Reaction of α,β-Unsaturated Acid Chlorides with β-Diketones. Synthesis of 4,6,7,8-Tetrahydro-2*H*-1-benzopyran-2,5(3*H*)-diones

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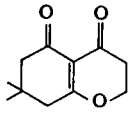
Reaction of an α,β-unsaturated acid chloride with the anion of 5,5-dimethyl-1,3-cyclohexanedione (**2**) gives either the enol ester (**4**) or a cyclized product (**5**), depending upon the reaction conditions. When the acid chloride is in excess, the ester is obtained. When the anion is in excess and the acid chloride is acryloyl or crotonyl, the cyclized product is obtained. A similar cyclized product (**9**) was formed from acryloyl chloride and an excess of the anion of 4-hydroxy-6-methyl-2-pyrone (**8**).

Recent studies have shown that cyclized products can be obtained from the reaction of α,β-unsaturated acid chlorides with enamines (1-3) and with 4-hydroxy-2-pyrones (4,5). We have found that α,β-unsaturated acid chlorides react with the anion of 5,5-dimethyl-1,3-cyclohexanedione (**2**) to yield either the enol ester (**4**) or a 4,6,7,8-tetrahydro-2*H*-1-benzopyran-2,5(3*H*)-dione (**5**), depending upon the reaction conditions.

When acryloyl chloride (**3a**) was reacted with an excess of anion, prepared by addition of sodium hydride to a solution of 5,5-dimethyl-1,3-cyclohexanedione (**1**) in dry tetrahydrofuran, 4,6,7,8-tetrahydro-7,7-dimethyl-2*H*-1-benzopyran-2,5(3*H*)-dione, (**5a**), the cyclized product was produced. The spectral properties of this compound are consistent with the assigned structure and eliminate other reasonable alternatives. The nuclear magnetic resonance spectrum shows no olefinic protons so all structures containing the acryloyl group, such as the enol ester (**4a**), are ruled out. The infrared absorption at 1782 cm^{-1} is characteristic of an enol lactone (6) rather than of an α,β-unsaturated ketone such as **6** (4). Cyclized products analogous to **6** have been isolated from the reaction of 4-hydroxy-2-pyrones with α,β-unsaturated acid chlorides in trifluoroacetic acid (4) and in pyridine (5). Products analogous to **5** were also obtained in pyridine (5).



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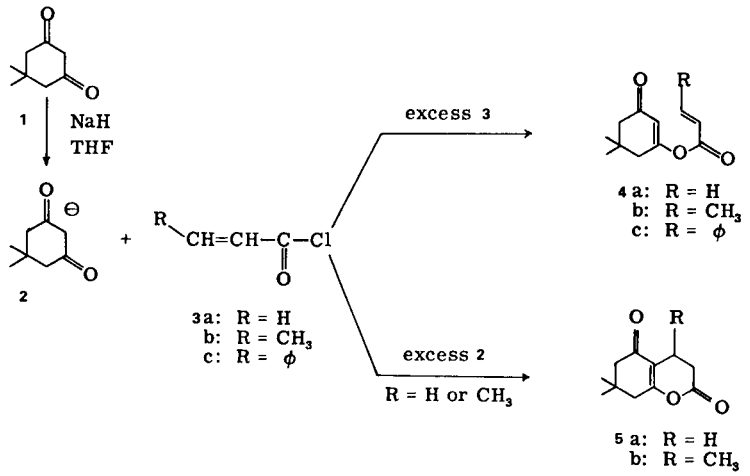
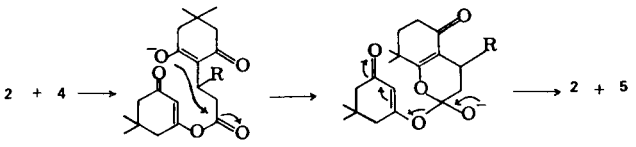
An analogous product was obtained from the reaction of crotonyl chloride (**3b**) with an excess of anion, but cinnamoyl chloride (**3c**) gave only the enol ester (**4c**). However, if the reaction conditions were varied so that the acid chloride rather than the anion was in excess, in all three cases the enol ester (**4**) was the only product formed. These products were easily identified from their spectra which are consistent with the enol ester structure.

The acrylate and crotonate esters could be cyclized to the corresponding tetrahydrobenzopyrans. Treatment of



4a or **4b** with about 10 mole per cent of anion in refluxing tetrahydrofuran for 5 hours gave essentially complete conversion to the cyclized product. This conversion could be easily followed by observation of the change in the nuclear magnetic resonance spectrum of the product. The cinnamate ester (**4c**) did not cyclize under these conditions. Treatment of the acrylate and crotonate esters with a small amount of acid chloride and sodium hydride in refluxing tetrahydrofuran gave back the starting ester.

Initially it was thought that cyclization was an intramolecular process occurring by way of anions derived from **4a** and **4b** in the presence of excess sodium hydride. However, the experimental results indicate that **2** acts as a catalyst in the cyclization. A resonable mechanism for this catalytic action is shown below. Michael addition (7) of



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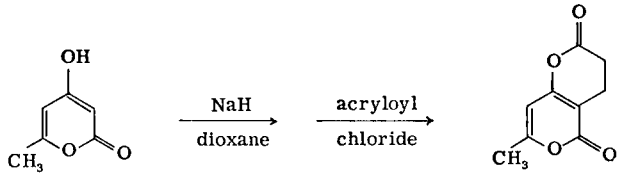
the anion (**2**) to the ester would give an intermediate Michael adduct (**7**). Cyclization can then proceed by intramolecular attack on the ester carbonyl and elimination of **2**, thus reforming the catalyst. Other conceivable intermolecular mechanisms involving participation of the acid chloride can be ruled out by our data although other possible mechanisms involving the anion can not.

A cyclized product was also obtained from the reaction of an excess of the anion of 4-hydroxy-6-methyl-2-pyrone (**8**) with acryloyl chloride in refluxing dioxane (8). Tetrahydrofuran proved to be an unsatisfactory solvent for this reaction, possibly because the pyrone is relatively insoluble in it. Analogous products have been reported from the



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reaction of **8** with crotonyl and 3,3-dimethylacryloyl chloride in pyridine. The mechanism of formation of these products may be similar to that reported here since mixtures of esters and cyclized products are formed under varying conditions (5).

EXPERIMENTAL

Melting points were determined in open capillaries on a Thomas-Hoover melting point apparatus and are uncorrected. Boiling points are uncorrected. Infrared spectra were recorded in chloroform solution relative to chloroform on a Perkin-Elmer IR7 spectrometer. Ultraviolet spectra were measured in 95% ethanol relative to 95% ethanol on a Cary 14 ultraviolet-visible spectrophotometer. Proton magnetic resonance spectra, reported in δ units relative to internal tetramethylsilane, were determined in deuteriochloroform solution on a Varian Associates Model A-60A high resolution spectrometer. Peak areas are assigned relative to the most intense peak in the spectrum. Microanalyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Michigan.

Tetrahydrofuran was refluxed over lithium aluminum hydride and distilled into the reaction flask. Dioxane was refluxed over sodium and distilled from sodium into the reaction flask. Sodium hydride (Alfa Inorganics, 50% dispersion in mineral oil) was freed from mineral oil by washing with pentane before addition to the reaction mixture. Cinnamyl chloride (Aldrich) and 5,5-dimethyl-1,3-cyclohexanedione (MCB) were used as received. Acryloyl chloride (Aldrich) and crotonyl chloride (Aldrich) were distilled prior to use. 4-Hydroxy-6-methyl-2-pyrone (Aldrich) was recrystallized from ethanol.

Preparation of 5,5-Dimethyl-1,3-cyclohexanedione Enol Crotonate (**4b**).

General Procedure.

To 150 ml. of tetrahydrofuran was added 3.92 g. (28 mmole) of 5,5-dimethyl-1,3-cyclohexanedione (**1**) and 700 mg. (29 mmole) of sodium hydride. After the evolution of hydrogen ceased, the reaction mixture was heated to reflux and 3 ml. (3.24 g., 31 mmole) of crotonyl chloride in 20 ml. of tetrahydrofuran added dropwise with stirring. The reaction mixture was heated and stirred at reflux for 3 hours, cooled and filtered to remove inorganic material. Evaporation of the solvent followed by vacuum distillation gave 4.85 g. (23.3 mmole, 83%) of a light yellow oil, b.p. 115-116° (1.0-1.2 mm Hg); n^{24} 1.4994; ν max 1740, 1675, 1120 cm^{-1}; NMR, δ 7.45-6.85 (multiplet, relative area 1, CH=C*H*–CH_3), 5.93 (doublet of quartets, J=15 cps and 1.7 cps, C*H*=CH–CH_3), 5.87 (triplet, J=1.3 cps, C=CH–CO), total area of two previous peaks: 2, 2.47 (doublet, 2, J=1.3 cps, CH_2), 2.27 (singlet, 2, CH_2), 1.92 (doublet of doublets, 3, J=6.5 cps and 1.7 cps, CH–C*H*$_3$), 1.11 (singlet, 6, *gem*-dimethyl).

Anal. Calcd. for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.22; H, 7.61.

On standing in the air a white solid precipitated from the ester. It was filtered off and identified as 5.5-dimethyl-1,3-cyclohexanedione (**1**), m.p. 143-145°, formed from hydrolysis of the ester.

5,5-Dimethyl-1,3-cyclohexanedione Enol Acrylate (**4a**).

This compound was obtained as a colorless oil from 3.91 g. (27.9 mmole) of **1**, 960 mg. (40 mmole) of sodium hydride, and 3 ml. (3.42 g., 37.8 mmole) of acryloyl chloride. Yield, 83%, b.p. 89-91° (0.7 mm Hg); ν max 1742, 1670, 1105 cm^{-1}; NMR, δ 6.83-5.97 (complex multiplet, 4, olefinic protons), 2.47 (singlet, 2, CH_2), 2.27 (singlet, 2, CH_2); 1.11 (singlet, 6, *gem*-dimethyl).

Anal. Calcd. for $C_{11}H_{14}O_3$: C, 68.02; H, 7.26. Found: C, 68.15; H, 7.33.

5,5-Dimethyl-1,3-cyclohexanedione Enol Cinnamate (**4c**).

This compound was obtained as a white crystalline solid from the reaction of 3.50 g. (25 mmole) of **1**, 700 mg. (39.1 mmole) of sodium hydride, and 4.28 g. (26 mmole) of cinnamyl chloride. Yield of crude ester, 85%. Prolonged heating of the reaction mixture at reflux with either the anion (**2**) or acid chloride in excess produced a yellowing of the reaction mixture. The product was purified by sublimation, m.p. 70.5-72°; ν max 1730, 1665, 1630,

1125 cm^{-1}; NMR, δ 7.87 (doublet, 1, J=16 cps, φ–C*H*=CH), 7.70-7.38 (multiplet, 5, aromatic H), 6.53 (doublet, 1, J=16 cps, φ–CH=C*H*), 6.08 (triplet, 1, J=1.3 cps, C=CH–CO), 2.50 (doublet, 2, J=1.3 cps, CH_2), 2.28 (singlet, 2, CH_2), 1.11 (singlet, 6, *gem*-dimethyl).

Anal. Calcd. for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.47; H, 6.77.

Preparation of 4,6,7,8-tetrahydro-4,7,7-trimethyl-2*H*-1-benzopyran-2,5(3*H*)-dione (**5b**).

General Procedure for Cyclization.

To 150 ml. of tetrahydrofuran was added 3.08 g. (22 mmole) of 5,5-dimethyl-1,3-cyclohexanedione (**1**) and 640 mg. (267 mmole) of sodium hydride. After the evolution of hydrogen ceased, the reaction mixture was heated to reflux and 2 ml. of crotonyl chloride (2.16 g., 20.7 mmole) in 20 ml. of tetrahydrofuran added dropwise with stirring. The reaction mixture was heated at reflux for 4 hours, cooled and filtered to remove inorganic material. Evaporation of the solvent followed by vacuum distillation of the product gave 3.87 g. (18.6 mmole, 90%) of a clear oil which crystallized in the receiver. This material could also be purified by sublimation, m.p. 82-83.5°; λ max 254 nm (ε, 12,100); ν max 1785, 1655, 1120 cm^{-1}; NMR, δ 3.10 (multiplet, 1, CH_3–C*H*–CH_2), 2.65 (apparent doublet, 2, CH_3–CH–C*H*$_2$), 2.40 (singlet, 2, CH_2), 2.28 (singlet, 2, CH_2), 1.10 (singlet, 7.5, *gem*-dimethyl plus half of CH_3–CH doublet), 0.98 (singlet, 1.5, half of C*H*$_3$–CH doublet).

Anal. Calcd. for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74; Molecular Weight, 208. Found: C, 68.96; H, 7.71; Molecular Weight, 207 (osmometric in benzene).

5,6,7,8-Tetrahydro-7,7-dimethyl-2*H*-1-benzopyran-2,5(3*H*)-dione (**5a**).

This compound was obtained as a white crystalline solid from the reaction of 3.92 g. (28 mmole) of **1** with 740 mg. (30 mmole) of sodium hydride and 2 ml. (2.28 g., 25.2 mmole) of acryloyl chloride (**3a**). The compound could be purified by distillation or sublimation. Yield, 80%, m.p. 56-58°; λ max 255 nm (ε, 11,000); ν max 1782, 1655, 1378, 1100 cm^{-1}; NMR, δ 2.71-2.21 (complex multiplet with sharp peaks at 2.61 and 2.28, 8, methylene protons), 1.12 (singlet, 6, *gem*-dimethyl).

Anal. Calcd. for $C_{11}H_{14}O_3$: C, 68.02; H, 7.26. Found: C, 67.90; H, 7.16.

3,4-Dihydro-7-methyl-2*H*,5*H*-pyrano-[4,3-*b*]pyran-2,5-dione (**9**).

To 200 ml. of dioxane was added 3.59 g. (28.5 mmole) of 4-hydroxy-6-methyl-2 pyrone (**8**) and 770 mg. (32 mmole) of sodium hydride. The reaction mixture was heated at reflux for 1 hour and 2 ml. (2.28 g., 25.3 mmole) of acryloyl chloride (**3a**) in 15 ml. of dioxane added dropwise with stirring. The reaction mixture was heated at reflux for 7 hours, cooled and filtered. Evaporation of the solvent gave an orange solid which was sublimed to give 3.81 g. (21.1 mmole, 84%) of a white crystalline solid, m.p. 129-131°; λ max 288 nm (ε, 6,000); ν max 1783, 1708, 1595, 1107 cm^{-1}; NMR, δ 5.93 (broad singlet, 1, =CH), 2.82 (singlet, 4. CH_2CH_2), 2.28 (singlet, 3, methyl).

Anal. Calcd. for $C_9H_8O_4$: C, 60.00; H, 4.44; Molecular Weight, 180. Found: C, 59.85; H, 4.49; Molecular Weight, 180 (mass spectrometric).

Cyclization of **4b** to **5b**.

To 30 ml. of tetrahydrofuran was added 700 mg. (3.4 mmole) of 5,5-dimethyl-1,3-cyclohexanedione enol crotonate (**4b**), 70 mg. (0.5 mmole) of 5,5-dimethyl-1,3-cyclohexanedione (**1**), and 30 mg. (1.3 mmole) of sodium hydride. The reaction mixture was heated to reflux. Aliquots were removed at various intervals and filtered. The solvent was then evaporated and the residue analyzed by NMR. Cyclization of the ester could be followed by observing the change in the NMR spectrum. After 5 hours cyclization was complete.

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