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Vinylsilane-Terminated Cycloacylation: A General Synthetic Approach to Four- to Six-Membered Cyclic Ketones and its Regiochemical Features

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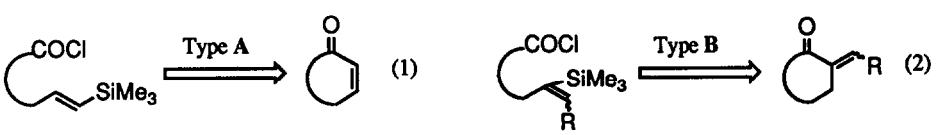
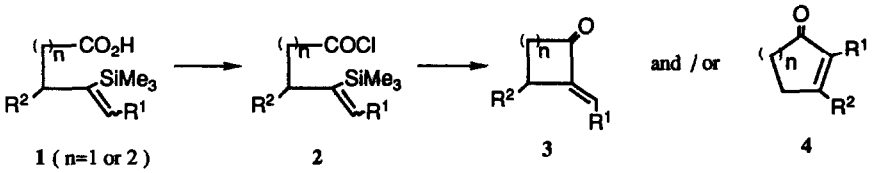
Abstract: *Intramolecular acylations of m-trimethylsilyl-m-alkenoyl chlorides (m=4 and 5) are described which afford the expected α-alkylidenecycloalkanone and/or the unexpected cycloalkenone, depending markedly upon the substitution pattern on the vinylsilane moiety and/or the chain length (m).*

The construction of carbocyclic systems by electrophilic additions to alkenes is a well-established, powerful methodology in organic synthesis.[1] The carbon-carbon bond forming cyclizations ("carbocyclization") have also been utilized to prepare heterocyclic systems.[2,3] A main subject of studies on these cation-induced reactions has been the development of an appropriate functionality to initiate or terminate the ring-forming processes. Vinylsilanes react readily with a wide range of electrophiles to give the products of substitution with retention of configuration. The regiochemistry of substitution is ensured by the so-called β-effect that carbenium ion development occurs at the carbon terminus β to the silicon.[4,5] Thus, the intramolecular acylation of vinylic silanes would provide a versatile synthetic method for cyclic ketones with high regio- and stereocontrol.[6] Of special interest are the cycloacylations of type A (endocyclic) and B (exocyclic) which are highly anticipated[7] to give, respectively, the cycloalkenone and the α-alkylidenecycloalkanone, valuable classes of intermediates in organic synthesis (eq 1 and 2).



We now wish to report the details of our studies on the exocyclic cycloacylation of vinylsilanes of type **1** which provides the expected α-alkylidenecycloalkanone and/or the unexpected cycloalkenone, the ratio depending markedly upon the substitution pattern on the vinylsilane moiety and/or the chain length (*n*) (Scheme 1).[8]



1 (n=1 or 2) **2** **3** **4**

Scheme 1.

RESULTS AND DISCUSSION

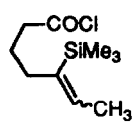
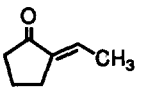
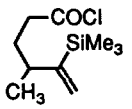
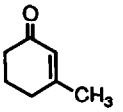
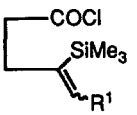
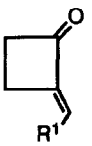
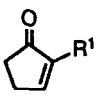
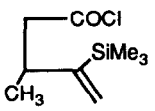
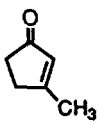
The availability of the starting acid (**1**) deserves special comment. In our continuing study on new synthetic applications of sigmatropic rearrangements, we have developed the sigmatropic variants of β-(trimethylsilyl)allyl alcohol derivatives which permit ready access to a variety of acid (**1**).[9] The Claisen rearrangement of β-(trimethylsilyl)allyl alcohols and the tandem [2,3]Wittig-oxy-Cope sequence[10] of β-(trimethylsilyl)allyl allyl ethers followed by Ag_2O oxidation (except for Ireland rearrangement) afford the acids (**1**) with n=1 and 2, respectively.

We examined the internal acylations of five acid chlorides using aluminum chloride as the activator. Typically, chloride **2** was added to a dilute suspension of aluminum chloride (3 equiv) in dichloromethane (1 mmol/200 ml) at 0 °C over a period of 3 h. The resulting mixture was stirred at 20-25 °C for 10 h, hydrolyzed with aqueous $NaHCO_3$ at 0 °C, and worked up as usual.[11] The cyclization products thus obtained are summarized in Table 1.

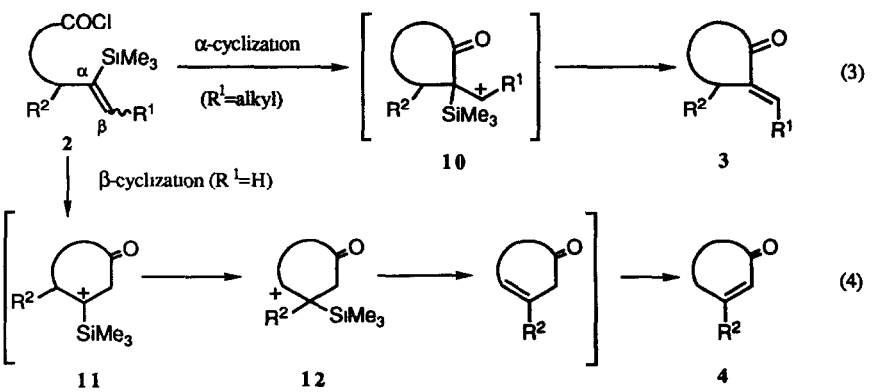
Inspection of Table 1 reveals notable regiochemical trends in the present cycloacylations which are not necessarily consistent with the regiochemical rule ("β-effect")[4,5] widely accepted for the intermolecular versions. First, the most striking is that vinylsilane **2b** afforded the unusual β-acylation product (**4b**), whereas **2a** gave the normal α-acylation product (**3a**), indicating that the substitution pattern on the vinylsilane moiety exerts a great influence in dictating product regiochemistry (*i.e.* mode of cyclization). Second, comparison of entry 1 vs. 3 reveals that the regiochemical course is also affected, at least partially, by the chain length (*n*). Third and more significantly, entries 2 and 4 obviously indicate the occurrence of migration of methyl group at the allylic position during the unusual β-cycloacylation.

The observed regiochemistry is rationalized (or predicted) by properly considering the relative stability of the incipient cations and/or the ring strain involved. In the cycloacylations of vinylsilane possessing the β-alkyl substituent such as **2a**, the secondary β-silylcarbenium ion (**10**) prevails to give the normal α-cyclization product (**3**) (eq 3). In the cycloacylations of vinylsilanes without β-alkyl substituent such as **2b** and **2e**, on the other hand, the tertiary α-silyl cation (**11**) predominates over the primary β-silyl one (**10**, R^1=H), thus leading to the unusual β-cyclization product (**4**) via the rearrangement of **11** to the β-silyl cation (**12**) accompanied by the migration of R^2 (eq 4).[12] While little has been known about the relative stability of tertiary α-silyl vs. primary β-silylcarbenium ion, the higher stability of the former is not unexpected.[13] Overall, these considera-

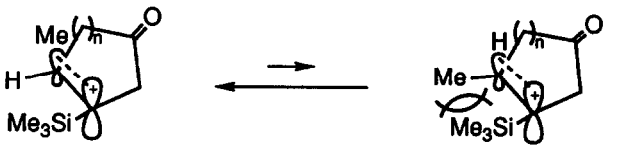
Table 1. Vinylsilane-Terminated Cycloacylation

Entry	Substrate [*E*/*Z*]	Product 3[a] (%Yield)[b]	Product 4[a] (%Yield)[b]
1			
	2a [80 : 20]	**3a**[18] (quant.) [*E*, >95%]	
2			
	2b		**4b**[19] (76)
3[c]			
	2c, R^1=CH_3 [52 : 48]	**3c** (38) [*E*, > 95%]	**4c**[20] (62)
	2d, R^1=n-C_5H_{11} [55 : 45]	**3d** (39) [*E*, > 95%]	**4d**[21] (54)
4			
	2e		**4e**[19] (quant.)

[a] The spectral data (IR and NMR) of these products are fully consistent with the assigned structures including stereochemistry. [b] Refers to isolated yields. [c] The two products were easily separated by column chromatography (silica gel, n-hexane / ether).



tions would suggest that, unless any steric restrictions are present, the relative stability of the carbenium ions concerned decreases in the order: tertiary trialkyl > secondary β-silyl > tertiary α-silyl > primary β-silyl.[14] The exclusive migration of the β-methyl observed in the reactions of **2b** and **2e** is rather surprising, because the β-hydride is known to migrate faster than the β-methyl in related carbocation reactions.[15] Thus, the exclusive β-methyl migration is best explained as a result of the stereoelectronic effect operating in the sterically favorable conformer **A** (eq 5) which better suits for the methyl migration in virtue of the better orbital overlap between the axial methyl and the p-orbital of the α-silyl cation. In the cyclization of **2c** or **2d** where the normal α-cyclization leading to the cyclobutanone (**3c** or **3d**)[16] is depressed apparently by the severe ring strain, the β-cyclization product (**4c** or **4d**) is formed as the major product.



A **B** (5)

The regiochemical aspect outlined here[8] not only offers the first example of the unprecedented β-cycloacylation of vinylic silanes[6], but also warrants that one should not overestimate the "β-effect" in the electrophilic reactions of vinylic silanes in general. Furthermore, the present work convincingly demonstrates the synthetic potential of the internal acylations of vinylic silanes for the construction of a variety of carbocyclic frameworks.

EXPERIMENTAL

B.ps are uncorrected. IR spectra were recorded on a JASCO A-102 spectrometer. NMR spectra were recorded at 90 MHz on a Varian EM-390 spectrometer and chemical shifts were reported in ppm using TMS or $CHCl_3$ as internal standard. UV spectra were recorded on a Shimazu UV-200 spectrometer. High resolution mass spectra were performed on a JEOL JMS-505H mass spectrometer (Acid chlorides **2** were too unstable to detect the parent peaks.). GC analyses were run on a Shimazu GC-3BT chromatograph using He as a carrier gas (1 kg cm^{-2}) and a 3 mm x 3 m column [20% PEG 20M on Chromosorb W (60-80 mesh)] at the indicated temperature. Benzene was dried by azeotropic distillation after drying with $CaCl_2$. CH_2Cl_2 and CCl_4 were dried by distillation from CaH_2. All reactions were performed under N_2 atmosphere. *E/Z* geometrical assignment and the isomeric ratio were determined by GC and/or NMR analyses according to the literature method.[17]

Preparation of m-trimethylsilyl-m-alkenoyl chlorides (m=4,5)

5-Trimethylsilyl-5-heptenoyl chloride (2a)

To a solution of **1a** (0.54 g, 2.7 mmol) in benzene (2 ml) was added dropwise slowly oxalyl chloride (0.31 ml, 3.6 mmol) at 0 °C and allowed to room temperature. After stirring for 1 h, the reaction mixture was concentrated *in vacuo* followed by distillation afforded acid chloride **2a** (0.52 g, 88%; *E/Z* = 80 : 20 by NMR):

b.p. 73-79 °/0.3 mmHg; IR (neat) 1800, 1615, 1250, 840, 755 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.00 (s, 9H), 1.35-1.92 (m, 2H), 1.63 (d, J=6.9 Hz, 3H), 2.00-2.38 (m, 2H), 2.68-3.04 (m, 2H), 5.90 and 5.97 (2q, J=6.9 Hz, 0.8 and 0.2H).

4-Methyl-5-trimethylsilyl-5-hexenoyl chloride (2b)

To a solution of **1b** (0.86 g, 4.3 mmol) in CCl_4 (1.5 ml) was added dropwise slowly thionyl chloride (0.9 ml, 12.3 mmol) at 0 °C and was heated at 55 °C for 3 h. The reaction mixture was concentrated *in vacuo* followed by distillation afforded acid chloride **2b** (0.79 g, 84%): b.p. 88-95 °/2 mmHg; IR (neat) 1800, 1250, 840, 760 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ -0.09 (s, 1H), 0.88 (d, J=6.3 Hz, 3H), 1.40-1.90 (m, 2H), 2.00-2.44 (m, 1H), 2.68 (t, J=8.1 Hz, 2H), 5.36 (d, J=2.4 Hz, 1H), 5.54 (d, J=2.4 Hz, 1H).

4-Trimethylsilyl-4-hexenoyl chloride (2c)

Acid chloride **2c** was prepared from **1c** (0.92 g, 4.9 mmol) by oxalyl chloride as described for the preparation of **2a** (0.57 g, 56%; *E*/*Z* ≈ 52 : 48 by NMR): b.p. 46-48 °/0.4 mmHg; IR (neat) 1805, 1620, 1255, 840, 760 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.03 and 0.13 (2s, 4.68 and 4.32H), 1.65 and 1.70 (2d, J=6.6 Hz, 1.56 and 1.44H), 2.27-3.00 (m, 4H), 5.93 and 6.10 (2q, J=6.6 Hz, 0.52 and 0.48H).

4-Trimethylsilyl-4-decenoyl chloride (2d)

Acid chloride **2d** was prepared from **1d** (2.65 g, 11.0 mmol) by oxalyl chloride as described for the preparation of **2a** (1.72 g, 60%; *E*/*Z* = 55 : 45 by NMR): b.p. 76-84 °/0.2 mmHg; IR (neat) 1800, 1610, 1250, 955, 835, 755 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.00 and 0.08 (2s, 4.95 and 4.05H), 0.67-0.97 (m, 3H), 1.05-1.50 (m, 6H), 1.80-2.20 (m, 2H), 2.24-2.60 (m, 2H), 2.64-3.04 (m, 2H), 5.80 and 6.00 (2t, J=6.6 Hz, 0.55 and 0.45H).

3-Methyl-4-trimethylsilyl-4-pentenoyl chloride (2e)

Acid chloride **2e** was prepared from **1e** (0.65 g, 3.5 mmol) by thionyl chloride as described for the preparation of **2b** (0.57 g, 80%): b.p. 127-128 °/0.2 mmHg; IR (neat) 1800, 1250, 840, 760 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.10 (s, 9H), 1.06 (d, 6.6 Hz, 3H), 2.68-3.23 (m, 3H), 5.43 (d, J=2.1 Hz, 1H), 5.64 (d, J=2.1 Hz, 1H).

Cyclization of m-trimethylsilyl-m-alkenoyl chlorides (m=4,5)

A typical procedure is shown in the cyclization of **2a**.

Cyclization of 2a

To a dilute suspension of $AlCl_3$ (0.26 g, 1.95 mmol) in anhydrous CH_2Cl_2 (120 ml) was added dropwise slowly a solution of **2a** (0.14 g, 0.65 mmol) in anhydrous CH_2Cl_2 (20 ml) over a period of 3 h at 0 °C. After stirring for 10 h at room temperature, the reaction mixture was poured into sat. $NaHCO_3$, $AlCl_3$ was filtered off and extracted with CH_2Cl_2. The organic extracts were washed with brine, dried with $MgSO_4$ and concentrated *in vacuo* to give 2-ethylidenecyclopentan-1-one, **3a**[18] as one isomer (0.11 g, quant.; *E*>95% by

NMR): IR (neat) 1710, 1650, 810 cm^{-1}; ^1H-NMR ($CDCl_3$) δ 1.64-2.77 (m, 6H), 1.88 (d, J=7.5 Hz, 3H), 6.50 (q, t, J=7.5 and 2.7 Hz, 1H).

Cyclization of 2b

The cyclization of 0.22 g (1.0 mmol) of **2b** gave 3-methyl-2-cyclohexen-1-one, **4b**[19] as one isomer after purification by preparative TLC (84 mg, 76%): TLC (n-hexane : Et_2O = 2 : 1) R_f=0.18; IR (neat) 1765, 1665, 1630, 885 cm^{-1}; ^1H-NMR (CCl_4) δ 1.40-2.46 (m, 6H), 1.83 (s, 3H), 5.83 (s, 1H) ; MS m/e 110 (M^+).

Cyclization of 2c

The cyclization of 0.45 g (2.2 mmol) of **2c** gave 2-ethylidenecyclobutan-1-one, **3c** (80 mg, 38%; *E*>95% by NMR) and 2-methyl-2-cyclopenten-1-one, **4c**[20] (0.13 g, 62%) as two isomers which were isolated by silica-gel column chromatography: **3c**; TLC (n-hexane : Et_2O = 2 : 1) R_f=0.30; IR (CCl_4) 1760, 1675, 1090 cm^{-1}; ^1H-NMR (CCl_4) δ 1.75 (d, J=7.5 Hz, 3H), 2.40-2.73 (m, 2H), 2.78-3.11 (m, 2H), 6.26 (q, t, J=7.5 and 2.8 Hz, 1H); GC (PEG 20M, 150 °C) R_t = 6.3 min; MS m/e 96.0571 (calcd for C_6H_8O, 96.0575): **4c**; TLC (n-hexane : Et_2O = 2 : 1) R_f=0.18; IR (CCl_4) 1705, 1640, 1065 cm^{-1}; ^1H-NMR (CCl_4) δ 1.73 (s, 3H), 2.17-2.37 (m, 2H), 2.40-2.64 (m, 2H), 7.12-7.27 (m, 1H); GC (PEG 20M, 150 °C) R_t = 7.3 min; MS m/e 96.0573 (calcd for C_6H_8O, 96.0575).

Cyclization of 2d

The cyclization of 0.52 g (2.0 mmol) of **2d** gave 2-hexylidenecyclobutan-1-one, **3d** (0.12 g, 39%; *E*>95% by NMR) and 2-pentyl-2-cyclopenten-1-one, **4d**[21] (0.17 g, 54%) as two isomers which were isolated by silica-gel column chromatography: **3d**; TLC (n-hexane : Et_2O = 1 : 1) R_f = 0.57; IR (neat) 1750, 1665, 1100 cm^{-1}; ^1H-NMR ($CDCl_3$) δ 0.64-1.00 (m, 3H), 1.07-1.66 (m, 6H), 1.84-2.30 (m, 2H), 2.38-2.68 (m, 2H), 2.74-3.00 (m, 2H), 6.23 (t, t, J=7.5 and 2.8 Hz, 1H); GC (PEG 20M, 180 °C) R_t = 16.6 min; MS m/e 152 (M^+); UV λ_{max} = 239 nm: **4d**; TLC (n-hexane : Et_2O = 1 : 1) R_f = 0.42; IR (neat) 1700, 1630, 1000, 790 cm^{-1}; ^1H-NMR (CCl_4) δ 0.73-1.07 (m, 3H), 1.11-1.67 (m, 6H), 2.00-2.72 (m, 6H), 7.23-7.40 (m, 1H); GC (PEG 20M, 180 °C) R_t = 17.5 min; MS m/e 152 (M^+); UV λ_{max} = 226 nm.

Cyclization of 2e

The cyclization of 0.57 g (2.8 mmol) of **2e** gave 3-methyl-2-cyclopenten-1-one, **4e**[19] as one isomer (0.24 g, quant.): TLC (n-hexane : Et_2O = 1 : 1) R_f = 0.17; IR (neat) 1700, 1670, 1620, 1180, 965 cm^{-1}; ^1H-NMR ($CDCl_3$) δ 2.09 (s, 3H), 2.29-2.67 (m, 4H), 5.80-5.97 (m, 1H); MS m/e 96 (M^+).

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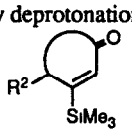

C

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