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Editor's Choice

1,3-Dialkynyl- and 1,3-Dialkenylisobenzofurans: New π-Extended Congeners Prepared by Double Nucleophilic Addition of Alkynyllithiums to *o*-Phthalaldehyde


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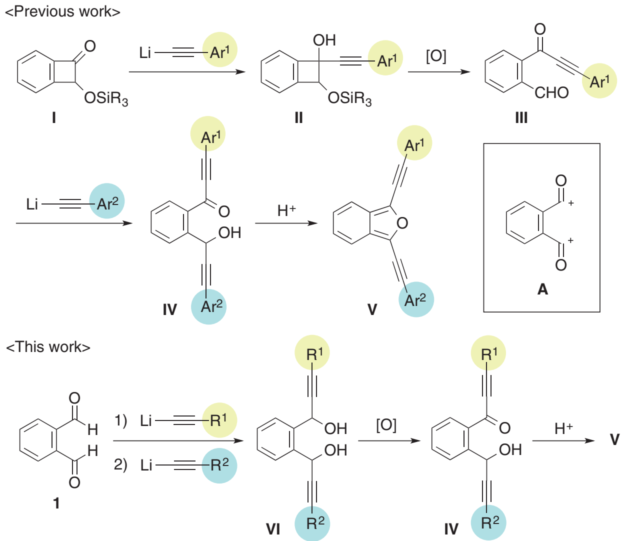
Efficient synthetic route to 1,3-dialkynyl- and 1,3-dialkenylisobenzofurans, new π-extended congeners of isobenzofurans, was reported. A three-step protocol including double nucleophilic additions of alkynyllithiums to *o*-phthalaldehyde and selective oxidation enables us to prepare various functionalized π-extended isobenzofurans. The photophysical properties of these π-extended isobenzofurans are also evaluated.

Keywords: 1,3-Dialkynylisobenzofuran | π-Extended congener | Three-step synthesis

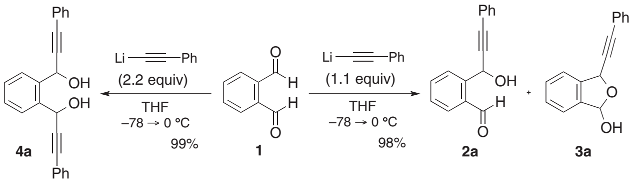
Isobenzofurans are 10π electron systems with a quinoid structure, which can serve as a useful building block for the construction of various natural/unnatural product syntheses.[1–3] In addition, based on their unique physical properties, they have potential utility as a component of functional materials, e.g. fluorophores, OLEDs, and photovoltaics.[4]

In this context, we previously reported a one-pot synthetic method of 1,3-diarylisobenzofurans by twofold additions of aryl metal species to *o*-formyl benzoate, allowing the rapid preparation of various functionalized derivatives, including an isobenzofuran dimer.[5] Further study, however, revealed that bis(arylethynyl)isobenzofurans **V**, new π-extended derivatives, was not accessible, due to the lower reactivity of the corresponding alkynyl metal species.[6]

Along these lines, an alternative approach to isobenzofurans has been recently developed by using benzocyclobutenones **I** as a masked form of intriguing species **A**, enabling the preparation of various bis(arylethynyl)isobenzofurans **V** (Scheme 1).[6,7] However, it still has a drawback in that multistep syntheses were required to prepare the starting material **I**, which hampered an efficient way to functionalize derivatives of **V**. Herein we wish to describe a new synthetic route to 1,3-dialkynylisobenzofurans **V** by using *o*-phthalaldehyde as a synthetic equivalent of **A**. As shown in Scheme 1, double nucleophilic additions of alkynyllithiums to *o*-phthalaldehyde (**1**), and subsequent selective mono-oxidation of diol **VI** efficiently gives isobenzofuran **V** after acid treatment of the resulting keto-alcohol **IV**. Importantly, stepwise introduction of two alkynyl groups to **1** allows for the selective preparation of symmetrical and unsymmetrical compounds **V**, including novel (alkenyl)ethynyl, (alkyl)ethynyl, and (silyl)ethynyl derivatives. Moreover, *dialkenyl*isobenzofuran, a new π-extended congener, is also accessible by appropriate introduction of two alkenyl groups onto the isobenzofuran core.

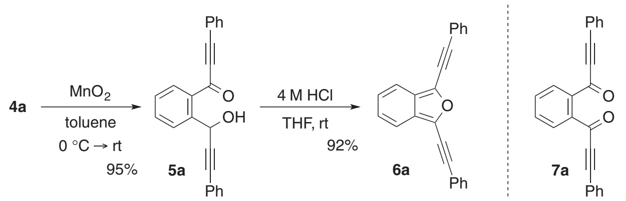


Scheme 1. Two synthetic routes to 1,3-dialkynylisobenzofurans.



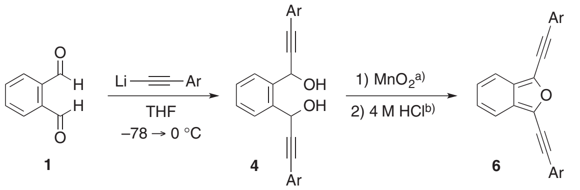
Scheme 2. Successive nucleophilic additions of phenylethynyllithium to *o*-phthalaldehyde (**1**).

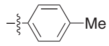
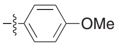
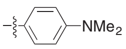
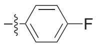
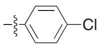
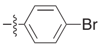
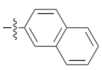
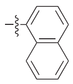
Scheme 2 shows the initial model study for successive introduction of two alkynyl groups to *o*-phthalaldehyde (**1**). Upon treatment of **1** with 1.1 equiv of phenylethynyllithium in THF at −78 °C, nucleophilic addition occurred selectively at one of the formyl groups in **1**, affording keto-alcohol **2a** and lactol **3a** as a mixture of products in 98% combined yield.[8] Importantly, the double additions to **1** did not entirely occur at −78 °C in spite of the treatment of excess amount of phenylethynyllithium (2.2 equiv). These results indicate that the reactivity of the lithio intermediates of **2a** with phenylethynyllithium is lower than **1** or suppressed by the predominant formation of the lithio intermediates of **3a** in the reaction media. Indeed, TLC analysis showed that second nucleophilic addition occurred gradually by warming the reaction to 0 °C. Quenching the reaction and purification by silica gel column chromatography gave diol **4a** in 99% yield.[9]



Scheme 3. Selective oxidation and acid-promoted cyclization to 1,3-bis(phenylethynyl)isobenzofuran (**6a**).

Table 1. Symmetrical 1,3-bis(arylethynyl)isobenzofurans



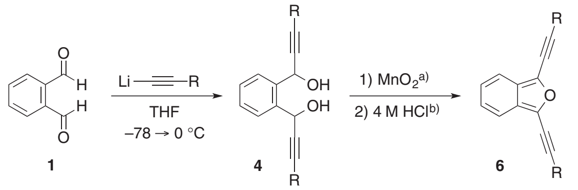
Entry	Ar	Yield of **4**/%	Yield of **6**/%
1		99 (**4b**)	71 (**6b**)
2		98 (**4c**)	91 (**6c**)
3		92 (**4d**)	58 (**6d**)
4		87 (**4e**)	72 (**6e**)
5		92 (**4f**)	82 (**6f**)
6		91 (**4g**)	77 (**6g**)
7		quant (**4h**)	71 (**6h**)
8		quant (**4i**)	71 (**6i**)

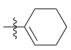
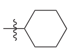
[a]1.2 equiv of MnO_2 in toluene at rt. [b]THF, 0 °C.

Selective mono-oxidation of diol **4a** turned out to be possible by using MnO_2 as an oxidant (Scheme 3). Upon treatment of **4a** with MnO_2 (1.2 equiv, MeCN, rt), the oxidation occurred smoothly to give keto-alcohol **5a** in 79% yield, accompanied by a small amount of diketone **7a** (7%). Screening of the reaction conditions revealed that the formation of diketone **7a** was almost completely suppressed by using toluene as a solvent, affording the essentially pure product **5a**. Keto-alcohol **5a**, thus obtained, was directly converted to 1,3-bis(phenylethynyl)isobenzofuran (**6a**) by acid-treatment (4 M HCl, THF, 0 °C → rt).

Various symmetrical (arylethynyl)isobenzofurans **6** were obtained through this three-step sequence (Table 1). Upon treatment of **1** with (4-methylphenyl)ethynyllithium, double nucleophilic additions occurred cleanly to give diol **4b**, which was smoothly converted to isobenzofurans **6b** by selective mono-oxidation and subsequent acid-promoted cyclization (Entry 1). Isobenzofuran **6c** with electron-donating methoxy group on the aromatic ring was efficiently prepared (Entry 2). It is noted that isobenzofuran **6d**, having an electron-donating dimethylamino group on the aromatic ring, should be purified by silica gel column chromatography *under Ar atmosphere* to avoid gradual oxidation with oxygen, affording **6d** as stable solids.[10] Halogenated derivatives **6e**–**6g** were also prepared by using (4-halophenyl)ethynyllithium as nucleophiles. Moreover, isomeric pair of alkynylisobenzofurans **6h** and **6i** with respect to the connection of the naphthyl group were selectively synthesized by using the corresponding naphthalenylethynyllithiums (Entries 7 and 8).

Table 2. Symmetrical 1,3-dialkynylisobenzofurans



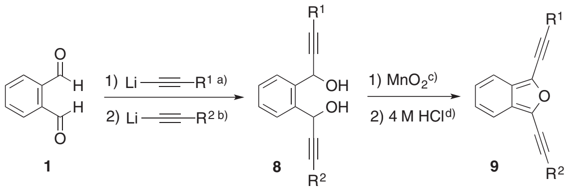
Entry[a]	Ar	Yield of **4**/%	Yield of **6**/%
1		86 (**4j**)	83 (**6j**)
2		97 (**4k**)	82 (**6k**)
3	$Si(i\text{-}Pr)_3$	92 (**4l**)	80 (**6l**)

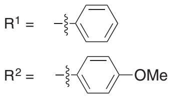
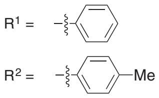
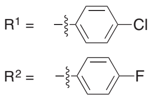
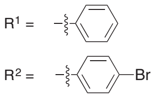
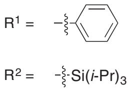
[a]1.2 equiv of MnO_2 in toluene at rt. [b]THF, 0 °C.

Less π-conjugated (alkenyl)ethynyl-, (alkyl)ethynyl, and (silyl)ethynyl derivatives **6j**–**6l** were also accessible (Table 2). Due to the potential instability, 1,3-dialkylisobenzofurans have been typically used by in situ generation from appropriate precursors or specially stabilized by steric protection, e.g. incorporating isobenzofuran into an alicyclophane macrocycle.[11] Fortunately, however, isobenzofuran **6k**, *alkynylogous* form[12] of the 1,3-dicyclohexylisobenzofuran, which would have an analogous electronic effect as with 1,3-dialkylisobenzofurans, could be carefully purified by silica gel column chromatography under Ar atmosphere.[10]

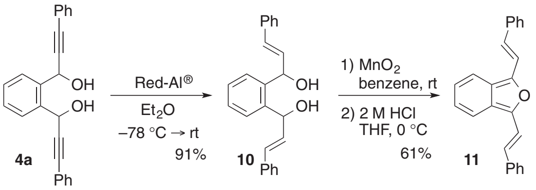
The unsymmetrical isobenzofurans were also efficiently accessible (Table 3). Taking advantage of the lower reactivity of the formyl group in monoadduct **2a** in comparison with **1** (vide supra), two alkynyl groups were selectively introduced by sequential addition of two kinds of alkynyllithiums to **1**, affording unsymmetrical diols **8a**–**8e**. Selective mono-oxidation of diols **8a**–**8e** was again achieved by using MnO_2 (1.2 equiv, toluene, rt), affording keto-alcohols (structure not shown) as a mixture of structural isomers (ca. 1:1), which were smoothly converted to unsymmetrical isobenzofurans **9a**–**9e** in good yields, respectively. As for the preparation of unsymmetrical isobenzofuran **9b**, this successive protocol including one-pot nucleophilic additions of two kinds of alkynyllithiums to **1** gave the high yield of the desired product **9b** and a very small amount of symmetrical isobenzofuran **6a**. Unfortunately, however, they could not be separated by silica gel column chromatography. In such a case, monoadducts **2a** and **3a** were purified before performing the second nucleophilic addition to avoid the incorporation of the symmetrical product at the final stage.

Table 3. Symmetrical 1,3-bis(arylethynyl)isobenzofurans



Entry^a	Ar^1 and Ar^2	Yield of **8**/%	Yield of **9**/%
1		78 (**8a**)	85 (**9a**)
2		78 (**8b**)	89 (**9b**)
3		92 (**8c**)	58 (**9c**)
4		87 (**8d**)	72 (**9d**)
5		92 (**8e**)	82 (**9e**)

^{a}THF, −78 °C. ^{b}THF, −78 → 0 °C. ^{c}1.2 equiv of MnO$_2$ in toluene at rt. ^{d}THF, 0 °C.



Scheme 4. Synthesis of 1,3-dialkenylisobenzofuran.

Moreover, a significant point to be emphasized is that *bis(arylethenyl)isobenzofuran*, a novel π-extended isobenzofuran, was firstly synthesized through the successive processes (Scheme 4). Starting from propargyl alcohol **4a**, double hydroalumination[13] by treatment with Red-Al® (Et$_2$O, −78 °C → rt), cleanly gave the high yield of bis-alcohol **10**, which cannot be straightforwardly obtained from our previous method (Scheme 1). Subsequent two-step protocols including the selective mono-oxidation of diol **10** to keto-alcohol gave isobenzofuran **11** in 61% yield. As for the stability, **11** can be stored in the solid state in a refrigerator for a several months, while it is readily decomposed in a no degassed solution.

The absorption and fluorescence spectra of selected isobenzofurans were measured in chloroform (Figures 1 and 2). 1,3-Bis(phenylethynyl)isobenzofuran (**6a**) has its absorption maximum at 424 nm and emission maximum at 484 nm with excellent fluorescence quantum yield (Φ_{F} 0.91), which are slightly red-shifted in comparison with 1,3-diphenylisobenzofuran (λ_{abs} 415 nm, λ_{em} 482 nm),[14] indicating the small effect on the photophysical properties by insertion of the two alkynyl groups. The absorption and emission spectra of less π-conjugated isobenzofuran **6k** were blue-shifted to 386 and 443 nm, respectively, which exhibited a lower fluorescence quantum yield than that of **6a** (Φ_{F} 0.62). Cyclohexenyl-substituted isobenzofuran **6j** showed a similar trend to **6a** in both spectra, although the fluorescence quantum yield was low (Φ_{F} 0.32). In sharp contrast, 1,3-bis(phenylethenyl)isobenzofuran **11**, the alkenyl congener of **6a**, showed a broad absorption band ranging from 380 to 530 nm, and peaking at 480 nm. The Stokes shift of **11** was increased to 88 nm and the emission peak was observed at 568 nm with a moderate fluorescence yield (Φ_{F} 0.48). In this manner, π-extension by ethenylation significantly affects the photophysical properties, and thus, these newly prepared derivatives would be promising probes for biological applications.[15]

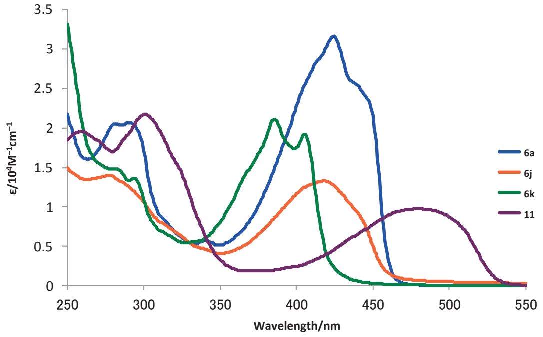


Figure 1. UV–vis absorption spectra of isobenzofuran.

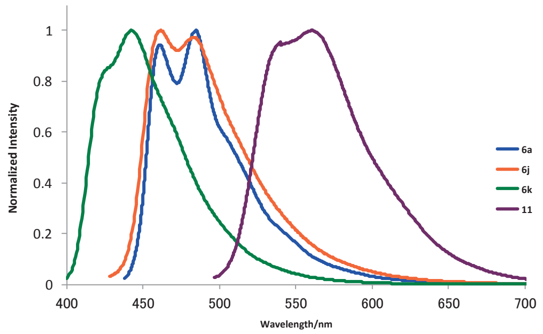


Figure 2. Fluorescence spectra of isobenzofuran.

In summary, we developed a new synthetic route to symmetrical and unsymmetrical 1,3-dialkynylisobenzofurans by sequential additions of *o*-phthalaldehyde with two identical or different alkynyllithium. This efficient synthetic method enables us to prepare new π-extended 1,3-dialkenylisobenzofurans. Further studies on synthetic applications and physical properties of these attractive molecules are currently in progress.

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Supporting Information is available on http://dx.doi.org/10.1246/cl.160884.

References and Notes

1. For reviews, see: a) A. O. Patil, A. J. Heeger, F. Wudl, *Chem. Rev.* **1988**, *88*, 183. b) J. Roncali, *Chem. Rev.* **1997**, *97*, 173. c) R. Rodrigo, *Tetrahedron* **1988**, *44*, 2093. d) W. Friedrichsen, *Adv. Heterocycl. Chem.* **1980**, *26*, 135. e) O. Peters, W. Friedrichsen, *Trends Heterocycl. Chem.* **1995**, *4*, 217. f) W. Friedrichsen, *Adv. Heterocycl. Chem.* **1999**, *73*, 1.
2. For selective examples of the syntheses of isobenzofuran, see: a) G. Wittig, L. Pohmer, *Chem. Ber.* **1956**, *89*, 1334. b) M. P. Cava, M. J. Mitchell, A. A. Deana, *J. Org. Chem.* **1960**, *25*, 1481. c) R. N. Warrener, *J. Am. Chem. Soc.* **1971**, *93*, 2346. d) J. T. Sharp, C. E. D. Skinner, *Tetrahedron Lett.* **1986**, *27*, 869. e) Y. Kuninobu, Y. Nishina, C. Nakagawa, K. Takai, *J. Am. Chem. Soc.* **2006**, *128*, 12376. f) D.-T. Hsu, C.-H. Lin, *J. Org. Chem.* **2009**, *74*, 9180. g) Y. Nishina, T. Kida, T. Ureshino, *Org. Lett.* **2011**, *13*, 3960.
3. For synthetic utility of isobenzofuran, see: a) G. Wittig, A. Krebs, *Chem. Ber.* **1961**, *94*, 3260. b) T. Sasaki, K. Kanematsu, K. Hayakawa, M. Sugiura, *J. Am. Chem. Soc.* **1975**, *97*, 355. c) W. C. Christopfel, L. L. Miller, *J. Org. Chem.* **1986**, *51*, 4169. d) H. N. C. Wong, *Acc. Chem. Res.* **1989**, *22*, 145. e) Y.-M. Man, T. C. W. Mak, H. N. C. Wong, *J. Org. Chem.* **1990**, *55*, 3214. f) P. Binger, P. Wedemann, R. Goddard, U. H. Brinker, *J. Org. Chem.* **1996**, *61*, 6462. g) D. Jiang, J. W. Herndon, *Org. Lett.* **2000**, *2*, 1267. h) T. Ernet, A. H. Maulitz, E.-U. Würthwein, G. Haufe, *J. Chem. Soc., Perkin Trans. 1* **2001**, 1929. i) K. Mikami, H. Ohmura, *Org. Lett.* **2002**, *4*, 3355. j) S.-H. Chan, C.-Y. Yick, H. N. C. Wong, *Tetrahedron* **2002**, *58*, 9413. k) Y. Luo, J. W. Herndon, *Organometallics* **2005**, *24*, 3099. l) J. E. Rainbolt, G. P. Miller, *J. Org. Chem.* **2007**, *72*, 3020.
4. a) S. T. Meek, E. E. Nesterov, T. M. Swager, *Org. Lett.* **2008**, *10*, 2991. b) H. Zhang, A. Wakamiya, S. Yamaguchi, *Org. Lett.* **2008**, *10*, 3591.
5. T. Hamura, R. Nakayama, *Chem. Lett.* **2013**, *42*, 1013.
6. K. Asahina, S. Matsuoka, R. Nakayama, T. Hamura, *Org. Biomol. Chem.* **2014**, *12*, 9773.
7. For our synthetic application of isobenzofurans to polyacene derivatives, see: a) S. Eda, T. Hamura, *Molecules* **2015**, *20*, 19449. b) R. Akita, K. Kawanishi, T. Hamura, *Org. Lett.* **2015**, *17*, 3094. c) S. Eda, F. Eguchi, H. Haneda, T. Hamura, *Chem. Commun.* **2015**, *51*, 5963. d) H. Haneda, S. Eda, M. Aratani, T. Hamura, *Org. Lett.* **2014**, *16*, 286.
8. Product ratio (**2a**/**3a**) was depending on the conditions of purification. Indeed, keto-alchohol **2a** was partially isomerized to lactol **3a** during the purification by silica gel column chromatography. For details, see Supporting Information.
9. For related double nucleophilic additions of alkynyllithiums to phthalaldehyde, see: a) D. Rodríguez, L. Castedo, D. Domínguez, C. Saá, *Org. Lett.* **2003**, *5*, 3119. b) Y.-C. Lin, C.-H. Lin, *Org. Lett.* **2007**, *9*, 2075. c) Y. Liu, S. Zhou, G. Li, B. Yan, S. Guo, Y. Zhou, H. Zhang, P. G. Wang, *Adv. Synth. Catal.* **2008**, *350*, 797.
10. For details, see Supporting Information.
11. a) S. L. Crump, B. Rickborn, *J. Org. Chem.* **1984**, *49*, 304. b) C. P. Casey, N. A. Strotman, I. A. Guzei, *Beilstein J. Org. Chem.* **2005**, *18*, 1. c) I. Saito, A. Nakata, T. Matsuura, *Tetrahedron Lett.* **1981**, *22*, 1697. d) R. N. Warrener, M. Shang, D. N. Butler, *Chem. Commun.* **2001**, 1550.
12. B. Xu, G. B. Hammond, *Synlett* **2010**, 1442.
13. a) E. J. Corey, H. A. Kirst, J. A. Katzenellenbogen, *J. Am. Chem. Soc.* **1970**, *92*, 6314. b) K. Ohmori, T. Suzuki, K. Taya, D. Tanabe, T. Ohta, K. Suzuki, *Org. Lett.* **2001**, *3*, 1057.
14. a) R. Adams, M. H. Gold, *J. Am. Chem. Soc.* **1940**, *62*, 2038. b) J. Jacq, S. Tsekhanovich, M. Orio, C. Einhorn, J. Einhorn, B. Bessières, J. Chauvin, D. Jouvenot, F. Loiseau, *Photochem. Photobiol.* **2012**, *88*, 633.
15. D. Song, S. Cho, Y. Han, Y. You, W. Nam, *Org. Lett.* **2013**, *15*, 3582.