[(3-Cyanopropyl)dimethylsilyl]acetylene, a Polar Analogue of (Trimethylsilyl)acetylene: Synthesis and Applications in the Preparation of Monoprotected Bisacetylenes

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The synthesis of well-defined oligomers in the range of several hundreds or thousands of daltons has been of continuing interest during the last several decades.[1] Two extreme synthetic strategies can be distinguished. On one hand small building blocks can be (sometimes in the presence of an appropriate end-capping agent) homocoupled or cocoupled with other building blocks. The desired product must then be isolated from the reaction mixture, a sometimes troublesome procedure. On the other hand, one can prepare the desired oligomers by a repetitive coupling approach. Unless a large excess of one component is used (excess approach), appropriate protective groups are generally necessary to mask that position of the molecule which will be needed for subsequent coupling steps (protective group approach).[2]

Our own recent research deals with the synthesis and investigation of shape-persistent macrocycles by the oxidative (template-directed) homocoupling of relatively large bisacetylenes, which requires an easy access toward these defined oligomers.[3,4] Key elements in their synthesis are the monoprotected diynes of the general structure **S** (Scheme 1). For their preparation we make use of the selective palladium-catalyzed coupling of terminal alkynes with aryl iodides in the presence of aryl bromides, and the site-selective removal of trimethylsilyl (TMS) groups in the presence of triisopropylsilyl (TIPS) groups (dormant group strategy).[5−7] Although several different monoprotected bisacetylenes are available in multigram quantities with this approach, essential prerequisites are both the availability of the corresponding bromo-iodo compounds, and the clean coupling reaction of the alkyne with the (less reactive) aryl-bromo positions of these compounds.

In the case that these prerequisites are not fulfilled, an alternative reaction is the coupling of the corresponding diiodo compound with 1 equiv of TMS-acetylene, separation of the product from the starting material and the bisethynylated byproduct, and reaction of the remaining second iodo position of the compound with TIPS-acetylene (or vice versa). The major drawback of this procedure is that aromatic iodides and the corresponding TMS-protected ethynylated compounds have similar R_f values, making a chromatographic purification after the first coupling step in most cases troublesome or impossible.[3b,8,9] Polar protecting groups at the acetylene moiety solve this problem. For example, Godt has shown that the use of hydroxymethyl (HOM)-protected acetylenes in the synthesis of oligo(*p*-phenyleneethynylene)s simplifies the isolation of pure compounds.[8] Schanze used the 2-hydroxypropan-2-yl (2-HP) protecting group to prepare and purify multigram quantities of phenylacetylene monomers containing metal complexing groups.[9] However, both of these protecting groups require strongly basic deprotection conditions, and higher temperatures (2-HP protecting group) or the presence of a large excess of the strongly oxidizing MnO_2 (HOM protecting group).

The goal of our own synthetic studies was to combine the mild conditions necessary to remove the TMS protecting group together with the high polarity of the hydroxyl-containing protecting groups. We therefore prepared and investigated the behavior of [(3-cyanopropyl)dimethylsilyl (CPDMS)]acetylene **1**. Compound **1** is readily available in large quantities in a one-step reaction by treating ethynylmagnesium bromide with (3-cyanopropyl)dimethylsilyl chloride (Scheme 2).

As expected, **1** can be reacted with aromatic diiodides under the same conditions as used for the Hagihara coupling reaction of other silyl-protected acetylene compounds. For example, palladium-catalyzed treatment of 1,4-diiodobenzene with 1 equiv of **1** results in a mixture of the starting material, the mono- and the bisethynylated products (Scheme 3).[10] Contrary to the analogue reaction using TMS-acetylene, the chromatographic separation of these compounds is facile because of their significantly different R_f values. In a mixture of hexanes/dichloromethane (1:1), **2** has a R_f value of 0.8, **3** has a R_f value of 0.5, and **4** of 0.2. This is clearly a consequence of the polar cyano functionality attached to the silyl-

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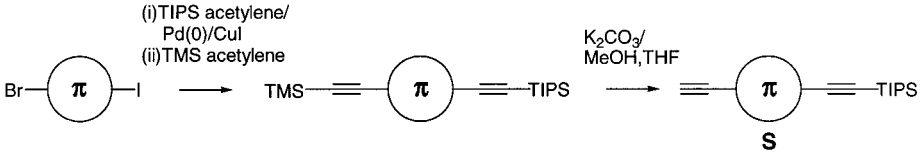
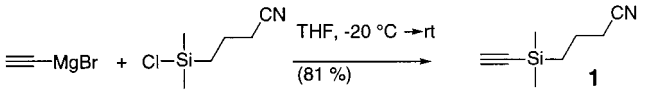
Scheme 1. Formation of Monoprotected Bisacetylenes by the Bromo-Iodo Strategy



Scheme 2



acetylene. Coupling of **3** with TIPS-acetylene, purification of **5** and subsequent treatment with potassium carbonate in MeOH/THF (1:1) overnight gives the mono-TIPS-protected bisacetylene **6** in nearly quantitative yield. This result clearly shows that **1** can be used in the desired way, although **6** is also readily available by the use of the bromo-iodo strategy mentioned above.[11] However, the protocol described here works also in cases where the bromo position of the bromo-iodo compounds is not reactive enough for a subsequent second acetylene coupling. Treatment of **7** with 1.1 equiv of **1**, and then with a small excess of TIPS acetylene in a one-pot reaction gives the CPDMS-TIPS-protected bisacetylene **8** in 33% isolated yield (Scheme 4). Again, all side products have significantly different R_f values enabling the easy separation of **8**. Potassium carbonate-induced deprotection of the CPDMS group gives the mono-TIPS-protected bisacetylene **9** in nearly quantitative yield. As already mentioned, **9** is not available by the bromo-iodo protocol because the intermediate aryl bromide does not undergo a clean Hagihara coupling under the typical conditions.[12]

In summary, we have shown that CPDMS-acetylene can be easily prepared from commercially available starting materials, can be coupled with aryl iodides under palladium/copper catalysis, and can be easily deprotected under the mild conditions used for the deprotection of the well-established TMS acetylene. In addition, its high polarity allows for the simple and high yield chromatographic separation of its palladium-catalyzed coupling products with aryl iodides. Applications of this new protective group in the synthesis of shape-persistent macrocycles are in progress and will be published elsewhere.

Experimental Section

General. Commercially available chemicals were used as received. 2,6-Diiodo-4-methylanisole was prepared according to the literature procedure.[13] THF was distilled from potassium prior to use. Piperidine was distilled from CaH_2 and stored under argon. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ or CD_2Cl_2 at 300 K (300 MHz for proton and 75.5 MHz for carbon), and chemical shifts are given relative to solvent signals or to TMS. Thin-layer chromatography was performed on aluminum plates precoated with Merck 5735 silica gel 60 F_{254}. Column chromatography was performed with Merck silica gel 60 (230−400 mesh). Microanalysis were performed by the University of Mainz. WARNING: (3-Cyanopropyl)dimethylsilyl chloride is a hazardous (toxic) compound. The synthesis of **1** as well as all subsequent applications should be carried out with care.

[(3-Cyanopropyl)dimethylsilyl]acetylene (1). Ethynylmagnesium bromide (800 mL, 0.5 M in THF; 0.40 mol, precooled to 5−8 °C) was added to a solution of (3-cyanopropyl)dimethylsilyl chloride (64.7 g, 0.40 mol) in THF (200 mL) at −20 °C over 1 h. The cooling bath was removed, and the dark mixture was allowed to stir overnight. After reduction of the solution volume to about 200 mL, ether (500 mL) and water (100 mL) were slowly added. The organic layer was separated and extracted with water and brine and dried over $MgSO_4$. Evaporation of the solvent gave a black oil which was purified by vacuum distillation to give **1** (49.3 g, 81%) as a colorless oil (bp: 62 °C, 1 mbar). ^1H NMR ($CDCl_3$) 2.41 (s, 1 H), 2.40 (t, J = 7.1 Hz, 2 H), 1.82−1.70 (m, 2 H), 0.81−0.75 (m, 2 H), 0.19 (s, 6 H); ^{13}C NMR ($CDCl_3$) 119.7, 94.7, 88.3, 20.6, 20.5, 15.5, −2.0. Anal. Calcd for $C_8H_{13}NSi$: C, 63.51; H, 8.66; N, 9.26. Found: C, 63.49; H, 8.77; N, 9.19.

1-[2-[(3-Cyanopropyl)dimethylsilyl]ethynyl]-4-iodobenzene (3). To a solution of 1,4-diiodobenzene (**2**) (2.00 g, 6.06 mmol) and **1** (0.91 g, 6.06 mmol) in piperidine (20 mL) were added $Pd(PPh_3)_2Cl_2$ (40 mg), PPh_3 (40 mg), and CuI (20 mg) at room temperature. After stirring for 3 h, dichloromethane and water were added. The organic phase was separated, extracted with water, 10% acetic acid, water, 10% aqueous NaOH, and brine, and dried over $MgSO_4$. Evaporation of the solvent yielded a brownish residue, which was chromatographed over silica gel using petroleum ether/dichloromethane (1:1; R_f = 0.52) as the eluent to afford **3** (830 mg, 39%) as a yellow oil which solidifies at room temperature. ^1H NMR ($CDCl_3$) 7.66−7.60 (m, 2 H), 7.18−7.12 (m, 2 H), 2.44 (t, J = 6.9 Hz, 2 H), 1.87−1.77 (m, 2 H), 0.88−0.82 (m, 2 H), 0.26 (s, 6 H); ^{13}C NMR ($CDCl_3$) 133.6, 122.5, 119.8, 105.6, 95.0, 94.0, 20.8, 20.7, 15.9, −1.7. Anal. Calcd for $C_{14}H_{16}INSi$: C, 47.60; H, 4.57; N, 3.96. Found: C, 47.69; H, 4.58; N, 3.87.

1-[2-[(3-Cyanopropyl)dimethylsilyl]ethynyl]-4-[2-(triisopropylsilyl)ethynyl]benzene (5). $Pd(PPh_3)_2Cl_2$ (15 mg), PPh_3 (15 mg), and CuI (10 mg) were added to a solution of **3** (291 mg, 0.82 mmol) and (triisopropylsilyl)acetylene (300 mg, 1.65 mmol) in piperidine (25 mL) at room temperature, and the mixture was then stirred for 3 h at 40 °C. After the reaction was cooled to room temperature, ether and water were added. The organic phase was separated and extracted with water, 10% acetic acid, water, 10% aqueous NaOH, and brine, and dried over $MgSO_4$. Evaporation of the solvent yielded an yellowish residue, which was chromatographed over silica gel using petroleum ether/dichloromethane (1:1; R_f = 0.70) as the eluent to afford **5** (315 mg, 94%) as a colorless oil. ^1H NMR ($CDCl_3$) δ 7.50−7.30 (m, 4 H), 2.44 (t, J = 6.9 Hz, 2 H), 1.88−1.78 (m, 2 H), 1.13 (s, 21 H), 0.95−0.80 (m, 2 H), 0.26 (s, 6 H). ^{13}C NMR ($CDCl_3$) 131.9, 131.8, 123.9, 122.5, 119.6, 106.5, 106.0, 94.0, 93.1, 20.7, 20.5, 18.7, 15.7, 11.3, −1.9. Anal. Calcd for $C_{25}H_{37}NSi_2$: C, 73.64; H, 9.15; N, 3.44. Found: C, 73.36; H, 9.18; N 3.95.

1-Ethynyl-4-[2-(triisopropylsilyl)ethynyl]benzene (6). K_2CO_3 (280 mg, 2.03 mmol) was added to a solution of **5** (300 mg, 0.74 mmol) in THF/MeOH (1:1; 10 mL), and the mixture was stirred overnight at room temperature. The mixture was poured into ether and water, and the organic layer was extracted with water and brine and dried over $MgSO_4$. Evaporation of the solvent yielded an yellowish residue, which was chromatographed over silica gel using petrolether/dichloromethane (2:1; R_f = 0.72) as the eluent to afford **6** (185 mg, 89%) as a slightly yellow oil which slowly solidified. ^1H NMR (CD_2Cl_2) 7.43 (s, 4 H), 3.23 (s, 1 H), 1.14 (s, 21 H). ^{13}C NMR (CD_2Cl_2) 132.3, 132.2, 124.4, 122.4, 106.7, 93.5, 83.4, 79.2, 18.8, 11.7. Anal. Calcd for $C_{19}H_{26}Si$: C, 80.78; H, 9.28. Found: C, 80.47; H, 9.35.

1-[2-[(3-Cyanopropyl)dimethylsilyl]ethynyl]-4-methyl-6-[2-(triisopropylsilyl)ethynyl]anisole (8). $Pd(PPh_3)_2Cl_2$ (40 mg), PPh_3 (40 mg), and CuI (20 mg) were added to a solution of 2,6-diiodo-4-methylanisole (**7**) (1.00 g, 2.67 mmol) and **1** (409 mg,

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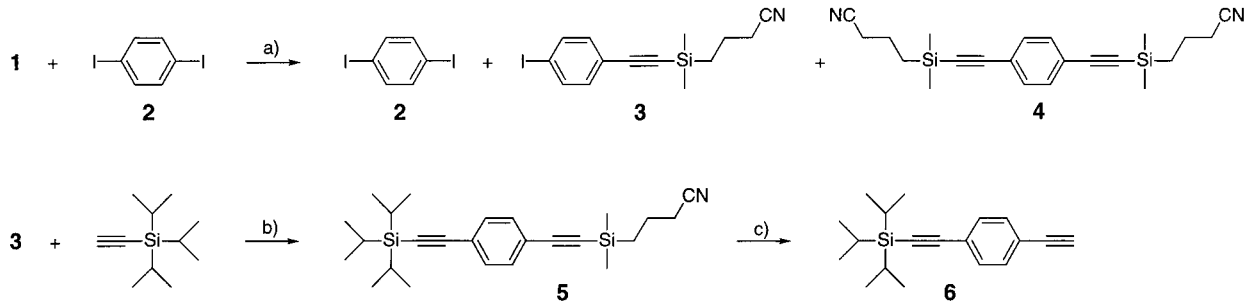
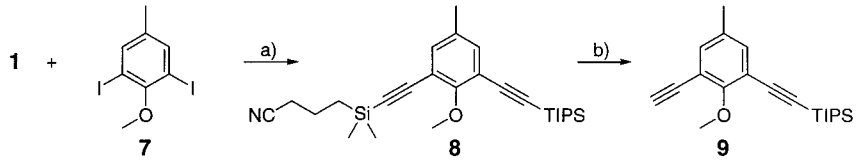
Scheme 3



[a] Reagents and conditions: (a) $Pd(PPh_3)_2Cl_2$, PPh_3, CuI, piperidine, 39%; (b) $Pd(PPh_3)_2Cl_2$, CuI, piperidine, 94%; (c) K_2CO_3, MeOH/THF (1:1), 89%.

Scheme 4



[a] Reagents and conditions: (a) (1) $Pd(PPh_3)_2Cl_2$, PPh_3, CuI, piperidine; (2) TIPS-acetylene, 34%; (b) K_2CO_3, MeOH/THF (1:1), 86%.

2.71 mmol) in piperidine (30 mL) at room temperature. After stirring overnight at 40 °C, 0.73 g (4.0 mmol) of (triisopropylsilyl)acetylene was added, and the mixture was additionally stirred overnight at 40 °C. After being cooled to room temperature, the mixture was poured into ether and water. The organic phase was separated, extracted with 10% acetic acid, water, 10% aqueous NaOH, and brine, and then dried over $MgSO_4$. Evaporation of the solvent yielded a dark residue, which was chromatographed over silica gel using petroleum ether/dichloromethane (2:1; $R_f = 0.37$) as the eluent to give **8** (315 mg, 34%) as a colorless oil. ^{1}H NMR (CD_2Cl_2) δ 7.24−7.22 (s, 1 H), 7.21−7.29 (s, 1 H), 3.95 (s, 3 H), 2.43 (t, $J = 6.9$ Hz, 2 H), 2.24 (s, 3 H), 1.88−1.78 (m, 2 H), 1.14 (s, 21 H), 0.87−0.82 (m, 2 H), 0.26 (s, 6 H); ^{13}C NMR (CD_2Cl_2) δ 135.4, 134.8, 133.6, 120.1, 117.8, 117.2, 102.9, 102.4, 97.1, 95.8, 61.4, 21.1, 20.8, 20.4, 18.8, 16.0, 11.8, −1.8. Anal. Calcd for $C_{27}H_{41}NOSi_2$: C 71.78; H 9.15; N 3.10. Found: C 71.94; H 9.16; N 3.35.

2-Ethynyl-4-methyl-6-[2-(triisopropylsilyl)ethynyl]anisole (9). K_2CO_3 (280 mg, 2.03 mmol) was added to a solution of **8** (300 mg, 0.67 mmol) in THF/MeOH (1:1; 10 mL), and the mixture was stirred overnight at room temperature. The mixture was poured into ether and water, and the organic layer was extracted with water and brine and dried over $MgSO_4$. Evaporation of the solvent yielded an yellowish residue, which was chromatographed over silica gel using petroleum ether/dichloromethane (2:1; $R_f = 0.60$) as the eluent to afford **9** (187 mg, 86%) as a slightly yellow oil. ^{1}H NMR (CD_2Cl_2) δ 7.27−7.24 (m, 1 H), 7.24−7.21 (m, 1 H), 3.96 (s, 3 H), 3.29 (s, 1 H), 2.25 (s, 3 H), 1.14 (s, 21 H). ^{13}C NMR (CD_2Cl_2) δ 161.3, 135.5, 135.0, 133.7, 117.8, 116.5, 102.9, 96.0, 81.3, 61.5, 20.4, 18.8, 11.8. Anal. Calcd for $C_{21}H_{30}Si$: C, 77.24; H, 9.26. Found: C, 77.17; H, 9.34.

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