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A new approach for the design of novel hexa-host molecules

Ahmed H. M. Elwahy*

Chemistry Department, Faculty of Science, Cairo University, Giza, Egypt

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Abstract—A synthesis of novel hexa-host molecules **1** and **2** by a Pd/Cu-catalyzed cross coupling reaction of the hexakis(4-iodophenoxymethyl)benzene **9** with the corresponding acetylenes **11** or **12** is described. © 2001 Published by Elsevier Science Ltd.

During recent decades organic hosts that form inclusion compounds have attracted a great deal of interest.[1,2] These compounds have been studied as models for the processes of molecular recognition via intermolecular interactions as well as for their abilities to store or separate guest molecules.[3,4] Certain structural features present in host compounds can maximize opportunities for inclusion complex formation. These features include, in addition to the shape of the host molecules, the presence of a rotational axis of symmetry.[5] A wide range of inclusion behavior has been established for molecules of the hexa-host type. Suitably hexa-substituted benzene derivatives as hosts and complex forming ligands with a great underlying potential have received considerable attention in recent years.[5,6]

In connection with current interest in the design of multimolecular host systems, we report herein our efforts to generate novel sixfold branched phenylacetylenes **1** and **2**, which are linked to the core via phenoxymethylene spacers.

Two strategies have been attempted for the synthesis of the target molecules **1** and **2**. In the first strategy (Scheme 1) we studied the synthesis of hexakis(4-ethynylphenoxymethyl)benzene **6** from the corresponding aldehyde **5** via a modified Corey–Fuchs reaction.[7] Compound **6** should then undergo a Pd/Cu-catalyzed cross coupling reaction with the appropriate aryl halides to give compounds **1** and **2**. For this purpose, hexakis(4-formylphenoxymethyl)benzene **5** was prepared in 80% yield by reacting the potassium salt of 4-hydroxybenzaldehyde **4** with hexakis(bromomethyl)benzene **3**[8] in refluxing DMF for 30 minutes. Unfortunately, attempted conversion of the aldehyde **5** into the corresponding alkyne **6** by a sequence of reactions starting from a Wittig-type condensation of **5** with the ylide derived from dibromomethyltriphenylphosphonium bromide in THF containing *t*-BuOK were unsuccessful. This may be attributed to the inherent insolubility of the aldehyde in the reaction mixture.

In the second strategy (Scheme 2) we attempted to prepare **6** by utilizing the elegant synthetic approach demonstrated by Hagihara[9] to mono- and diethynylarenes and the modified synthetic approach by Vollhardt and others[10] to poly(ethynyl)arenes. In these synthetic approaches, aryl halides and trimethylsilylacetylene (TMSA) are coupled in the presence of catalytic copper(I) iodide–dichlorobis(triphenylphosphine) palladium(II) with secondary or tertiary amines as solvent and base. For this, hexakis(4-iodophenoxymethyl)benzene **9** was prepared and coupled with (TMSA) at 100°C in a triethylamine–piperidine mixture. Unfortunately, under these conditions we could not isolate a pure sample of the corresponding hexakis(4-trimethylsilylethynylphenoxymethyl)benzene **11**. The reaction instead gave a mixture of products that were not easily handled and have not been characterized as yet. Compound **9** was obtained in 77% yield by sixfold substitution of **3** with six equivalents of the potassium salt of **8** in refluxing DMF for 30 minutes. We could also prepare hexakis(phenoxymethyl)benzene **10** by reacting **3** with potassium phenoxide in refluxing DMF in a moderate yield (70%) and short time (30 min) after modification of the literature procedure.[11] It is noteworthy to mention that inclusion behavior has been established for **8** and other related compounds.[6,11,12]

Keywords: ethynylbenzenes; Pd/Cu-cross coupling reaction; poly(phenylethynylphenoxymethyl)benzenes.

* Corresponding author. E-mail: aelwahy@chem-sci.cairo.eun.eg

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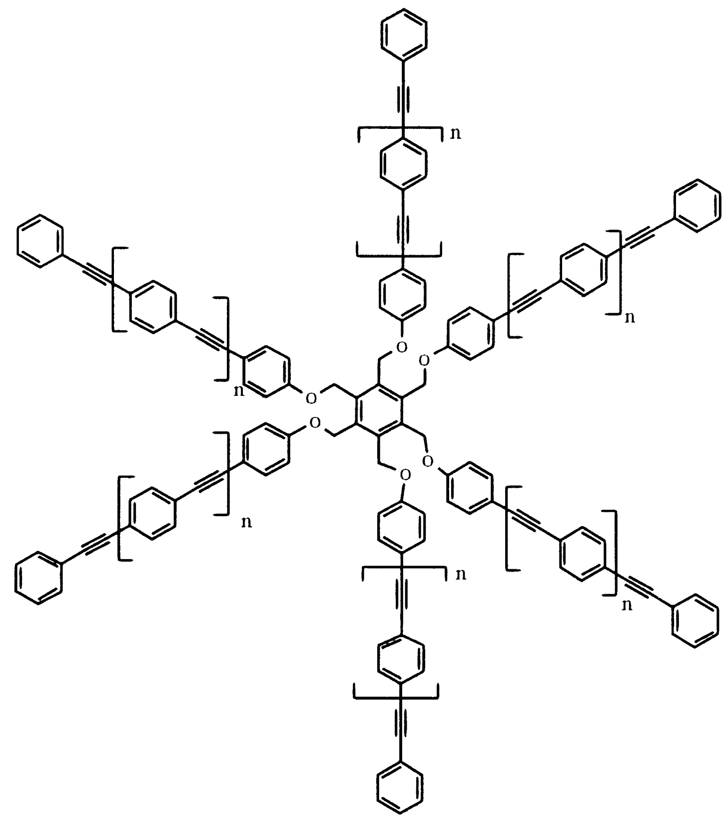


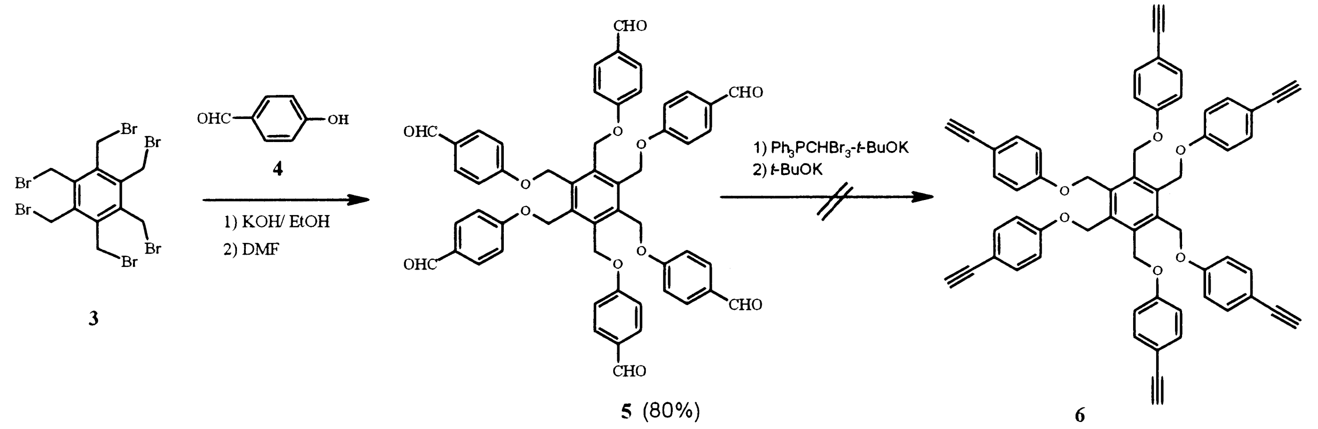
1, n = 0
2, n = 1

In a search for an expedient pathway to prepare **1** and **2** our attention focused on compound **9** as a precursor which should then undergo further coupling with the appropriate ethynylarenes with the Pd/Cu catalytic system. Thus, six equivalents of phenylacetylene could be coupled with **9** at 100°C in the presence of bis-(triphenylphosphine) palladium chloride and CuI in a triethylamine–piperidine mixture to give a 75% yield of **1** as pale yellow crystals.

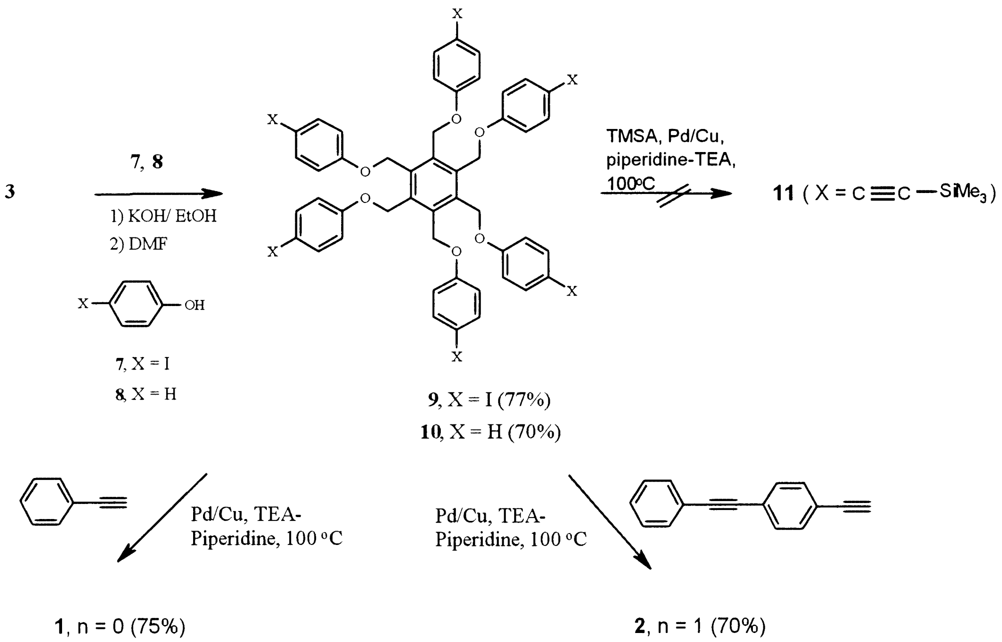
The same methodology can be extended to the preparation of **2**. Thus, reaction of **9** with 6 equivalents of 1-ethynyl-4-(phenylethynyl)benzene **12**[13] under similar conditions afforded **2** in 70% yield, as orange crystals. The symmetry of compounds **1** and **2** are manifested by a single set of signals in the ^{1}H and ^{13}C NMR spectra.

*Physical data for compounds **1**, **2**, **5**, **9** and **10***[14,15]

1: Pale yellow crystals (ethyl acetate/petroleum ether), mp 276–278°C; MS (ESI) *m*/*z* (%) 1316 (100%); ^{1}H NMR ($CDCl_3$) δ 5.23 (s, 12H, OCH_2), 6.85–7.51 (m, 54H, ArH); ^{13}C NMR ($CDCl_3$) δ 63.79 (OCH_2), 88.55, 89.13 (C≡C), 114.74, 116.52, 123.52, 128.11, 128.40, 131.58, 133.28, 137.90, 158.33.



Scheme 1.



Scheme 2.

2: Orange crystals (DMF), mp 238–240°C; ^{1}H NMR (DMSO) δ 5.39 (s, 12H, OCH_2), 6.9–7.54 (m, 78H, ArH); ^{13}C NMR (DMSO) δ 63.96 (OCH_2), 87.23, 88.34, 90.56, 90.58 (C≡C), 114.49, 114.84, 121.66, 122.45, 127.82, 127.95, 130.66, 130.72, 132.15, 136.92, 158.20.

5: Colorless crystals (acetic acid), mp 224–225°C; MS (ESI) m/z (%) 905 [M^++Na, 100%]; ^{1}H NMR ($CDCl_3$) δ 5.45 (s, 12H, OCH_2), 7.08 (d, $J=8.7$ Hz, 12H, ArH), 7.74 (d, $J=8.7$ Hz, 12H, ArH), 9.79 (s, 6H, CHO).

9: Colorless crystals (DMF/ethanol), mp 275–277°C; ^{1}H NMR (DMSO) δ 5.34 (s, 12H, OCH_2), 6.74 (d, $J=8.8$ Hz, 12H, ArH), 7.53 (d, $J=8.8$ Hz, 12H, ArH); ^{13}C NMR (DMSO) δ 64.9 (OCH_2), 83.74 (=C-I), 118.24, 137.85, 138.34, 158.78.

10: Colorless crystals (toluene), mp 225–227°C (lit.[11] 228–229°C); MS (FD): m/z (%) 715 [M^+, 100%]; ^{1}H NMR (DMSO) δ 5.19 (s, 12H, OCH_2), 6.86–7.27 (m, 30H, ArH); ^{13}C NMR (DMSO) δ 63.83 (OCH_2), 114.97, 121.58, 129.76, 138.18, 158.73.

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14. The new compounds described gave correct elemental analyses.
15. NMR spectra were recorded with a Bruker NMR spectrometer WM 300 in $CDCl_3$ or DMSO with tetramethylsilane as internal standard. Mass spectra (MS) were obtained with a Varian 311A instrument.