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Abstract—An efficient synthetic approach to a variety of unsymmetrically substituted conjugated diynes has been developed, starting from the readily available 1,4-bis(trimethylsilyl)-1,3-butadiyne, based upon the selective and sequential substitution of the trimethylsilyl groups with alkyl, aryl and vinyl groups.

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Compounds containing chains of conjugated triple bonds are present in a broad series of natural products. Many of these compounds possess interesting biological properties, such as antitumor,¹ antibacterial² and anti-inflammatory activity.³ Moreover they display a wide range of potential applications in material science. Butadiynes, in particular, have been widely utilized as substructures in the formation of new photonic materials,⁴ oligomers and polymers.⁵

A commonly used tactic for the synthesis of unsymmetrical 1,3-diynes is based upon the Cadiot–Chodkiewicz reaction,⁶ the coupling reactions of terminal alkynes with 1-bromoalkynes in the presence of a copper(I) salt and a suitable amine.^{1a,2b,7} A number of interesting variations has been developed.^{8,9} The predominant limitation of these methods is in the requirement of the prior synthesis of a terminal alkyne for one or both of the coupling partners. However, only a few examples of



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the direct coupling of 1,3-diynes with the appropriate halides have been reported.¹⁰

In connection with our ongoing work¹¹ in which we succeeded in synthesizing stereodefined conjugated polyunsaturated systems and a series of natural products¹² using unsaturated silylated compounds, we decided to develop a direct and flexible route yielding unsymmetrically substituted conjugated diynes. For this purpose, we decided to start from the readily available 1,4-bis(trimethylsilyl)-1,3-butadiyne **1a**.

It is known¹³ that compound **1a** undergoes selective monodesilylation with MeLi–LiBr complex in ether, leading quantitatively to the corresponding lithium salt, which can be alkylated with alkyl halides.^{13b} Moreover, a procedure has recently¹⁴ been developed for the direct coupling of monosilylated acetylenes with vinyl triflates and aryl iodides, in the presence of K₂CO₃/MeOH and a catalytic amount of AgCl and Pd(PPh₃)₄. On the basis of these findings and in order to prepare a variety of unsymmetrical diynes, we have devised a general procedure as reported in Scheme 1.

The diynes **4** (R¹=aryl or vinyl and R²=alkyl) were synthesized according to two different approaches. The first approach required the selective mono-desilylation of the diyne **1a** with MeLi–LiBr complex¹³ and the isolation of the monosilylated diyne **1b**,¹⁵ which was easily coupled with an aryl or vinyl halide (R¹X), according to the Sonogashira protocol,¹⁶ to give the monosubstituted diynes **2**. A further desilylation reaction of the diynes **2** with MeLi–LiBr complex afforded the lithium salts of the terminal diynes, which were coupled with an alkyl halide (R²X) leading to the diynes **4** (R¹=aryl, R²=alkyl). The second approach required the selective mono-desilylation of the diyne **1a** with MeLi–LiBr complex and the direct coupling reaction of the lithium salt with an alkyl halide^{13b} (R²X) to lead to the monosubstituted diynes **3**. We have also found that the monosilylated diynes **3** can be coupled efficiently and directly with aryl iodides or vinyl bromides in the presence of K₂CO₃/MeOH and a catalytic amount of AgCl and Pd(PPh₃)₄ to give the diynes **4** (R¹=aryl, vinyl, R²=alkyl). Accordingly, to obtain the disubstituted diynes **5** (R¹, R³=aryl, vinyl) it was only necessary to perform the direct coupling reaction of the monosilylated diynes **2** with aryl or vinyl halides. Finally, the preparation of disubstituted diynes **6** possessing two alkyl groups was carried out using a one-pot procedure starting directly from the bis-silylated diyne **1a** without isolation of the mono-alkylated silylated diyne **3**. The addition of more MeLi–LiBr complex, followed by the other alkyl halide (R⁴X) then gave diynes **6**. The overall results are reported in Table 1.

Compound **2a** (entry 1) and compound **2b** (entry 5) were synthesized in good yields (70 and 89%) by cross-coupling reactions of mono-silylated diyne **1b**¹⁵ respectively with iodobenzene and with (*E*)-1-bromo-2-trimethylsilylethene in the presence of PdCl₂–

(PPh₃)₂, CuI and Et₃N in THF.^{12d} To obtain compound **3** (entry 9), the reagent **1a** (1 equiv.) was dissolved in THF (0.5 M) and selectively desilylated by the addition of 1.1 equiv. of MeLi–LiBr complex (1.5 M) in ether at room temperature. After complete desilylation, the reaction mixture was cooled to –78°C and 1.1 equiv. of 1-iodoheptane and 2 equiv. of HMPA were added, then the mixture was slowly brought to room temperature, leading to a 69% yield of diyne **3**. Compound **6** was obtained using a one-pot procedure (entry 9, 52% overall yield), without isolation of the mono-alkylated silylated diyne **3**, by adding more MeLi–LiBr complex (1.1 equiv.), followed by 1-iodopentane (1.1 equiv.), according to the same procedure described for the preparation of compound **3**. Compound **4a** (entry 1, 65% yield) was synthesized by direct alkylation of the lithium salt of **2a**, prepared with MeLi–LiBr complex, with 1-iodopentane according to the same procedure reported above. In contrast, compound **4b** (entry 5, 57% yield) was prepared by reaction of 1-iodopentane with the lithium salt of **2b**, obtained by desilylation of **2b** with K₂CO₃/MeOH, isolation of the terminal alkyne and subsequent reaction with *n*-BuLi. The unsymmetrically substituted diynes **5** (entries 2–4 and 6–8), **4c** and **4d** (entries 10 and 11) were obtained in high yields (63–88%) according to the general procedure reported below.

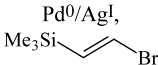
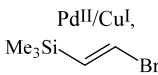
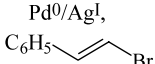
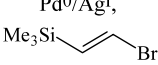
In conclusion, the procedure described here appears to be a straightforward and general route to a variety of unsymmetrical conjugated diynes, substituted with alkyl, aryl and vinyl groups. Moreover, the ready availability of the starting materials, the mild reaction conditions, and the simplicity of the operations involved are additional features making the methodology very promising.

General procedure for the synthesis of unsymmetrically substituted 1,3-diynes **4c**, **4d**, and **5**

To a solution of vinyl- or aryl halide (1 equiv.) in anhydrous DMF (0.4 M) at room temperature under nitrogen were successively added Pd(PPh₃)₄ (0.05 equiv.), AgCl (0.2 equiv.) and K₂CO₃ (8 equiv.). The resulting mixture was stirred for 5 min, then MeOH (8 equiv.) was added followed by a solution of the 1-trimethylsilyldiyne (1 equiv.) in anhydrous DMF (0.4 M). The reaction mixture was warmed to 40°C and stirred at the same temperature until the disappearance of the desilylated diyne, formed by in situ deprotection of the starting silylated diyne, then quenched with aqueous NH₄Cl and extracted with ethyl acetate (3×15 mL). The organic extracts were washed with water (3×15 mL), dried over anhydrous Na₂SO₄ and concentrated under vacuum. The residue was purified by silica gel column chromatography using petroleum ether or the appropriate mixture of petroleum ether and ethyl acetate as eluent.

Full spectroscopic data have been obtained for all compounds reported herein.

Table 1. Synthesis of unsymmetrically substituted 1,3-diynes **4–6**

Entry	Compounds 1	Reaction Conditions	Monosilylated diynes 2,3 Yields (%)	Reaction Conditions	Disubstituted diynes 4–6 Yields (%)
1	1b	PdII/CuI, C ₆ H ₅ I	C ₆ H ₅ —C≡C—C≡C—SiMe ₃ 2a (70)	MeLi-LiBr, <i>n</i> -C ₅ H ₁₁ I	C ₆ H ₅ —C≡C—C≡C—C ₅ H ₁₁ - <i>n</i> 4a (65)
2			2a	Pd ⁰ /AgI, <i>p</i> -Me-C ₆ H ₄ I	C ₆ H ₅ —C≡C—C≡C—C ₆ H ₄ -Me- <i>p</i> 5a (82)
3			2a	Pd ⁰ /AgI, 	C ₆ H ₅ —C≡C—C≡C—  5b (87)
4			2a	Pd ⁰ /AgI, 	C ₆ H ₅ —C≡C—C≡C—CH=CH-SiMe ₃ 5c (83)
5	1b	PdII/CuI, 	Me ₃ Si—CH=CH—C≡C—C≡C—SiMe ₃ 2b (89)	<i>n</i> -BuLi, ^a <i>n</i> -C ₅ H ₁₁ I	Me ₃ Si—CH=CH—C≡C—C≡C—C ₅ H ₁₁ - <i>n</i> 4b (57)
6			2b	Pd ⁰ /AgI, <i>p</i> -MeO-C ₆ H ₄ I	Me ₃ Si—CH=CH—C≡C—C≡C—C ₆ H ₄ -OMe- <i>p</i> 5d (63)
7			2b	Pd ⁰ /AgI, <i>p</i> -O ₂ N-C ₆ H ₄ I	Me ₃ Si—CH=CH—C≡C—C≡C—C ₆ H ₄ -NO ₂ - <i>p</i> 5e (76)
8			2b	Pd ⁰ /AgI, 	Me ₃ Si—CH=CH—C≡C—C≡C—CH=CH-C ₆ H ₅ 5f (88)
9	1a	MeLi-LiBr, <i>n</i> -C ₇ H ₁₅ I	<i>n</i> -C ₇ H ₁₅ —C≡C—C≡C—SiMe ₃ 3 (69)	MeLi-LiBr, <i>n</i> -C ₅ H ₁₁ I	<i>n</i> -C ₇ H ₁₅ —C≡C—C≡C—C ₅ H ₁₁ - <i>n</i> 6 (52) ^b
10			3	Pd ⁰ /AgI, 	<i>n</i> -C ₇ H ₁₅ —C≡C—C≡C—  4c (76)
11			3	Pd ⁰ /AgI, 	<i>n</i> -C ₇ H ₁₅ —C≡C—C≡C—CH=CH-SiMe ₃ 4d (75)

^a The reaction with *n*-BuLi was performed on the isolated terminal alkyne, obtained by desilylation of **2b** with K₂CO₃/MeOH;^b Overall yield of the product prepared by a one-pot procedure.

Selected spectral data: (**4b**) yellow oil; $\nu_{\max}$ (neat) 2957, 2932, 2872, 2861, 2234, 1566, 1466, 1427, 1250, 1209, 972, 865, 841, 726 cm⁻¹; δ_{H} (500 MHz, CDCl₃) 6.55 (1H, d, *J*=19.2 Hz), 5.90 (1H, d, *J*=19.2 Hz), 2.29 (2H, t, *J*=7.0 Hz), 1.56–1.48 (2H, m), 1.39–1.22 (4H, m), 0.87 (3H, t, *J*=7.1 Hz), 0.06 (9H, s); δ_{C} (125.7 MHz, CDCl₃) 148.7, 122.3, 85.2, 74.8, 65.1, 30.9, 27.9, 22.1, 19.5, 13.9, -1.8; MS *m/z* 218 (M⁺, 11), 204 (16),

203 (81), 177 (50), 159 (8), 147 (22), 133 (14), 123 (13), 120 (13), 109 (12), 107 (13), 105 (10), 83 (19), 73 (53), 59 (100), 53 (18), 45 (47), 43 (50), 41 (20%). (**4c**) pale yellow oil; $\nu_{\max}$ (neat) 3107, 3078, 2929, 2856, 2232, 2150, 1465, 1425, 1210, 852, 830, 701 cm⁻¹; δ_{H} (500 MHz, CDCl₃) 7.27–7.20 (2H, m), 6.93 (1H, dd, *J*=5.0, 3.6 Hz), 2.36 (2H, t, *J*=7.1 Hz), 1.60–1.51 (2H, m), 1.45–1.23 (8H, m), 0.89 (3H, t, *J*=6.9 Hz); δ_{C} (125.7

MHz, CDCl₃) 133.7, 127.9, 126.9, 122.4, 87.1, 78.6, 67.6, 65.0, 31.6, 28.8, 28.7, 28.2, 22.6, 19.6, 14.0; MS *m/z* 230 (M⁺, 38), 215 (4), 201 (12), 187 (34), 173 (39), 160 (18), 153 (19), 147 (71), 146 (26), 145 (70), 132 (25), 128 (20), 121 (18), 115 (30), 102 (18), 101 (23), 97 (28), 93 (17), 87 (17), 79 (17), 75 (18), 69 (32), 63 (17), 55 (18), 51 (15), 45 (95), 43 (50), 41 (100%). (5c) yellowish oil; $\nu_{\max}$ (neat) 3081, 3063, 2994, 2956, 2897, 2213, 1561, 1490, 1442, 1249, 1208, 972, 865, 839, 754, 688 cm⁻¹; δ_{H} (500 MHz, CDCl₃) 7.53–7.47 (2H, m), 7.38–7.28 (3H, m), 6.69 (1H, d, *J*=19.3 Hz), 6.05 (1H, d, *J*=19.3 Hz), 0.13 (9H, s); δ_{C} (125.7 MHz, CDCl₃) 149.9, 132.4, 129.1, 128.3, 122.0, 121.8, 81.9, 81.7, 74.2, 74.0, -1.8; MS *m/z* 224 (M⁺, 25), 210 (21), 209 (100), 184 (14), 183 (71), 169 (6), 155 (5), 153 (7), 129 (12), 105 (10), 98 (5), 92 (21), 77 (11), 73 (11), 59 (28), 53 (14), 45 (30), 43 (40%). (5e) whitish solid (petroleum ether, mp 116–118°C); $\nu_{\max}$ (KBr) 3104, 2957, 2898, 2208, 1593, 1518, 1342, 1251, 1105, 982, 974, 867, 852, 842, 747, 684 cm⁻¹; δ_{H} (500 MHz, CDCl₃) 8.16 (2H, d, *J*=8.9 Hz), 7.59 (2H, d, *J*=8.9 Hz), 6.72 (1H, d, *J*=19.3 Hz), 6.01 (1H, d, *J*=19.3 Hz), 0.09 (9H, s); δ_{C} (125.7 MHz, CDCl₃) 151.8, 147.3, 133.1, 128.7, 123.6, 121.3, 84.4, 79.4, 78.9, 73.2, -1.9; MS *m/z* 269 (M⁺, 19), 255 (21), 254 (100), 229 (11), 228 (53), 214 (6), 208 (8), 182 (21), 167 (10), 165 (5), 115 (4), 91 (7), 73 (14), 59 (63), 53 (10), 45 (34), 43 (33%). (5f) brown oil; $\nu_{\max}$ (neat) 3060, 3029, 2957, 2898, 2196, 1561, 1491, 1448, 1249, 972, 951, 864, 840, 747, 690 cm⁻¹; δ_{H} (500 MHz, CDCl₃) 7.44–7.28 (5H, m); 7.10 (1H, d, *J*=16.2 Hz), 6.69 (1H, d, *J*=19.2 Hz), 6.27 (1H, d, *J*=16.2 Hz), 6.08 (1H, d, *J*=19.2 Hz), 0.16 (9H, s); δ_{C} (125.7 MHz, CDCl₃) 149.6, 144.3, 135.6, 129.1, 128.6, 126.3, 122.1, 106.8, 82.3, 81.8, 76.2, 74.6, -1.9; MS *m/z* 250 (M⁺, 46), 235 (48), 233 (21), 219 (15), 210 (12), 209 (56), 207 (11), 205 (12), 195 (15), 191 (15), 181 (10), 179 (12), 169 (19), 165 (22), 155 (14), 145 (9), 135 (10), 105 (16), 103 (11), 83 (12), 73 (100), 59 (93), 53 (22), 45 (59), 43 (81%).

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