

Unexpected preparation of (*Z*)-chloromethyleneketals and their sulfur analogues by a novel three-component condensation*

Dedicated to the burning memory of Professor Heinz Gunter Viehe

Florian Schevenels and István E. Markó*

*Université catholique de Louvain, Bâtiment Lavoisier, Place Louis Pasteur 1, B-1348
Louvain-la-Neuve, Belgium.*

Experimental section

General: ^1H and ^{13}C NMR spectra were recorded at room temperature with a Bruker Avance 300 instrument operating at a frequency of 300 MHz for ^1H and 75 MHz for ^{13}C . In cases of ambiguous assignments, spectra were recorded with a Bruker 500. ^1H NMR spectra were recorded in CDCl_3 and referenced to CHCl_3 ($\delta = 7.26$) as an internal standard. ^{13}C NMR spectra were referenced to the CDCl_3 ($\delta = 77.16$ ppm) signal. Mass spectra were recorded using Varian Matt 44S and Finnigan-Matt TSQ-70. High-resolution mass data were obtained with a Kratos MS50TC instrument. Infrared spectra were recorded on a SHIMATZU-FTIR-8400S spectrometer and recorded in cm^{-1} . Elemental analyses were carried out at the University of Stuttgart, Germany. X-Ray diffraction studies were carried out by Pr. B. Tinant (UCL) and Pr. J. Wouters (FUNDP).

General procedure for chloromethyleneketals

To 25 mL of anhydrous THF, the ketone **27** (10 mmol, 2 eq.), ethylene dichloride **9** (0.40 mL, 5.0 mmol, 1 eq.) and potassium tert-butoxide (1.12 g, 10 mmol, 2 eq.) were added sequentially. After 1 to 4 h, as indicated by tlc, the mixture was filtered through a pad of silica using 300 mL of a 3:1 mixture of petroleum ether : ethyl acetate. The solvents were removed under vacuum. If necessary, the product was purified by silicagel column chromatography.

Cyclohexyl-chloromethyleneketal (**5**)

No further purification was needed and 1.24g (4.8 mmol, 97%) of **5** were obtained as a yellowish oil.

$R_f=0.88$ (EP/EtOAc 5:1). ^1H NMR (300 MHz): $\delta = 4.90$ (s, 1 H), 1.15 to 1.80 (m, 20 H) ppm. ^{13}C NMR (75 MHz): $\delta = 159.0, 113.0, 85.6, 82.8, 38.8, 37.7, 25.0, 24.8, 23.7, 22.3$ ppm. MS (ESI): $m/z = 257$. I.R. (neat): ν 2934, 2858, 1682. Anal. Calcd for $\text{C}_{14}\text{H}_{21}\text{ClO}_2$; C, 65.49; H, 8.24; Cl, 13.81. Found: C, 65.29; H, 8.09; Cl, 13.88.

4-*tert*-butyl-cyclohexyl-chloromethyleneketal (**21**)

No further purification was needed and 1.70 g (4.6 mmol, 92%) of **21** were obtained as a white crystalline material. This consisted of a mixture of four diastereoisomers in a 1:2:10:3 ratio.

$R_f=0.88$ (EP/EtOAc 5:1). $^1\text{H NMR}$ (300 MHz): $\delta = 4.89$ (s, 1 H), 1.30 to 1.99 (m, 16 H), 1.03 (t, $J = 12.0$ Hz, 2 H), 0.86 (s, 18 H) ppm. $^{13}\text{C NMR}$ (75 MHz): $\delta = 158.9, 113.3, 85.0, 82.4, 46.6, 46.4, 39.1, 37.5, 32.4, 32.2, 27.5, 27.4, 24.5, 23.2$, ppm. MS (ESI): $m/z = 369$. I.R. (neat): ν 2945, 2868, 1684. Anal. Calcd for $\text{C}_{22}\text{H}_{37}\text{ClO}_2$; C, 71.61; H, 10.11; Cl, 9.61. Found: C, 71.63; H, 10.30; Cl, 9.67. mp 76-80 °C.

4-NBoc-piperidyl-chloromethyleneketal (**22**)

The crude product was purified by column chromatography (silica, petroleum ether/ethyl acetate 3:1) to yield 2.16 g (4.7 mmol, 94%) of **22** as a white crystalline material.

$R_f=0.40$ (EP/EtOAc 5:1). $^1\text{H NMR}$ (300 MHz): $\delta = 5.01$ (s, 1 H) 4.03 (m, 2 H), 3.56 (t, $J = 5.7$ Hz, 4 H), 3.04 (t, $J = 12.0$ Hz, 2 H), 1.57 to 1.86 (m, 8 H), 1.45 (s, 18 H) ppm. $^{13}\text{C NMR}$ (75 MHz): $\delta = 157.1, 154.8, 154.7, 111.7, 87.7, 81.3, 80.0, 79.9, 41.5, 41.3, 38.2, 37.3, 28.5$ ppm. MS (ESI): $m/z = 459$. I.R. (neat): ν 2972, 1690. Anal. Calcd for $\text{C}_{22}\text{H}_{35}\text{ClN}_2\text{O}_6$; C, 57.57; H, 7.69; N, 6.10; Cl, 7.72. Found: C, 57.58; H, 7.70; N, 5.81; Cl, 7.84. mp 69-73 °C.

Tetraethyl-chloromethyleneketal (**17**)

Crude mixture was purified on column chromatography (silica, petroleum ether/ethyl acetate 10:1) to yield 530 mg (2.3 mmol, 45%) of **17** as a colourless oil.

$R_f=0.81$ (EP/EtOAc 10:1). $^1\text{H NMR}$ (300 MHz): $\delta = 4.87$ (s, 1 H) 1.58 to 1.82 (m, 8 H), 0.90 to 0.98 (m, 12 H) ppm. $^{13}\text{C NMR}$ (75 MHz): $\delta = 157.2, 116.2, 87.2, 85.8, 31.7, 30.7, 8.5, 8.4$ ppm. MS (ESI): $m/z = 184$. I.R. (neat): ν 2974, 2941, 1682. Anal. Calcd for $\text{C}_{12}\text{H}_{21}\text{ClO}_2$; C, 61.92; H, 9.09; Cl, 15.23. Found: C, 61.76; H, 8.94; Cl, 15.23.

1-chloroethynyl-cyclohexanol (**12**)

A mixture of 12 mL of THF and 0.78 mL (5.5 mmol, 2.2 eq.) of diisopropylamine was cooled to 0°C. At this temperature, 2.2 mL (5.5 mmol, 2.2 eq.) of BuLi 2.5 M in hexane were added dropwise. After 20 minutes under stirring, the mixture was cooled to -78°C and 0.22 mL (2.75 mmol, 1.1 eq.) of ethylene dichloride were added. The temperature was slowly raised to 0°C and 0.26 mL (2.5 mmol, 1 eq.) of cyclohexanone were added. After 1 hour at 0°C, the reaction was quenched with 10 mL of saturated aqueous NH_4Cl . The aqueous phase was extracted with 3 x 10 mL of diethylether. The organic layers were pooled, dried over magnesium sulphate, filtered and concentrated to yield 390 mg (2.45 mmol, 98%) of **12** as a yellowish oil.

$R_f=0.52$ (EP/EtOAc 5:1). $^1\text{H NMR}$ (300 MHz): $\delta = 2.40$ (s, 1 H) 1.84 (m, 2 H), 1.67 (m, 2 H), 1.24 (m, 5 H), 1.08 (m, 1 H) ppm. $^{13}\text{C NMR}$ (75 MHz): $\delta = 73.0, 69.2, 62.7, 39.9, 25.2, 23.2$ ppm. MS (CI): $m/z = 158$. I.R. (neat): ν 3339, 2934, 2858, 2224. Anal. Calcd for $\text{C}_8\text{H}_{11}\text{ClO}$; C, 60.57; H, 6.99; Cl, 22.35. Found: C, 60.44; H, 6.82; Cl, 22.39.

1-chloro-3-ethylpent-1-yn-3-ol (**14**)

A mixture of 120 mL of THF and 7.8 mL (55 mmol, 2.2 eq.) of diisopropylamine was cooled to 0°C. At this temperature, 22 mL (55 mmol, 2.2 eq.) of BuLi 2.5 M in hexane were added dropwise. After 20 minutes under stirring, the mixture was cooled to -78°C and 2.2 mL (27.5 mmol, 1.1 eq.) of ethylene dichloride were added. The temperature was slowly raised to 0°C and 2.7 mL (25 mmol, 1 eq.) of 3-pentanone were added. After 1 hour at 0°C, the reaction was quenched with 100 mL of saturated aqueous NH₄Cl. The aqueous phase was extracted with 3 x 100 mL of diethylether. The organic layers were pooled, dried over magnesium sulphate, filtered and concentrated to yield 3.60 g (24.5 mmol, 98%) of **14** as a yellowish oil.

R_f=0.72 (EP/EtOAc 2:1). ¹H NMR (300 MHz): δ = 2.90 (s, 1 H) 1.59 (q, *J* = 7.8 Hz, 4 H), 0.94 (t, *J* = 7.5 Hz, 6 H) ppm. ¹³C NMR (75 MHz): δ = 72.6, 71.9, 62.4, 34.2, 8.4 ppm. MS (CI): *m/z* = 147. I.R. (neat): ν 3394, 2970, 2227. Anal. Calcd for C₇H₁₁ClO; C, 57.35; H, 7.56; Cl, 24.18. Found: C, 57.50; H, 7.74; Cl, 24.41.

Cyclohexyl-thiophenylmethyleneketal (**23**)

To 25 mL of THF, 1.05 mL (10 mmol, 2 eq.) of cyclohexanone, 860 mg (5 mmol, 1 eq.) of (*E*)-(2-chlorovinyl)(phenyl)sulfane and 1.12 g (10 mmol, 2 eq.) of potassium *tert*-butoxide were added sequentially. After 2 hours at room temperature, the crude mixture was filtered through a pad of silica using 300 mL of a 3:1 mixture of petroleum ether : ethyl acetate to yield 1.48 g (4.5 mmol, 90%) of **23** as a yellowish oil.

R_f=0.84 (EP/EtOAc 5:1). ¹H NMR (300 MHz): δ = 7.21 to 7.38 (m, 4 H) 7.04 to 7.18 (m, 1 H), 4.90 (s, 1 H), 1.88 (m, 2 H), 1.52 to 1.80 (m, 16 H), 1.30 to 1.48 (m, 2 H) ppm. ¹³C NMR (75 MHz): δ = 165.4, 138.3, 128.8, 126.6, 125.0, 113.1, 83.3, 82.3, 38.9, 37.9, 25.2, 24.9, 23.8, 22.4 ppm. MS (CI): *m/z* = 330. I.R. (neat): ν 2932, 2857, 1636, 1583. Anal. Calcd for C₂₀H₂₆O₂S; C, 72.69; H, 7.93; S, 9.70. Found: C, 72.40; H, 7.98; S, 9.98.

4-NBoc-piperidinyl-thiophenylmethyleneketal (**24**)

To 12 mL of THF, 1.00 g (5.0 mmol, 2 eq.) of Bocpiperidone, 430 mg (2.5 mmol, 1 eq.) of (*E*)-(2-chlorovinyl)(phenyl)sulfane and 0.56 g (5 mmol, 2 eq.) of potassium *tert*-butoxide were added sequentially. After 4 hours, the reaction mixture was filtered through a pad of silica gel using 300 mL of a 2:1 mixture of petroleum ether : ethyl acetate. Purification over column chromatography (silica, petroleum ether/ethyl acetate) provided 1.17 g (2.2 mmol, 88%) of **24** as a white crystalline material.

R_f=0.44 (EP/EtOAc 5:1). ¹H NMR (300 MHz): δ = 7.27 (m, 4 H) 7.15 (m, 1 H), 5.01 (s, 1 H), 4.11 (br, 2 H), 3.53 (s, 4 H), 3.08 (br, 2 H), 1.78 (m, 8 H), 1.48 (s, 9 H), 1.46 (s, 9 H) ppm. ¹³C NMR (75 MHz): δ = 161.3, 154.7, 154.6, 137.2, 129.0, 127.3, 125.6, 111.3, 85.9, 81.5, 79.9, 79.8, 41.3, 40.2, 38.1, 37.2, 28.5 ppm. MS (ESI): *m/z* = 532. I.R. (neat): ν 2974, 2930, 2872, 1693, 1674. H.R.M.S. (ESI): Calcd for C₂₈H₄₀N₂O₆SNa; 555.2505. Found: 555.2529. mp 59-63 °C.

Cyclohexyl-phenylmethyleneketal (**27**)

A solution of THF (17 mL) and NMP (12 mL), containing 220 mg (0.3 mmol, 0.2 eq.) of Fe(acac)₃ and 380 mg (1.48 mmol, 1 eq.) of ketal **5**, was cooled to -10°C. At this temperature, 1.6 mL (4.44 mmol, 3 eq.) of phenylmagnesium bromide (2.8 M in diethylether) were added dropwise. The temperature was raised to 20°C. After stirring for 1 hour, 40ml of saturated

aqueous NaCl (brine) were added carefully. The aqueous phase was extracted 3 times with 40 mL of ether. The organic layers were pooled, dried over magnesium sulphate, filtered and concentrated. The crude product was purified by column chromatography (silica, petroleum ether/ethyl acetate 50:1) to yield 430 mg (1.44 mmol, 97%) of **27** as a greenish oil.

$R_f=0.63$ (EP/EtOAc 40:1) ^1H NMR (300 MHz): $\delta = 7.61$ (d, $J = 7.2$ Hz, 2 H) 7.45 (t, $J = 7.5$ Hz, 2 H), 7.36 (t, $J = 7.2$ Hz, 1 H), 4.95 (s, 1 H), 1.80 (t, $J = 12.9$ Hz, 2 H), 1.57 to 1.74 (m, 14 H), 1.34 to 1.51 (m, 3 H), 1.10 to 1.32 (m, 1 H) ppm. ^{13}C NMR (75 MHz): $\delta = 159.2$, 141.4, 128.9, 127.4, 127.3, 113.3, 85.7, 83.0, 39.0, 37.9, 25.1, 24.9, 23.9, 22.5 ppm. MS (CI): $m/z = 298$. I.R. (neat): ν 2931, 2858, 1682. HRMS (ESI): Calcd for $\text{C}_{20}\text{H}_{26}\text{O}_2$: 298.1927. Found: 298.1932.

Cyclohexyl-allylsilanemethyleneketal (**25**)

A solution of 3 mL of THF, 115 mg (0.21 mmol, 0.05 eq.) of $\text{NiCl}_2(\text{dppp})$, and 1.10 g (4.28 mmol, 1 eq.) of ketal **5** was cooled to 0°C . At this temperature, 3.6 mL (4.7 mmol, 1.1 eq.) of ((trimethylsilyl)methyl)magnesium chloride (1.3 M in THF) were added dropwise. The reaction mixture was then refluxed during 3 hours. After this time, 0.05 eq. of catalyst and 1.1 eq. of the Grignard reagent were added. After 3 hours under reflux, 0.3 equivalent of the Grignard reagent were added every hour until the starting material fully disappeared. Then, 20 mL of water and 20 mL of 1 M HCl were added. The aqueous phase was extracted with 3 x 40 mL of ether. The organic layers were pooled, dried over magnesium sulphate, filtered and concentrated. The crude reaction product was purified by column chromatography (silica, petroleum ether/ethyl acetate 50:1) to yield 1.06 g (3.44 mmol, 80%) of **25** as a yellowish oil.

$R_f=0.75$ (EP/EtOAc 40:1). ^1H NMR (300 MHz): $\delta = 4.07$ (t, $J = 8.4$ Hz, 1 H) 1.53 to 1.76 (m, 15 H), 1.32 to 1.48 (m, 4 H), 1.42 (d, $J = 8.4$ Hz, 2 H), 1.12 to 1.28 (m, 1 H), -0.01 (s, 9 H) ppm. ^{13}C NMR (75 MHz): $\delta = 156.3$, 109.9, 89.7, 81.2, 39.3, 38.0, 25.4, 25.2, 24.0, 22.8, 14.8, -1.7 ppm. MS (CI): $m/z = 308$. I.R. (neat): ν 2931, 2858, 1697. Anal. Calcd for $\text{C}_{18}\text{H}_{32}\text{SiO}_2$; C, 70.07; H, 10.45. Found: C, 69.86; H, 10.32.

1-(1-hydroxycyclohexyl)-3-(trimethylsilyl)propan-1-one (**26**)

Pyridine was added dropwise to an aqueous solution of CAN (1.40 g, 2.59 mmol, 1 eq.) until the pH reached 3.0-3.5. The resulting solution was then added to a mixture of 10 mL of acetonitrile and 800 mg (2.59 mmol, 1 eq.) of cyclohexyl-allylsilylmethyleneketal **25**. The reaction mixture was heated to 60°C during 1 hour. Then, 10 mL of saturated aqueous NH_4Cl were added. The aqueous phase was extracted with 3 x 20 mL of diethylether. The organic layers were pooled, dried over magnesium sulphate, filtered and concentrated. The crude reaction product was purified by column chromatography (silica, petroleum ether/ethyl acetate 10:1) to yield 530 mg (2.33 mmol, 90%) of **26** as a colourless oil.

$R_f=0.67$ (EP/EtOAc 5:1). ^1H NMR (300 MHz): $\delta = 3.57$ (s, 1 H) 2.52 (t, $J = 8.1$ Hz, 2 H), 1.58 to 1.80 (m, 7 H), 1.39 to 1.56 (m, 2 H), 1.18 to 1.36 (m, 1 H), 0.76 (t, $J = 8.1$ Hz, 2 H), -0.01 (s, 9 H) ppm. ^{13}C NMR (75 MHz): $\delta = 215.7$, 78.2, 34.3, 30.3, 25.4, 21.3, 10.2, -1.7 ppm. MS (CI): $m/z = 228$. I.R. (neat): ν 3489, 2934, 1699. Anal. Calcd for $\text{C}_{12}\text{H}_{24}\text{O}_2\text{Si}$; C, 63.10; H, 10.59. Found: C, 63.10; H, 10.94.

2-chloro-1-(1-hydroxycyclohexyl)ethanone (**7**)

Pyridine was added dropwise to an aqueous solution of CAN (1.80 g, 3.23 mmol, 1 eq.) until pH reached 3.0-3.5. The resulting solution was added to a mixture of 12 mL of acetonitrile and 830 mg (3.23 mmol, 1 eq.) of cyclohexyl-chloromethyleneketal **5**. The reaction mixture was heated to 60°C during 5 hours. Then, 10 mL of saturated aqueous NH₄Cl were added. The aqueous phase was extracted with 3 x 10 mL of diethylether. The organic layers were pooled, dried over magnesium sulphate, filtered and concentrated. The crude product was purified by column chromatography (silica, petroleum ether/ethyl acetate 5:1). A mixture of cyclohexanone and the desired product was carefully heated under vacuum to yield 455 mg (2.58 mmol, 80%) of **7** as colourless crystals.

R_f=0.40 (EP/EtOAc 5:1). ¹H NMR (300 MHz): δ = 4.56 (s, 2 H) 2.72 (s, 1 H), 1.52 to 1.82 (m, 9 H), 1.19 to 1.39 (m, 1 H) ppm. ¹³C NMR (75 MHz): δ = 206.3, 79.0, 46.1, 34.2, 25.0, 20.9 ppm. MS (EI): *m/z* = 177. I.R. (neat): ν 3481, 2941, 2867, 1726. Anal. Calcd for C₈H₁₃ClO₂; C, 54.40; H, 7.42; Cl, 20.07. Found: C, 54.40; H, 7.35; Cl, 20.12. mp 51-53 °C.

Dicyclohexyl-lactoketal (**6**)

A solution of 80 mL of dichloromethane and 2.30 g (9.0 mmol, 1 eq.) of cyclohexyl-chloromethyleneketal **5** was cooled to -78°C. Ozone was bubbled until the appearance of a blue-purple colour. Nitrogen was then bubbled through the solution until the colour disappeared. Then, 2.82 g (10.8 mmol, 1.2 eq.) of PPh₃ were added. The mixture was stirred 3 hours at room temperature. The dichloromethane was evaporated under vacuum and the crude product was purified by column chromatography (silica, petroleum ether/ethyl acetate 100:1) to yield 600 mg (2.65 mmol, 30%) of **6** as a colourless oil, identical to an authentic sample.

¹H NMR (300 MHz): δ = 1.30 to 1.87 (m, 20 H) ppm. ¹³C NMR (75 MHz): δ = 174.9, 109.7, 78.0, 38.1, 34.9, 24.6, 24.3, 23.0, 21.2 ppm. MS (EI): *m/z* = 224.