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A Facile Synthesis of Large Extraannular-Functionalized Phenyl-Ethynyl Macrocycles Containing *m*-Terphenyl Units

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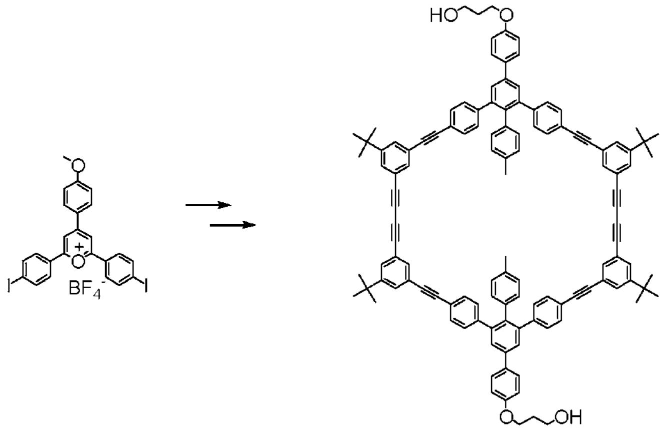
ABSTRACT



Two large extraannular-functionalized phenyl-ethynyl macrocycles containing *m*-terphenyl units are described. The synthesis of the *m*-terphenyl building blocks is based on the transformation of pyrylium salts to arenes.

Shape-persistent macrocycles based on the phenylene or phenylene-ethynylene backbone are fairly rigid structures having a lumen (interior size) in the range of one to several nanometers. Although some of the compounds are based on purely para-substituted aromatics, most macrocycles prepared to date have a polygonic shape. They contain corner pieces of ortho- or meta-substituted aromatics that introduce kinks into the structure, necessary to form the ring.[1]

During our work on large rigid macrocycles synthesized by the intermolecular oxidative dimerization of ethynyl-terminated phenyl-ethynyl-oligomers, it became apparent that the synthesis of rings with a large internal void is often highly time-consuming.[2] We therefore searched for a simple synthesis of expanded aromatic structures containing halogens (bromide or iodide) in an arrangement as it is found in meta-substituted benzene derivatives so that these structures can be used as corner pieces of a macrocyclic backbone. Moreover, the synthesis of these extended building blocks should allow the introduction of functional groups at various positions because this allows the preparation of macrocycles with a predetermined functional group orientation. If a polygonic macrocycle is based on the phenyl-ethynyl backbone that contains meta- and also para-substituted aromatic

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(1) Reviews about shape-persistent macrocycles: (a) Moore, J. S. *Acc. Chem. Res.* **1997**, *30*, 402. (b) Höger, S. *J. Polym. Sci., Part A* **1999**, *37*, 2685. (c) Haley, M. M.; Pak, J. J.; Brand, S. C. *Topic Curr. Chem.* **1999**, *201*, 81. (d) Grave, C.; Schlüter, A. D. *Eur. J. Org. Chem.* **2002**, 3075.

(2) Höger, S.; Meckenstock, A.-D.; Müller, S. *Chem. Eur. J.* **1998**, *4*, 2421.

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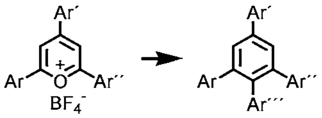
structures, only the latter can rotate freely. Their orientation can be influenced by an external parameter, while the orientation of the functional groups at the corner pieces is given by the actual structure of these building blocks.[3]

Here we report a new approach toward functionalized 4,4″-diiodo-*m*-terphenylenes and their use in the synthesis of shape-persistent macrocycles.[4,5] The key step in our reaction sequence is the transformation of a 2,4,6-triarylpyrylium salt to the corresponding arene by the reaction with sodium phenylacetate as described by Zimmermann and Fischer (Scheme 1).[6]

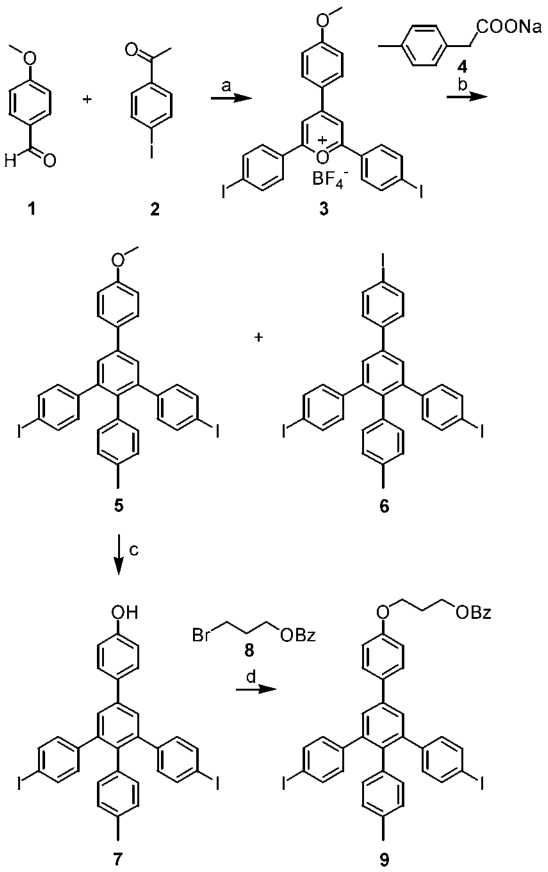
Scheme 1. Arenes from Pyrylium Salts



Pyrylium salts containing a variety of functional groups are easily available in large quantities. Their synthesis and subsequent transformation to arenes tolerate bromo and iodo groups, thus avoiding protective group transformation (e.g., TMS to I[7] or N_3Et_2 to I[8]) prior to the macrocycle synthesis.[9] In addition, Ar′ and Ar′′′ may contain functional groups. This strategy therefore allows the synthesis of macrocycles with intraannular as well as extraannular functional groups. The synthesis of these structures is of increasing interest because intraannular-functionalized macrocycles can act as host molecules for appropriate guest molecules.[10] Extraannular-functionalized macrocycles have shown to be versatile building blocks for new materials showing interesting aggregation phenomena.[11]

Scheme 2 shows the synthesis of a building block for the preparation of extraannular-functionalized macrocycles. Condensation of 1 equiv of 4-methoxy-benzaldehyde (**1**) with 2 equiv of 4-iodo-acetophenone (**2**) in the presence of $BF_3\cdot Et_2O$ at 100 °C for 2 h gave **3** in 48% yield.

Scheme 2[a]



[a] Reaction conditions: (a) $BF_3\cdot Et_2O$ (48%); (b) Ac_2O, $AgBF_4$ (20%); (c) BBr_3 (98%); (d) K_2CO_3 (78%).

Compound **3** was refluxed in acetic anhydride with **4** for 1.5 h, and **5** was isolated after chromatographic purification in 9−17% yield. This yield is remarkably low and to some extent due to the formation of the side product **6**. The nucleophilic substitution of the methoxy group by iodide is a result of the activating para-positioned electron-withdrawing pyrylium ring. Reacting **3** and **4** in the presence of 1 equiv of $AgBF_4$ (as an iodide scavenger) increased the yield up to 20%.[12] Nevertheless, the preparation of several grams of **5** can be performed without difficulties due to the simple preparation of **3**. Treatment of **5** with BBr_3 afforded **7** (98%), which was alkylated with 3-bromopropyl benzoate (**8**) to give **9** (78%) (Scheme 2).

Recrystallization of the phenyl-substituted 4,4″-diiodo-*m*-phenylene **5** from acetic acid gave crystals suitable for X-ray

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[3] (a) Okuyama, K.; Hasegawa, T.; Ito, M.; Mikami, N. *J. Phys. Chem.* **1984**, *88*, 1711. (b) Höger, S.; Enkelmann, V. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2713. (c) Morrison, D. L.; Höger, S. *J. Chem. Soc., Chem. Commun.* **1996**, 2313. (d) Höger, S.; Enkelmann, V.; Bonrad, K.; Tschierske, C. *Angew. Chem., Int. Ed.* **2000**, *39*, 2268. (e) Höger, S.; Morrison, D. L.; Enkelmann, V. *J. Am. Chem. Soc.* **2002**, *124*, 6734.

[4] Efficient and simple routes to *m*-terphenyls were reported by Hart et al.: (a) Du, C.-J. F.; Hart, H.; Ng, K.-K. D. *J. Org. Chem.* **1986**, *51*, 3162. (b) Saednya, A.; Hart, H. *Synthesis* **1996**, 1455. However, that approach has limitations with respect to 4,4″-dihalogenated compounds.

[5] For an oligo(het)arylene building block in macrocycle synthesis, see, for example: Manickam, G.; Schlüter, A. D. *Eur. J. Org. Chem.* **2000**, 3475.

[6] Zimmermann, T.; Fischer, G. W. *J. Prakt. Chem.* **1987**, *329*, 975. See also: Dimroth, K.; Neubauer, G. *Chem. Ber.* **1959**, *92*, 2042.

[7] Manickam, G.; Schlüter, A. D. *Eur. J. Org. Chem.* **2000**, 3475.

[8] Moore, J. S.; Weinstein, E. J.; Wu, Z. *Tetrahedron Lett.* **1991**, *32*, 2465.

[9] Balaban, A. T.; Dinculescu, A.; Dorofeenko, G. N.; Fischer, G. W. Koblik, A. V.; Mezheritskii, V. V.; Schroth, W. *Adv. Heterocycl. Chem., Supp. 2*; Academic Press: New York, 1982.

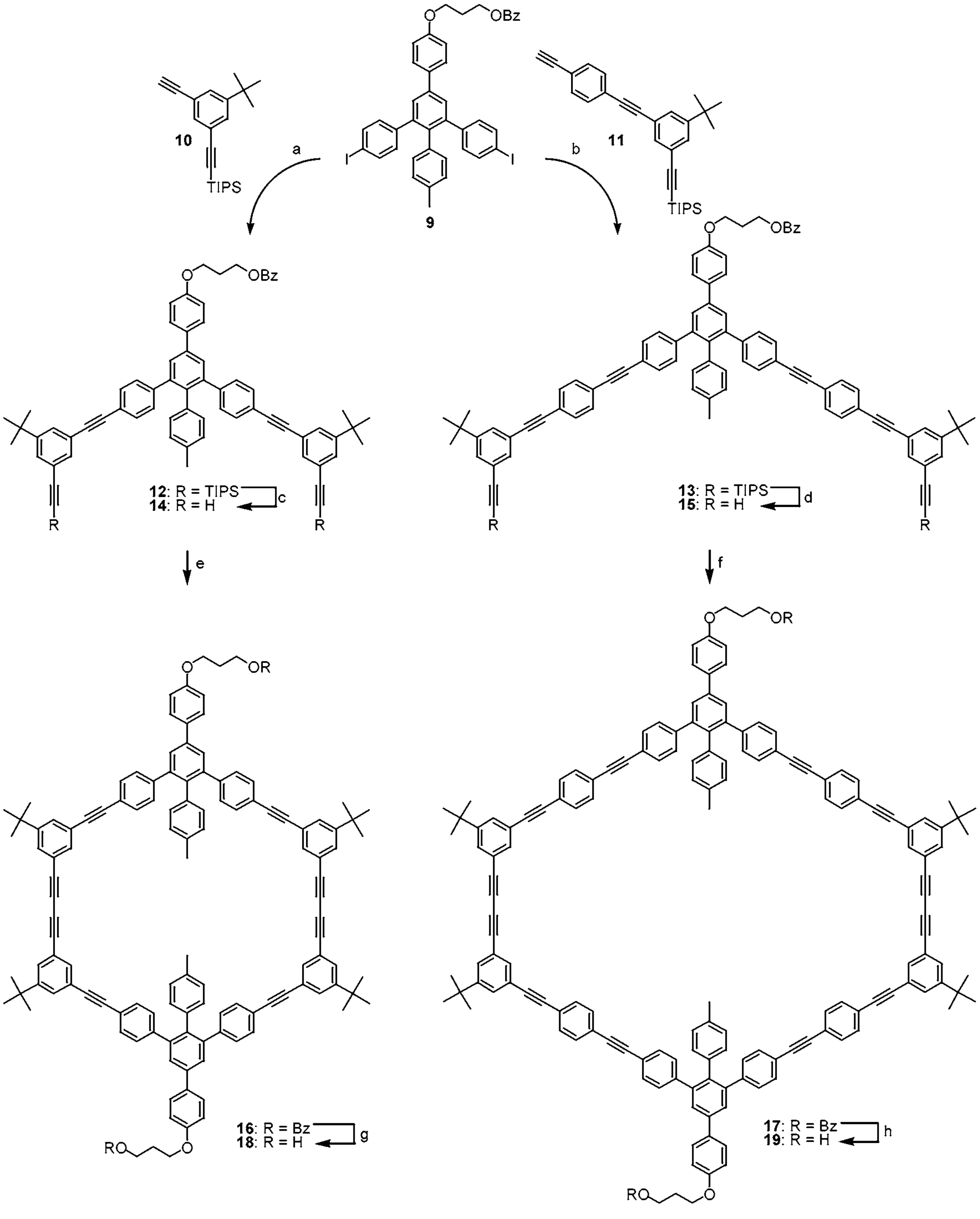
[10] For the concept of intraannular functional groups, see, for example: (a) Vögtle, F.; Neumann, P. *Tetrahedron* **1970**, *26*, 5299. (b) Weber, E.; Vögtle, F. *Chem. Ber.* **1976**, *109*, 1803.

[11] (a) Rosselli, S.; Ramminger, A.-D.; Wagner, T.; Silier, B.; Wiegand, S.; Häussler, W.; Lieser, G.; Scheumann, V.; Höger, S. *Angew. Chem., Int. Ed.* **2001**, *40*, 3138. (b) Höger, S.; Bonrad, K.; Rosselli, S.; Ramminger, A.-D.; Wagner, T.; Silier, B.; Wiegand, S.; Häussler, W.; Lieser, G.; Scheumann, V. *Makromol. Symp.* **2002**, *177*, 185. (c) Höger, S. Bonrad, K.; Mourran, A.; Beginn, U.; Möller, M. *J. Am. Chem. Soc.* **2001**, *123*, 5651.

[12] The use of an excess of $AgBF_4$ led to an undefined product mixture.

[13] **5·AcOH**: $C_{32}H_{24}I_2O\cdot AcOH$, monoclinic, $P2_1/a$, colorless, a = 18.581(1) Å, b = 7.4812(7) Å, c = 22.069(1) Å, β = 96.821(3) °, Z = 4, D_x = 1.610 g/cm, T = 195 K, 4568 reflections measured, 3525 unique reflections, 1843 observed reflections. Refinement on F with anisotropic C, O, and N; H with fixed isotropic temperature factors in the riding mode; R = 0.0569, R_w = 0.0527, GOF = 0.857.

Scheme 3[a]



[a] Reaction conditions: (a) $Pd_2(dba)_3$, CuI, PPh_3 (83%); (b) $Pd_2(dba)_3$, CuI, PPh_3 (92%); (c) Bu_4NF, THF (78%); (d) Bu_4NF, THF (91%); (e) CuCl, $CuCl_2$, pyridine (53%); (f) CuCl, $CuCl_2$, pyridine (20%); (g) KOH, LiOH (87%); (h) KOH, LiOH (91%).

analysis (Figure 1). Due to steric reasons, the methyl- and the iodo-substituted aromatic rings cannot be in plane with the central aromatic ring but adopt a propeller-like conformation. The crystals include one molecule of acetic acid per asymmetric unit, which forms hydrogen-bonded dimers in the crystal.[13]

Compound **9** is a suitable precursor for the formation of shape-persistent macrocycles containing extraannular substituents. Palladium-catalyzed coupling with **10** or **11** in the presence of CuI and PPh_3 provided the two-half rings in their TIPS-protected forms (**12** and **13**) in about 80−90% yield. Subsequent deprotection of **12** and **13** using tetrabutylammonium fluoride in THF gave bisacetylenes **14** and **15**, respectively (80−90% yield) (Scheme 3). The cyclization of **14** and **15** under pseudo high-dilution conditions was carried out by adding a solution of the bisacetylenes in

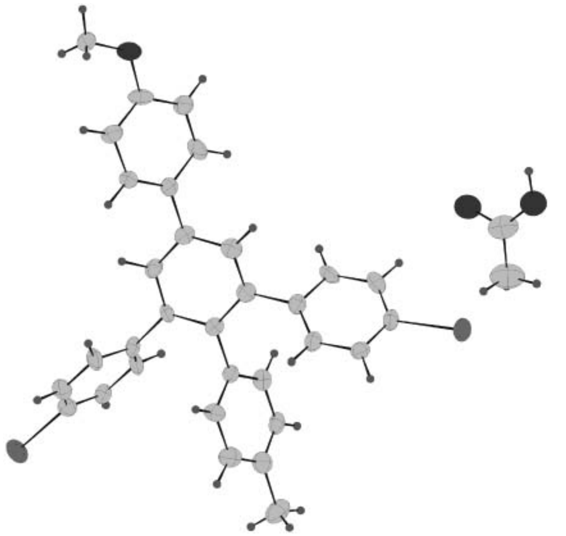


Figure 1. Crystal structure of **5**·AcOH.

pyridine in 96 h to a slurry of CuCl/$CuCl_2$ in the same solvent at 55 °C. The cyclization reaction is a statistical reaction, so the cyclic dimers **16** and **17** are formed along with cyclic trimers, oligomers, and polymers. According to the data of the gel permeation chromatography (GPC), the crude cyclization product of **14** contains **16** in about 80%. It could be easily purified by column chromatography and **44** was isolated in 53% yield. The crude cyclization product of **15** contains about 65% **17** but its purification was not possible by column chromatography. Pure **17** was obtained by recrystallization from 1,2-dichloroethene in only 20%. Deprotection of the macrocycles **15** and **17** was performed using a mixture of NaOH/LiOH in THF/water. After refluxing overnight, complete deprotection was achieved as confirmed by TLC, NMR spectra, and mass spectra. Both macrocycles were obtained in about 90% yield.

In conclusion, we have for the first time shown that 2,6-(4,4″-diiodo)-diphenyl pyryliums salts are valuable precursors for diiodo-*m*-terphenyl units. As shown here, functionalized pyrylium salts led to diiodo compounds that were used to prepare extraannular-functionalized shape-persistent macrocycles. The possibility of performing the pyrylium salt to arene transformation also with functionalized phenyl acetic acids allows the easy synthesis of large intraannular-functionalyzed macrocycles.[14]

Supporting Information Available: Detailed experimental procedures and characterization of all compounds in the text and X-ray data of **5**·HOAc. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Höger, S. Unpublished results.