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A RE-EXAMINATION OF THE ACID-CATALYSED REACTION OF KETALS WITH 1,2-BIS(TRIMETHYLSILOXY)CYCLOPENTENE

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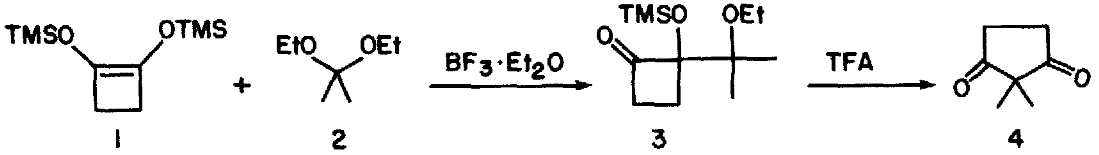
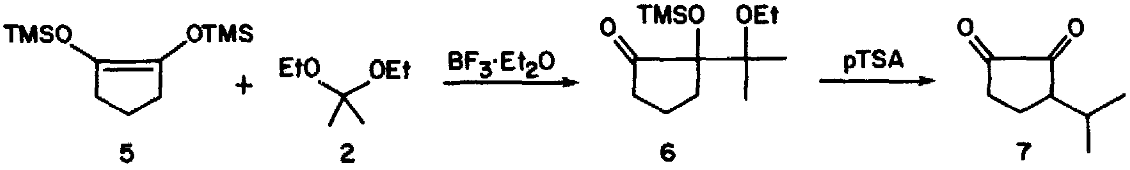
Abstract: Ketals react with 1,2-bis(trimethylsiloxy)cyclopentene in the presence of a large excess of boron trifluoride etherate to provide 2,2-disubstituted 1,3-cyclohexanediones in very good yields.

Kuwajima and coworkers[1] demonstrated that 1,2-bis(trimethylsiloxy)cyclobutene (**1**) reacts with a ketal (e.g. **2**), under catalysis by BF_3 etherate, to give a cyclobutanone product **3**. In trifluoroacetic acid **3** rearranges to a 2,2-disubstituted 1,3-cyclopentanedione **4**. An excess of BF_3 etherate and a longer reaction time provides **4** directly in a better yield.[2] In contrast, Pattenden and Teague[3] reported that 1,2-bis(trimethylsiloxy)cyclopentene (**5**) reacts initially with **2** in an analogous fashion to give the cyclopentanone **6**, but when this is treated with *para*-toluenesulfonic acid rearrangement to 2,2-dimethyl-1,3-cyclohexanedione (**8**) does not occur; instead the product (21%) was suggested to be 3-isopropyl-1,2-cyclopentanedione (**7**).





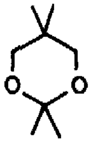
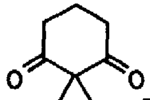
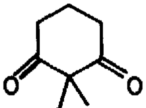
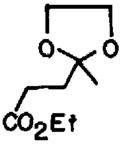
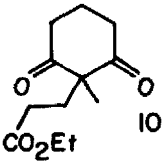
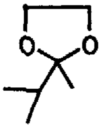
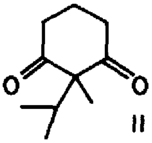
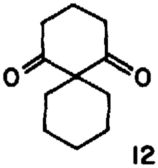
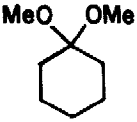
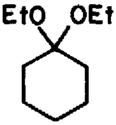
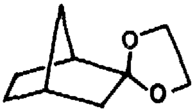
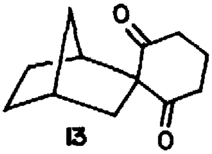
We have examined the reactions of **5** with a variety of ketals in the presence of a large excess of BF_3 etherate. The substrates included dimethyl and diethyl ketals, 1,3-dioxolanes and a 1,3-dioxane (Table). In every instance one major product was observed, and in every instance this product was undoubtedly a 2,2-disubstituted 1,3-cyclohexanedione.[4] The number of resonances in the ^{13}C nmr spectra of the pure products **8** - **12** in every case indicated the presence of a symmetrical molecule, and the carbonyl resonances confirmed a nonconjugated (i.e. nonenolized) structure. The product **13** derived from the norcamphor ethylene ketal gave rise to two nonenolized carbonyl resonances. The infrared spectrum of each product displayed two bands in its carbonyl region, consistent with many other 2,2-disubstituted 1,3-cyclohexanediones described in the literature.[5]

Comparing the reactions of **5** and **1**[2] qualitatively, we found the crude reaction products of the former to be much darker in color. Careful chromatography was necessary to remove this color. It was perhaps because of this that quantitatively we realized slightly lower isolated yields of the pure cyclohexanediones, but GC-MS analysis of the *crude* product mixtures from the reactions of **5** showed nearly complete conversion of ketals to cyclohexanediones in most cases. Thus, the reaction of a ketal with **5** is an efficient method for the preparation of a 2,2-disubstituted 1,3-cyclohexanedione. This is clearly an attractive alternative to double alkylation of 1,3-cyclohexanedione, a process that in most instances provides a poor yield of product due to the formation of unwanted O-alkylation products and ring cleavage.[6] Products like **10** and **11** would be especially difficult to obtain by double alkylation. Furthermore, for the synthesis of **12** the reaction of a cyclohexanone ketal with **5** is shorter and more efficient than the route via acid-catalysed rearrangement of an α,β-epoxy ketone.[7]

The following is a representative procedure: A solution of cyclohexanone ethylene ketal (336.3 mg, 2.36 mmol) in dry CH_2Cl_2 (30 mL) was cooled to -78°C under N_2. Freshly distilled BF_3 etherate (4.4 mL, 36 mmol) was added followed by the dropwise addition of a solution of **5**[8] (3.56 mmol) in dry CH_2Cl_2 (8 mL). The mixture was stirred overnight during which time the mixture attained room temperature. Water (10 mL) was added, then the aqueous layer was re-extracted (3 x 10 mL) with CH_2Cl_2. The combined organic solutions were washed with brine (2 x 20 mL), dried over $MgSO_4$ and evaporated at reduced pressure. The dark residue was purified by flash chromatography (SiO_2, petroleum ether-acetone) to afford **12** as colorless crystals (379.4 mg, 89%).[4]

We are grateful to the Natural Sciences and Engineering Research Council of Canada for financial support of this work.

Table. Reactions of ketals with 1,2-bis(trimethylsiloxy)cyclopentene (**5**)

Entry	Substrate	Product	Yield (%)
1		 8	75^{a}
2		 9	86^{a}
3		 10	83^{a}
4		 11	84^{a}
5		 12	89^{a}
6		12	80^{b}
7		12	$>95^{b}$
8		 13	81^{a}

a. Yield of pure, isolated product. b. From GC-MS of the crude reaction mixture.

References and Notes

1. E. Nakamura and I. Kuwajima, *J. Am. Chem. Soc.* **99**, 961 (1977); J. Shimada, K. Hashimoto, B.H. Kim, E. Nakamura and I. Kuwajima, *J. Am. Chem. Soc.* **106**, 1759 (1984); E. Nakamura and I. Kuwajima, *Org. Synth.* **65**, 17 (1987).
2. Y.-J. Wu and D.J. Burnell, *Tetrahedron Lett.* **29**, 4369 (1988).
3. G. Pattenden and S. Teague, *Tetrahedron Lett.* **23**, 1403 (1982).
4. Compound **8**: mp 34-35°C (lit.[9] 35°C); ir: 1720 and 1690 cm^{-1}; ^1H nmr (300 MHz, $CDCl_3$/TMS) δ: 1.307 (6H, s), 1.961 (2H, quintet) and 2.710 (4H, t, J = 6.6 Hz); ^{13}C nmr δ (multiplicity): 17.9 (q), 22.1 (t), 37.2 (t), 61.6 (s) and 210.3 (s); ms m/z: 140.0845 (M^+, 140.0837 reqd). Compound **9**: oil ; ir: 1725 and 1695 cm^{-1}; ^1H nmr δ: 0.796 (3H, t, J = 7.4 Hz), 1.206 (3H, s), 1.847 (2H, q, J = 7.4 Hz), 1.86 (1H, m), 2.05 (1H, m) and 2.675 (4H, m); ^{13}C nmr δ: 9.1 (q), 17.7 (t), 17.9 (q), 30.8 (t), 37.9 (t), 66.2 (s) and 210.4 (s); ms m/z: 154.0987 (M^+, 154.0993 reqd). Compound **10**: oil; ir: 1725 (br) and 1690 cm^{-1}; ^1H nmr δ: 1.242 (3H, t, J = 7.2 Hz), 1.268 (3H, s), 1.97 (2H, m), 2.16 (4H, m), 2.685 (4H, m) and 4.090 (2H, q, J = 7.2 Hz); ^{13}C nmr δ: 14.1 (q), 17.5 (t), 20.8 (q), 29.4 (t), 30.4 (t), 37.7 (t), 60.5 (t), 64.3 (s), 172.7 (s) and 209.7 (s); ms m/z (%): 226.1201 (M^+, 226.1204 reqd). Compound **11**: oil; ir: 1720 and 1690 cm^{-1}; ^1H nmr δ: 0.848 (6H, d, J = 6.7 Hz), 1.059 (3H, s), 1.66 (1H, m), 2.12 (1H, m), 2.54 (3H, m) and 2.83 (2H, m); ^{13}C nmr δ: 9.0 (q), 17.2 (q), 18.3 (t), 34.6 (d), 37.6 (t), 71.7 (s) and 209.6 (s); ms m/z: 168.1147 (M^+, 168.1150 reqd). Compound **12**: mp 71-72°C; ir: 1720 and 1690 cm^{-1}; ^1H nmr δ: 1.42 (2H, m), 1.58 (4H, m), 1.90 (6H, m) and 2.687 (4H, apparent t, J = 7.0 Hz); ^{13}C nmr δ: 18.4 (t), 22.4 (t), 25.5 (t), 30.9 (t), 37.2 (t), 67.6 (s) and 209.6 (s); ms m/z: 180.1167 (M^+, 180.1149 reqd). Compound **13**: mp 49-50°C; ir: 1720 and 1690 cm^{-1}; ^1H nmr δ: 1.13-1.31 (3H, m), 1.39-1.51 (3H, m), 1.69 (1H, m), 1.822 (1H, dd, J = 2.6, 12.4 Hz), 2.10-2.24 (2H, m), 2.30 (1H, br, bridgehead H), 2.54-2.76 (3H, m), 2.74 (1H, br, bridgehead H) and 2.94 (1H, m); ^{13}C nmr δ: 18.2 (t), 25.2 (t), 27.6 (t), 27.7 (t), 36.5 (d), 37.1 (t), 37.9 (t), 39.3 (d), 76.0 (s), 206.9 (s) and 207.4 (s); ms m/z: 192.1150 (M^+, 192.1149 reqd).
5. See especially: S.N. Ananchenko, I.V. Berezin and I.V. Torgov, *Izvest. Akad. Nauk SSSR, Otdel. Khim. Nauk*, 1644 (1960).
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