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Synthesis of Sequence Specific Phenylacetylene Oligomers on an Insoluble Solid Support

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We have previously reported synthetic routes to precisely defined dendrimeric,[1] linear,[2] and macrocyclic[3] poly(phenylacetylene)-based nanoarchitectures.[4,5] In this communication, methods are described for synthesizing phenylacetylene oligomers on an insoluble polymer matrix. Terminal acetylene and aryl halide moieties are orthogonally masked as (trimethylsilyl)acetylene and 1-aryl-3,3-dialkyltriazene groups, respectively, during our macromolecule construction. Selective and facile removal of these protecting groups precedes Pd(0)-catalyzed coupling of the terminal acetylene group to an aryl iodide. The efforts described here focus on the strategy of using the insoluble polymer as a masked aryl iodide by attaching functionalized aromatic monomers to polystyrene beads via the 1-aryl-3,3-dialkyltriazene group (Figure 1). These robust triazene linkers lead to advantages over traditional solution methods by obviating the need to handle toxic 1-aryl-3,3-dialkyltriazene solutions as well as by leading to the simplified purifications and enhanced yields associated with the solid phase technique.[6] The initial goals of this investigation were to identify suitable linking strategies, modify the coupling and deprotection conditions to be compatible with the swelling characteristics of the polymer, develop qualitative monitoring methods that accurately reflect the reaction completeness at any stage, and probe the limits of polymer-bound oligomeric growth.

Scheme 1 illustrates the fragment condensation approach we investigated.[7] During this process, a portion of the supported oligomeric sequence is liberated from the polymer and then coupled to the remaining supported sequence that has had the trimethylsilyl protecting group previously removed. The first synthetic target for polymer-supported synthesis chosen was a hexameric precursor to our first reported phenylacetylene macrocycle,[3] allowing a direct comparison with the solution-based chemistry. Peptide coupling of a triazene−acid linker to aminomethylated polystyrene was estimated to be >90% complete by Kaiser's qualitative ninhydrin test.[8] The unreacted benzylamines of resin **1** were "capped" as their acetamides to give a negative ninhydrin test (<0.1% free NH_2). Conservative estimates of theoretical yields were calculated by adjusting the original substitution of the polymer to account for the mass gain or loss for each transformation. At each step, the completeness of reaction was assessed by liberating the oligomer from the support followed by characterization of the substrate. The overall yield to pure, unbound hexamer after a total of 10 reactions was 61%, which is much higher than for solution methods.[3] The liberated hexamer was contaminated with trace impurities,[9] as assessed by TLC, GPC, and ^{1}H NMR, that were easily removed by filtration through SiO_2. At this stage, the polymer-supported approach was deemed superior to the solution synthesis, mainly because it is much easier to purify the intermediate sequences. A key issue, lacking with this linking protocol, involves assessing the completeness of reactions on the polymer-bound material. The broad amide N−H stretch of the peptide linker made IR monitoring impractical because of its overlap with the terminal acetylenic C−H stretch at 3311 cm^{-1}. The inability to quickly and efficiently monitor polymer-bound reactions was a significant drawback in this preliminary study.

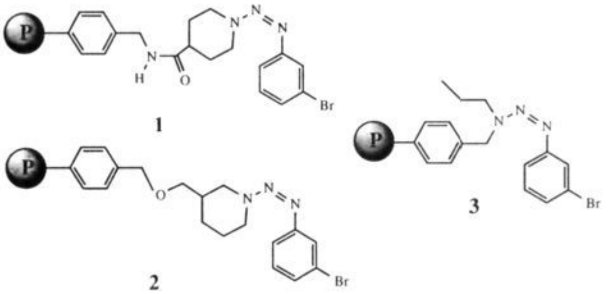

Figure 1. Functionalized aromatic monomers linked to polystyrene beads via the 1-aryl-3,3-dialkyltriazene functional group.

Etherification of chloromethylated polystyrene[10] with an excess of an alcohol−triazene provided the supported aryl bromide **2,** which was further elaborated to the corresponding protected phenylacetylene by Pd(0)-catalyzed coupling with (trimethylsilyl)acetylene. The nonlinear repetitive doubling strategy was pursued without incident through the hexadecamer stage. The completeness of each reaction was estimated by infrared analysis of the polymer bound substrate as shown in Figure 2. Absorptions at 3311 cm^{-1} (strong) and 2109 cm^{-1} (weak) are characteristic of the terminal acetylenic carbon−hydrogen and carbon−carbon stretches, respectively and an absorption at 2156 cm^{-1} (strong) is assigned to the carbon−carbon stretch of the trimethylsilyl-protected terminal acetylene.[11] The coupling reaction is accompanied by the disappearance of the 3311 cm^{-1} band and the appearance of the 2156 cm^{-1} absorption. The trimethylsilyl deprotection step was similarly monitored, in that the 2156 cm^{-1} band disappears and the 3311 cm^{-1} band appears. The reliability of this "null to null" infrared monitoring was confirmed by removal and characterization of the trimethylsilyl-protected product. The hexadecamer was obtained in 50% overall yield for the 11 steps.[12] Attempts to double oligomer length from 16 to 32 were only partially successful, due largely to solubility problems. Not only was the liberated hexadecamer poorly soluble in media suitable for the Pd(0)-catalyzed cross coupling reaction but perhaps more critically the swelling behavior of the polymer was diminished at the present level of loading. The diminished swelling was initially observed during the postcoupling washing procedure, which involves repetitive shrinking and swelling of the resin. The infrared analysis is also adversely affected to the point where it is no longer an accurate indictor of reaction

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[9] The crude purity is typically 95+%, and the unidentified contaminants are higher in molecular weight than the product.

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[12] The high molecular weight impurities become difficult to separate by (SiO_2) chromatography from the hexadecamer stage on.

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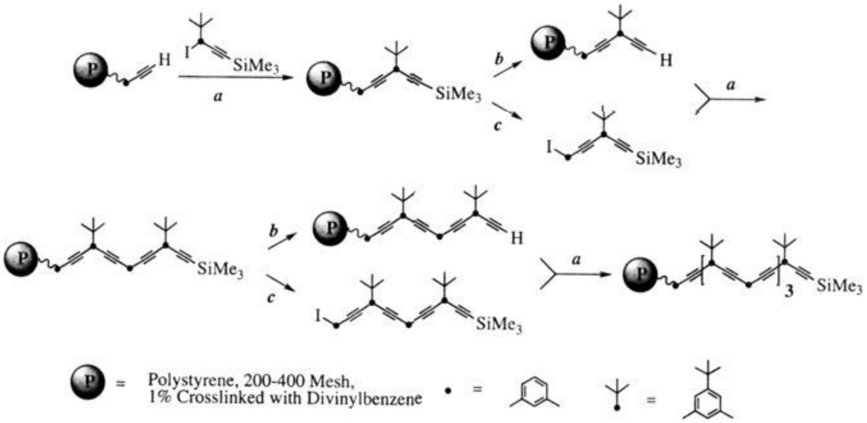
Scheme 1. Nonlinear Repetitive Growth Scheme for the Sequence Specific Synthesis of Phenylacetylene Oligomers[a]



[a] Reagents: (***a***) bis(dibenzylideneacetone)palladium(0), cuprous iodide, triphenylphosphine, triethylamine, DMF, 65 °C, 24 h; (***b***) potassium hydroxide, THF, MeOH, 75 °C, 1 h; (***c***) methyl iodide, 110 °C, 6 h.

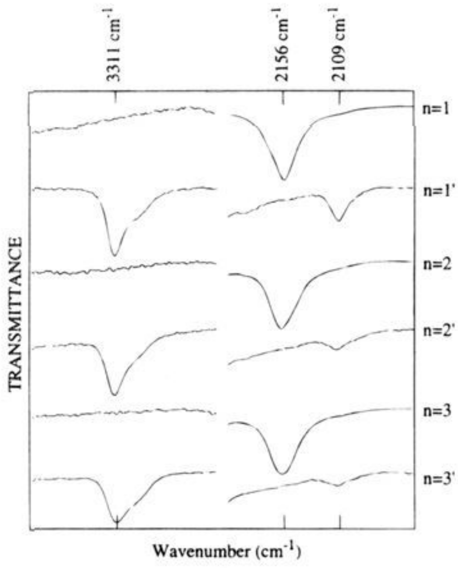


Figure 2. Monitoring of coupling and deprotection reactions on polymer-bound oligomers by infrared spectroscopy. Observations of nulls at 3311 cm^{-1} or 2156 cm^{-1} correspond to complete acetylene coupling and (trimethylsilyl)acetylene deprotection, respectively (n represents the number of repetitive reaction cycles, where $n = 1$ and $n = 1'$ correspond to trimethylsilyl-protected and unprotected dimers, respectively).

completeness, presumably because the sample preparation involves swelling the polymer with carbon tetrachloride. The best coupling conditions gave product a with a 95 to 5 ratio of the desired 32-mer product to unreacted hexadecamer. The solid support that contained this mixture of 32-mer and hexadecamer was subjected to the doubling sequence to produce a 64-mer and the expected lower homologues. This mixture still contained unreacted hexadecamer, suggesting that, since there is no apparent onus on the oligomer length, these sites were becoming inaccessible. These experiments lead us to believe that the synthesis of monodisperse high molecular weight linear phenylacetylenes may be possible by lessening the polymer loading and incorporating more solubilizing groups.[13]

Finally, we have developed a direct triazene link to polystyrene (e.g., **3**) that allows for infrared monitoring and incorporation of a wider range of pendant functional groups and eliminates the need to synthesize the trifunctional triazenes needed to prepare resins **1** and **2**. With the efficient way these polymer-bound reactions can be monitored, the combined time for the Pd(0) cross coupling, trimethylsilyl deprotection, and liberation has been reduced to only 31 hours.

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Supplementary Material Available: Figures displaying characterization data for the linkers and oligomeric sequences and text describing general procedures for polymer-supported reactions are presented (11 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfiche version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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