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Benzotrifuranone: Synthesis, Structure, and Access to Polycyclic Heteroaromatics

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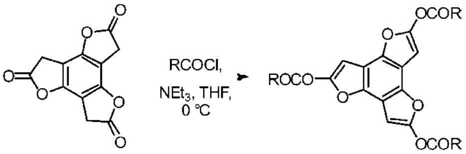
ABSTRACT



Functionalized benzotrifurans can be accessed in one efficient acylation step from previously unreported benzotrifuranone. DFT calculations have confirmed the aromaticity of the heteroaromatic system and determined its electronic structure that is relevant to applications in materials and supramolecular chemistry.

Benzofuranone **1** (Figure 1) is a common substructure in a number of natural products,[1] pigments,[2] and polymer processing stabilizers (e.g., Irganox HP-136) and boasts a rich chemical profile. Among the well-characterized reactions of **1** is O-acylation, effected by a weak base and suitable electrophile,[3] to afford the aromatic[4] benzofuran system **2** (Figure 1). It is surprising that this chemistry has yet to be extended to multiple lactone rings around a central arene scaffold where it could rapidly produce polyfuran ring systems, motifs undergoing a resurgence for broad-based materials applications.[5] In particular demand are efficient synthetic approaches to fused C_3-symmetric heteroaromatics that can display useful self-assembly and electronic properties.[6] Along these lines, we demonstrate how a simple deprotonation/acylation sequence can efficiently access benzotrifurans, sparsely studied molecules that are otherwise prepared via relatively low-yielding and high-temperature cyclotrimerization reactions.[6b,7]

The work begins with the synthesis of previously unknown benzotrifuranone **3** (Scheme 1)—drawing on our synthetic experience with phloroglucinol (1,3,5-trihydroxybenzene)[8]—

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(1) See, for example:(a) Wu, B.; He, S.; Wu, X.-D.; Wu, D.-K.; Pan, Y.-J. *Helv. Chim. Acta* **2007**, *90*, 1586–1592. (b) Kwon, Y.-J.; Sohn, M.-J.; Zheng, C.-J.; Kim, W.-G. *Org. Lett.* **2007**, *9*, 2449–2451. (c) Ge, H. M.; Zhu, C. H.; Shi, D. H.; Zhang, L. D.; Xie, D. Q.; Yang, J.; Ng, S. W.; Tan, R. X. *Chem.—Eur. J.* **2008**, *14*, 376–381.

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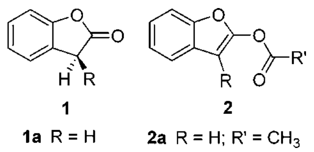
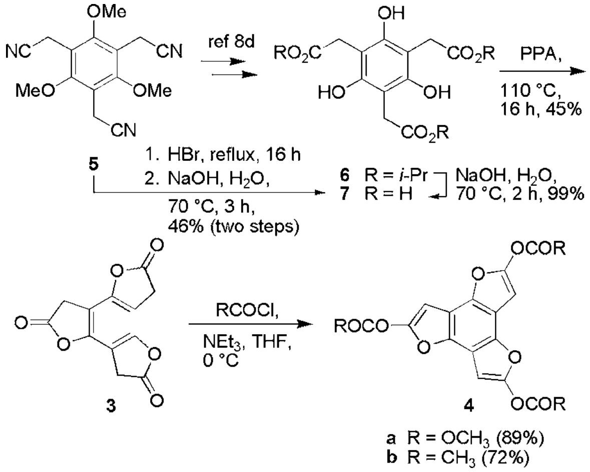


Figure 1. Benzofurans **2** can be accessed via O-acylation of benzofuranones **1**. Derivatives shown have been prepared as model compounds in the current study.

Scheme 1. Synthesis of Benzotrifuranone **3** and Heteroaromatic Benzotrifurans **4**



as the immediate precursor to representative benzotrifuran derivatives **4**. Demonstrated for **3** are rare polar crystal formation and subtle electronic coupling between the three lactone rings, properties incommensurate with its simple structure and high symmetry. Subsequently shown is O-acylation of **3** using representative electrophiles and efficient generation of the benzotrifuran core of **4**. Spectroscopic measurements and DFT calculations go on to address the aromaticity and delocalized electronic structure of the polycyclic system and confirm features prerequisite for materials applications of the molecules.

Our synthetic approach to **3** begins from triester **6** (available from **5** in three steps as reported previously[8d]) that is easily saponified to give its corresponding triacid **7** (Scheme 1). Intermediate **7** can alternatively be prepared more directly via dimethylation and hydrolysis of **5**, as shown. Subsequent dehydrative lactonization of **7** with polyphosphoric acid (PPA) affords a modest, but reproducible, supply of benzotrifuranone **3** on a gram scale. The identity of highly symmetric **3** is quickly confirmed by NMR analysis (DMSO-d_6) where it shows a single peak in the ^{1}H NMR spectrum at $\delta = 4.01$ ppm for the six chemically equivalent methylene protons and just four peaks by ^{13}C NMR analysis ($\delta = 30.1$ (CH$_2$), 101.9 ($\text{O}-\text{C}{=}\underline{\text{C}}$), 148.8 ($\text{O}-\underline{\text{C}}{=}\text{C}$), and 173.4 ($\text{C}{=}\text{O}$) ppm).[9] Further proof is available from X-ray crystallographic analysis (vide infra). The compound is isolated as an off-white powder that is reasonably soluble in organic solvents that include DMSO, THF, CH_2Cl_2, and $CHCl_3$. Alternative strategies to synthesize **3** are conceivable (and have been attempted) based on those reported for simpler **1** in the literature. Scheme 1 emerges as particularly successful since it reduces contamination by partially cyclized intermediates (e.g., benzofuranones and benzodifuranones) that are difficult to separate from or further convert to the target.[10]

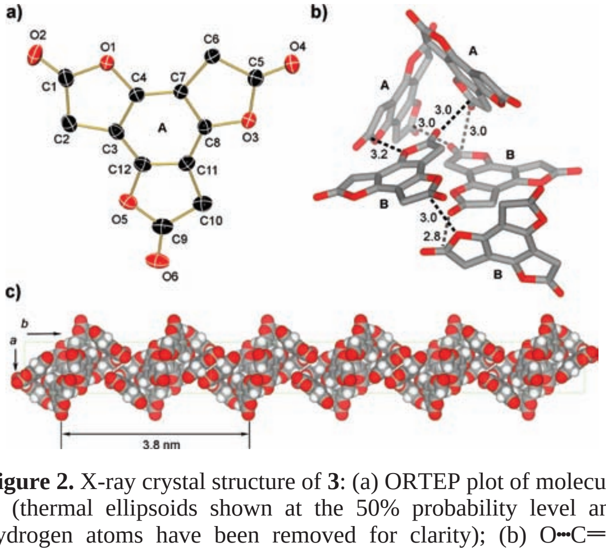


Figure 2. X-ray crystal structure of **3**: (a) ORTEP plot of molecule **A** (thermal ellipsoids shown at the 50% probability level and hydrogen atoms have been removed for clarity); (b) $\text{O}\cdots\text{C}{=}\text{O}$ interactions between molecules **A** and **B** that define the molecular packing (distances in Å); (c) helical arrangement of **3** along the *b* axis.

A single crystal of **3** could be obtained by slow diffusion of pentane into its chloroform solution; the X-ray crystal structure is shown in Figure 2, and experimental and calculated (at the RB3LYP/6-311+G* level) structural data are given in Table S6 (Supporting Information). Most surprisingly, the crystal is *noncentrosymmetric* and occupies the orthorhombic space group *aba2* (point group *mm2*); the

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(6) See, for example:(a) Destrade, C.; Tinh, N. H.; Mamlok, L.; Malthete, J. *Mol. Cryst. Liq. Cryst.* **1984**, *114*, 139–150. (b) Destrade, C.; Tinh, N. H.; Gasparoux, H.; Mamlok, L. *Liq. Cryst.* **1987**, *2*, 229–233. (c) Nicolas, Y.; Blanchard, P.; Levillain, E.; Allain, M.; Mercier, N.; Roncali, J. *Org. Lett.* **2004**, *6*, 273–276. (d) Roncali, J.; Leriche, P.; Cravino, A. *Adv. Mater.* **2007**, *19*, 2045–2060. (e) Patra, A.; Wijsboom, Y. H.; Shimon, L. J. W.; Bendikov, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 8814–8818. (f) Lai, W.-Y.; He, Q.-Y.; Zhu, R.; Chen, Q.-Q.; Huang, W. *Adv. Funct. Mater.* **2008**, *18*, 265–276. (g) Talarico, M.; Termine, R.; García-Frutos, E. M.; Omenat, A.; Serrano, J. L.; Gómez-Lor, B.; Golemme, A. *Chem. Mater.* **2008**, *20*, 6589–6591. (h) Rose, K. G.; Jaber, D. A.; Gondo, C. A.; Hamilton, D. G. *J. Org. Chem.* **2008**, *73*, 3950–3953. (i) Kashiki, T.; Shinamura, S.; Kohara, M.; Miyazaki, E.; Takimiya, K.; Ikeda, M.; Kuwabara, H. *Org. Lett.* **2009**, *11*, 2473–2475. (j) Taerum, T.; Lukoyanova, O.; Wylie, R. G.; Perepichka, D. F. *Org. Lett.* **2009**, *11*, 3230–3233. (k) Wu, Y.-T.; Tai, C.-C.; Lin, W.-C.; Baldridge, K. K. *Org. Biomol. Chem.* **2009**, *7*, 2748–2755.

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(8) (a) Li, H.; Homan, E. A.; Lampkins, A. J.; Ghiviriga, I.; Castellano, R. K. *Org. Lett.* **2005**, *7*, 443–446. (b) Lampkins, A. J.; Abdul-Rahim, O.; Li, H.; Castellano, R. K. *Org. Lett.* **2005**, *7*, 4471–4474. (c) Lampkins, A. J.; Abdul-Rahim, O.; Castellano, R. K. *J. Org. Chem.* **2006**, *71*, 5815–5818. (d) Lampkins, A. J.; Li, Y.; Al Abbas, A.; Abboud, K. A.; Ghiviriga, I.; Castellano, R. K. *Chem.—Eur. J.* **2008**, *14*, 1452–1463.

result defines a relatively rare example of polar crystal formation from an achiral, C_3-symmetric species (vide infra).[11] Two slightly different molecules comprise the unit cell. In one, **A**, the central benzene ring and three fused lactone rings are essentially planar; the most that any non-hydrogen ring-containing atom deviates from the C3−C4−C7 plane is 0.05 Å. The second molecule, **B**, is slightly distorted with respect to its central six-membered and peripheral five-membered rings; here the most that any non-hydrogen ring-containing atom is removed from the C3−C4−C7 plane is 0.18 Å (for C9B). Although these small deviations are not reproduced in electronic structure calculations that predict a planar **3**, the calculated and experimental bond lengths and angles agree within 0.02 Å and 1.5°, respectively (Table S6, Supporting Information). Worth noting, the experimentally determined parameters for **3** are also similar to those reported for simple 5-hydroxy-2(3*H*)benzofuranone (CSD code: BIZCIW)[12] and calculated for **1a**.

The packing structure of **3** (Figures 2b and 2c) is surprisingly devoid of stacking arrangements and is instead dominated by O···C═O dipolar interactions[13] and C−H···O contacts.[14] The former come in two forms: C═O···C═O interactions[15] defined by an O···C distance of 2.8−3.0 Å and an O···C═O angle of 97−107° (approaching the Bürgi−Dunitz angle[16]) and (O═C)O···C═O interactions, also defined by short distances (3.0−3.2 Å) and an O···C═O angle of 76−98°. Most striking is the consequence of these contacts on the packing structure where a helical arrangement develops with a repeat distance defined by the *b* unit cell dimension (37.939(4) Å). Helices are rarely presented by planar, achiral molecules in the context of acentric crystals,[17] although the motifs are relevant to the design of nonlinear optics, ferroelectrics, and electrooptics.[18]

Spectroscopic studies have been performed to further explore the unique structure of **3**. Its IR spectrum (KBr pellet) shows a single C═O stretch (1822 cm^{-1}) that is higher in energy than **1a** (1807 cm^{-1}) and comparable to four-membered ring β-butyrolactone (1825 cm^{-1}; neat[19]); these trends are also reproduced in DFT vibrational frequency calculations.[20] The implied strengthening of the carbonyl π-bond of **3** versus **1a** is further consistent with the ^{1}H and ^{13}C NMR data.[21] Although the electronic effects are subtle and not neatly borne out in the X-ray structural data (Table 1), they likely surface in the chemical reactivity of **3**.[22] The UV/vis spectrum of **3** in CH$_3$CN (Figure 3) shows a strong absorption band at $\lambda_{max} = 215$ nm ($\varepsilon = 22\,400$ M^{-1} cm^{-1}), a shoulder at intermediate energy, and a very weak absorption at lower energy ($\lambda_{max} = 270$ nm; $\varepsilon = 710$ M^{-1} cm^{-1}).[23]

Table 1. Total NICS Values (ppm) Calculated for the Central and Heterocyclic Rings of Benzofuran, **3**, and **4b**[a]

	central ring		heterocyclic ring	
	NICS(0)	NICS(1)	NICS(0)	NICS(1)
benzofuran	−9.96 (−9.96)[b]	−10.98 (−10.99)[b]	−10.23 (−9.56)[b]	−8.40 (−8.26)[b]
3	−10.32	−8.93	−1.43	−1.90
4b	−13.18	−11.28	−10.96	−7.17

[a] NICS values were calculated for the ring centers as defined by the center of mass, NICS(0), and 1 Å above the ring centers, NICS(1). Calculations performed at the RB3LYP/6-311+G* level on RB3LYP/6-311+G* minimized structures. [b] Values reported in ref 4b.

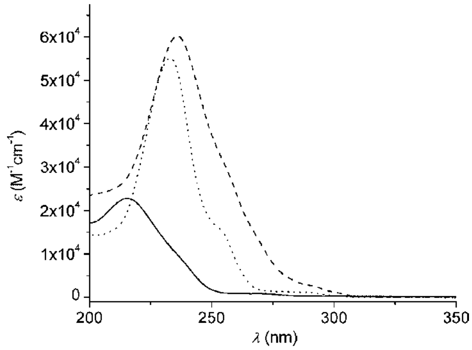

Figure 3. UV/vis absorption spectra of **3** (—), **4a** (····), and **4b** (----) in CH$_3$CN.

Both spectroscopic experiments (e.g., IR) and preliminary calculations have found that the enol tautomers of **3** are unstable (consistent with **1**[24]), even though complete tautomerism would generate the fully aromatic benzotrifuran ring system (vide infra). The aromatic enolate[25] of **3** could

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(9) The corresponding protons for **1a** (Figure 1) appear slightly upfield at $\delta = 3.90$ ppm. The corresponding carbons appear at $\delta = 32.6$, 110.1, 154.1, and 174.4 ppm.

(10) See the Supporting Information for details. A benzodifuranone does appear as a characterized intermediate in the synthesis of triacid **7**.

(11) A search of the Cambridge Structural Database (version 5.30), for example, reveals no C_3-symmetric molecules in the *aba2* space group.

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(18) Nalwa, H. S.; Miyata, S. *Nonlinear Optics of Organic Molecules and Polymers*; CRC Press, Inc.: Boca Raton, 1997.

(19) Iida, M.; Araki, T.; Teranishi, K.; Tani, H. *Macromolecules* **1977**, *10*, 275–284.

(20) Calculated (DFT-RB3LYP/6-311+G*) C═O vibrational frequencies (unscaled): **1a** (1877 cm^{-1}); **3** (1891 cm^{-1}); β-butyrolactone (1909 cm^{-1}).

(21) The NMR data show for **3** versus **1a**: (a) commensurate weakening of the C1−O1 bond (with enhanced δ^- character on O1) and (b) deshielding of the C2 protons.

(22) For example, in terms of ring-opening kinetics with respect to common nucleophiles. Quantitative comparisons of **3** versus **1** are being pursued.

(23) The calculated (ZINDO/S) excitation energy with the largest oscillator strength is identical to the maximum absorption (i.e., 215 nm) and arises from multiple degenerate excitations (see the Supporting Information for details).

(24) Heathcote, D. M.; De Boos, G. A.; Atherton, J. H.; Page, M. I. *J. Chem. Soc., Perkin Trans. 2* **1998**, 535–540.

be generated under mild conditions (NEt_3, THF, 0 °C)[3] and trapped with two test electrophiles, methyl chloroformate and acetyl chloride (Scheme 1), to produce benzotrifurans **4a** and **4b**, respectively.[26] Using **4b** as an example (the data for **4a** is similar), the high symmetry of the product yields a simple ^{1}H NMR spectrum in $CDCl_3$ with two peaks, $\delta = 2.41$ (CH_3) and 6.60 (CH) ppm; the latter resonance is downfield of the equivalent proton for **2a** (Figure 1) that appears at $\delta = 6.34$ ppm.[27] The UV/vis spectra of **4** in CH_3CN (Figure 2) show that the main absorption band (**4a**: $\lambda_{max} = 233$ nm; $\varepsilon = 54\,500$ M^{-1} cm^{-1}; **4b**: $\lambda_{max} = 236$ nm; $\varepsilon = 59\,600$ M^{-1} cm^{-1}) is red-shifted and intensified (~3-fold) relative to **3**, consistent with extension of the benzene conjugation to include the fused furan ring system.[28] The same absorption band is comparably intense but blue-shifted relative to benzotrithiophene ($\lambda_{max} = 263$ nm; $\varepsilon = 70\,600$ M^{-1} cm^{-1} in MeOH).[29] Finally, the extinction coefficient of **4** is significantly enhanced (~5-fold) relative to **2a**.[30]

DFT calculations provide a way to explore the electronic properties of **4**. The aromaticity of **4b** has been probed by calculating its nucleus-independent chemical shifts (NICS).[4b] On the basis of the NICS values (that are large in magnitude), both its central and heterocyclic rings are aromatic, analogous to simple benzofurans (Table 1).[4b] The same calculations on **3** show, expectedly, essentially nonaromatic peripheral heterocyclic rings. Also accessible from calculations are HOMO and LUMO density plots (Figure 4) for the lowest-energy conformation of **4b** (bearing C_{3h} symmetry) that confirm delocalization of π-electron density over the entire benzotrifuran system and a HOMO−LUMO gap (4.77 eV) that is lower than **2a** (4.99 eV) or recently studied benzodifurans.[5i] Taken together, the results bode well for the use of appropriately functionalized versions of **4** as components of self-assembled conjugated materials.[31]

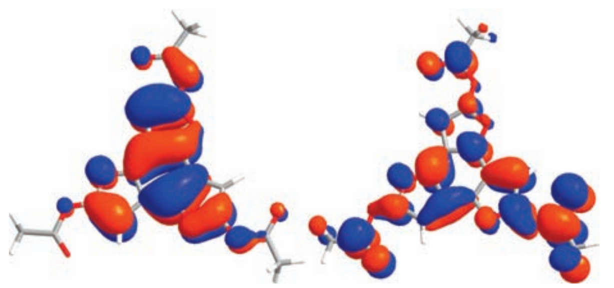

Figure 4. HOMO (left) and LUMO (right) plots of benzotrifuran **4b** calculated from its RB3LYP/6-311+G* optimized geometry.

To conclude, polycyclic heteroaromatic benzotrifurans **4** have been prepared from a versatile C_3-symmetric benzotrifuranone scaffold (**3**) under mild acylation conditions. The synthetic approach presented is suitable for accessing a number of functionalized molecules given the broad availability of alkyl and aryl chloroformates and acyl chlorides; presumably, even other electrophiles will work effectively. Future targets will contribute to the current interest in O-containing fused heteroaromatic systems for optoelectronic and materials applications,[5] frameworks that in many cases show π-stacking and optical properties unique from their more typically explored sulfur congeners.[5i]

Acknowledgment. This work was financially supported by the National Science Foundation CAREER program (CHE-0548003) and the University of Florida. B.G.S. and R.K.C. thank the Center for Nanophase Materials Sciences (CNMS), sponsored by the Division of Scientific User Facilities, U.S. Department of Energy, for resources (user grant CNMS2007-029 to R.K.C.). A.J.L. and M.B.B. were supported by University of Florida Alumni Graduate Fellowships. K.A.A. thanks the National Science Foundation and University of Florida for funding the X-ray crystallography equipment.

Supporting Information Available: Experimental procedures, copies of ^{1}H and ^{13}C NMR spectra for all new compounds, UV/vis, X-ray, and CV (for **4a**) data, and computational details. This material is available free of charge via the Internet at http://pubs.acs.org.

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(25) Bordwell, F. G.; Fried, H. E. *J. Org. Chem.* **1991**, *56*, 4218–4223.

(26) This simple acylation procedure has neither been demonstrated in the literature for derivatives of **1a** nor been performed with **1** (where R = alkyl or aryl) using simple acid chlorides.

(27) See the Supporting Information for the synthesis and characterization of **2a**.

(28) ZINDO/S calculations performed on **4b** predict degenerate transitions at multiple wavelengths (278, 254, 238, and 207 nm). Data have been included in the Supporting Information.

(29) Jayasuriya, N.; Kagan, J.; Owens, J. E.; Kornak, E. P.; Perrine, D. M. *J. Org. Chem.* **1989**, *54*, 4203–4205.

(30) For **2a**: $\lambda_{max} = 245$ nm; $\varepsilon = 12\,000$ M^{-1} cm^{-1}.

(31) Attempts to refine the X-ray diffraction data obtained from needle-like crystals of **4b** have been unsuccessful. A crystal structure of 2,6,10-trimethyl-substituted **4b** has been obtained and shows the anticipated π-stacking (plane-to-plane distance = 3.4 Å) in the context of 1D columns. These data will be reported separately.