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Facile and efficient synthesis of C_3-symmetric benzoxazine: a novel tri-arm molecular scaffold

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ABSTRACT

Six novel C_3-symmetric benzoxazines (**1a–f**) were synthesized via a one-pot condensation, in which twelve covalent bonds were formed up to 96% yield. Two X-ray crystal structures confirmed their proposed conformations and showed their potential as a novel tri-arm molecular scaffold.

With a diverse array of known applications, calixarenes and their derivatives are one of the most useful macrocyclic scaffolds.[1] Their applications include: self-organized nanostructures,[2] supramolecular assemblies,[3] ionophores,[4] as well as sensors for cations,[5] anions,[6] and neutral organic molecules.[7] The versatility of the calixarene scaffold is a result of its preorganized 'chalice' shape,[8] which consists of four phenolic units connected by methylene bridges. Synthetic advances over the last several decades have produced methodology to append various functional groups to the aromatic rings.[1] These groups are selected to interact with specific guest molecules.[9]

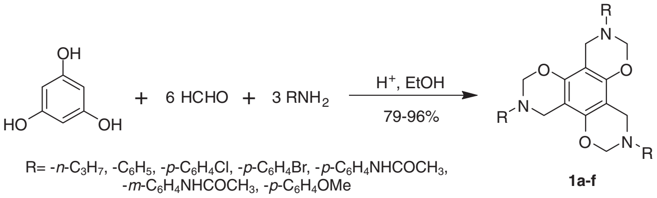
Recently, a new family of bowl-shaped compounds have been synthesized from phloroglucinol and ninhydrin.[10] They exhibit interesting cavities, but their applications are limited because they are difficult to be further functionalized.

Herein we report a facile and efficient synthesis of a new family of cup-shaped benzoxazines (**1a–f**, Scheme 1). By a one-pot condensation between phloroglucinol, formaldehyde, and anilines,[11] the C_3-symmetric benzoxazine was synthesized in 79–96% yield. It is notable that twelve covalent bonds are formed in a single reaction step with medium to nearly quantitative yield.

In a typical reaction, phloroglucinol, formaldehyde, and aniline were mixed in 1:6:3 ratios in EtOH in the presence of catalytic amount of glacial acetic acid. Requisite tri-arm benzoxazines started to precipitate from the reaction mixture within an hour and was isolated by simple filtration. The reaction could be carried out in an open flask with wet solvent.

A diverse array of C_3-symmetric benzoxazines can be easily synthesized because of the multitude of amine and aniline derivatives that are commercially available and/or easy to synthesize. The reaction between phloroglucinol, formaldehyde, and *n*-propylamine only offered polybenzoxazine.[12] However, Table 1 includes six examples with different substituents attached to the three aromatic arms in the symmetrical molecule. The ability to introduce different functionality onto C_3-symmetric benzoxazine shows its potential application in serving as a novel tri-arm molecular scaffold.[13] Either electron donating groups (OMe and $NHCOCH_3$) or weak electron withdrawing groups (Cl and Br) can be introduced onto the benzoxazines with electron donating groups offering better yields with shorter reaction time. This is presumably due to change in nucleophilicity of the anilines in the Mannich aminomethylation and sequential ring closure condensation. The trihalides are valuable since they can be converted into a large variety of functional derivatives by metal-catalyzed transformations.

X-ray quality crystals of **1d** were obtained by diffusion of water vapor into DMSO solution of **1d**. The X-ray structure of **1d** shows a



Scheme 1. Synthesis of C_3-symmetric benzoxazines (**1a–f**).

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Table 1
Reaction conditions and yields of benzoxazines

Entry	*R*	Temp	Time (h)	Product	Yield[a] (%)
1	$-n\text{-}C_3H_7$	rt	12	polymer	NA
2	$-C_6H_5$	rt	10	**1a**	84[b]
3	$-p\text{-}C_6H_4Cl$	rt	12	**1b**	82
4	$-p\text{-}C_6H_4Br$	rt	12	**1c**[c]	79
5	$-p\text{-}C_6H_4NHCOCH_3$	rt	12	**1d**	95
6	$-m\text{-}C_6H_4NHCOCH_3$	rt	12	**1e**	91
7	$-p\text{-}C_6H_4OMe$	rt	8	**1f**	96

[a] Yield of isolated product by simple filtration.
[b] Containing some polymer.
[c] 9% 1,3,5-tri-*p*-bromophenyl-hexahydro-1,3,5-triazine was isolated as a by-product.

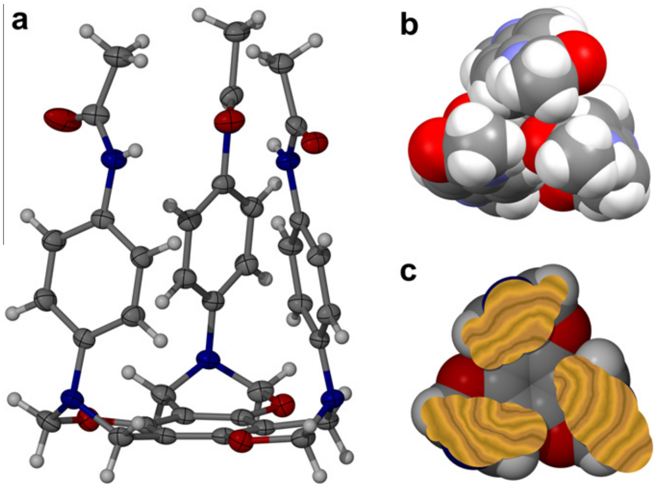

Figure 1. Crystal structure of **1d**. (a) Oak Ridge Thermal Ellipsoid Plot (ORTEP) representation at 50% electron density; (b) top view in space filling style; (c) a sliced top view in space filling style showing the prism-shaped cavity.

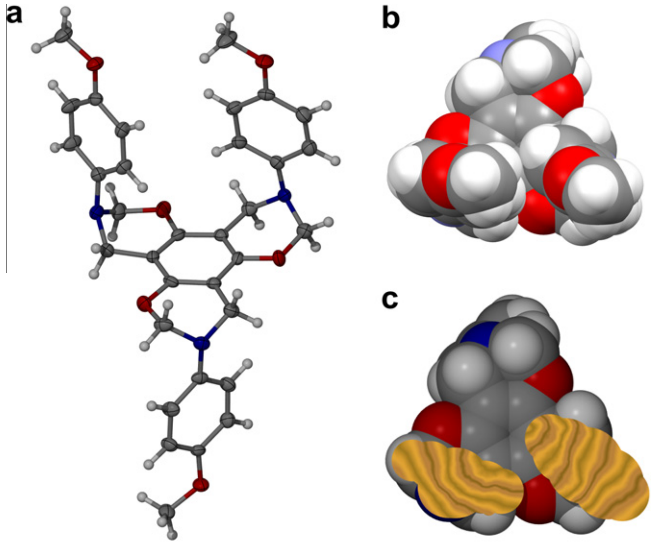

Figure 2. Crystal structure of **1f**. (a) ORTEP representation at 50% electron density; (b) top view in space filling style; (c) a sliced top view in space filling style.

cup-shaped conformation (Fig. 1).[14,15] Three aromatic arms are approximately perpendicular to benzo-trioxazine ring. As a consequence of the conformation, a small prism-shaped cavity has formed. The compound is chiral due to the orientation of three oxazine rings.[11b] It crystallized out as a racemic mixture with a pair of enantiomers in each unit cell. However, the two enantiomers are inseparable because they undergo interconversion in solution by pyramidal inversion of nitrogen trigonal pyramids at room temperature.

Just as calix[4]arenes can exist in four possible conformations,[1] the tri-arm benzoxazines exist as 'cup' or 'chair' conformer. The cup-shaped conformation of **1d** is presumably due to the favorable hydrogen bonding between the amide substituents. Each amide group forms hydrogen bonds either within the cup-shaped molecule or between the two neighboring molecules (See Supplementary material).

The chair-shaped conformation was observed by the crystal structure of **1f**, which is obtained by slow evaporation of CH_2Cl_2 solution of **1f** (Fig. 2).[14,15] It is interesting to notice that the aromatic arms twist around the N–Ar bond to achieve close packing in the solid-state.

In summary, we have synthesized and characterized six C_3-symmetric benzoxazines with different substituents attached. The facile and efficient synthesis will make the tri-arm benzoxazine a novel C_3-symmetric molecular scaffold.[13] Two crystal structures confirmed their conformation and showed the flexibility of the three aromatic arms, which can be tailored toward specific guests by introducing suitable binding groups.[9,10a] C_3-symmetric benzoxazine will also provide useful precursors for the generation of new molecular hosts, synthetic ionophores, and chemical sensors.[2–7,16] In addition, they might also be used as monomers for newly developed thermosetting polybenzoxazine resins.[12]

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Supplementary data

Supplementary data (experimental procedures, ^1H, ^{13}C NMR and IR data of the compounds and CIF files of the crystal structures.) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.10.162.

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14. Crystal data for compound **1d**: colorless, 0.10 × 0.10 × 0.20 mm, $C_{36}H_{36}N_6O_6$, M = 648.71, Triclinic, $p\bar{1}$, a = 10.8717(3) Å, b = 12.6249(3) Å, c = 12.8831(3) Å, α = 71.8360(10)°, β = 72.8500(10)°, γ = 68.5970(10)°, V = 1531.14(7) Å^3; T = 173 (2) K, D_{calc} = 1.407 g cm^{-3}, Z = 2, reflections collected = 19634, independent reflections = 5401 (R_{int} = 0.0267), R values [$I > 2\sigma(I)$, 4232 reflections]: R_1 = 0.0382, wR_2 = 0.1060; S = 0. 914; CCDC 833788.
   Crystal data for compound **1f**: colorless, 0.25 × 0.30 × 0.60 mm, $C_{33}H_{33}N_3O_6$, M = 539.60, Triclinic, $p\bar{1}$, a = 10.1872(9) Å, b = 16.4822(15) Å, c = 16.9613(16) Å, α = 70.936(5)°, β = 83.198(5)°, γ = 89.978(6)°, V = 2670.6(4) Å^3; T = 173 (2) K, D_{calc} = 1.342 g cm^{-3}, Z = 4, reflections collected = 82580, independent reflections = 9257 (R_{int} = 0.0545), R values [$I > 2\sigma(I)$, 7134 reflections]: R_1 = 0.1018, wR_2 = 0.2450; S = 1.069; CCDC 833789.
15. (a) All crystallographic calculations were conducted using SHELXL-97: G. M. Sheldrick, SHELXL-97, Program for Refinement of Crystal Structure, University of Göttingen, Göttingen, Germany, 1997; (b) Crystal figures are generated by X-Seed: Barbour, L. J. *J. Supramol. Chem.*, **2001**, *1*, 189–191.
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