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Tetrahedron Letters
Tetrahedron Letters 48 (2007) 6075–6079

Synthesis of penta-*p*-phenylenes with oligo(ethylene glycol) side chains

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Received 18 May 2007; revised 26 June 2007; accepted 29 June 2007
Available online 7 July 2007

Abstract—We report an efficient synthesis of a series of penta-*p*-phenylene derivatives with four side chains of various lengths, including deca(ethylene glycol) groups. The key feature of the synthesis is that the side chains are efficiently introduced in the last step, facilitating optimization of the side chains for different applications. Raman spectroscopy study indicates a similarly high rigidity for all these compounds, even those with long oligo(ethylene glycol) side chains. The deca(ethylene glycol)-substituted penta-*p*-phenylene derivatives are versatile building blocks for construction of nanometric, tripod-shaped adsorbates for biological applications.

The control of the orientation and spacing between functional groups in organic thin films, and the availability of methods for its high fidelity derivatization, will greatly facilitate the development of molecular scale devices for many applications. For instance, the alignment of molecules is necessary for obtaining non-linear optical phenomena and orientation-dependent electronic and optical properties of conjugated molecules.[1] For biosensor applications, it is highly desirable to control the spacing between the adjacent probe molecules in order to achieve maximum loading, and yet not to hinder the interaction between the probe and target molecules.[2]

Currently, a common method to prepare functional organic thin films is based on self-assembly of monolayers of monodentate adsorbates with a long alkyl chain, such as alkylsiloxanes on polar surfaces, or alkylthiolate on gold surfaces.[3,4] The orientation of the flexible molecules in these monolayers is maintained by the close packing of the alkyl chains through van der Waals forces. Although the average density of the functional groups on these monolayer surfaces can be adjusted by co-deposition with inert analogous adsorbates, it is not possible to avoid non-randomized mixing at the nanoscale that prevents the control of the nanoscale spacing between the functional surface groups.[4]

For the development of molecular scale devices, it is highly desirable to develop large, shape-persistent and self-standing adsorbate molecules. Several of such molecules have been reported, including 'molecular caltrops' with four phenylacetylene arms extending from a tetrahedral silicon corn,[5] conically shaped dendron adsorbates with a functional group at the corn,[6] and tripod-shaped molecules with three oligophenylene heptamers as the tripod legs and one bromophenyl group as the functional arm, joined together at a single silicon atom.[7] Tripodal rigid adsorbates (compound **1**) have been deposited on hydrogen-terminated silicon surfaces through surface hydrosilylation.[8] The orientation of the bromophenyl groups at the focal point of the tripods in the film is believed to be perpendicular to the surface since the Suzuki coupling of these groups with arylboronic acid derivatives gave a very high yield (>90%).[8] In comparison, the same reaction only gave <50% yield for bromophenyl groups on films derived from carbosilane dendrimers, likely because a substantial amount of these groups had an unfavourable orientation and some of them were even buried inside the films due to the flex-

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doi:10.1016/j.tetlet.2007.06.167

ibility of the dendrimer, and hence could not undergo the reaction.[6b–d] These results show the promise of controlling the orientation of functional moieties on free-standing individual adsorbate molecules. We are interested in generating single molecule patterns of similar tripod molecules to control the orientation and location of the individual functional moieties on surfaces, and use such well defined model systems to study multivalent and multi-component interactions in biological systems. The reported tripod derivatives **1** cannot be used for this purpose, since the hydrophobic tripod framework and its hexyl side chains are well known to interact non-specifically with protein molecules, thus interfering with the specific interaction of target molecules with the ligand on the focal point of the tripod. To overcome this problem, we must develop tripod molecules that are modified with side chains that do not interact with protein molecules. The most common materials for resisting non-specific interaction with proteins are poly- or oligo(ethylene glycol) (PEG or OEG).[3,9] Monolayers presenting OEG groups on gold or silicon substrate surfaces have been shown to strongly resist protein adsorption.[3a] Therefore, our goal is to develop an efficient synthesis of the tripod adsorbates with OEG side chains. In this Letter, we report an efficient method for preparing the key building block of these molecules: penta-*p*-phenylenes with OEG side chains (compounds **2** in Fig. 1).

The initial plan of synthesis of **2** adapted our previously reported route[7] involving the preparation of the monomer **I**, followed by Suzuki coupling with triphenyl diiodide. The attempted preparation of **I** began with the reaction of **3** with NBS in the presence of AIBN in refluxing CCl_4 to provide the tetrabromine derivative **4** in 63% yield (Scheme 1).[10] OEG groups were introduced to **4** through substitution with commercial tri(ethylene glycol) monomethyl ether (**5**). Initially, the reaction was run in refluxing THF using KO-*t*-Bu as the base, leading to a low yield of **6** (25%) and formation of the monodebromination product of **6** (21%). We then found that using toluene as the solvent, NaH as the base and performing the reaction at a lower temperature (20 °C) resulted in a good yield of **6** (71%). Unfortunately, the monolithiation of the dibromide **6** followed by reaction with trimethoxy borate failed. Only unreacted product or complex reaction mixtures were obtained under several reaction temperatures (−78 °C, −40 °C and 20 °C). This result was in contrast with several reports of monolithiation of *p*-dibromo benzene derivatives.[11] We speculate that the failure in our system is probably due to the following factors: (1) protonation of the phenyl anion by the relatively acidic benzylic protons to form benzylic anion which is stabilized by the benzylic oxygen atom and the complexation of the Li^+ by the OEG side chain; and (2) difficulties of eliminating water absorbed by the hydrophilic OEG side chains.

Owing to these results, we decided to first construct the penta-*p*-phenylene backbone by Suzuki coupling of the boronic acids **8** with *p*-diiodoterphenyl (**9**, Scheme 2), and to incorporate the OEG groups at the end of the synthesis. In addition to the OEG substituted penta-*p*-phenylenes, we also prepared several other derivatives to allow a systematic study by Raman spectroscopy (see below). The boronic acids used, **8a**,**b**, were pur-

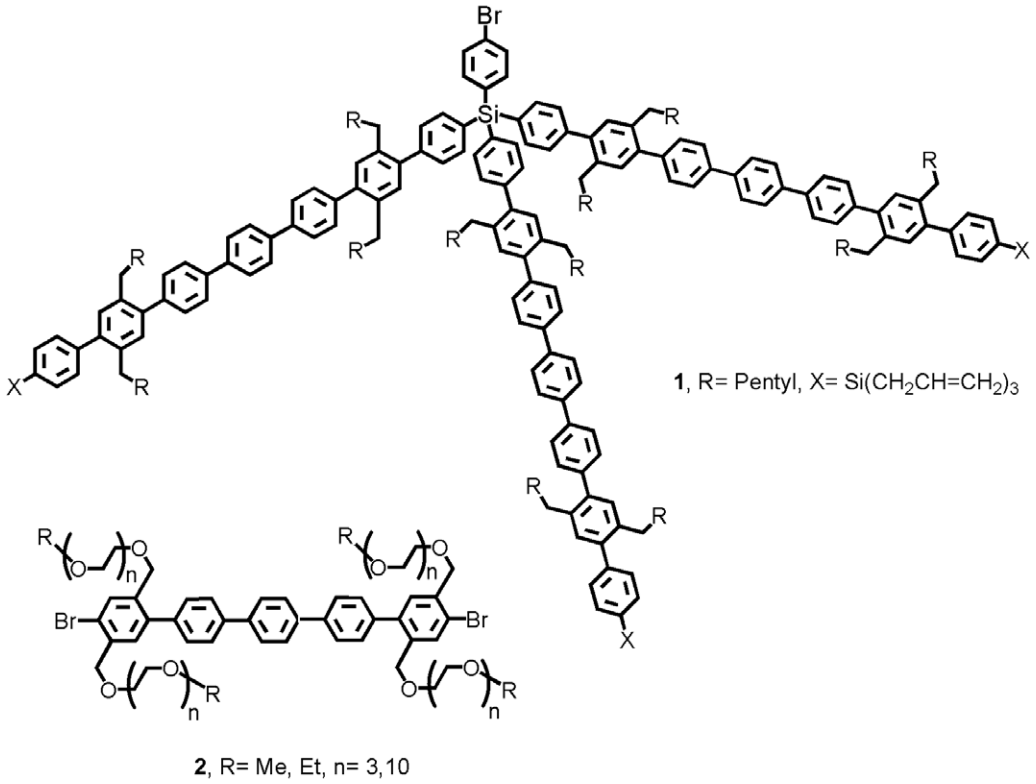
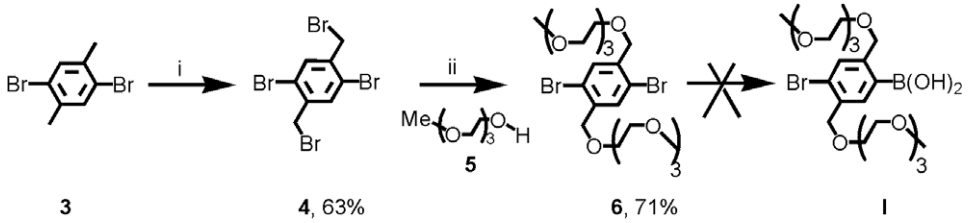
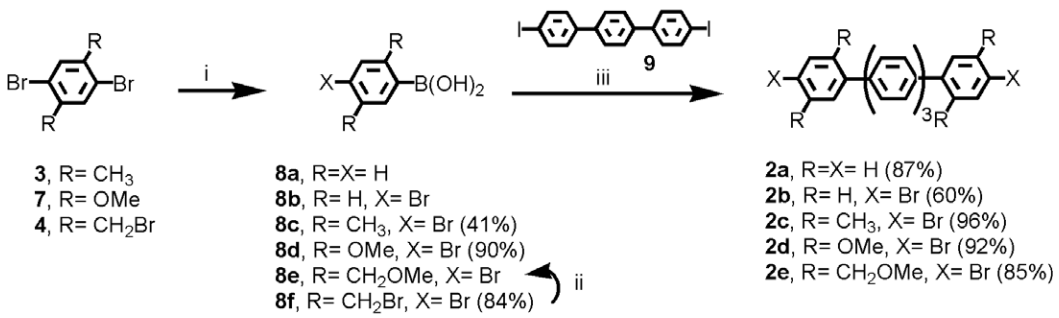


Figure 1.



Scheme 1. Reagents and conditions: (i) NBS/AIBN/CCl_4, reflux; (ii) NaH/toluene, 20 °C.



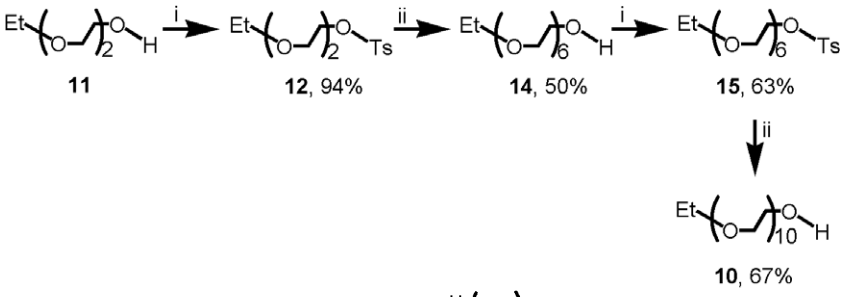
Scheme 2. Reagents and conditions: (i) (1) *n*-BuLi/THF, −78 °C, (2) $B(OMe)_3$/THF, (3) HCl; (ii) Na/MeOH, 20 °C; (iii) $Pd(PPh_3)_4$ (5 mol %)/1 M Na_2CO_3/DME, reflux, 18 h.

chased from Aldrich, and **8c**, **8d** and **8f** were prepared from compounds **3**, **7** and **4**, respectively, by monolithiation with *n*-buthyl lithium, followed by reaction with trimethoxy borate (Scheme 2).[12] The treatment of **8f** with an excess of sodium methoxide in methanol gave **8e**. Subsequent coupling with **9** under standard Suzuki conditions in refluxing DME gave penta-*p*-phenylenes **2a**–**e** in good yields, which were purified by recrystallization from toluene (Scheme 2). Under these reaction conditions no polymerization of compound **8** was observed.

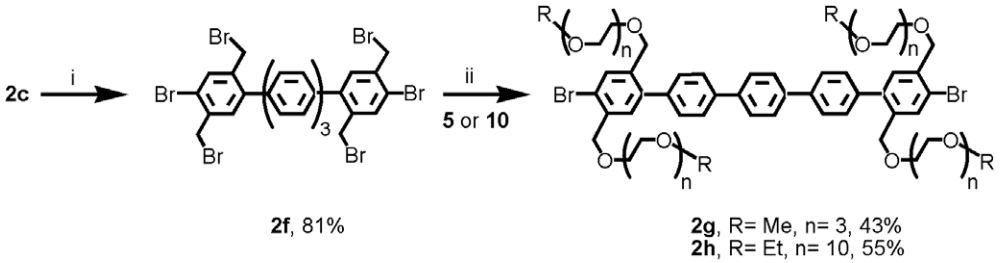
We chose the deca(ethylene glycol) **10** as the side chains for the oligophenylenes, since we anticipated that long OEG groups are needed to mask the penta-*p*-phenylene backbone to render it resistant to the non-specific interactions with proteins.[3a] The deca(ethylene glycol) derivative was prepared by the reaction sequence shown in Scheme 3. Treatment of compound **11** with tosyl chloride in a mixture of THF and H_2O at 20 °C for 24 h gave tosylate **12** in a 94% yield. This compound was coupled with an excess of tetraethylene glycol (**13**) in the presence of KOH to provide, after washing the reaction mixture with water, the hexa(ethylene glycol) **14** in 50% yield. No chromatography was needed to purify the compound. Tosylation of **14** afforded **15** in 63% yield. The coupling of **15** with an excess of **13** provided deca(ethylene glycol) monomethyl ether (**10**) in 67% yield.

The synthesis of the oligo(ethylene glycol) substituted penta-*p*-phenylenes was efficiently accomplished with the tetramethyl penta-*p*-phenylene **2c** (Scheme 4). Bromination of the four methyl groups in **2c** with NBS (1.1 equiv for each methyl group) and AIBN (4.4 mol %) in refluxing CCl_4 gave the hexabromine compound **2f** in very good yield (81%).

The reaction conditions for the coupling of **2f** with OEG derivatives were optimized with commercial tri(ethylene glycol) monomethyl ether (**5**). Out of the conditions we tested, the reaction was best run in toluene at 20 °C with NaH as the base and a molar ratio of **2f**/**4** = 1:4.4, leading to **2g** in 43% yield. We were glad to find that under the same conditions, the final product **2h** was obtained in 55% yield from **2f** and the deca(ethylene glycol) **10** (Scheme 4).



Scheme 3. Reagents and conditions: (i) TsCl/NaOH/THF–H_2O, 20 °C; (ii) **13**, KOH, 70 °C.



Scheme 4. Reagents and conditions: (i) NBS/AIBN/CCl_4; (ii) NaH/toluene, 20 °C.

We have described an efficient synthesis of a series of penta-*p*-phenylene derivatives **2a**–**h**. Without alkyl substitution, the penta-*p*-phenylene derivatives **2a**,**b** are barely soluble in common solvents such as chloroform, ethyl ether, THF or toluene. However, compounds with four side chains (**2c**–**h**) are soluble in these organic solvents, and the solubility increases with the chain length. The OEG substituted penta-*p*-phenylenes **2g** and **2h** are also soluble in aqueous solvents, which is necessary for biological applications. With these compounds in hand, we are interested in studying their physical especially spectroscopy properties, since poly- and oligo(*p*-phenylene)s are attractive materials for potential applications involving photo- and electroluminescence. In addition, the backbone of oligo(*p*-phenylene)s is relatively rigid and hence is attractive to be used as the framework of self-standing molecular adsorbates.

Herein, we report the Raman spectroscopy study of these compounds.[13] It has been established that the relative intensities of the Raman active modes of oligo(*p*-phenylene)s recorded at 1220, 1280 and 1600 cm^{-1} depend on the combined effect of π-electron delocalization and intra-ring confinement. Therefore their intensities are very sensitive to the conjugation length of these molecules.[14,15] Overall, the intensity ratio I_{1280}/I_{1220} decreases with increasing effective conjugation length, which can be caused by either increasing the number of repeat units in the oligomer, or by reducing the inter ring torsion angle. For this reason these bands have been used to monitor the quality of synthetic routes to poly(*p*-phenylene)s.[16]

Figure 2 shows the Raman spectra of **2a**–**h**.[17] The characteristic bands of the penta-*p*-phenyl frame can be seen at ca. 1210, 1270 and 1600 cm^{-1}, assigned to C–H in-plane bend, C–C inter-ring stretch and C=C on-ring stretch, respectively. The ratio of I_{1280}/I_{1220} (ca. 3:1) is approximately the same for compounds **2b**–**h**. The higher I_{1280}/I_{1220} ratio of 1:1 for compound **2a** can be explained by a higher planarity in its structure, as can be expected in this case due to the absence of substituents. It is remarkable that no significant differences of the I_{1280}/I_{1220} ratio were observed for compounds **2b**–**h**, even though the lengths of the side chains are very different in these compounds, the OEG side chains in compound **2h** being the longest. This result strongly indicates that the length of the four OEG side chains in the oligo(*p*-phenylene)s does not significantly affect the planarity and rigidity of the backbone of the oligomers, probably because the sufficient separation between the sides reduces steric hindrances.

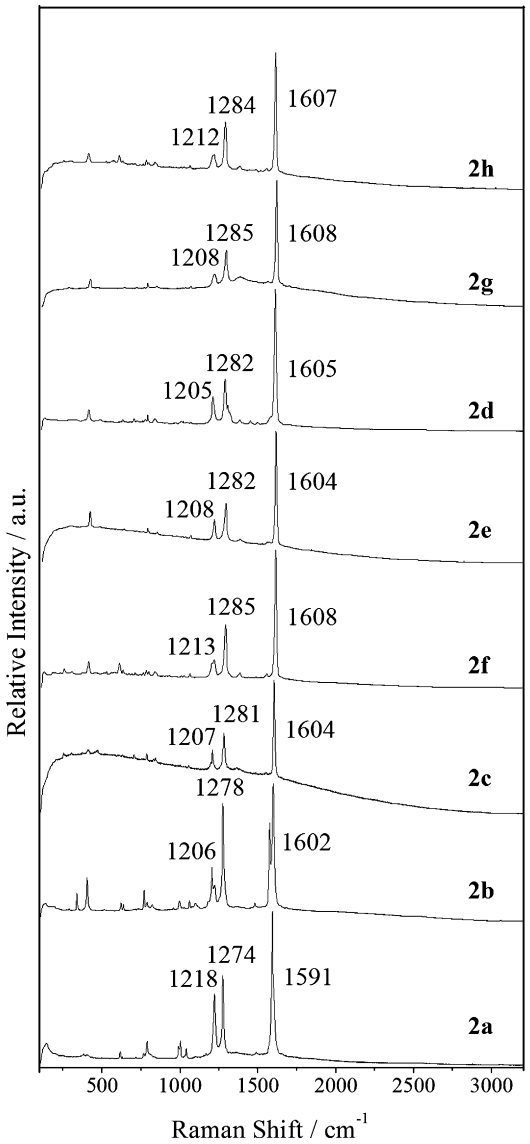


Figure 2. Raman spectra of penta-*p*-phenylenes **2a**–**h**.

In summary, a series of penta-*p*-phenylene derivatives have been efficiently synthesized. The key feature of our synthetic approach is that different side chains can easily be introduced into the oligophenylene backbone

in the last step of the synthesis, making it versatile for optimizing the side chains for different purposes. Using this synthetic route, we prepared the penta-*p*-phenylene **2h** with four deca(ethylene glycol) side chains as versatile building blocks for construction of shape-persistent adsorbate molecules for biological applications. Raman analyses show a similarly high rigidity for all these compounds, even those with long OEG side chains. The synthesis of the tripod-shaped adsorbates of using **2h** is currently under study.

Acknowledgements

This research was supported by the Nanotechnology Spanish Research Projects NAN04-09312 C03-01, -02 and -03, CTQ2006-02330, and the Junta de Andalucía Project P06-FQM-01895. R.M.M. and E.G. thanks the project NAN04-09312 C03-02 for the contracts CI-05-138 and CI-06-151, respectively.

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12. Elemental analyses and spectroscopic data of new compounds were in agreement with their structures. Compound **2h**: yellowish syrup; UV ($CDCl_3$) λ_{max}: 300, 242 nm; FTMs-APPI: 2534.22 ($C_{122}H_{204}{}^{79}Br_1{}^{81}Br_1O_{44}$); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 1.19 (t, $J = 14.2$ Hz, 12H), 3.52 (q, $J = 14.2$ Hz, 8H), 3.56–3.65 (m, 160H), 4.44 (s, 4H), 4.64 (s, 4H), 7.39 (s, 2H), 7.50 (d, 4H), 7.73–7.77 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 15.6, 60.2, 62.1, 62.5, 67.1, 70.3, 70.6, 70.78, 70.82, 70.91, 70.99, 71.05, 71.1, 72.9, 123.0, 127.1, 127.5, 129.1, 129.5, 132.9, 135.1, 137.1, 137.4, 137.5, 139.2, 140.1. Only one synthesis of compound **8c** has been reported in Ref. 11a, but no experimental details or yields are included for this product. Purchased compounds were used without purification. Triethylene glycol monomethyl ether (**5**), diethylene glycol monoethyl ether (**11**) and tetraethylene glycol (**13**) were commercial, and purchased from Aldrich. *p*-Diiodoterphenyl (**9**) was prepared from terphenyl following reported procedures: Unroe, M. R.; Reinhardt, B. A. *Synthesis* **1987**, 981.
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17. Raman spectra were recorded on neat products on a Renishaw InVia Reflex Raman Microscope System using the 785 nm line from a diode laser. The laser power at the sample position was 5 mW and the spectra were recorded using a Leica microscope with a 50× objective working at a resolution of 4 cm^{-1}.