra*). Second nucleophilic addition to **VIII** occurs selectively at formyl side due to the high electrophilic character of aldehyde (step 3), and subsequent formation of lactol from adduct **IX** and acid promoted dehydration effectively gives symmetrical and unsymmetrical dialkynylisobenzofuran **X** (step 4).[11]



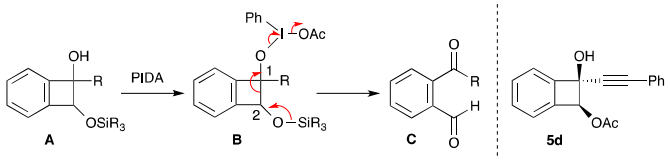
Scheme 3 A synthetic route to dialkynylisobenzofuran by using alkoxybenzocyclobutenone as a reactive platform.

Scheme 4 shows the preparation of keto-aldehyde **7a**. Upon treatment of siloxybenzocyclobutenone **4**[12,13] with 1.1 equiv. of (phenylethynyl)lithium at –78 ˚C, the nucleophilic addition occurred stereoselectively to give cis adduct **5a** in 95% yield as a single isomer. The stereochemistry of **5a** was determined by NOE after conversion of **5a** to reduced product **6a** (Pd/C, H_2, EtOH). Subsequent oxidative ring opening of **5a** was promoted by treatment of MnO_2 (20 equiv., CH_3CN, r.t., 2 h), affording keto-aldehyde **7a** in 82% yield. Screening of oxidizing agents revealed that phenyliodine diacetate (PIDA) was most effective (1.1 equiv., HFIP–H_2O, r.t., 10 min), affording **7a** in 90% yield.[14] Treatment of **5a** with pyridinium dichromate (PDC) gave also **7a** in moderate yield.[15] Keto-aldehydes **7b** and **7c** having an electron donating and electron withdrawing groups on the aromatic ring were also conveniently prepared by using these two–step sequences.



Scheme 4 Preparation of keto-aldehydes **7**.

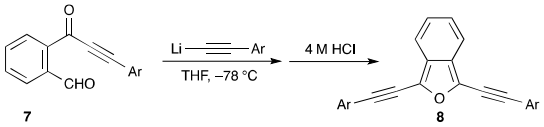
The plausible reaction mechanism of oxidative ring cleavage of the cyclobutenol is shown in Scheme 5. In the first step, the alcohol oxygen in **A** reacted with PIDA to give iodine complex **B**. Subsequent C_1–C_2 bond cleavage on the four-membered ring promoted by the siloxy group at C_2 position underwent the oxidation of the alcohol to produce keto-aldehyde **C**. Importantly, the presence of the electron donating group on the four-membered ring is necessary for the ring opening: when the acetoxy substrate **5d** was treated under the similar conditions (PIDA, HFIP–H_2O, r.t., 20 h), prolonged reaction time was required to consume the starting material to give **7a** in 59% yield.

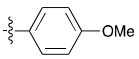
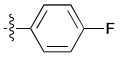


Scheme 5 Plausible reaction mechanism of oxidative ring cleavage of benzocyclobutenol.

The next step is a second nucleophilic addition to keto-aldehyde **7** and acid promoted cyclization (Table 1). Upon treatment of **7a** with (phenylethynyl)lithium (1.1 equiv.) at –78 ˚C, nucleophilic addition occurred cleanly and subsequent acid treatment (4 M HCl) gave 1,3-bis(phenylethynyl)-isobenzofuran (**8a**) in 68% yield (entry 1).[16] In this case, the use of TFA as an acid also promoted the cyclization, affording **8a** in moderate yield (entry 2).[5] Similarly, treatment of **7b** and **7c** with [(4-methoxyphenyl)ethynyl]lithium or [(4-fluorophenyl)ethynyl]lithium gave isobenzofurans **8b** and **8c** in 59% and 68% yields, respectively (entries 3 and 4).

Table 1 Symmetrical 1,3-bis(arylethynyl)isobenzofuran

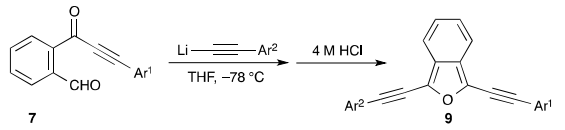


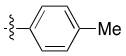
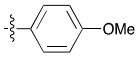
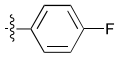
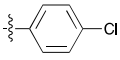
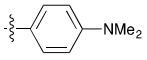
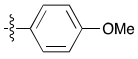
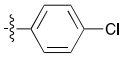
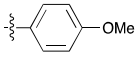
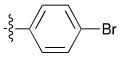
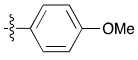
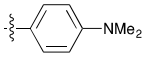
Entry	Ar	Product	Yield (%)
1		**8a**	68
2[a]		**8a**	41
3		**8b**	59
4		**8c**	68

[a]TFA was used as an acid.

Unsymmetrical 1,3-dialkynylisobenzofuran was also easily accessed by using two different alkynyllithiums (Table 2). When keto-aldehyde **7a**, selectively obtained by nucleophilic addition of (phenylethynyl)lithium to **4**, followed by oxidative ring cleavage (*vide supra*), was treated with [(4-methylphenyl)ethynyl]lithium (–78 °C), unsymmetrical dialkynylisobenzofuran **9a** was obtained in 70% yield after acidic work-up (entry 1). In a similar manner, the reactions of **7a** with (arylethynyl)lithiums having an electron donating or an electron deficient group on the benzene ring gave isobenzofurans **9b**–**9d**, respectively (entries 2–4). When [(4-dimethylaminophenyl)ethynyl]lithium was used as a nucleophile, acid-promoted dehydration by 4 M HCl did not occur cleanly, only giving the complex mixture of products. In this case, however, Ac_2O was effective for dehydration, affording the desired product **9e** in 43% yield (entry 5).[2f]

Table 2 Unsymmetrical 1,3-bis(arylethynyl)isobenzofuran

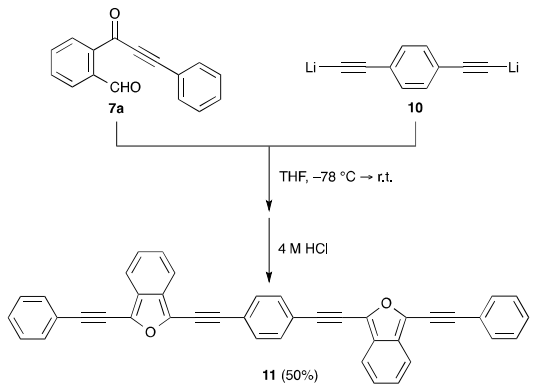


Entry	Ar^1	Ar^2	Product	Yield (%)
1			**9a**	70
2			**9b**	52
3			**9c**	53
4			**9d**	59
5[a]			**9e**	43
6			**9f**	66
7			**9g**	62
8[a]			**9h**	50

[a]Ac_2O was used for dehydration.

Moreover, the dual reactions in the combination of [(4-methoxyphenyl)ethynyl]lithium with substituted nucleophiles gave the corresponding products **9f**–**9h**, respectively (entries 6–8).[17]

Lastly, an important point to emphasize is that structurally attractive bis-isobenzofurans,[18] where two isofuran moieties are connected by extended π-unit, was easily accessible by using this method. Indeed, bis-isobenzofuran **11**, connected by 1,4-diethynylbenzene, was obtained from the keto-aldehyde **7a** in good yield by double nucleophilic addition of bis-alkynyllithium **10** to **7a**, and subsequent cyclization–dehydration of bis-adduct (structure not shown) under the acidic conditions (Scheme 6).[19]



Scheme 6 Preparation of bis-isobenzofuran **11**.

In summary, we developed an efficient synthetic method of symmetrical and unsymmetrical 1,3-dialkynylisobenzofurans, a new class of π-extended derivatives, by sequential reactions of siloxybenzocyclobutenone with two identical or different alkynyllithiums. Further studies on synthetic applications and physical properties of these attractive molecules are currently in progress.

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Notes and references

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†Electronic Supplementary Information (ESI) available: Experimental details and characterization data. See DOI: 10.1039/c000000x/

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6 Use of (phenylethynyl)lithium as a nucleophile gave the phthalide **2** in 32% yield.

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12 According to an efficient synthetic method of benzocyclobutene derivatives developed by Suzuki, benzocyclobutenone **4** was prepared by [2+2] cycloaddition of benzyne and ketene silyl acetal. For details, see supporting information. See also ref. 13.

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15 Other oxidizing agents, e.g. SO_3•pyr and Dess–Martin Periodinane, only gave the starting material.

16 All new compounds were fully characterized by spectroscopic means. For details, see supporting information.

17 Alkynyllithiums, having no aryl group, could also be used for this reaction. For example, treatment of **7a** with 1-hexynyllithium gave the corresponding unsymmetrical dialkynylisobenzofuran in 71% yield. Reactivity and physical property of 1,3-dialkynylisobenzofurans are now in progress, which will be reported in due course.

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