Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Radical Cyclization of Bromomethyldimethylsilyl Propargyl Ethers; a General Method for the Stereoselective Synthesis of Variously Substituted Trimethylenemethane (TMM) Precursors

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Published online: 23 Sep 2006.

SYNTHETIC COMMUNICATIONS, 24(9), 1215-1221 (1994)

RADICAL CYCLIZATION OF BROMOMETHYLDIMETHYLSILYL PROPARGYL ETHERS ; A GENERAL METHOD FOR THE STEREOSELECTIVE SYNTHESIS OF VARIOUSLY SUBSTITUTED TRIMETHYLENEMETHANE (TMM) PRECURSORS.

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Abstract : The radical cyclization of bromomethyldimethylsilyl propargyl ethers allows the regio- and stereoselective preparation of variously substituted 2-trimethylsilylmethyl-2-propen-1-ol derivatives in good yields. After acetylation of the alcohol function, these compounds are useful precursors of trimethylenemethane (TMM) in [3+2] cycloaddition reactions using the Trost methodology.

The palladium-catalyzed trimethylenemethane (TMM) [3+2] cycloaddition reactions have great appeal for selective five-membered ring formation.[1] Such precursors are not of an easy access and a very few methods have been described.[2] For the synthesis of trisubstituted double bonds, the carbocupration has been used.[3]

We have recently proposed a short and efficient synthesis of 2-trimethylsilylmethyl-2-propen-1-ol[4] and we want to report now a general and straightforward route to these kinds of variously substituted compounds. The key step of our strategy is the radical cyclization of bromomethyldimethylsilyl propargyl ethers which affords, regio- and stereoselectively, trisubstituted olefins.[5] Moreover, it is

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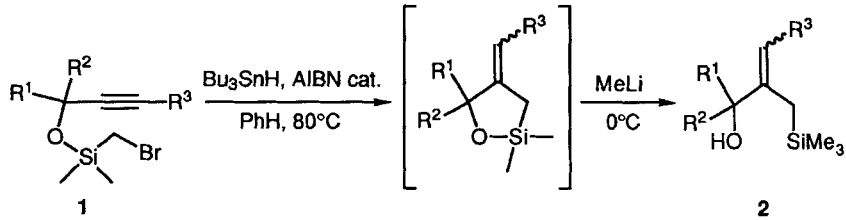
noteworthy that this reaction is performed under mild conditions and is compatible with the presence of a variety of functionalities.

The silyl ethers **1** are readily obtained in quantitative yields by treatment of propargyl alcohols with commercially available bromomethylchlorodimethylsilane and triethylamine in dichloromethane with 4-dimethylaminopyridine (4-DMAP) as catalyst at room temperature. The radical cyclization of **1** is carried out in boiling benzene by the slow addition of tributyltin hydride in the presence of a catalytic amount of azabis-isobutyronitrile (AIBN). The oxa-silacyclopentene intermediate is then treated *in situ* with methyllithium at 0°C to afford the allyl silane derivative **2** after hydrolysis (Scheme 1 and Table 1).



1 **2**

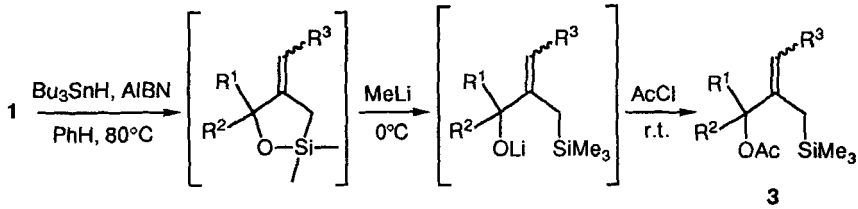
Scheme 1

Table 1

Entry	R^1	R^2	R^3	Ratio (*E* / *Z*)[a]	**2** (Yield %)
1a	H	H	H	/	70
1b	H	H	n-C_5H_{11}	50 / 50	76
1c	n-C_5H_{11}	H	H	/	60
1d	n-C_5H_{11}	H	n-C_4H_9	0 / 100	70
1e	CH_3	CH_3	$(CH_2)_3OTHP$	0 / 100	60
1f	CH_3	CH_3	Ph	75 / 25	77
1g	CH_3	CH_3	SPh	40 / 60	78
1h	CH_3	H	SPh	40 / 60	41
1i	CH_3	H	$SiMe_3$	70 / 30	61

*a) The stereochemistry of olefins **2** was assigned by γ-gauche effects in the ^{13}C-NMR spectra. For the discussion of the stereoselectivity during H-abstraction of the trisubstituted vinyl radicals, see reference 5.*

Then, the alcohols **2** can be treated with acetyl chloride and triethylamine in dichloromethane in the presence of 4-DMAP as catalyst at room temperature to furnish the acetate derivatives **3** as reagents for the [3+2] cycloaddition reactions. Nevertheless, this method requires two steps and it is noteworthy that compounds **3** can be also obtained in only one step when the alkoxide anion is trapped *in situ* with acetyl chloride at room temperature (Scheme 2 and Table 2).



Scheme 2

Table 2

Entry	R^1	R^2	R^3	Ratio (*E* / *Z*)	**3** (Yield %)
1a	H	H	H	/	67
1b	H	H	*n*-C_5H_{11}	50 / 50	65
1d	*n*-C_5H_{11}	H	*n*-C_4H_9	0 / 100	60
1j	CH_3	H	C_2H_5	30 / 70	65[a]
1k	CH_3	H	H	/	58

a) The carbonate derivative was prepared instead of the acetate.

In summary, we have described a short and efficient preparation of variously substituted trimethylenemethane (TMM) precursors as reagents for the [3+2] cycloaddition reactions.

EXPERIMENTAL

^{1}H-NMR spectra were taken on 200 MHz Bruker AC 200 and 400 MHz Jeol GSX 400 spectrometers. ^{13}C-NMR spectra were recorded on 50 MHz Bruker AC 200 and 100 MHz Jeol GSX 400 instruments. Deuteriated solvents (chloroform and benzene) were used and no TMS was included to the solutions ; chemical shifts

are reported in ppm referenced to the residual proton resonances of the solvents. Infrared (IR) spectra were obtained on a Perkin-Elmer 298 infrared spectrophotometer. Elemental analyses were performed by the Elemental Analyses Center of Université Pierre et Marie Curie. Thin layer chromatography (TLC) was performed on Merck silica gel 60F-254. Silica gel 60 (35-70μm) from Amicon was used for column chromatography by the method of Still.[6] The structures of the known compounds (**2a**, **3a**)[4] and **2e**[7] were confirmed by the comparison of their spectroscopic data with those of literature.

Typical Procedure for Preparation of Alcohol Derivatives 2. A benzene solution (5 mL) of *n*-Bu_3SnH (480 mg, 1.65 mmol) containing AIBN (21 mg, 0.15 mmol) was added by a syringe pump over 5 h to a solution of bromomethyldimethylsilyl propargyl ether **1** (1.5 mmol) in refluxing benzene (40 mL) under argon. After completion of the addition, the mixture was allowed to reflux for 2 additional hours. The reaction mixture was then cooled at 0°C and methyllithium (1.6M in ether, 2.75 mL, 4.5 mmol) was added dropwise. The reaction was monitered by TLC and stirred for 1 h under argon. The organic phase was washed with brine and dried over Na_2SO_4. After evaporation of the solvent, the residue was chromatographed with a mixture of petroleum ether and ether (7 : 3) as eluent.

(*E*) and (*Z*)-2-Trimethylsilylmethyl-2-octen-1-ol (2b) : oil (76%) ; unseparable stereoisomers ; ^{1}H-NMR (400 MHz, C_6D_6) δ 5.29 and 5.13 (1H, *J*= 6.9 Hz, t), 4.06 and 3.94 (2H, s), 2.06 and 1.94 (2H, *J*= 6.9 Hz, q), 1.80-1.55 (2H, m), 1.41-1.19 (6H, m), 0.88 and 0.87 (3H, *J*= 6.9 Hz, t), 0.03 and 0.02 (9H, s) ; IR (neat) 3350, 2950, 1650, 1460, 1370, 1245, 840, 750 cm^{-1} ; Anal. Calcd. for $C_{12}H_{26}OSi$: C, 67.22 ; H, 12.22. Found : C, 67.06 ; H, 12.35.

2-Trimethylsilylmethyl-1-octen-3-ol (2c) : oil (60%); ^{1}H-NMR (200 MHz, $CDCl_3$) δ 4.87 (1H, br. s), 4.63 (1H, br. s), 3.90 (1H, *J*= 7.3 and 4.9 Hz, dd), 1.48 (2H, *J*= 41.0 Hz, AB), 1.34-1.22 (8H, m), 0.86 (3H, *J*= 6.9 Hz, t), 0.15 (9H, s) ; ^{13}C-NMR (50 MHz, $CDCl_3$) δ 150.2, 107.0, 75.8, 35.7, 31.8, 25.4, 22.6, 22.4, 13.9, -1.2 ; IR (neat) 3400, 3075, 2950, 1660, 1460, 1245, 840, 750 cm^{-1} ; Anal. Calcd. for $C_{12}H_{26}OSi$: C, 67.22 ; H, 12.22. Found : C, 66.96 ; H, 12.28.

(*Z*)-7-Trimethylsilylmethyl-7-dodecen-6-ol (*Z*-2d) : oil (70%); ^{1}H-NMR (400 MHz, C_6D_6) δ 5.43 (1H, *J*= 7.1 Hz, t), 4.17 (1H, *J*= 6.0 Hz, t), 2.29 (2H, *J*= 7.1 Hz, q), 1.63 (2H, *J*= 38.6 Hz, AB), 1.47-1.31 (12H, m), 1.02 (3H,

J= 7.1 Hz, t), 0.99 (3H, J= 6.9 Hz, t), 0.20 (9H, s) ; ^{13}C-NMR (100 MHz, C_6D_6) δ 141.0, 122.5, 77.1, 36.8, 32.6, 32.5, 28.5, 26.4, 23.3, 23.1, 18.7, 14.5, -0.2 ; IR (neat) 3400, 2950, 1650, 1460, 1245, 840 cm^{-1}.

(*Z*)-2-Methyl-3-trimethylsilylmethyl-4-phenyl-3-buten-2-ol (Z-2f) : oil (19%); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.32-7.17 (5H, m), 6.43 (1H, s), 1.94 (2H, s), 1.45 (6H, s), -0.09 (9H, s) ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 147.9, 139.1, 128.8, 128.1, 125.7, 119.0, 74.1, 30.0, 17.7, 0.1 ; IR (neat) 3300, 3000, 2950, 1620, 1585, 1490, 1230, 850, 680 cm^{-1} ; Anal. Calcd. for $C_{15}H_{24}OSi$: C, 72.52 ; H, 9.74. Found : C, 72.38 ; H, 9.79.

(*E*)-2-Methyl-3-trimethylsilylmethyl-4-phenyl-3-buten-2-ol (E-2f) : m.p= 38°C (58%) ; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.28-7.16 (5H, m), 6.24 (1H, s), 1.69 (2H, s), 1.28 (6H, s), 0.12 (9H, s) ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 146.8, 140.2, 128.9, 128.0, 126.2, 122.9, 74.9, 30.7, 24.2, -0.5 ; IR (neat) 3300, 3000, 2950, 1620, 1585, 1490, 1230, 850, 680 cm^{-1} ; Anal. Calcd. for $C_{15}H_{24}OSi$: C, 72.52 ; H, 9.74. Found : C, 72.95 ; H, 9.83.

(*Z*)-2-Methyl-3-trimethylsilylmethyl-4-phenylthio-3-buten-2-ol (Z-2g) : oil (46%) ; ^{1}H-NMR (400 MHz, C_6D_6) δ 7.38 (2H, J= 7.7 Hz, d), 7.07 (2H, J= 7.7 Hz, t), 6.96 (1H, J= 7.7 Hz, t), 6.21 (1H, s), 1.97 (2H, s), 1.20 (6H, s) 0.26 (9H, s) ; ^{13}C-NMR (100 MHz, C_6D_6) δ 149.8, 137.9, 129.2, 128.8, 126.0, 113.4, 73.4, 29.9, 20.5, 0.4 ; IR (neat) 3440, 3050, 2950, 1650, 1580, 1470, 1370, 1240, 840, 730 cm^{-1} ; Anal. Calcd. for $C_{15}H_{24}OSSi$: C, 64.23 ; H, 8.62. Found : C, 64.46 ; H, 8.51.

(*E*)-2-Methyl-3-trimethylsilylmethyl-4-phenylthio-3-buten-2-ol (E-2g) : oil (32%) ; ^{1}H-NMR (400 MHz, C_6D_6) δ 7.39 (2H, J= 8.2 Hz, d), 7.09 (2H, J= 7.7 Hz, t), 6.97 (1H, J= 7.1 Hz, t), 5.81 (1H, s), 1.71 (2H, s), 1.51 (6H, s) 0.09 (9H, s) ; ^{13}C-NMR (100 MHz, C_6D_6) δ 150.7, 138.8, 129.2, 128.9, 126.1, 112.9, 73.6, 29.6, 25.7, -0.5 ; IR (neat) 3440, 3050, 2950, 1650, 1580, 1470, 1370, 1240, 840, 730 cm^{-1}.

(*E*) and (*Z*)-3-Trimethylsilylmethyl-4-phenylthio-3-buten-2-ol (2h): oil (41%) ; unseparable stereoisomers ; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.17-7.31 (5H, m), 6.18 and 5.77 (1H, s), 4.94-4.86 and 4.31-4.23 (1H, m), 1.82-1.66 (2H, m), 1.35 and 1.30 (3H, J= 6.6 Hz, d) 0.11 and 0.10 (9H, s) ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 149.7, 147.8, 138.0, 137.5, 129.5, 129.2, 128.5, 126.5, 126.4, 114.4, 113.7, 72.8, 68.9, 23.5, 22.8, 21.5, 0.6, 0.2 ; IR (neat) 3440, 3050, 2950, 1650, 1580, 1470, 1370, 1240, 840, 730 cm^{-1}.

(Z)-4-Trimethylsilyl-3-trimethylsilylmethyl-3-buten-2-ol (Z-2i): oil (18%) ; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 5.08 (1H, s), 4.47 (1H, *J*= 6.4 Hz, q), 1.63 (2H, *J*= 17.7 Hz, AB), 1.23 (3H, *J*= 6.4 Hz, d), 0.09 (9H, s), -0.01 (9H, s) ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 159.7, 123.1, 71.4, 23.2, 22.0, 0.9, -0.8 ; IR (neat) 3350, 2950, 1610, 1410, 1360, 1240, 1150, 1040, 840 cm^{-1} ; Anal. Calcd. for $C_{11}H_{26}OSi_2$: C, 57.32 ; H, 11.37. Found : C, 57.67 ; H, 11.50.

(E)-4-Trimethylsilyl-3-trimethylsilylmethyl-3-buten-2-ol (E-2i): oil (43%) ; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 5.34 (1H, s), 4.07 (1H, *J*= 6.3 Hz, q), 1.75 (2H, *J*= 36.5 Hz, AB), 1.25 (3H, *J*= 6.3 Hz, d), 0.09 (9H, s), 0.05 (9H, s) ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 160.7, 116.1, 72.1, 24.4, 22.7, 0.4, -0.5 ; IR (neat) 3350, 2950, 1610, 1410, 1360, 1240, 1150, 1040, 840 cm^{-1} ; Anal. Calcd. for $C_{11}H_{26}OSi_2$: C, 57.32 ; H, 11.37. Found : C, 57.56 ; H, 11.42.

Typical Procedure for Preparation of Acetate Derivatives 3. The radical cyclization was performed as described before. After the addition of methyllithium at 0°C, the reaction mixture was stirred for 1 h and acetyl chloride (0.3 mL, 4.5 mmol. Or methyl chloroformate for the preparation of **3j** : 0.35 mL, 4.5 mmol) was added dropwise. The reaction mixture was warmed at room temperature and stirred for 1 additional hour. The organic phase was washed with brine and dried over Na_2SO_4. After evaporation of the solvent, the residue was chromatographed with a mixture of petroleum ether and ether (95 : 05) as eluent.

(E) and (Z)-1-Acetoxy-2-trimethylsilylmethyl-2-octene (3b) : oil (65%) ; unseparable stereoisomers ; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.32 and 5.23 (1H, *J*= 7.2 Hz, t), 4.51 and 4.40 (2H, s), 2.04 and 1.94 (2H, *J*= 7.2 Hz, q), 2.00 and 1.98 (3H, s), 1.80-1.52 (2H, m),1.38-1.22 (6H, m), 0.88 and 0.87 (3H, *J*= 7.1 Hz, t), 0.02 and 0.01 (9H, s) ; IR (neat) 3080, 2970, 1740, 1650, 1460, 1370, 1250, 1040, 840 cm^{-1} ; Anal. Calcd. for $C_{14}H_{28}O_2Si$: C, 65.57 ; H, 11.00. Found : C, 65.29 ; H, 11.08.

(Z)-7-Acetoxy-6-trimethylsilylmethyl-5-dodecene(Z-3d): oil (60%); ^{1}H-NMR (200 MHz, $CDCl_3$) δ 5.24 (1H, *J*= 6.9 Hz, t), 5.08 (1H, *J*= 6.5 Hz, t), 2.01 (3H, s), 1.90 (2H, *J*= 7.1 Hz, q), 1.63 (2H, *J*= 38.6 Hz, AB), 1.36-1.24 (12H, m), 0.87 (3H, *J*= 6.7 Hz, t), 0.85 (3H, *J*= 5.8 Hz, t), 0.02 (9H, s) ; ^{13}C-NMR (50 MHz, $CDCl_3$) δ 170.8, 135.9, 122.7, 79.3, 33.8, 32.2, 32.0, 28.4, 25.8, 23.0, 22.9, 21.9, 18.6, 14.5, 0.1 ; IR (neat) 3080, 2970, 1735, 1650, 1460, 1360, 1240, 1010, 840 cm^{-1} ; Anal. Calcd. for $C_{18}H_{36}O_2Si$: C, 69.17 ; H, 11.61. Found : C, 69.09 ; H, 11.71.

(*Z*)-3-Trimethylsilylmethyl-3-hexen-2-methylcarbonate (*Z*-3j) : oil (45%) ; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.30 (1H, *J*= 7.4 Hz, t), 5.00 (1H, *J*= 6.9 Hz, q), 3.72 (3H, s), 1.91 (2H, *J*= 7.4 Hz, q), 1.55-1.41 (2H, m), 1.30 (3H, *J*= 6.9 Hz, d), 0.91 (3H, *J*= 7.4 Hz, t), 0.02 (9H, s) ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 155.9, 136.1, 128.8, 79.3, 55.0, 21.5, 20.5, 18.9, 15.3, 0.0 ; IR (neat) 2950, 1745, 1650, 1440, 1370, 1265, 1040, 840 cm^{-1}.

(*E*)-3-Trimethylsilylmethyl-3-hexen-2-methylcarbonate (*E*-3j) : oil (20%) ; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.55 (1H, *J*= 6.9 Hz, q), 5.08 (1H, *J*= 7.8 Hz, t), 3.70 (3H, s), 2.08 (2H, *J*= 6.4 Hz, q), 1.48-1.35 (2H, m), 1.25 (3H, *J*= 6.8 Hz, d), 0.92 (3H, *J*= 7.6 Hz, t), -0.01 (9H, s) ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 155.9, 135.1, 126.7, 73.9, 55.0, 21.4, 20.3, 20.0, 14.5, -0.3 ; IR (neat) 2950, 1745, 1650, 1440, 1370, 1265, 1040, 840 cm^{-1}.

3-Acetoxy-2-trimethylsilylmethyl-1-butene (3k) : oil (58%) ; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 4.89 (1H, br. s), 4.65 (1H, br. s), 3.95 (1H, *J*= 6.8 Hz, q), 2.01 (3H, s), 2.00 (3H, s), 1.41 (2H, *J*= 26.5 Hz, AB), 1.33 (3H, *J*= 6.8 Hz, d), 0.03 (9H, s) ; IR (neat) 3080, 2960, 1740, 1640, 1470, 1250, 1050, 850 cm^{-1} ; Anal. Calcd. for $C_{10}H_{20}O_2Si$: C, 59.95 ; H, 10.06. Found : C, 59.66 ; H, 10.14.

Acknowledgment. S. B. thanks GLAXO for a grant.

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(Received in the UK 11 October 1993)