DIMERIZATION OF 2,2-DISUBSTITUTED 1,3-DICARBONYL COMPOUNDS. A SYNTHESIS OF 2,4,6,8-TETRAOXA-ADAMANTANE DERIVATIVES

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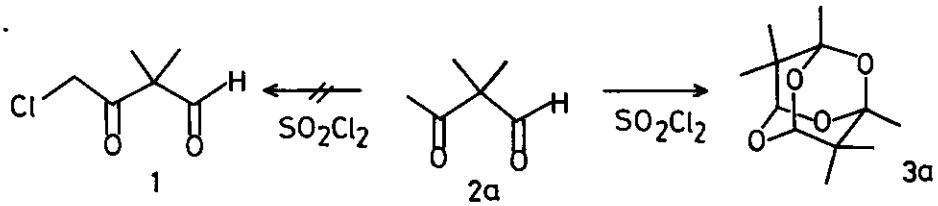
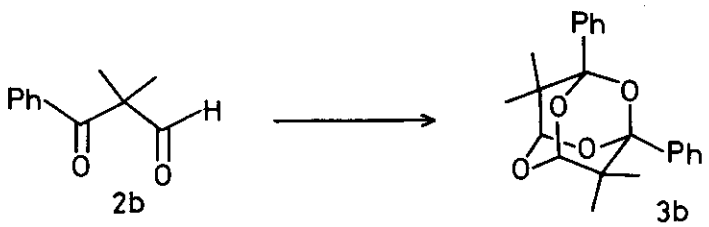
Abstract— Treatment of 2,2-dimethyl-3-oxobutanal and 2,2-dimethyl-3-oxopentanal with sulfuryl chloride gave 1,3,9,9,10,10-hexamethyl-2,4,6,8-tetraoxa-adamantane and 1,3-diethyl-9,9,10,10-tetramethyl-2,4,6,8-tetraoxa-adamantane in 100% and 70% yields, respectively. Thionyl chloride and hydrogen chloride also catalyzed the dimerization.

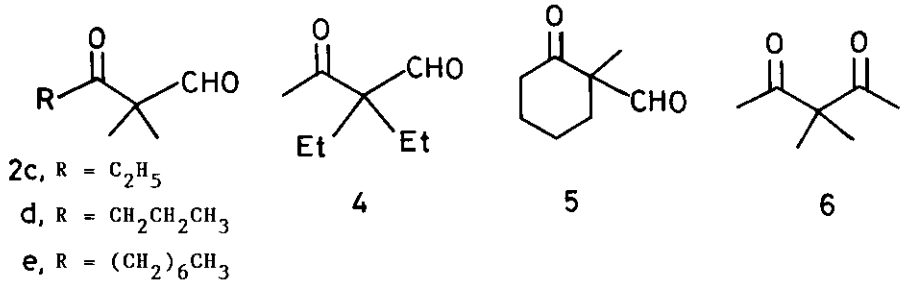
Recently, we required 4-chloro-2,2-dimethyl-3-oxobutanal (**1**) for the study of Favorskii-type rearrangement. Sulfuryl chloride treatment of 2,2-dimethyl-3-oxobutanal (**2a**) to obtain **1**, however, caused a cyclization to afford crystals which (based on spectral data) were supposed to be either the structural isomer of **2a** or the dimer. Our X-ray crystalographic study[1] definitely revealed that it is 1,3,9,9,10,10-hexamethyl-2,4,6,8-tetraoxatricyclo[3.3.1.1^{3,7}]decane, that is, 1,3,9,9,10,10-hexamethyl-2,4,6,8-tetraoxa-adamantane (**3a**) which is an unique dimerization product of two molecules of **2a**. The dimerization of **2a** and 2,2-dimethyl-3-oxo-3-phenylpropanal (**2b**) in the presence of $BF_3 \cdot OMe_2$ or $ZnCl_2$-CH_3CO_2H has been reported by Almqvist.[2,3] Further investigation as to dimerization of other 2,2-disubstituted 1,3-dicarbonyl compounds, its catalysts, and the stability of the products has not been mentioned by these authors. Here we describe further investigation of this interesting dimerization for various 1,3-dicarbonyl compounds.



1 2a 3a

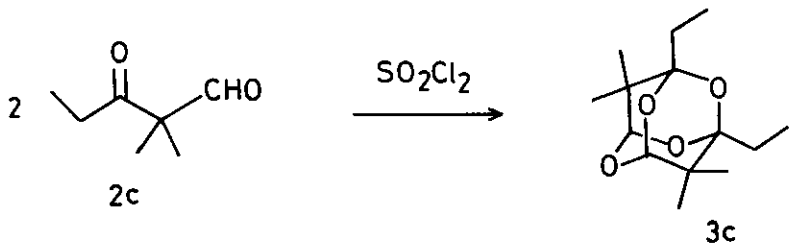


Compounds **2c-e**, **4**, **5**, and **6**, in addition to **2a** and **2b**, were prepared and allowed to react with sulfuryl chloride in carbon tetrachloride. Treatment of **2a** with 1.2 equivalents of sulfuryl chloride at room temperature gave a quantitative yield of



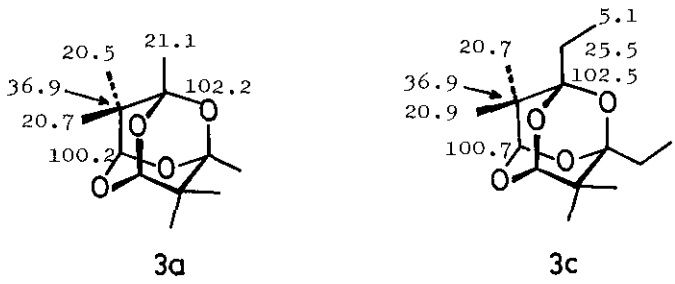
3a in 2 h. When a catalytic amount (0.03 equiv) of sulfuryl chloride was used for the reaction, it took longer than 24 h to complete the dimerization. Its spectral data and melting point were identical with those of an authentic sample.[2]

Similar treatment of **2c** with one equivalent of sulfuryl chloride for 40 h gave 1,3-diethyl-9,9,10,10-tetramethyl-2,4,6,8-tetraoxa-adamantane (**3c**) in 76% yield. Its IR spectrum showed no signals due to C-O and C-C multiple bonds at 2800-1500 cm^{-1} but several strong peaks due to acetal groups at 1200-1000 cm^{-1}.



Proton NMR spectrum also exhibited characteristic signals of the structure **3c** at 0.95, 1.05, 1.10, 1.60, and 4.70 ppm. Carbon-13 NMR spectra of **3a** and **3c** were measured and assigned as shown in Figure 1. The chemical shifts were assigned with reference to those of 2,4,6,8-tetraoxa-adamantane.[4] The signal due to $CH_2\underline{C}H_3$ of **3c** appeared at unusually high field (5.1 ppm). This high field shift will be due to the steric hindrance between methyl and ethyl groups and/or to the magnetic

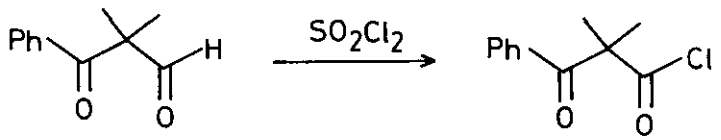
anisotropy of the neighboring oxygen atoms. These data afford a strong support for the structural determination of **3**.



3a 3c

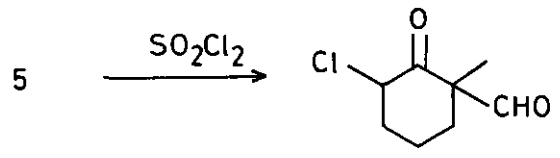
Fig 1. ^{13}C NMR spectral data of tetraoxa-adamantanes **3a** and **3c**.

Treatment of other aldehydes (**2d** and **2e**) with sulfuryl chloride resulted in the recovery of the starting materials. Attempted synthesis of **3b** from **2b** with sulfuryl chloride was unsuccessful but led to the formation of 2,2-dimethyl-3-oxo-3-phenylpropanoyl chloride (**7**) in 52% yield, which is in contrast to the result obtained by Almqvist[2] under different conditions. Compound **4** was recovered intact



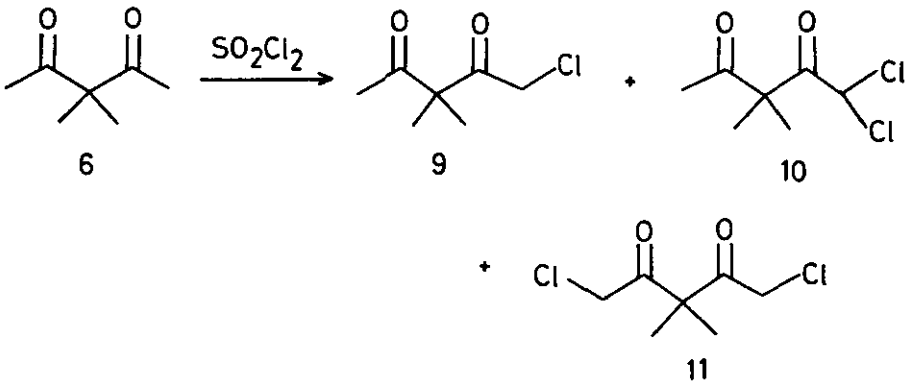
2b 7

by this treatment. Reaction of **5** with sulfuryl chloride proceeded normally to give cis-trans mixture (1:1) of **8** in 69% yield. Compound **6** similarly underwent



8

chlorination in the usual manner to give **9**, **10**, and **11** in a ratio of 58:9:14.



In addition to sulfuryl chloride, thionyl chloride and hydrogen chloride also catalyzed the dimerization of 1,3-dicarbonyl compounds. While the following could not catalyze the dimerization: $SOBr_2$, Br_2, $AlCl_3$, $CoCl_2$, $PdCl_2$, Al_2O_3, and p-toluenesulfonic acid. Solvents such as chloroform, dichloromethane, and benzene were effective for the dimerization of **2**, while the reactions carried out in acetonitrile, ethanol, and diethyl ether failed. Tetraoxa-adamantane **3** are pretty stable both to acid (10% HCl) and base (10% NaOH) even at higher temperature (100 °C, 60 min). Compound **3a** is distillable at 100-110 °C (26 mm).

The present dimerization would be initiated by the protonation of a carbonyl oxygen with hydrogen chloride generated from sulfuryl chloride or thionyl chloride. The strict limitation of the present dimerization would be due to steric hindrance between substitution groups of 1,3-dicarbonyl compounds.

EXPERIMENTAL

The melting points and boiling points are uncorrected. Elemental analyses were carried out by Eiichiro Amano of our laboratory. Analytical determinations by GLC were performed on a Hitachi Model 163 gas chromatograph fitted with 10% Silicone SE-30 on Chromosorb W column (3 mm o.d. x 1 m); carrier gas, N_2 (1 kg/cm^2); detecter, FID. Preparative GLC were performed on a Yanagimoto G-80 model gas chromatograph fitted with 10% Apiezone Grease L on Chromosorb W (3 mm o.d. x 1 m); carrier gas, He (25 ml/min).

Compounds **2** and **4** were prepared by the reaction of 4-(2-methyl-1-propenyl)morpholine with acyl chloride as described by Inukai and Yoshizawa.[6]

2,2-Dimethyl-3-oxobutanal (2a):[6] bp 60 °C (20 mm)[lit.[6] 43-44 °C (8 mm)]; ^{13}C NMR ($CDCl_3$) δ 19.1 (q), 26.6 (q), 60.2 (s), 201.1 (d), 207.6 (s).

2,2-Dimethyl-3-oxo-3-phenylpropanal (2b):[6] bp 150 °C (15 mm)(short path distillation)[lit.[6] 87-89 °C (1 mm)].

2,2-Dimethyl-3-oxopentanal (2c): bp 62 °C (15 mm); IR (neat) 1730, 1700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.60 (s, 1H), 2.46 (q, 2H, J = 7 Hz), 1.30 (s, 6H,), 1.03 (t, 3H, J = 7 Hz), ^{13}C NMR ($CDCl_3$) δ 210.0 (s), 201.3 (d), 60.1 (s), 32.3 (t), 19.3 (q), 7.5 (q). Found: C, 65.35; H, 9.26%. Calcd for $C_7H_{12}O_2$: C, 65.60; H, 9.44%.

2,2-Dimethyl-3-oxohexanal (2d): IR (neat) 1735, 1710 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.60 (s, 1H), 2.40 (t, 1H, J = 7 Hz), 1.9-1.0 (m, 2H), 1.29 (s, 6H), 0.90 (t, 3H, J = 7 Hz). Found: C, 67.34; H, 9.82%. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.92%.

2,2-Dimethyl-3-oxodecanal (2e): bp 130 °C (10 mm); IR (neat) 1730, 1705 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.61 (s, 1H), 2.39 (q, 2H, J = 6 Hz), 1.30 (s, 6H), 1.28 (broad s, 10H), 0.88 (t, 3H, J = 6 Hz). Found: C, 72.51; H, 11.05%. Calcd for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18%.

2,2-Diethyl-3-oxobutanal (4): bp 150 °C (10 mm)(short path distillation): IR (neat) 1730, 1710 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.67 (s, 1H), 2.15 (s, 3H), 1.92 (q, 4H, J = 8 Hz), 0.83 (t, 6H, J = 8 Hz). Found: C, 67.41; H, 9.82%. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.92%.

1-Methyl-2-oxocyclohexanecarbaldehyde (5).[7] The procedure described in the literature[7] was applied for this synthesis. To a cooled solution of 0.8 g (20 mmol) of sodium hydroxide in 7.5 ml of water was added 1.7 g (10 mmol) of *tetrabutylammonium hydrogensulfate*. This mixture was added to a stirred solution of 1.22 g (10 mmol) of 2-oxocyclohexylcarbaldehyde and 1.42 g (10 mmol) of methyl iodide in 7.5 ml of dichloromethane. The mixture was stirred for 30 min and then worked up as described in the literature[7] to give 1.14 g (81%) of **5** as a clean oil: IR (neat) 1730, 1710 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.50 (s, 1H), 1.4-2.8 (m, 8H), 1.23 (s, 3H).

3,3-Dimethyl-2,4-pentanedione (6) was obtained by the reaction of acetylacetone with methyl iodide:[8] 78% yield; short path distillation, bp 95 °C (27 mm); mp 26 °C (lit.[9] 26 °C).

1,3,9,9,10,10-Hexamethyl-2,4,6,8-tetraoxatricyclo[3.3.1.1^{3,7}]decane (3a). To a solution of 0.114 g (1 mmol) of **2a** in 0.8 ml of dry carbon tetrachloride was added

0.1 ml (0.16 g, 1.2 mmol) of sulfuryl chloride with an injector over a period of 30 min, and the mixture was stirred for 2 h at room temperature. Carbon tetrachloride (10 ml) was added and the mixture was poured into 40 ml of cold water. The mixture was stirred for 30 min and the organic layer was separated, washed with water, and dried over $MgSO_4$. Removal of the solvent gave 0.114 g (10%) of **3a** as white crystals: mp 79-80 °C (from pentane)(lit.[2] 78-79 °C). ^1H NMR and mass spectra were identical with those described in the literature.[2]

1,3-Diethyl-9,9,10,10-tetramethyl-2,4,6,8-tetraoxatricyclo[3.3.1.1^{3,7}]decane (3c). The similar manner as for **3a** was used. A mixture of 0.32 g (2.5 mmol) of **2c**, 68 mg (0.5 mmol) of sulfuryl chloride, and 15 ml of carbon tetrachloride was stirred for 40 h at room temperature. The mixture was worked up as described in **3a** to give 0.243 g (70%) of **3c** as white crystals: mp 67-69 °C (from hexane) ; IR (KBr) 1170, 1110, 1070; ^1H NMR ($CDCl_3$) δ 4.70 (s, 1H), 1.60(q, 2H, J = 8 Hz), 1.10 (s, 3H), 1.05 (s, 3H), 0.95 (t, 3H, J = 8 Hz). Found: C, 65.60; H, 9.44%. Calcd for $C_{14}H_{24}O_4$: C, 65.53; H, 9.34%.

2,2-Dimethyl-3-oxo-3-phenylpropanoyl Chloride (7). The similar manner as for **3a** was used. A mixture of 0.164 g (1 mmol) of **2b**, 0.162 g (0.93 mmol) of sulfuryl chloride, and 1 ml of carbon tetrachloride was stirred for 3 h at room temperature, and then worked up as described in **3a**, giving 0.148 g of crude **7** as white crystals. Purification of the crude product by preparative TLC (silica gel PF_{254}, 2:1 hexane:acetone, R_f = 0.67) gave 0.101 g (52%) of **7**: mp 96-98 °C; IR (KBr) 1800, 1770, 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.2-8.2 (m, 5H), 1.66 (s, 6H). Found: C, 62.57; H, 5.22%. Calcd for $C_{11}H_{11}ClO_2$: C, 62.72; H, 5.26%.

3-Chloro-1-methyl-2-oxocyclohexanecarbaldehyde (8). The similar manner as for **3a** was used. A mixture of 0.14 g (1 mmol) of **5**, 0.162 g (1.2 mmol) of sulfuryl chloride, and 0.8 ml of carbon tetrachloride was stirred for 3 h at room temperature. After evaporation of the solvent, the residue was poured into cold water. The organic layer was extracted with chloroform. The combined extracts were washed with water, dried ($MgSO_4$), and concentrated to give 0.12 g (69%, 1:1 cis, trans mixture) of **8**: IR (neat) 1730, 1715, 1450, 785 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.56 (s, 0.5 H), 9.42 (s, 0.5 H), 4.9-4.4 (m, 1H), 2.9-1.5 (m, 6H), 1.35 (s, 1.5 H), 1.30 (s, 1.5 H). The compound was too labile for elemental analysis.

Reaction of 6 with Sulfuryl Chloride. A mixture of 0.265 g (2 mmol) of **6**, 0.30 g (0.18 ml, 2.2 mmol) of sulfuryl chloride, and 1.8 ml of carbon tetrachloride was stirred for 4 h at room temperature. Removal of the solvent gave 0.313 g of a

clean oil. GLC analysis (column temp. 100°C) showed 4 peaks. Peaks, retention times (min), and integrated percentages (%) were: 1, 0.6, 19; 2, 1.73, 58; 3, 3.2, 9; 4, 6.2, 14. Each component was separated by preparative GLC, and identified by spectral data.

Peak 1: **6.**

Peak 2: **1-chloro-3,3-dimethyl-2,4-pentanedione (9):** IR (neat) 1730, 1705 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.19 (s, 2H), 2.15 (s, 3H), 1.41 (s, 6H). Found: C, 51.74; H, 6.81%. Calcd for $C_7H_{11}ClO_2$: C, 51.70; H, 6.82%.

Peak 3: **1,1-dichloro-3,3-dimethyl-2,4-pentanedione (10):** IR (neat) 1730, 1705 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.20 (s, 1H), 2.20 (s, 3H), 1.50(s, 6H). Found: C, 42.78; H, 5.02%. Calcd for $C_7H_{10}Cl_2O_2$: C, 42.67; H, 5.11%.

Peak 4: **1,5-dichloro-3,3-dimethyl-2,4-pentanedione (11):** IR (neat) 1720 (C=O), 1035, 782 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.28 (s, 4H), 1.50 (s, 6H). Found: C, 42.76; H, 4.88%. Calcd for $C_7H_{10}Cl_2O_2$: C, 42.67; H, 5.11%.

Attempts of the Dimerization of 2a with Various Reagents. (1) Following the procedure with sulfuryl chloride, the dimerization of **2a** (0.114 g, 1 mmol) with thionyl chloride (0.13 g, 1.1 mmol) was carried out to give 62 mg (54%) of **3a**: mp 77-79 °C. *IR and ^1H NMR spectra were identical with those of the authentic sample.*

(2) Dimerization of **2a** with hydrogen chloride was carried out by bubling HCl gas into the solution of **2a** (0.228 g, 2 mmol) in carbon tetrachloride (1 ml) at room temperature for 3 h. Removal of the solvent gave 0.157 g (69%) of **3a**: mp 77-79 °C. IR and ^1H NMR spectra were identical with those of the authentic sample.

(3) Thionyl bromide and bromine, respectively was treated with **2a** as shown in the *reaction with sulfuryl chloride, and gave some products which were assumed to be* brominated. The mixture was not further investigated.

(4) The reactions of **2a** with an equimolar amount of $AlCl_3$, $CoCl_2$, $PdCl_2$, Al_2O_3, p-toluenesulfonic acid were carried out respectively as shown in the reaction with sulfuryl chloride to give the starting material recovered.

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