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Efficient one-pot synthesis of chlorinated cyclopentenones from hexachlorocyclopentadiene

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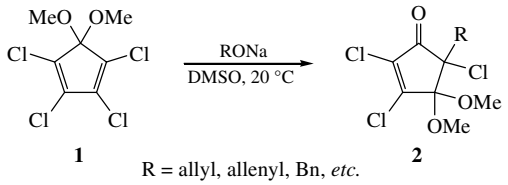
The interaction of hexachlorocyclopentadiene ($CpCl_6$) with KOH in MeOH followed by acidic treatment of the reaction mass results in synthetically valuable 2,3,5-trichloro-4,4-dimethoxy- or 2,5-dichloro-3,4,4-trimethoxycyclopent-2-en-1-ones.

Oxygenated chlorocyclopentenones are of interest for the synthesis of chlorine-containing natural compounds (chlorovulones,[1] pynaglandines,[2] cryptosporiopsine,[3] *etc.*), heterocycles[4] and chlorine-free cyclopentanoids (prostaglandins,[5] cyclopentenone antibiotics,[6] carbanucleosides,[7] *etc.*).

Earlier,[8] we proposed original one-stage procedures for the transformation of dimethoxy derivative **1**,[9] easily available from $CpCl_6$, into synthetically valuable 5-substituted trichlorocyclopentenones **2** by treatment with allyl, propargyl, benzyl and other sodium alcoholates.



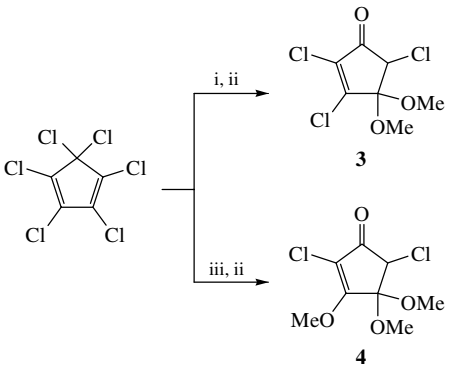
1 **2**

R = allyl, allenyl, Bn, *etc.*

Scheme 1

Here, we describe an efficient method for the preparation of chlorocyclopentenones **3**[10,11] and **4** directly from $CpCl_6$ using inexpensive reagents (KOH, MeOH and H_2SO_4).

In order to synthesise cyclopentenone **3**, a mixture of $CpCl_6$ and KOH in a molar ratio of 1:(7–10) in MeOH (1 g of $CpCl_6$ in 5 ml of MeOH) was stirred at room temperature for 24 h and then hydrolysed with 50% H_2SO_4 at 50 °C for 10 h. The usual treatment of the reaction mass and vacuum distillation of the crude product gave chlorocyclopentenone **3** in >70% yield (Scheme 2).† If compared with other multistep syntheses of this compound,[12,13] our one-pot procedure is direct, simple and practical.



Scheme 2 *Reagents and conditions*: i, KOH–MeOH, 20 °C, 24 h; ii, 50% H_2SO_4, 50 °C, 10 h, 75%; iii, KOH–MeOH, 80 °C, 10 h, 58%.

The same reaction, but at more vigorous alkaline treatment (70–80 °C, 10 h), resulted in trimethoxy derivative **4** in 58% yield.‡

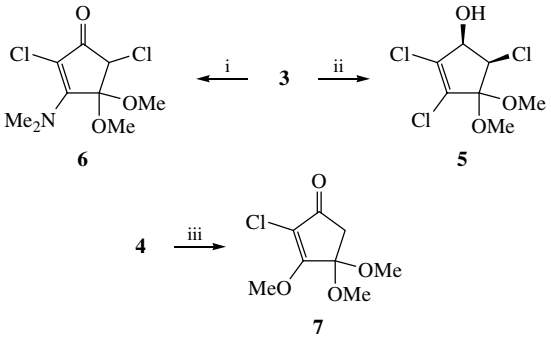
These experiments demonstrate that the one-pot reaction which combines the methanolysis of chlorine substituents with partial acid hydrolysis is a very efficient method for the synthesis of heavily functionalised chlorocyclopentenones directly from $CpCl_6$.

The reactivity of compounds **3** and **4** was tested in reactions typical of trichlorocyclopentenones **2**.[13–15] Thus, the hydride reduction of **3** with $NaBH_4$ led to sterically homogeneous *cis*-chlorohydrine **5**.§ The Ad_N-E-type regioselective reaction of C^3-Cl_3 with dimethylamine resulted in the formation of vinylogous amide **6**.¶ The reductive dechlorination of **4** with Zn–NH_4Cl in

† The NMR spectra were recorded on a Bruker AM-300 spectrometer at 300 (^{1}H) or 75.47 MHz (^{13}C) in $CDCl_3$ with TMS as a standard. The IR spectra were recorded on Specord M-80 and UR-20 (in Vaseline oil). The progress of the reactions was monitored by TLC on Silufol plates using light petroleum (PE)–ethyl acetate (AcOEt) as an eluent and visualised with an alkaline solution of $KMnO_4$.[16]

2,3,5-Trichloro-4,4-dimethoxycyclopent-2-en-1-one **3**. A mixture of pulverised KOH (42 g, 750 mmol) and $CpCl_6$ (30 g, 100 mmol) in 100 ml of MeOH was stirred at 20 °C for 24 h (total conversion by TLC), then a 50% H_2SO_4 solution was added at 0 °C to pH 3, and the reaction mass was stirred at 50 °C for 10 h (TLC). The solvent was removed under reduced pressure, a 10% $NaHCO_3$ solution was added to pH 7, and the product was extracted with AcOEt (3×30 ml). The combined organic extracts were washed with brine and dried ($MgSO_4$). After evaporation of the solvent, the crude product was purified by distillation to give 17.2 g (75%) of **3** as a yellow oil (bp 103–105 °C/0.2 Torr), R_f 0.42 (Silufol, PE–AcOEt, 9:1), which crystallised in a refrigerator. Crystalline pale yellow solid, mp 53–54 °C (lit.,[13] 52–54 °C). ^{1}H NMR, δ: 3.51 (s, 3H, OMe), 3.53 (s, 3H, OMe), 4.64 (s, 1H, C^5H). ^{13}C NMR, δ: 52.03 and 52.07 (OMe), 62.19 (C^5), 100.49 (C^4), 133.77 (C^2), 157.65 (C^3), 186.17 (C^1). IR (ν/cm^{-1}): 1070 (O–C–O), 1605 (C=C), 1760 (C=O). Found (%): C, 34.10; H, 2.82; Cl, 43.40. Calc. for $C_7H_7Cl_3O_3$ (%): C, 34.25; H, 2.87; Cl, 43.33.

‡ *2,5-Dichloro-3,4,4-trimethoxycyclopent-2-en-1-one* **4**. A mixture of pulverised KOH (4.2 g, 75 mmol) and $CpCl_6$ (3.0 g, 10 mmol) in MeOH (10 ml) was stirred at 80 °C for 10 h (TLC), then a 50% H_2SO_4 solution was added at 0 °C to pH 3, and the reaction mixture was stirred at 50 °C for 10 h (TLC). The resulting mixture was treated as described above for compound **3**, and the crude product was purified by column chromatography on silica gel (PE–AcOEt, 7:3) to give 1.40 g (58%) of compound **4** as a red oil. R_f 0.31 (Silufol, PE–AcOEt, 9:1). ^{1}H NMR, δ: 3.41 and 3.46 (s, 6H, OMe), 4.47 (s, 3H, OMe), 4.48 (s, 1H, C_5H). ^{13}C NMR, δ: 52.02 and 51.70 (OMe), 60.44 (C^5), 100.13 (C^4), 108.14 (C^2), 173.75 (C^3), 187.05 (C^1). IR (ν/cm^{-1}): 1080 (O–C–O), 1610 (CCl=CCl), 1740 (C=O). Found (%): C, 39.65; H, 4.30; Cl, 29.65. Calc. for $C_8H_{10}Cl_2O_4$ (%): C, 39.86; H, 4.18; Cl, 29.41.



Scheme 3 *Reagents and conditions*: i, Me_2NH·HCl, KOH, MeOH, 20 °C, 76%; ii, $NaBH_4$, MeOH, 0 °C, 64%; iii, Zn–NH_4Cl, MeOH, 20 °C, 78%.

MeOH led chemoselectively to C^5-dechlorination product **7**[††] (Scheme 3).

Thus, chlorocyclopentenones **3**–**7** with the reactive ring carbon atoms of 'orthogonal' functionalization are easily available. Their prospects for synthetic applications are evident.

[§] *2,3,5-Trichloro-4,4-dimethoxycyclopent-2-en-1-ol* **5**. Sodium borohydride (0.11 g, 2.4 mmol) was added to a solution of ketone **3** (0.2 g, 0.8 mmol) in MeOH (10 ml) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h; then, acetone (3 ml) was added. The solution was concentrated, and the product was extracted with AcOEt. The combined organics were washed with a saturated NaCl solution, dried ($MgSO_4$), and concentrated *in vacuo* to furnish the corresponding reduction product. This was purified by column chromatography on silica gel using a mixture of PE–AcOEt (7:3) as an eluent, to give 0.19 g (95%) of compound **5** as a crystalline white solid, mp 82–84 °C, R_f 0.57 (PE–AcOEt, 7:3). ^{1}H NMR, δ: 2.5 (d, 1H, OH, *J* 10.5 Hz), 3.47 (s, 3H, OMe), 3.48 (s, 3H, OMe), 4.50 (d, 1H, C^5H, *J* 5.0 Hz), 4.65 (dd, 1H, C^1H, *J* 5.0 and 10.5 Hz). ^{13}C NMR, δ: 50.81 (OMe), 51.89 (OMe), 65.33 (C^5), 73.13 (C^1), 103.97 (C^4), 130.86 (C^3), 136.09 (C^2). IR (ν/cm^{-1}): 1085 (O–C–O), 1640 (CCl=CCl), 3450 (OH). Found (%): C, 33.85; H, 3.52; Cl, 42.74. Calc. for $C_7H_9Cl_3O_2$ (%): C, 33.97; H, 3.67; Cl, 42.97.

[¶] *3-Dimethylamino-2,5-dichloro-4,4-dimethoxycyclopent-2-en-1-one* **6**. A mixture of Me_2NH·HCl (0.13 g, 1.6 mmol) and KOH (1.4 g, 2.0 mmol) was added to a solution of ketone **3** (0.2 g, 0.8 mmol) in MeOH (3 ml) at 20 °C. The reaction mixture was stirred at 20 °C for 7 h. After completion of the reaction, the solvent was evaporated and water (10 ml) was added. The product was extracted with AcOEt and the combined organics were washed with a 10% aqueous HCl, saturated NaCl solution, dried ($MgSO_4$), and concentrated *in vacuo* to furnish the corresponding adduct. This was purified by column chromatography on silica gel using a mixture of PE–AcOEt (1:1) as an eluent to give 0.16 g (76.2%) of compound **6**; crystalline yellow solid, mp 89–90 °C, R_f 0.4 (Silufol, PE–AcOEt, 1:1). ^{1}H NMR, δ: 3.27 (s, 3H, OMe), 3.73 (s, 6H, NMe_2), 3.52 (s, 3H, OMe), 4.60 (s, 1H, C^5H). ^{13}C NMR, δ: 41.74 (NMe_2), 51.48 and 52.87 (OMe), 60.69 (C^5), 102.56 (C^2), 103.29 (C^4), 159.68 (C^3), 183.84 (C^1). IR (ν/cm^{-1}): 1080 (O–C–O), 1610 (CCl=CCl), 1740 (C=O). Found (%): C, 42.42; H, 5.21; Cl, 27.77; N, 5.64. Calc. for $C_9H_{13}Cl_2NO_3$ (%): C, 42.54; H, 5.16; Cl, 27.90; N, 5.51.

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[††] *2-Chloro-3,4,4-trimethoxycyclopent-2-en-1-one* **7**. A mixture of Zn dust (1.31 g) and NH_4Cl (0.32 g) was added to a solution of ketone **3** (0.31 g, 1.3 mmol) in MeOH (13 ml), and the reaction mixture was refluxed with stirring for 1 h (TLC) and then cooled. The pricipitate was filtered off, the solvent was evaporated and water (7 ml) was added. The product was extracted with CH_2Cl_2, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (PE-AcOEt, 8:2) to give 0.21 g (78%) of compound **7** as a colourless oil. R_f 0.2 (Silufol, PE–AcOEt, 9:1). ^{1}H NMR, δ: 2.63 (s, 2H, C^5H), 3.35 (s, 6H, OMe), 4.33 (s, 3H, OMe). ^{13}C NMR, δ: 43.15 (C^5), 51.31 (C^4OMe), 59.97 (C^3OMe), 102.02 (C^4), 109.06 (C^2), 173.69 (C^3), 192.43 (C^1). IR (ν/cm^{-1}): 1065 (O–C–O), 1605 (CCl=CCl), 1740 (C=O). Found (%): C, 46.59; H, 5.26; Cl, 17.38. Calc. for $C_8H_{11}ClO_4$ (%): C, 46.50; H, 5.37; Cl, 17.16.

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Additions and Corrections

Synthesis and optical properties of linear and branched bithienylsilanes

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In the second footnote of this communication the values of melting points for compounds **2** and **3** were erroneously indicated as 5 °C and 44 °C, respectively, and should be replaced by the correct ones: mp 44 °C for **2** and mp 34 °C for **3**. The corrected footnote is below.

‡ *Trimethyl-5-(5′-hexyl-2,2′-bithienyl)silane* **1**. A 2.5 M solution of butyllithium in hexane (1.24 ml, 3.1 mmol) was added dropwise to a solution of 5-hexyl-2,2′-bithiophene (0.78 g, 3.1 mmol) in 15 ml of dry THF, keeping the temperature in the interval between –18 and 0 °C. Then, the cooling bath was removed and the temperature was allowed to rise to 0 °C. After cooling the reaction mixture again to –18 °C, a solution of trimethylchlorosilane (0.4 ml, 3.1 mmol) in 1.5 ml of absolute THF was added dropwise. After that, the cooling bath was removed and the temperature was allowed to rise to 20 °C. For isolation of the product, 100 ml of diethyl ether and 50 ml of ice water were added to the reaction mixture. The organic phase was separated, washed several times with water to pH 7 and dried over Na_2SO_4; the solvent was evaporated. As a result, 1.04 g of the substance, containing according to GPC 88% of the product, was obtained. Purification by column chromatography on silica gel (eluent, hexane) gave the pure product (0.647 g, 65%), mp 17 °C. ^{1}H NMR ($CDCl_3$) δ: 0.31 (s, 9H, SiMe), 0.88 (t, 3H, CH_2Me, J 6.7 Hz), 1.23–1.45 (overlapped peaks, 6H, $CH_2CH_2CH_2$), 1.67 (m, 2H, thiophene-CH_2CH_2, M = 5, J 7.3 Hz), 2.77 (t, 2H, thiophene-CH_2CH_2, J 7.3 Hz), 6.66 [d, 1H, thiophene-H(4′), J 3.7 Hz], 6.97 [d, 1H, thiophene-H(3′), J 3.7 Hz], 7.09 [d, 1H, thiophene-H(3), J 3.7 Hz], 7.13 [d, 1H, thiophene-H(4), J 3.7 Hz]. MS, *m/z*: 322 (M^+). Found (%): C, 63.37; H, 8.26; S, 19.72; Si, 8.68. Calc. for $C_{17}H_{26}S_2Si$ (%): C, 63.29; H, 8.12; S, 19.88; Si, 8.71.

Dimethylbis(5′-hexyl-2,2′-bithien-5-yl)silane **2** was obtained by a similar procedure from 5-hexyl-2,2′-bithiophene (1.18 g, 4.7 mmol) and dimethyldimethoxysilane (0.27 ml, 2.0 mmol). After purification by column chromatography on silica gel (eluent, hexane), the pure product was obtained (0.859 g, 78%), mp 44 °C. ^{1}H NMR ($CDCl_3$) δ: 0.63 (s, 6H, SiMe), 0.88 (t, 6H, CH_2Me, J 6.7 Hz), 1.23–1.45 (overlapped peaks, 12H, $CH_2CH_2CH_2$), 1.66 (m, 4H, thiophene-CH_2CH_2, J 7.3 Hz, M = 5), 2.77 (t, 4H, thiophene-CH_2CH_2, J 7.3 Hz), 6.66 [d, 2H, thiophene-H(4′), J 3.7 Hz], 6.98 [d, 2H, thiophene-H(3′), J 3.7 Hz], 7.16 [dd, 4H, thiophene-H(3),H(4), J_1 3.7 Hz, J_2 8.5 Hz]. MS, *m/z*: 556 (M^+). Found (%): C, 64.70; H, 7.26; S, 23.42; Si, 5.09. Calc. for $C_{30}H_{40}S_4Si$ (%): C, 64.69; H, 7.24; S, 23.03; Si, 5.04.

Methyltris(5′-hexyl-2,2′-bithien-5-yl)silane **3** was obtained by a similar procedure from 5-hexyl-2,2′-bithiophene (0.9 g, 3.6 mmol) and methyltriethoxysilane (0.14 ml, 1.0 mmol). After purification by column chromatography on silica gel (eluent, hexane–toluene, 10:1) the pure product was obtained (3.69 g, 54%), mp 34 °C. ^{1}H NMR ($CDCl_3$) δ: 0.88 (t, 9H, CH_2Me, J 6.7 Hz), 0.92 (s, 3H, SiMe), 1.23–1.45 (overlapped peaks, 18H, $CH_2CH_2CH_2$), 1.66 (m, 6H, thiophene-CH_2CH_2, J 7.3 Hz, M = 5), 2.77 (t, 6H, thiophene-CH_2CH_2, J 7.3 Hz), 6.66 [d, 3H, thiophene-H(4′), J 3.7 Hz], 7.01 [d, 3H, thiophene-H(3′), J 3.7 Hz], 7.18 [d, 3H, thiophene-H(3), J 3.7 Hz], 7.27 [d, 3H, thiophene-H(4), J 3.7 Hz]. MS, *m/z*: 790 (M^+). Found (%): C, 65.47; H, 7.03; S, 24.35; Si, 3.39. Calc. for $C_{43}H_{54}S_6Si$ (%): C, 65.26: H, 6.88; S, 24.31; Si, 3.55.

Tetrakis(5′-hexyl-2,2′-bithien-5-yl)silane **4** was obtained by the similar procedure from 5-hexyl-2,2′-bithiophene (1.99 g, 8.0 mmol) and tetraethoxysilane (0.37 ml, 1.7 mmol). After purification by column chromatography on silica gel (eluent, hexane), the pure product was obtained (1.22 g, 72%), mp 50 °C. ^{1}H NMR (DMSO, CCl_4) δ: 0.88 (t, 12H, CH_2Me, J 6.7 Hz), 1.23–1.45 (overlapped peaks, 24H, $CH_2CH_2CH_2$), 1.66 (m, 8H, thiophene-CH_2CH_2, J 7.3 Hz, M = 5), 2.77 (t, 8H, thiophene-CH_2CH_2, J 7.3 Hz), 6.72 [d, 4H, thiophene-H(4′), J 3.7 Hz], 7.1 [d, 4H, thiophene-H(3′), J 3.7 Hz], 7.28 [d, 4H, thiophene-H(3), J 3.7 Hz], 7.37 [d, 4H, thiophene-H(4), J 3.7 Hz]. MS, *m/z*: 1024 (M^+). Found (%): C, 65.33; H, 6.59; S, 25.38; Si, 2.61. Calc. for $C_{56}H_{68}S_8Si$ (%): C, 65.57; H, 6.68; S, 25.01; Si, 2.74.