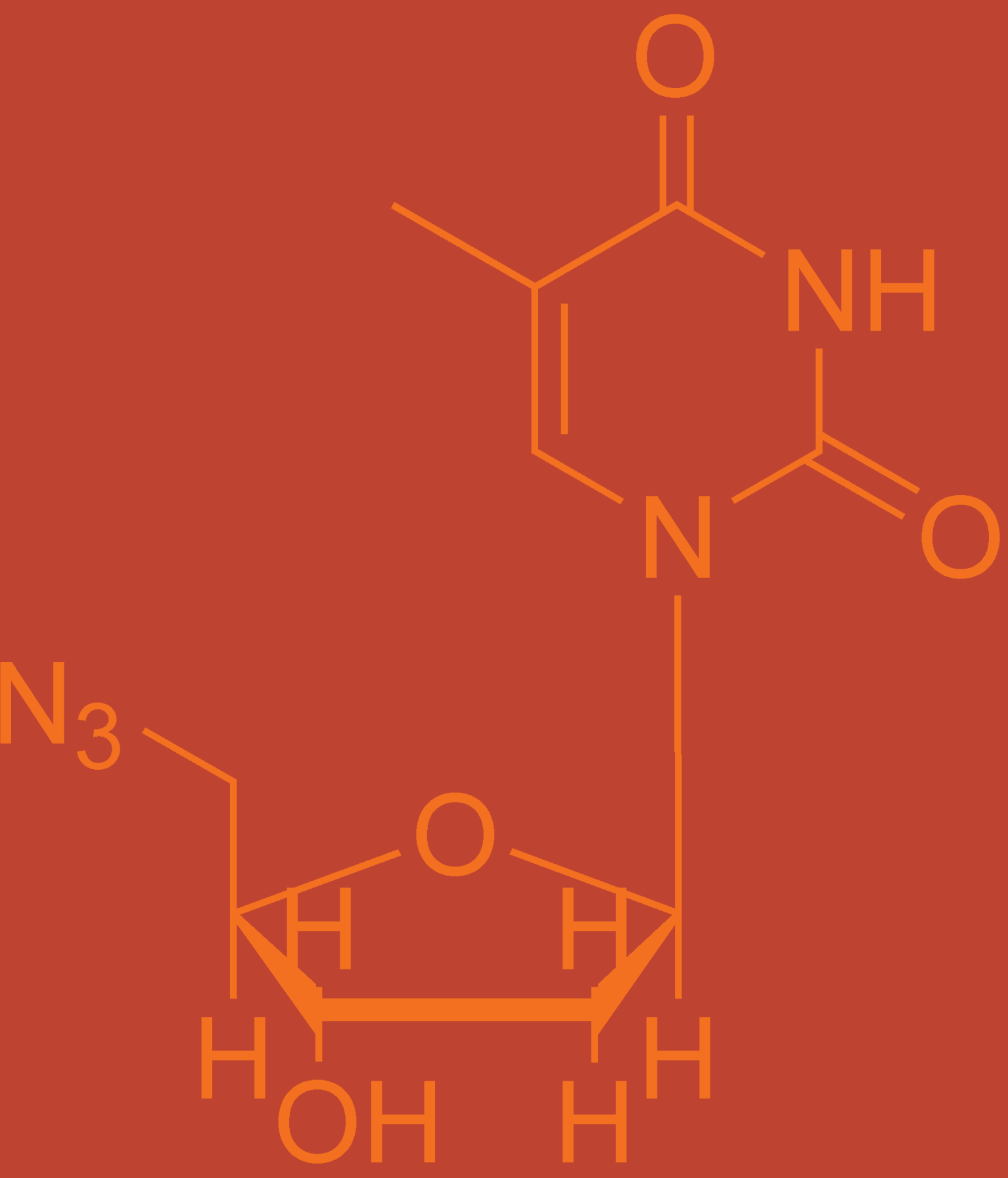
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Progress toward "Click"-Based Small-Molecule DNA Hybrids: Syntheses of Precursors to Acetylene-Terminated Cores and Azide-Functionalized Arms

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Abstract

This paper reports the synthesis of an azide-functionalized deoxynucleoside as a precursor for azide-terminated oligonucleotides. Also reported is the synthesis of an acetylene-terminated precursor, which can be used to make a diverse array of silyl-protected acetylene-terminated small molecule cores. Both of these precursors serve as basic building blocks en route to stable "click"-based small-molecule DNA hybrids.

Introduction

There are nearly 4,000 known genetic diseases affecting the human population today, with new ones discovered every year. Many of these genetic disorders are caused by minor deviations in the normal genetic code, often in the form of single-base mutations or single-nucleotide polymorphisms (SNPs). Diagnosing such diseases requires detection assays that are both highly selective and highly sensitive. While excellent DNA detection strategies have been developed over the last decade, an easily-deployed, fast and accurate system has yet to be achieved.

Recently, several DNA detection systems have been developed based on the sharpened melting profile (compared with that of free DNA) exhibited by aggregated DNA hybrids (Figure 1). When duplex DNA is heated, it denatures into two strands over a range of temperatures. The percent of hybridized DNA at a given temperature can be measured and used to construct a "melting curve" whose inflection point is defined as the melting point (mp) of the DNA sample. Because duplex DNA containing mismatched base pairs has fewer complimentary interactions (hydrogen bonds) than a fully complementary DNA duplex of comparable length, the former would melt at a lower temperature than the latter, and the difference in melting points can be used as a basis for SNP detection.

Interestingly, for aggregate systems where DNA strands are bundled together in parallel or near-parallel geometry, the associated duplexes melt significantly more sharply than comparable free DNA duplexes. This property accentuates the melting point differences between fully

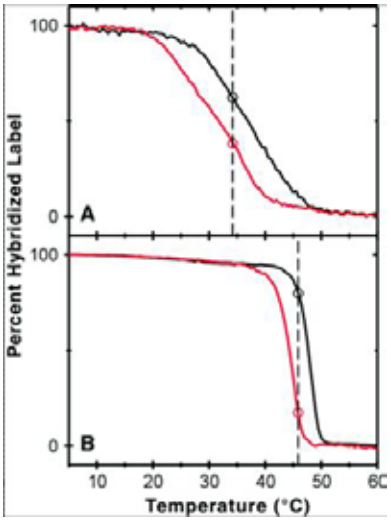

Figure 1. The difference in melting profiles for free DNA (A) and aggregate DNA (B) (adapted from Taton et al. *Science* 2000, 289, 1757–60). The graphs indicate the percent of intact duplexes for perfectly complementary DNA pairs (black) and DNA pairs having a single base-pair mismatch (red). The free DNA system — one where each individual "unit structure" has only a single DNA strand attached — is represented in the top picture by fluorescein-labeled DNA probes. The aggregate system — one where each individual "unit structure" has multiple DNA strands attached — is represented in the bottom picture by the DNA-gold nanoparticle hybrids.

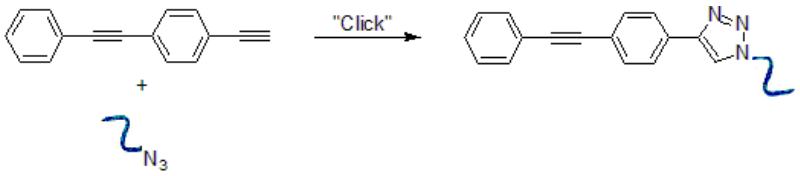

Figure 2. Proposed strategy for linking DNA to small molecule using click chemistry.

complementary and mismatched duplexes in the melting region (Figure 1, cf a and b), and allows for the selective removal of the latter via stringency washes at the temperature where there is the biggest difference in the percent of hybridized DNAs. It is difficult to use stringency washes to discriminate between complementary and mismatched DNA duplexes of comparable lengths when the melting profile is broad (Figure 1a), because both melt over a shared temperature range (Figure 1). Although aggregate systems demonstrating these sharp melting transitions recently have been implemented in commercial prototypes for DNA detection, a complete description of the parameters that govern such sharp melting behavior has not been achieved.

To improve the hybrid DNA materials currently used in DNA detection applications, it is critical to fully understand the processes governing the interactions between such materials and a target DNA sequence (i.e., the sequence that marks a particular disease). In this sense, small-molecule DNA hybrids (SMDHs) possessing fixed geometries and a number of DNA strands can serve as an ideal model system for deciphering structure-property relationships in hybrid DNA materials. The parameters that affect the observed sharp melting transitions can be systematically unraveled because the structure of the SMDHs can be tuned in a modular fashion, which enables superior detection methods.

Stepp and colleagues have recently synthesized a three-armed SMDH with a rigid phenylacetylene core that is ideal for maintaining a fixed geometry between parallel DNA arms.[1] While this SMDH exhibits sharp melting when treated with its complementary SMDH at very dilute concentration, its low stability — a consequence of the labile benzylic phosphate-ester linkage between the core and the DNA arms — prohibited further studies. In addition, the divergent approach used to synthesize these SMDHs requires a tedious multistep process that is not ideal for creating a diversity of core molecules — any variation of the intended core structure would require a significant reworking of the synthetic route. Hence, there is interest in synthesizing more stable SMDHs using a more convergent method based on modular synthons and readily available starting materials.

The synthesis of triazole-linked SMDHs through the connection of azide-terminated DNA strands to acetylene-terminated small molecules using click chemistry (Figure 2) is proposed to prevent instability and ease diversification.[2] By attaching DNA to rigid phenylacetylene-based core structures through a stable triazole linkage, stronger and more stable SMDHs can be produced. In addition, the modular synthetic approach will ease diversification, thereby permitting a wide range of SMDH materials to be synthesized and studied. This will lead to the development of improved DNA detection systems.

Background

C.A. Mirkin and coworkers demonstrated that treating DNA-modified gold nanoparticles (GNP) with complementary DNA-modified GNPs results in the formation of aggregate structures with sharp melting transitions. This discovery has led to use of these structures as DNA-detection probes.[3–4] Such probes can selectively report a mismatch between a single base-pair in a short DNA duplex where similar assays like molecular fluorophore probes cannot (Figure 1). However, due to difficulty in controlling synthetic variables such as oligonucleotide density,[3] DNA-GNP aggregates do not make an ideal model for studying the sharp melting phenomena in depth.

Alternatively, ROMP (ring-opening metathesis polymerization)-based polymer DNA hybrids have been synthesized and used as electrochemical probes for DNA detection.[5] Similar to the gold nanoparticles, aggregates of these hybrids also exhibit sharp melting behaviors. But they too permit only limited control over certain properties, including DNA orientation and spacing, which makes them less than ideal models to further study DNA melting properties.

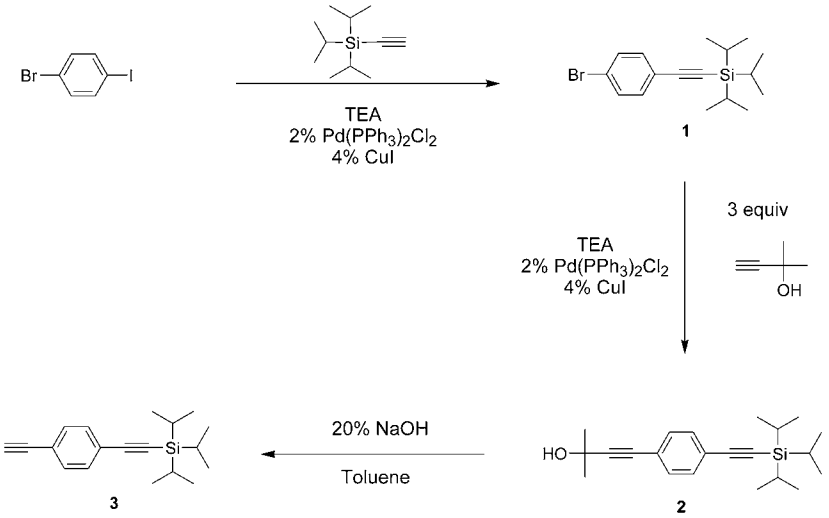

Figure 3. Synthesis of precursor 3.

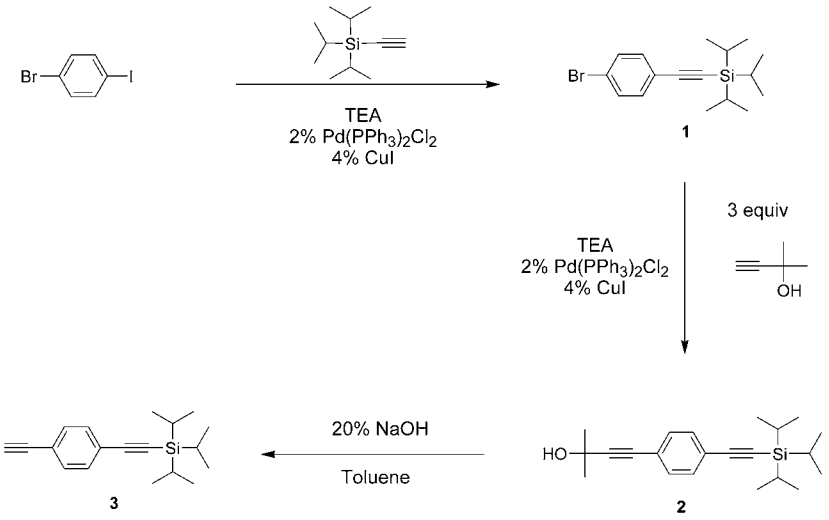

Figure 4. Synthesis of Small Molecule 1 (SM1).

Progress toward "Click"-Based Small-Molecule DNA Hybrids: Syntheses of Precursors to Acetylene-Terminated Cores and Azide-Functionalized Arms *(continued)*

Approach

As shown in Figure 2, click-coupling requires both an azide-terminated molecule and an acetylene-terminated molecule to form a triazole linkage. Applying this strategy to SMDH formations is appealing because click reactions have been shown to be high yielding and very selective.[2] In addition, triazoles are known to have excellent stability and should afford more stable SMDHs than the benzylic phosphate ester analogs. Once these stable click-based SMDHs are made, detailed studies can delineate the fundamental parameters that govern the unique melting properties of materials possessing multiple DNA strands.

To access a variety of acetylene-terminated small-molecule cores, a versatile synthon like (4-ethynylphenyl) triisopropylsilylacetylene (**3**) is desired. Precursor **3** is an efficient building block because it can be combined readily with many different aryl halides to afford geometrically well-defined SMDH cores.[6,7] After these small-molecule cores with silyl-protected peripheries are made, the triisopropylsilyl (TiPs) group can be easily deprotected to leave terminal acetylene reactive sites for click chemistry, which is where DNA will be linked to the core molecule.

In the synthesis of **3**, 1-bromo-4-iodobenzene was first coupled to triisopropylsilylacetylene to afford **1** (Figure 3) in good yield. A second coupling between **1** and 3-hydroxy-3-methylbutyne, to add a second acetylene group to the opposite side of the phenyl ring, resulted in **2**. Selective deprotection of **2** then yielded the acetylene-terminated precursor **3**.

Once precursor **3** was synthesized, it was coupled to a variety of aryl halides to give one-, two-, and three-armed cores with silyl-protected periphery acetylenes. Given their higher reactivities compared with the chloride analogs, mono-, di-, and tribromobenzene derivatives were initially employed in these reactions. However, yields ranged from low for bromobenzene to nonexistent for 1,3,5-tribromobenzene. By comparison, the coupling of **3** with 1,4-diiodobenzene afforded much better yields, suggesting that the increased reactivity of aryl iodides may make them better substrates in the synthesis of SMDH cores. Although microwave irradiation was employed in a few of these couplings, attempts were not made to directly compare thermal and microwave reactions.

Attaching DNA to our SMDH core via click chemistry requires an azide-functionalized base that can be incorporated in solid-phase DNA synthesis. To this end, 5'-azido-2'-deoxythymidine was successfully synthesized in two steps. Reacting 2'-deoxythymidine with methanesulfonyl chloride resulted in 5'-O-methanesulfonyl-2'-deoxythymidine (**8**) in moderate yield. Treating **8** with an excess of lithium azide afforded 5'-azido-2'-deoxythymidine (**9**) in 88% yield.[8,9]

For **9** to be usable in the solid-phase synthesis of DNA, it must first be converted to a 3'-phosphoramidite. This process will result in an azide-terminated DNA strand that is ready to be linked to the acetylene-terminated SMDH cores (Figure 2). Due to time limitations, these last steps were not attempted.

Results

*Synthesis of (4-Bromophenyl)triisopropylsilylacetylene (**1**)*
Under a nitrogen atmosphere, triisopropylsilylacetylene (1.24 g, 6.81 mmol) was added to a 25-mL round-bottom flask containing 1-bromo-4-iodobenzene (2.12 g, 7.49 mmol), $(PPh_3)_2PdCl_2$ (0.099 g, 0.14 mmol), CuI (0.025 g, 0.13 mmol), and triethylamine (TEA, 10 mL). The reaction mixture was allowed to stir under nitrogen overnight before being evaporated to dryness. The resulting oil was dissolved in a minimum amount of hexanes and was purified using silica gel chromatography (8 cm diameter x 10 cm length) and hexanes as the eluent. After solvent removal, the isolated product appeared as a clear liquid (1.91 g, 5.65 mmol, 75%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.4 (d, 2H), 7.2 (d, 2H), 1.051 (s, 21H); the methine protons of the TiPS group could not be identified, consistent with literature observations.[8]

*Synthesis of 2-Methyl-4-{4-[(triisopropylsilyl)ethynyl]phenyl} but-3-yn-2-ol (**2**) (Figure 3)*
Under a nitrogen atmosphere, 3-hydroxy-3-methylbutyne (1.41 g, 16.8 mmol) was added to a 50-mL round-bottom flask containing **1** (1.89 g, 5.60 mmol), $(PPh_3)_2PdCl_2$ (0.076 g, 0.11 mmol), CuI (0.020 g, 0.11 mmol), and triethylamine (10 mL). The reaction mixture, allowed to reflux under nitrogen overnight, revealed crystallization when cooled to room temperature. Enough diethyl ether was then added to dissolve the crystals, the reaction was filtered over a Buchner funnel and the filtrate was evaporated to dryness using a rotary evaporator. The remaining residue was dissolved in a mixture of pentane:ethyl acetate (9/1 v/v), and purified using silica gel

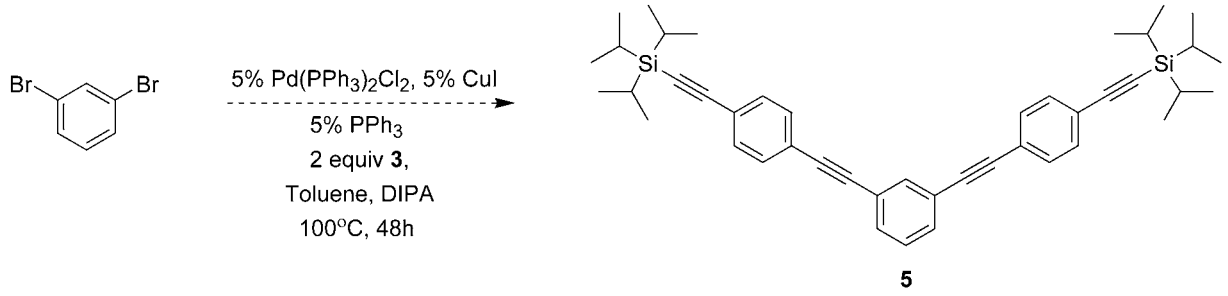

Figure 5. The final attempt to synthesize Small Molecule 2 (SM2).

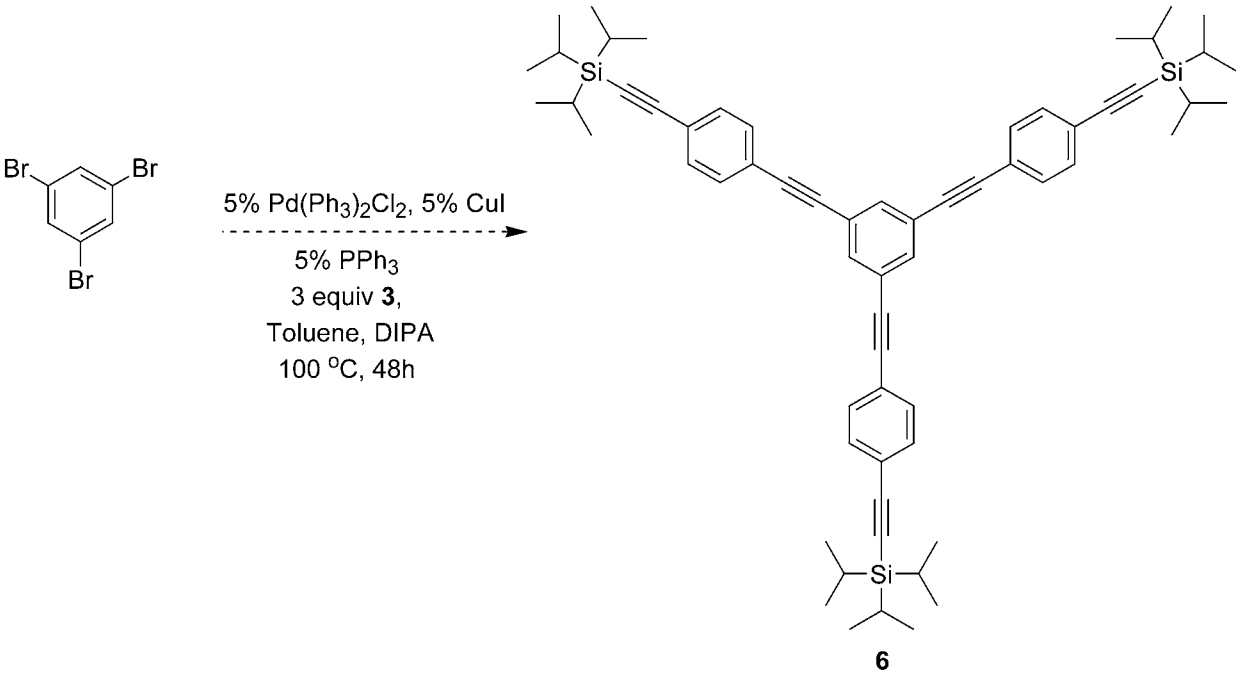

Figure 6. An attempt to synthesize Small Molecule 3 (SM3).

chromatography (8 cm diameter x 10 cm length) and a mixture of pentane:ethyl acetate (9/1 v/v) as the eluent. After solvent removal, the isolated product appeared as a light- brown solid (0.903 g, 2.65 mmol, 51%). ^{1}H-NMR (400 MHz. $CDCl_3$): δ 7.42 (d, 2H), 7.39 (d, 2H), 1.626 (s, 6H), 2.05 (s, 1H), 1.131 (s, 21H); the methine protons of the TiPS group could not be identified, consistent with literature observations.[8]

*Synthesis of (4-ethynylphenyl)triisopropylsilylacetylene (**3**) (Figure 3)*
Selective deprotection of **2** was accomplished by adding NaOH (0.021 g, 0.53 mmol) to a solution of **2** (0.90 g, 2.60 mmol) in dry toluene (~ 20 mL) and allowing the resulting mixture to reflux under nitrogen overnight (Figure 3). After cooling to room temperature, the reaction mixture was evaporated to dryness in vacuo. The remaining crude product was dissolved in a minimum amount of hexanes:ethyl acetate (4/1 v/v), and was purified by silica gel chromatography (8 cm diameter x 5 cm length) using hexanes:ethyl acetate (4/1 v/v) as the eluent. After solvent removal, the isolated product appeared as a light-brown solid (0.355 g, 1.26 mmol, 61%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.427 (s, 1H), 1.132 (s, 21H); the methine protons of the TiPS group could not be identified, consistent with literature observations.[8]

*Synthesis of Small Molecule 1 (**SM1**) (Figure 4)*
In an inert atmosphere glovebox, precursor **3** (0.144 g, 0.50 mmol) was added to a 5-ml vial containing bromobenzene (0.08 g, 0.51 mmol), CuI (0.001 g, 5.2 mmol), $(PPh_3)_2PdCl_2$ (0.004 g, 5.0 mmol), and triethylamine (4 mL). This reaction mixture was microwave-irradiated (Biotage Initiator) for 4 hr at 80° C. GC-MS analysis of the reaction mixture at this point suggested incomplete reaction even though bromobenzene was completely consumed. Another equivalent of bromobenzene was added and the reaction was irradiated for an additional 2 hr at 80° C and reanalyzed with GC-MS, again showing incompletion. Only after an additional 3 hr of irradiation at 90° C did the reaction go to completion. The reaction mixture was then diluted with excess ethyl ether (20 mL), washed with 1N aqueous HCl (20 mL), dried over sodium sulfate, and filtered though a Buchner funnel. The collected organic was evaporated to dryness, redissolved in a minimum amount of methylene chloride, and passed through a silica gel column (8 cm diameter x 5 cm length) using methylene chloride as an eluent. After solvent removal, the isolated product appeared as a brown solid (0.040 g, 0.11 mmol, 22%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (t, 2H), 7.45 (t, 4H), 7.36 (d, 2H), 7.27 (s, 1H), 1.132 (s, 21H); the methine protons of the TiPS group could not be identified, consistent with literature observations.[8]

*Attempted Synthesis of Small Molecule 2 (**SM2**) (Figure 5)*
The synthesis of **SM2** was attempted multiple times using reaction conditions described above for **SM1** as a starting point. Each time two equivalents of **3** were used in combination with 1,3-dibromobenzene, and the reaction was carried out in an air-free environment. Although both starting materials were consumed, as detected by TLC, the desired product was not observed after reaction work-up, either via NMR or GC-MS.

On the first attempt, $(PPh_3)_2PdCl_2$ (1 mol%) and CuI (2 mol%) were employed with triethylamine as the solvent. The reaction was microwave-irradiated (Biotage Initiator, regular absorption setting) for 5 hr at 90° C and again for 4 hr at 110° C. TLC analysis of the reaction mixture using pentane eluent and UV visualization suggested several new species that are different from the starting materials. After work-up, the reaction mixture was separated using silica-gel chromatography with pentane as the eluent. However, ^{1}H NMR analysis of the three collected fractions did not give commensurate integration of the aromatic and TiPS protons (there were fewer TiPS protons than aromatic). It is possible that the high temperature conditions used in this reaction may cause degradation of the TiPS group.

On the second attempt, a matrix of solvent and temperature conditions was applied, again with $(PPh_3)_2PdCl_2$ (1 mol%) and CuI (2%) as the catalyst components; all reactions were microwave-irradiated (Biotage Initiator, regular absorption setting) for 4 hr. The four conditions were TEA as the solvent with heating at 120° C; TEA as the solvent with heating at 150° C; DMF:DIPEA (3/1 v/v) as the solvent with heating at 120° C; and DMF:DIPEA (3/1 v/v) as the solvent with heating at 150° C. DMF (dimethyl formamide) and DIPEA (diisopropylethyl amine) were employed to allow for higher temperature. Starting materials still remained after 4 hr. Further heating for an additional 6 hr followed. TLC analysis of the reaction mixtures using pentane eluent and UV visualization suggested several new species were formed in the reaction using the conditions of TEA solvent with heating

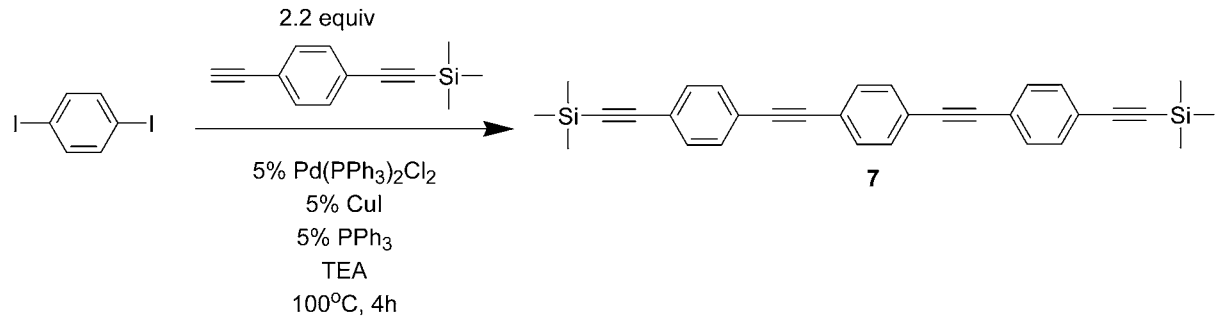

Figure 7. Synthesis of Bis(TMS-protected)-1,4-analog of SM2.

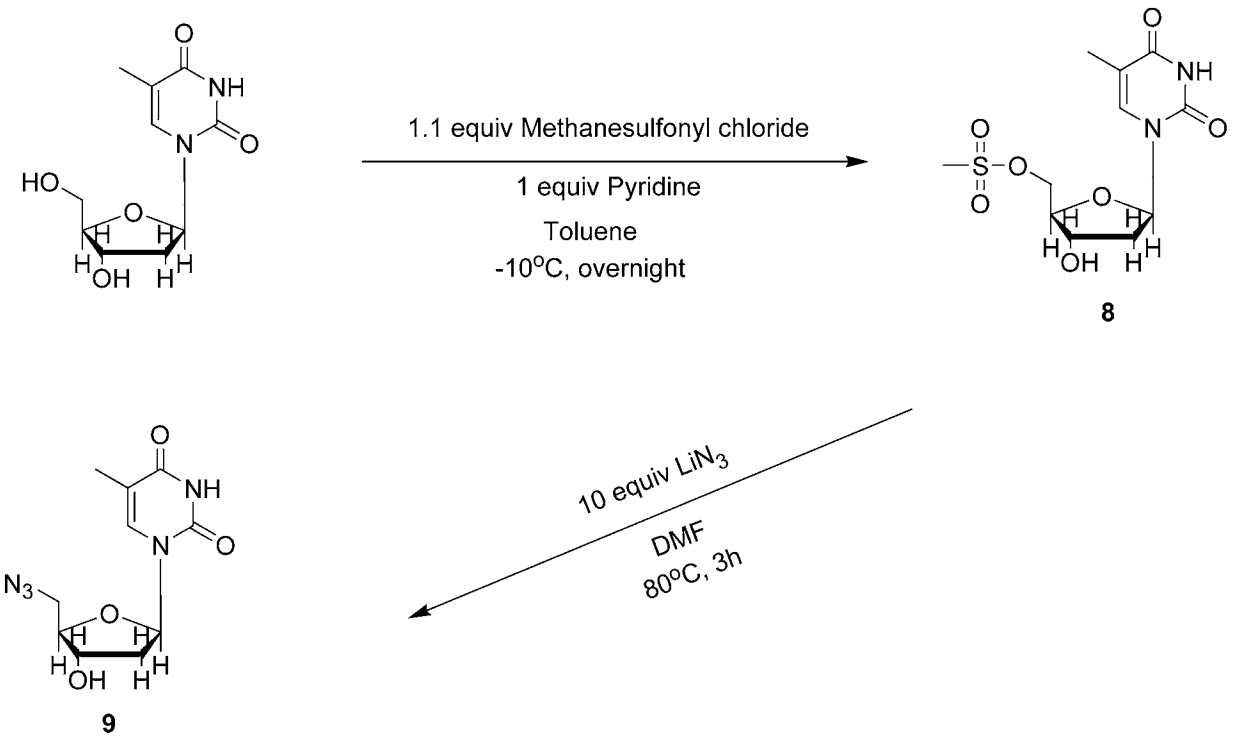

Figure 8. Synthesis of 5'-azido-2'-deoxythymidine.

at 120° C. The three other conditions showed little change from the initial starting materials. After work-up, the reaction mixture containing newly formed species was separated using silica-gel chromatography with pentane as the eluent. However, ^{1}H NMR analysis of the three collected fractions did not give commensurate integration of the aromatic and TiPS protons (there were fewer TiPS protons than aromatic). It is possible that high temperature conditions used in this reaction may cause degradation of the TiPS group.

On the final attempt, the concentrations for both catalyst components were increased to 5 mol% and excess PPh3 (5 mol%) was included as a stabilizer for the catalyst (Figure 5). This reaction was carried out at 100° C in a DIPEA:toluene (50/50 v/v) mixture for 48 hr. After cooling to room temperature, ethyl ether (~ 20 mL) was added to the reaction mixture, which was filtered through a Buchner funnel. The filtrate was washed with hexanes, evaporated to dryness, redissolved in pentane:ethyl acetate (19/1 v/v) and purified using silica gel chromatography with pentane:ethyl acetate (19/1 v/v) as the eluent. However, ^{1}H NMR analysis of the two collected fractions did not give commensurate integration of the aromatic and TiPS protons (there were fewer TiPS protons than aromatic). It is possible that the high temperature conditions used in this reaction may cause degradation of the TiPS group.

*Synthesis of Small Molecule 3 (**SM3**) (Figure 6)*
The synthesis of **SM3** was also attempted multiple times using reaction conditions described above for **SM1** as a starting point. Each time three equivalents of precursor **3** were used in combination with 1,3,5-tribromobenzene, and the reaction was carried out in an air-free environment.

As was the case for **SM2**, TLC analysis of the reaction mixture using UV visualization suggested several new species that are different from the starting materials. After work-up, the reaction mixture was separated using silica-gel chromatography with pentanes:ethyl acetate (9/1 v/v) as the eluent. However, ^{1}H NMR analysis of the four collected fractions did not give commensurate integration of the aromatic and TiPS protons (there were fewer TiPS protons than aromatic). It is possible that the high temperature conditions used in this reaction may cause degradation of the TiPS group.

*Synthesis of Bis(TMS-protected)-1,4-analog of Small Molecule 2 (**7**) (Figure 7)*
Given that the bromo-substituted benzenes were not successful when used in the synthesis of **SM2** and **SM3**, it is hypothesized that aryliodides, which traditionally react faster than arylbromides in Sonogashira coupling reactions, may help. To support this conjecture, 1,4-diiodobenzene was coupled to (4-ethynylphenyl)trimethylsilylacetylene (the TMS analog of **3**) to create a 1,4-disubstituted phenyl ring with trimethylsilyl-protected terminal acetylene groups as a model for our revised strategy. Both precursors were chosen because of their ready availability.

In an inert atmosphere glovebox, the (4-ethynylphenyl) trimethylsilylacetylene (0.31 g, 1.56 mmol) was added to a 5-mL vial containing 1,4-diiodobenzene (0.23 g, 0.70 mmol), $(PPh_3)_2PdCl_2$ (0.060 g, 0.08 mmol), CuI (0.008 g, 0.08 mmol), PPh_3 (0.023 g, 0.08 mmol), and TEA (5 mL). The reaction mixture was then microwave-irradiated (Biotage Initiator, regular absorption setting) for 4 hr at 100° C. After cooling to room temperature, the reaction mixture was then diluted with excess ethyl ether (20 mL) and was filtered though a Buchner funnel. The filtrate was evaporated to dryness, redissolved in a minimum amount of hexanes, and purified by silica gel chromatography (8 cm diameter x 10 cm length) with hexanes as the eluent. After solvent removal, the isolated product appeared as white crystals (0.110 g, 0.234 mmol, 33%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.486 (d, 4H), 7.451 (s, 4H), 7.393 (d, 4H), 0.262 (s, 18H).

*Synthesis of 5'-O-methanesulfonyl-2'-deoxythymidine (**8**) (Figure 8)*
Compound **8** was synthesized using a modification of the procedure reported by Grinstaff and coworkers.[9] Thymidine (2.8 g, 11.6 mmol) was added to a 100-mL Schlenk flask containing dry pyridine (50 mL), and the reaction flask was placed under nitrogen. After stirring this mixture at -10° C for 35 min, methanesulfonyl chloride (1.48 g, 12.9 mmol) was added to the reaction mixture using a syringe pump (~ 1 mL/h). The reaction was then warmed up to -2° C and allowed to stir for 48 hr before being warmed to 10° C and quenched with methanol (60 mL). The reaction mixture was evaporated to dryness in vacuo overnight (100 mTorr) to remove any excess pyridine. The crude product was dissolved in a minimum amount of methylene chloride and purified by silica gel chromatography (8 cm diameter x 10 cm length) using methylene chloride:methanol (9/1 v/v) as the eluent. After solvent removal, the isolated product appeared as a white solid (1.86 g, 5.53 mmol, 44%). ^{1}H NMR (400MHz, $DMSO_6$): δ 11.346 (s, 1H), 7.438 (s, 1H), 5.5 (s, 1H), 6.22 (t, 1H), 5.49 (d,

1H), 4.36-4.41 (m, 2H), 3.97 (q, 1H), 3.23 (s, 3H), 2.1-2.2 (m, 2H), 1.78 (s, 3H).

*Synthesis of 5'-azido-2'-deoxythymidine (**9**)*
Compound **9** was synthesized using a modification of the procedure by Grinstaff and coworkers.[10] Under nitrogen, compound **8** (0.3 g, 0.94 mmol) and dry lithium azide (0.46 g, 9.4 mmol) were combined in DMF (15 mL) in a 50-mL Schlenk flask equipped with a magnetic stir bar. The reaction mixture was subsequently heated at 80° C for 3 hr (Figure 8). After cooling, the reaction was evaporated to near dryness. Toluene (50 mL) was then added to the slushy residue, and the resulting mixture was again evaporated in vacuo to drive off any remaining DMF. The remaining solid crude material was dissolved in a minimum amount of acetonitrile:methylene (3/2 v/v) and purified by silica gel chromatography (8 cm diameter x 10 cm length) with acetonitrile:methylene chloride (3/2 v/v) as the eluent. After solvent removal, the isolated product appeared as a brown-orange solid (0.22 g, 0.82 mmol, 88%). ^{1}H NMR (400MHz, DMSO-d_6): δ 11.339 (s, 1H), 7.496 (s, 1H), 6.119 (t, 1H), 5.41 (s, 1H), 4.17-4.18 (m, 1H), 3.84 (q, 1H), 3.33- 3.55 (m, 2H), 2.236 (m, 2H), 1.789 (s, 3H).

Conclusion

Although the key precursor **3** was successfully synthesized and coupled with bromobenzene to give **SM1**, attempts to make **SM2** and **SM3** using the corresponding bromobenzene derivatives failed. Suspecting that iodobenzene derivatives may perform better in Sonigashira coupling, it was possible to couple the TMS analog of **3** with 1,4-diiodobenzene to give the bis(TMS-protected)-1,4-analog of **SM2** in moderate yields. As such, further work will entail the coupling of 1,3-diiodobenzene and 1,3,5-triiodobenzene with either **3** or its TMS analog. Following the synthesis of **SM2** and **SM3**, the silyl protecting groups will be removed to give the acetylene-terminated small molecule cores ready to be coupled to DNA.

Additionally, azide-functionalized thymidine, the second key precursor in our plan to connect DNA strands to acetylene-terminated small molecule cores, was successfully synthesized in a two-step approach. This can be converted to a 3'-phosphoramidite and subsequently used as a modified base in solid-phase DNA synthesis. Doing so will result in an azide-terminated DNA strand that is ready for click-coupling reactions.

Stable SMDHs can be synthesized once the azide-terminated DNA and the acetylene-terminated small molecule cores have been obtained. Subsequent studies on the melting behaviors of SMDH:SMDH hybrids should shed light on the parameters that control sharp melting in cooperative DNA-based materials. Such knowledge will enable the development of more accurate and selective DNA detection systems.

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References

(1) Stepp, B. R.; Gibbs-Davis, J. M.; Koh, D. L-F.; Nguyen, S. T. *Unpublished results.*

(2) Lutz, J.-F. *Angew. Chem. Int. Ed.* **2007,** *46,* 1018–1025.

(3) Jin, R.; Wu, G.; Li, Z.; Mirkin C. A.; Schatz, G. C. J. *Am. Chem. Soc.* **2003,** 125, 1643–1654.

(4) Park, S. Y.; Lee, J.-S.; Georganopoulou, D.; Mirkin, C. A.; Schatz, G. C. *J. Phys. Chem. B* **2006,** *1101,* 12673–12681.

(5) Gibbs, J. M.; Park, S.-J.; Anderson, D. R.; Watson, K. J.; Mirkin, C. A.; Nguyen, S. T. J. *Am. Chem. Soc.* **2005,** *127,* 1170–1178.

(6) Erdélyi, M.; Gogoll, A. *J. Org. Chem.* **2001,** *66,* 4165–4169.

(7) Petricci, E.; Radi, M.; Corelli, F.; Botta, M. *Tetrahedron Lett.* **2003,** *44,* 9181–9184.

(8) Chandra, K. L.; Zhang, S.; Gorman, C. B. *Tetrahedron* **2007,** *63,* 7120–7132.

(9) Hu, X.; Tierney M. T.; Grinstaff, M. W. *Bioconjugate Chem.* **2002,** *13,* 83–89.

(10) Hashimi, S. A. N.; Hu, X.; Immos, C. E.; Lee, S. J.; Grinstaff, M.W. *Org. Lett.* **2002,** *4,* 4571–4574.