



Regioselectivity of Diels–Alder reactions between 6,7-dehydrobenzofuran and 2-substituted furans

Neil Brown, Keith R. Buszek*

Department of Chemistry, University of Missouri-Kansas City, 205 Spencer Chemical Laboratories, 5100 Rockhill Road, Kansas City, MO 64110, USA

The University of Kansas Center of Excellence in Chemical Methodologies and Library Development, Structural Biology Center, 2121 Simons Drive, Lawrence, KS 66047, USA

ARTICLE INFO

Article history:

Received 11 February 2011

Revised 24 May 2012

Accepted 24 May 2012

Available online 30 May 2012

Keywords:

Arynes

Benzofurans

Furans

Dehydrobenzofuran

Benzofuranyne

Indole

Indolyne

Diels–Alder

Cycloaddition

Regioselective

ABSTRACT

We describe the first report of the generation of 6,7-dehydrobenzofuran(6,7-benzofuranyne) from 6,7-dihalobenzofurans via metal–halogen exchange and elimination, in a manner similar to our previous work with 6,7-indole arynes. This benzofuranyne undergoes highly regioselective Diels–Alder cycloadditions with 2-substituted furans.

© 2012 Elsevier Ltd. All rights reserved.

The existence of the benzyne reactive intermediate **1** has been known since 1953 (Fig. 1).¹ Since that initial landmark account, several other metastable benzenoid arynes have appeared in the literature, including the naphthalynes **2a–b** and the pyridynes **3a–b**.² Over the last several years our group first^{3a–f} followed by the Garg laboratory^{4a–f} published numerous reports involving arynes derived from the three benzenoid positions of the ubiquitous indole nucleus (i.e., indolynes, **4a–c**, Fig. 1).

Indolynes have already demonstrated their value in the synthesis of complex natural products,^{3b,d,4e} and have also been used recently in the construction of unique polycyclic indole libraries.^{3f} The regioselectivity within various indolyne reaction manifolds has also been explored by our group and others.^{3,4} Our investigations in particular revealed, *inter alia*, that 6,7-indolynes show remarkable regioselectivity in Diels–Alder cycloadditions with 2-substituted furans (Scheme 1).^{3c,e}

The observed contrasteric regioselectivity has been rationalized in terms of the highly polarized nature of the 6,7-indolyne which imparts substantial asynchronous electrophilic character to the initial bond-forming step in the cycloaddition reaction.^{3e}

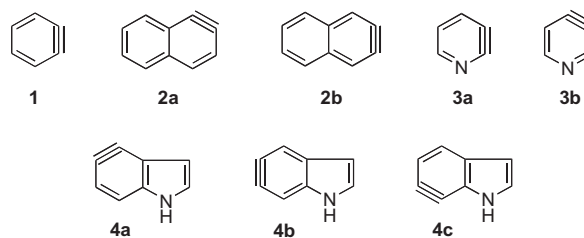
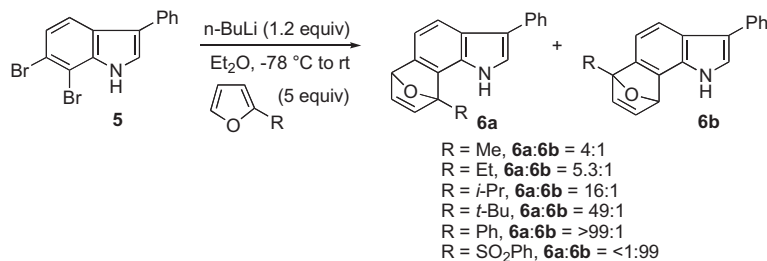


Figure 1. Benzyne and other common and recent arynes.

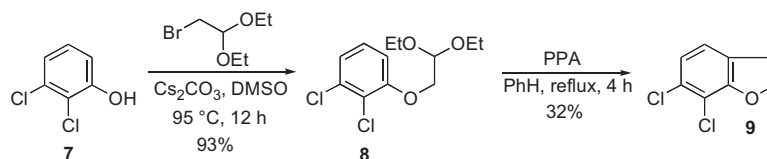
Surprisingly, arynes derived from the common heterocycle benzofuran are apparently unknown. Just as the indole nucleus appears in many natural products and commercial drugs,⁵ the related benzofuran moiety is also present in many natural products⁶ and therapeutically useful entities including the antiarrhythmia drug dronedarone (marketed in the United States by Sanofi–Aventis as Multaq).⁷ Benzofuran derived arynes would offer a rapid entry into novel functionalized and annulated benzofurans. We are pleased to report the first generation of 6,7-benzofuran arynes (6,7-benzofuranynes) and their regioselective cycloaddition with 2-substituted furans.

* Corresponding author. Tel.: +1 816 235 2292; fax: +1 816 235 5502.

E-mail address: buszekk@umkc.edu (K.R. Buszek).



Scheme 1. Regioselectivity in 6,7-indolynes cycloadditions.



Scheme 2. Synthesis of 6,7-dichlorobenzofuran.

In our earlier work with indolynes, we chose to generate the reactive intermediate via metal–halogen exchange, utilizing *o*-dihalo substituted indoles.³ Based on our success with this general method, we attempted to prepare the 6,7-benzofuranyne in the same manner. Our initial objective was the synthesis of 6,7-dichlorobenzofuran (Scheme 2).

Commercially available 2,3-dichlorophenol was alkylated with bromoacetaldehyde diethyl acetal with Cs₂CO₃ in DMSO to give **8** in 93% yield.⁸ Many conditions were investigated to effect the cyclocondensation to give 6,7-dichlorobenzofuran. After much experimentation optimal results were achieved using polyphosphoric acid under Dean–Stark conditions to give the desired product **9** in 32% yield.⁹

Since the metal–halogen exchange of *o*-dichloroindoles required the use of excess *t*-BuLi, we also sought the synthesis of the corresponding 6,7-dibromobenzofuran (Scheme 3) which would be amenable to more facile aryne formation via *n*-BuLi. Thus, commercially available 3-bromophenol was first protected as its carbamate **11** with *N,N*-diethylcarbamoyl chloride in pyridine in quantitative yield.¹⁰ The *ortho* bromine was then introduced with 1,2-dibromoethane via directed *ortho* metallation (DoM)¹¹ using LiTMP to afford the desired *o*-dibromobenzene **12** in 75% yield.

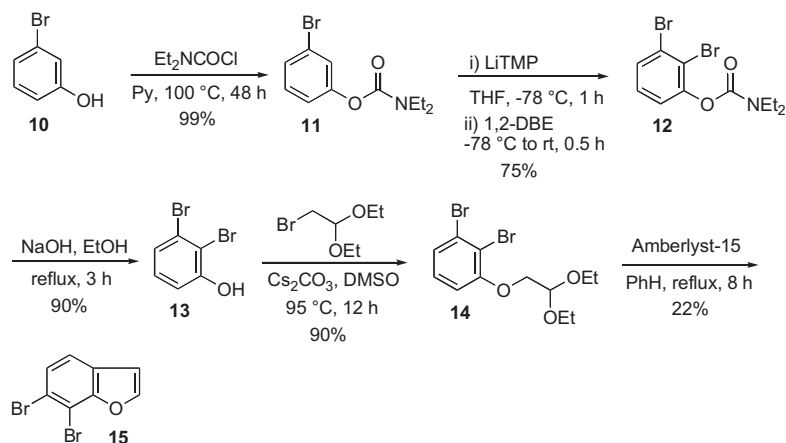
The carbamate was hydrolyzed in ethanolic sodium hydroxide to give 2,3-dibromophenol **13** in 90% yield. Alkylation with bromoacetaldehyde diethyl acetal as described above produced the desired

intermediate **14** in 90% yield. Cyclocondensation was achieved in this case with Amberlyst-15 resin under the same conditions to give 6,7-dibromobenzofuran **15** in 22% yield.¹² Attempts to optimize the yield with various other conditions (e.g., PPA as before) unfortunately gave no improvement. We attribute the modest yields in both cyclocondensation reactions to the slow reaction kinetics coupled with a self-condensation reaction that dominates the product distribution with increased but necessary reaction times. This cyclocondensation is the subject of continuing investigations.

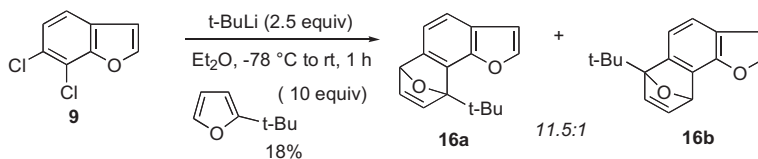
With the necessary aryne precursors in hand, the generation of the 6,7-dehydrobenzofuran via metal–halogen exchange and elimination was attempted. Thus, the reaction of *o*-dichlorobenzofuran **9** in the presence of excess 2-*t*-butylfuran and 2.5 equiv of *t*-BuLi in ether at –78 °C gave an 11.5:1 mixture of cycloadducts **16ab** albeit in only 18% isolated yield (Scheme 4). Changing the reaction solvent to THF decreased the yield to just 5% but without affecting the regioisomeric ratio.

We previously found that with 6,7-indole arynes, the presence of excess *t*-BuLi yielded primarily regioselective and exoselective ring-opened cycloadducts in high yield (Scheme 5).^{3c} Interestingly, no analogous ring-opened products were detected with the putative 6,7-dehydrobenzofuran cycloadducts.

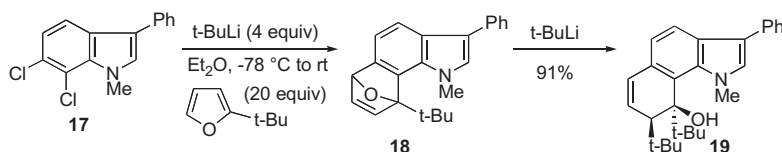
We also found that 6,7-indolynes could be prepared from the corresponding 6,7-dibromoindole in consistently much higher yield and without concomitant ring opening using a slight excess of *n*-BuLi.



Scheme 3. Synthesis of 6,7-dibromobenzofuran.



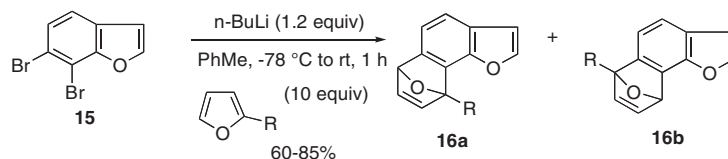
Scheme 4. Generation of 6,7-dehydrobenzofuran and trapping with 2-*tert*-butylfuran.



Scheme 5. Ring opening of the 6,7-indole aryne cycloadduct with *t*-BuLi.

Table 1

Regioselective Diels–Alder cycloadditions between 6,7-dehydrobenzofuran and 2-substituted furans



Entry	Furan, R	16a	16b	Yield (%)
1	Me	65	35	72
2	Et	78	22	85
3	<i>n</i> -Pr	73	27	83
4	<i>n</i> -Bu	75	25	60
5	<i>t</i> -Bu	92	8	62
6	Ph	>99	<1	63
7	SO ₂ Ph	<1	>99	72

In accordance with this observation, 6,7-dibromobenzofuran was subjected to aryne generation and trapping as before with 1.2 equiv of *n*-BuLi in ether or toluene (Scheme 6). Gratifyingly this gave a much improved 62% yield of cycloadducts, again as an 11.5:1 mixture of regioisomers. The nature of the regiochemical outcome is that the contrasteric product **16a** dominates.

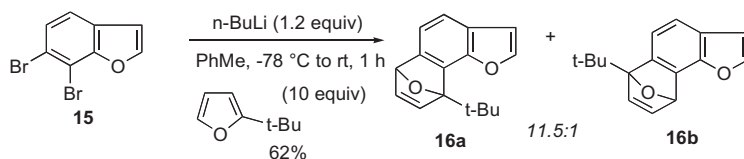
This experimental observation can be explained by our aforementioned hypothesis that polarized arynes of this type, similar to the 6,7-indolyne, imparts substantial asynchronous electrophilic character to the initial bond forming step with asymmetrically substituted dienes.^{3e}

In a previous report we described the calculated free energies of activation in Diels–Alder cycloadditions with indolynes, benzofuranynes, and benzothiophenyne with 2-substituted furans.^{3e} Low barriers to reaction are predicted in either gas phase or continuum solution leading to the contrasteric product with 2-*tert*-butylfuran in these three systems. The benzofuran case was predicted to have the lowest energies of activation by a small margin as expected given the greater electrophilicity of this heterocycle. This prediction is now confirmed in the case of 6,7-benzofuranyne by the experimental results presented here.

The previously reported regiochemical outcome of 6,7-indolyne Diels–Alder reactions with various 2-substituted furans was compared to the similar reaction with 6,7-benzofuranyne (Table 1). As is shown, the results parallel those seen in the 6,7-indolyne case except that it was generally found that the regioisomeric ratios were lower across the board with 6,7-benzofuranyne.

The exceptions were entries 6 and 7 in which 2-phenylfuran gave only the contrasteric isomer, and 2-phenylsulfonylfuran gave only the opposite isomer, respectively. These results are consistent with the view that electron-donating groups favor the more sterically crowded product while electron-withdrawing groups give the opposite regioisomer.

In conclusion we have provided the first example of an aryne derived from 6,7-dihalobenzofuran, namely, 6,7-dehydrobenzofuran (6,7-benzofuranyne), via metal–halogen exchange and elimination. As predicted, this aryne also exhibits remarkable regioselectivity in reactions with 2-substituted furans. Further investigations into this aryne and the related 6,7-dehydrobenzothiophene are in progress and the results will be reported in due course.



Scheme 6. Generation and trapping of 6,7-dehydrobenzofuran from 6,7-dibromobenzofuran.

Acknowledgments

We acknowledge support of this work by the National Institutes of Health, Grant No. R01 GM069711 (K.R.B.). We also acknowledge additional support of this work by the National Institutes of Health, the University of Kansas Chemical Methodologies and Library Development Center of Excellence (KU-CMLD), NIGMS Grant P50 GM069663. We thank Mr. Ben Neuenswander (KU-CMLD) for providing select high-resolution mass spectral data. This paper is warmly dedicated to Professor Michael E. Jung on the occasion of his 65th birthday.

Supplementary data

Supplementary data (a general experimental procedure for the generation and Diels–Alder trapping of 6,7-dehydrobenzofuran and select HRMS and NMR data) associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.tetlet.2012.05.118>.

References and notes

- (a) Roberts, J. D.; Simmons, H. E., Jr.; Carlsmith, L. A.; Vaughan, C. W. *J. Am. Chem. Soc.* **1953**, *75*, 3290–3291; (b) Roberts, J. D.; Semenow, D. A.; Simmons, H. E., Jr.; Carlsmith, L. A. *J. Am. Chem. Soc.* **1956**, *78*, 601–611.
- For a review of arynes, see: (a) Gampe, C. M.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2012**, *51*, 3766–3778; (b) Hoffmann, R. W. *Dehydrobenzene and Cycloalkynes*; Academic: New York, 1967; (c) Pellissier, H.; Santelli, M. *Tetrahedron* **2003**, *59*, 701–730; (d) Wenk, H. H.; Winkler, M.; Sander, W. *Angew. Chem., Int. Ed.* **2003**, *42*, 502–528; (e) Reinecke, M. G. *Tetrahedron* **1982**, *38*, 427–498; Pyridynes: (f) Kauffmann, T.; Boettcher, F. P. *Angew. Chem.* **1961**, *73*, 65–66; (g) Martens, R. J.; den Hertog, H. J. *Tetrahedron Lett.* **1962**, 643–645; Naphthalynes: (h) Bunnett, J. F.; Brotherton, T. K. *J. Org. Chem.* **1958**, *23*, 904–906; (i) Huisgen, R.; Zirngibl, L. *Chem. Ber.* **1958**, *91*, 1438–1452.
- (a) Buszek, K. R.; Luo, D.; Kondrashov, M.; Brown, N.; VanderVelde, D. *Org. Lett.* **2007**, *9*, 4135–4137; (b) Buszek, K. R.; Brown, N.; Luo, D. *Org. Lett.* **2009**, *11*, 201–204; (c) Brown, N.; Luo, D.; VanderVelde, D.; Yang, S.; Brassfield, A.; Buszek, K. R. *Tetrahedron Lett.* **2009**, *50*, 63–65; (d) Brown, N.; Luo, D.; Decapo, J. A.; Buszek, K. R. *Tetrahedron Lett.* **2009**, *50*, 7113–7115; (e) Garr, A. N.; Luo, D.; Brown, N.; Cramer, C. J.; Buszek, K. R.; VanderVelde, D. *Org. Lett.* **2010**, *12*, 96–99; (f) Thornton, P. D.; Brown, N.; Hill, D.; Neuenswander, B.; Lushington, G. H.; Santini, C.; Buszek, K. R. *ACS Comb. Sci.* **2011**, *13*, 443–448.
- (a) Bronner, S. M.; Bahnck, K. B.; Garg, N. K. *Org. Lett.* **2009**, *11*, 1007–1010; (b) Tian, X.; Hutters, A. D.; Douglas, C. J.; Garg, N. K. *Org. Lett.* **2009**, *11*, 2349–2351; (c) Cheong, P. H.-Y.; Paton, R. S.; Bronner, S. M.; Im, G.-Y. J.; Garg, N. K.; Houk, K. N. *J. Am. Chem. Soc.* **2010**, *132*, 1267–1269; (d) Im, G.-Y. J.; Bronner, S. M.; Goetz, A. E.; Paton, R. S.; Cheong, P. H.-Y.; Houk, K. N.; Garg, N. K. *J. Am. Chem. Soc.* **2010**, *132*, 17933–17944; (e) Bronner, S. M.; Goetz, A. E.; Garg, N. K. *J. Am. Chem. Soc.* **2011**, *133*, 3832–3835; (f) Goetz, A. E.; Bronner, S. M.; Cisneros, J. D.; Melamed, J. M.; Paton, R. S.; Houk, K. N.; Garg, N. K. *Angew. Chem.* **2012**, *124*, 2812–2816.
- For a recent review see: Kochanowska-Karamyan, A. J.; Hamann, M. T. *Chem. Rev.* **2010**, *110*, 4489–4497.
- McCallion, G. D. *Curr. Org. Chem.* **1999**, 67–76.
- Hoy, S. M.; Keam, S. J. *Drugs* **2009**, *69*, 1647–1663.
- Wei, L.; Jianchang, L.; DeVincentis, D.; Mansour, T. S. *Tetrahedron* **2008**, *64*, 7871–7876.
- Barker, P.; Finke, P.; Thompson, K. *Synth. Commun.* **1989**, *19*, 257–265.
- Dallaire, C.; Kolber, I.; Gingras, M. *Org. Synth.* **2002**, *78*, 42–50.
- For a review of DoM see: Snieckus, V. *Chem. Rev.* **1990**, *90*, 879–933.
- Dixit, M.; Sharon, A.; Maulik, P. R.; Goel, A. *Synlett* **2006**, 1497–1502.