Towards Aza helicenes

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Progress towards the synthesis of aza helicenes is described in this paper. The synthetic strategy entails polymerization by Stille coupling of a polyphenylene followed by imine bridge formation results in a rigid helicene. Work towards the synthesis of 6,8-diaza-dibenzoanthracene has been carried out in order to create a test case complex. Successful completion of this complex will demonstrate the feasibility of this synthetic strategy. The synthesis towards the monomeric subunit needed for the formation of the test case helicene is presented within.

Introduction

Helicenes which were first synthesized by Lednicer and Newman in 1955.1 They are nonplanar, chiral, ortho-fused, aromatic structures composed of repeating benzenoid rings.1 Due to steric hindrance, ortho-helicenes with six or more benzenoid rings twist out of a planar geometry to form a chiral helix (Figure 1) numbered as shown.2

In 2003, a new class of helicene was proposed by Balaban. In his work, Balaban described the synthesis of \([n, 3, 1]\) helicenes, where \(n\) represents the number of \(\beta\)-vinylacenic groups.3 This paper will present the progress made toward the synthesis of \([n, 3, 1]\) helicenes containing nitrogen functionality; specifically \(m\)-aza-helicenes (Figure 2).
Aza-helicenes possess unique properties. Flexible helical structures can be found in the synthesis of poly (m-phenylenes) (PMPs)\textsuperscript{4} which are useful as a copolymer in poly (p-phenylene) (PPPs). Such materials are used as colored tuned light emitting diodes (LED’s)\textsuperscript{5,6}.

The inclusion of basic sites allows for multiple protonations of the polymer chain.\textsuperscript{7} This allows polymers such as these to participate in acid/base chemistry which causes the helicene to expand and contract when protonated and deprotonated, respectively. Protonation of the bridging imine allows the helicene to expand.\textsuperscript{7} The ability of these molecules to expand and contract is motivated by molecular dynamics calculations. Rempala and King have demonstrated that protonation of bridging nitrogens causes a reversible 160\% increase in the length of the helicene.\textsuperscript{8} With this in mind, it is potentially feasible to control the length of the helicene simply by controlling pH. Several synthetic strategies for the formation of imine-bridged PPPs have been studied by Tour et. al.\textsuperscript{9} In their work, polymerization was achieved through an A, B step polymerization using the monomers shown in Figure 3.
Addition of acid to the polymer deprotects the Boc-protected amines and catalyzes imine formation. Using this synthetic strategy as a model, but extending it to a PMP system, we hope to synthesize a large m-aza-helicene (Scheme 1).

**Experimental**

Unless otherwise stated all reactions were carried out under nitrogen atmosphere using conventional schlenk techniques. NMR spectra were obtained at 300, and 500 MHz in CDCl₃ (unless otherwise noted), and chemical shifts were reported in ppm. Chemical shifts for ¹¹⁵Sn NMR were found with respect to a reference sample of tributyl tin chloride. All solvents were purchased from Acros Organics, Alfa-Aesar, Fischer or Aldrich and used as received unless
otherwise stated. All catalysts were dispensed in a glove box under Ar. Dry, degassed tetrahydrofuran was dispensed in the glove box and kept dry under molecular sieves.

**2,4-dibromo-**m-xylene (1)**

Bromine (48.40 mL, 941.8 mmol) was introduced over a period of one hour to a solution of m-xylene (57.86 g, 470.9 mmol) and iodine (0.597 g, 2.354 mmol) at 0°C being careful to exclude light from the reaction. The solution was warmed to room temperature for 24 h. The resulting orange solid was quenched with a potassium hydroxide solution (10% w/w, 100 mL). The resulting white solid was filtered and collected. The solid was recrystallized in 95% ethanol and dried to yield 1 (60.2131 g) in 48.4% yield. Spectra were identical to those reported in previous literature.**

**2,4-dibromo isophthalic acid (2)**

To a stirred solution of 1 (29.78 g, 112.8 mmol) in 200 mL butanol and 200 mL water, potassium permanganate (34.98 g, 221.4 mmol) was added. The solution was allowed to reflux at 100°C for 1 h, after which an additional amount of potassium permanganate (37.37 g, 236.2 mmol) was added. The reaction was refluxed at 100°C until a purple color was no longer observed. The mixture was filtered and washed with distilled water. The filtrate was slowly acidified to pH~1 with 3M HCl and the resulting white suspension was extracted with ethyl acetate. The solvent was removed and the solid recrystallized with water and dried to afford 2 (20.79 g) in 56.9% yield (based on recovered starting material). Spectra were identical to those reported previously.**

**N,N'-bis(tert-butoxycarbonyl)-1,5-diamino-2,4-dibromobenzene (3)**

In a nitrogen atmosphere, tert-butanol (55 mL) was added to a three neck round bottom flask. Triethylamine (0.86 mL, 6.174 mmol), diphenylphosphoryl azide (1.33 mL, 6.17 mmol)
and 2 (1.000 g, 3.087 mmol) were added. The stirred solution was allowed to reflux for 1 d. The solvent was removed. column chromatography (hexane/dichloromethane (1:1)) afforded 3 (0.499 g, 1.410 mmol) in 42.8% yield. \(^1\)H NMR (C\(_6\)D\(_6\)) \(\delta\): 7.20, 7.05 (C\(_6\)D\(_6\)), 6.80, 1.25, 0.30 ppm. \(^{13}\)C NMR (CDCl\(_3\)) \(\delta\): 151.97, 136.41, 134.36, 134.23, 129.33, 81.47, 26.34 ppm.

\(\text{N, N'-bis(tert-butoxycarbonyl)-1,5-bis(tri-n-butylstanyl)benzene (4)}\)^\(13\)

Under N\(_2\) atmosphere, 3 (200 mg, 0.5263 mmol), was dissolved in THF (15 mL) and diethyl ether (15 mL) and cooled to -78\(^\circ\) C. Methyl lithium (1.670 mL, 4.505 mmol) was added over 10 minutes. The solution was allowed to stir for 10 minutes before it was slowly warmed to 0\(^\circ\) C. The solution was recooled to -78\(^\circ\) C and tert-butyl lithium (6.940 ml, 1.7 M, 9.653 mmol) was added dropwise. The solution was slowly warmed to 0\(^\circ\) C, and then stirred for 4 h. The reaction was cooled again to -78\(^\circ\) C, and tri-butyltin chloride (1.510 mL, 5.577 mmol) was added dropwise. The solution was warmed slowly to 0\(^\circ\) C and then to room temperature. Water was added and the aqueous layer was extracted twice with ethyl acetate. The combined organic extracts were washed twice with water then brine, and dried over sodium sulfate. Flash chromatography was run with hexane as the eluent, flushing with ethyl acetate. Flash chromatography was run a second time with only hexane to yield 4 (0.320g, 16.86%). \(^1\)H NMR (CDCl\(_3\)) \(\delta\): 7.63, 7.25, 6.88, 1.50, 1.30, 1.13, 0.88 ppm. \(^{115}\)Sn NMR (CDCl\(_3\)) \(\delta\): -342 ppm.

**Formation of flexible terphenyl (5) by Stille Coupling\(^{9(c)}\)**

In a Schlenk flask, N-methyl-2-pyrrolidine (1.5 mL) and THF (1.5 mL) were stirred. Tri (t-buty) phosphate (0.400 mL, 0.008 mmol), copper (I) iodide (1 mg, 0.0053 mmol), o-bromobenzaldehyde (40 mg, 0.176 mmol), and 4 (80 mg, 0.088 mmol) were added. Palladium dichloride (1.2 mg, 0.029 mmol) and cesium fluoride (27 mg, 0.176 mmol) were added and the solution was stirred at 100\(^\circ\) C for 2 days. The reaction was quenched with water and extracted
three times with ethyl acetate. The combined extracts were washed twice with water and then with brine. Column chromatography was performed using ethyl acetate/hexane as the eluent (1:10). Like fractions were collected and the solvent removed. $^1$H NMR (CDCl$_3$) $\delta$: 12.32, 12.15, 12.03, 10.74, 8.83, 8.73, 7.84, 7.24 ppm.

**6,8-diaza-dibenzoanthracene (6)**

The flexible terphenyl, 5 (100mg, 0.165mmol), was dissolved in 1 mL d$_6$-DMSO. NMR data was taken at 25, 90, and 120° C looking for a change in the spectrum indicating cyclization. Current results show no indication of polymerization reaction.

**Results and Discussion**

The synthetic route towards one of the monomers needed to form the $m$-aza-helicene is shown in Scheme 2.

![Scheme 2](image_url)
The first step involves the bromination of \( \text{m-xylene, 1.}^{10} \) An oxidation protocol to afford \( \text{2,4-dibromo-m-xylene, 1} \) was developed.\(^{11} \) This required direct oxidation, which is performed using potassium permanganate in butanol and water. This reaction however, has presented challenges. The oxidation results in a large amount of unreacted starting material (~50%). The reported yield is based on recovered starting material with optimized conditions. \( \text{3} \) was synthesized through a Curtius rearrangement using diphenylphosphoryl azide, DPPA, and triethylamine in refluxing \( \text{t-butanol. This reaction occurs in fair yields (43.7%).}^{12} \)

To perform the Pd-catalyzed polymerization one monomer must be metalated. This is achieved through a lithium-halogen exchange which selectively monolithiates when one equivalent of butyllithiumis used. This step was optimized with previously synthesized \( \text{2,4-dibromo-m-xylene (Scheme 3).}^{8} \)

\[
\begin{align*}
\text{Br} & \quad \text{organolithium} & \quad \text{Sn(Bu)}_3\text{Cl} \\
\text{Br} \quad \text{Li} & \quad \text{Li} & \quad \text{(Bu)}_3\text{Sn} \\
\text{Sn(Bu)}_3 & \quad \text{Sn(Bu)}_3
\end{align*}
\]

\textbf{Scheme 3.} general reaction for lithium halogen exchange

Dilithiation requires a strong lithiating agent. Test lithiations were run and it was determined that \text{t\textsubscript{er}t-BuLi} was the optimal lithiating agent. However, methyl lithium must first be used. The lithium-halogen exchange with \text{t-BuLi} (but not MeLi) is faster than the deprotonation of the BOC-protected imine and the result is the reduction of the complex.\(^{13} \) Optimal conditions were found when MeLi (1.1 eq) followed by \text{t\textsubscript{er}t-BuLi} (2.2 eq) were used.

Two scenarios can be envisioned for the Pd-catalyzed polymerization. In the first, the BOC-protected diamine bears the stannyl functionality and the acetal-protected dialdehyde bears the halogens. In the other, the BOC-protected diamine bears the halogens and the acetal-
protected dialdehyde bears the stannyl functionality. Due to the electron withdrawing effect of the acetals, the Pd-catalyzed polymerization will only proceed under the functionalization of the diBOC protected dibromo compound (4). Metalation was achieved by lithiation followed by quenching with tri-butyltin chloride (Scheme 4). The resulting mixture was purified by column chromatography to afford a clear oil. The remaining impurities are removed by subsequent chromatography with a less polar solvent. This compound can potentially be purified by preparative HPLC.

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\begin{align*}
\text{Scheme 4. Formation of 4} \\
\end{align*}
\]

6,8-diaza-dibenzoanthracene is synthesized in the Stille coupling of 4 with 2-(2-Bromo-phenyl)[1,3]dioxane (Scheme 5). Synthesis of this monomer will demonstrate the polymerization to form an aza helicene. Work towards the completion of 5 and 6 is in progress. The reaction is followed by a water workup and then column chromatography (10% ethyl acetate in hexanes) to afford a yellow oil. Characterization of this complex has not yet been completed.
Scheme 5. Formation of 6,8-diaza-dibenzoanthracene

Future Studies

Flexible terphenyl 5 can form 6 by acid promoted deprotection and imine formation. The reaction can be monitored by NMR.

The synthesis of m-aza-helicenes, 8, will be achieved by co-polymerization of monomers 4 and 7 followed by imine bridge formation. The general strategy is expressed in Scheme 6.

Scheme 6. Stille coupling to form polymer
In order for the polymerization reaction to succeed, it must be possible to synthesize both of the monomers in high yield and purity. Due to the low yield of 4, an alternate route may be necessary. The abundance of coupling strategies as well as the ability to functionalize either monomer presents an array of options that have yet to be explored. As such, it may be desirable in the future to try different combinations of monomers in an attempt to produce longer polymer chains.

**Conclusion**

The work done towards the synthesis of large, imine bridged helicenes has been introduced. Various monomers have been synthesized to participate in the polymerization reaction. Characterization of the flexible terphenyl as well as the closed terphenyl has not yet been completed. With the efficient synthesis of each monomer and evidence of a successful test case, it is possible to produce a large helical chain.

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References


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