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Conversion of Furans into γ-Hydroxybutenolides: Use of Sodium Chlorite

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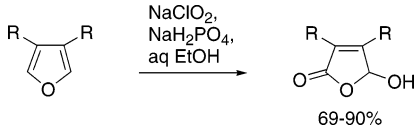


3,4-Disubstituted furans are converted into γ-hydroxybutenolides by treatment with $NaClO_2$ in aqueous EtOH containing NaH_2PO_4.

Discussion

During synthetic studies on the core of CP-225,917, the furan **1** (Scheme 1) was treated with $NaClO_2$ under the standard conditions used for oxidizing an aldehyde to a carboxylic acid. In the event, the aldehyde group of **1** was indeed converted into a carboxyl; at the same time, the furan subunit of **1** was oxidized, and a mixture of the regioisomeric γ-hydroxybutenolides **2** and **3** was obtained.[1,2]

The conversion of 2,3-disubstituted furans into γ-hydroxy-butenolides has normally been done by exposure to singlet oxygen and treatment of the product with an organic base,[3] although other oxidizing agents have occasionally been used: NBS,[4a,b] MCPBA,[4a,c,d] chromic acid,[4e,f] and H_2O_2−V(IV).[4g,h]

We have found that $NaClO_2$ is a general reagent for oxidizing furans to γ-hydroxybutenolides (Table 1).

SCHEME 1

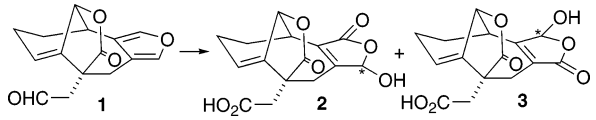
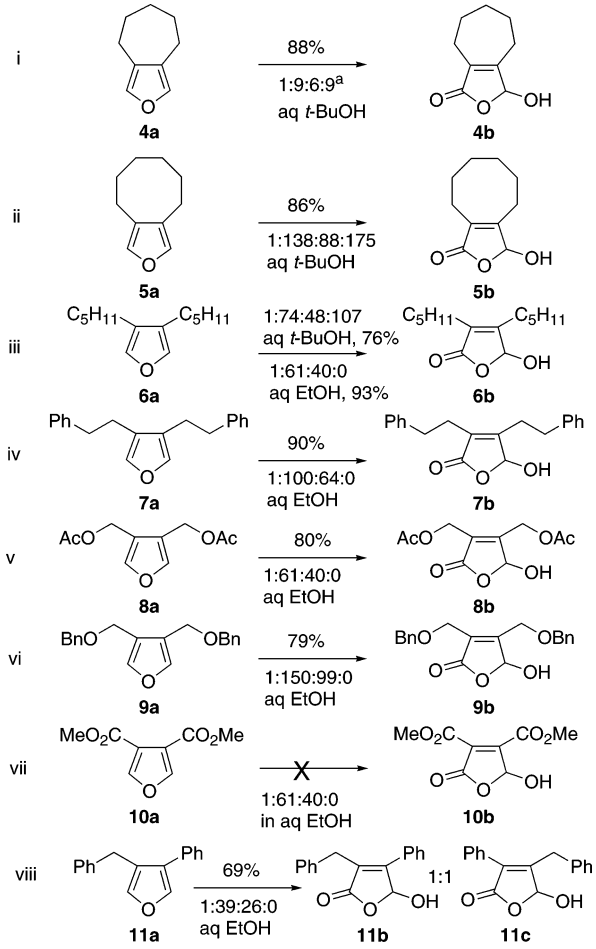


TABLE 1. Oxidation of Furans to Hydroxybutenolides



[a] Molar ratio of furan:$NaClO_2$:$NaHPO_4$:olefin.

In the case of furans **4a** and **5a**, we used our original conditions[1,5] ($NaClO_2$, $NaH_2PO_4 \cdot H_2O$, 2-methyl-2-butene, *t*-BuOH, water) and obtained **4b** and **5b** in 88 and 86% yields, respectively. The oxidation was carried out under a slight static pressure of nitrogen, but in later experiments with some of the other furans listed in Table 1, we found that reaction in an open flask gave higher yields, suggesting that evaporation of the 2-methyl-2-butene facilitated the process. Brief optimization studies with **8a** quickly established that oxidations in the absence of olefin were indeed fast and gave an improved yield. Use of other scavengers such as sulfamic acid (H_2NSO_3H) or 1,3-benzenediol[6] also inhibited the oxidation.

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(2) Stereochemistry at starred atoms not established.
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Finally, we decided to use aqueous EtOH as the solvent. This modification (with **8a**) led to an increased yield and a significantly shorter reaction time (ca. 13 vs 34 h). The modified process was then applied to examples **6a**−**11a**. An experiment with **8a** in which $NaH_2PO_4 \cdot H_2O$ was omitted gave no oxidation product. Our results (Table 1) show that two ester groups attached directly to the furan ring prevent oxidation, but the reaction works with alkyl and substituted alkyl groups. With the unsymmetrical furan **11a**, both regioisomeric products **11b** and **11c** were formed (1:1, 70%). In this case, the standard method of singlet oxygen oxidation was also tried, and again a 1:1 mixture was obtained (78%). Compound **11c** has been isolated[7] from a fungus.

We have not established the mechanism of the oxidations but have excluded HOCl as the effective reagent. It is known[6] that HOCl and ClO_2 are formed during $NaClO_2$ oxidations; we therefore treated **8a** with NaOCl at pH 4.5 (in the presence of NaH_2PO_4) but found that **8b** is not formed (^{1}H NMR). If the effective reagent is actually ClO_2, our experiments show that $NaClO_2$ is a convenient alternative source; ClO_2 itself has not been used for oxidation of furans.

Experimental Section

General Procedures. The symbols s, d, t, and q used for ^{13}C NMR signals indicate 0, 1, 2, or 3 attached hydrogens, respectively, the assignments being made from APT spectra.

3-Hydroxy-3,4,5,6,7,8-hexahydrocyclohepta[*c*]furan-1-one (4b). In the following experiment, a cold container of 2-methyl-2-butene (just removed from the refrigerator) was opened, and a portion was taken up into a syringe.

$NaClO_2$ (1.00 g, 11.1 mmol) and $NaH_2PO_4 \cdot H_2O$ (1.00 g, 7.25 mmol) were dissolved in water (10 mL), and an aliquot (3 mL) of this freshly made solution was added to a stirred solution of **4a**[8,9,10] (176.5 mg, 1.3 mmol) and 2-methyl-2-butene (0.9 mL) in *t*-BuOH (4 mL). Stirring at room temperature was continued overnight (mixture open to the air), by which stage the color of solution had become yellow. Some **4a** remained (TLC, silica, 3:7 EtOAc−hexane). $NaClO_2$ (0.50 g, 5.53 mmol) and $NaH_2PO_4 \cdot H_2O$ (0.500 g, 3.62 mmol) were dissolved in water (5 mL), and an aliquot (3 mL) of this freshly made solution was added to the reaction mixture. Stirring was continued for 18 h. EtOAc (20 mL) was added, and the pH was adjusted to 3 (pH paper) by addition of 1 N hydrochloric acid. The aqueous layer was saturated with NaCl and extracted with EtOAc (4 × 15 mL). The combined organic extracts (yellow) were dried (Na_2SO_4) and evaporated. During the evaporation, the residue became colorless, but the distillate was yellow. Flash chromatography of the residue over silica gel (21 cm × 2 cm), using 3:7 EtOAc−hexane, gave **4b** (191.3 mg, 88%) as a colorless oil: FTIR (CH_2Cl_2 cast) 3351, 1736 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.61−1.80 (m, 6 H), 2.36−2.59 (m, 4 H), 4.59 (br s, 1 H), 5.87 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.8 (t), 26.7 (t), 26.8 (t), 27.6 (t), 30.1 (t), 97.6 (d), 131.7 (s), 161.4 (s), 172.4 (s), exact mass *m/z* calcd for $C_9H_{12}O_3$ 168.07864, found 168.07885.

5-Hydroxy-3,4-dipentyl-5*H*-furan-2-one (6b). A freshly made solution of $NaClO_2$ (0.500 g, 5.53 mmol) and $NaH_2PO_4 \cdot H_2O$ (0.500 g, 3.6 mmol) in water (5 mL) was added to a stirred solution of **6a** (19.5 mg, 0.094 mmol) in EtOH (5 mL). Stirring was continued for 12 h (mixture open to the air), and the mixture was diluted with EtOAc (15 mL). Aqueous $NaHSO_3$ (1 M, 11 mL) was added, and the solution became colorless. The aqueous layer was saturated with NaCl and extracted with EtOAc (4 × 20 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (25 × 2.4 cm), using 1:4 EtOAc−hexane gave **6b** (21 mg, 93%): FTIR (CH_2Cl_2 cast) 3377, 1742 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.88−0.93 (m, 6 H), 1.30−1.70 (m, 12 H), 2.24 (t, J = 8 Hz, 2 H), 2.38−2.44 (m, 2 H), 3.43 (d, J = 8 Hz, 1 H), 5.95 (d, J = 7.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.9 (q), 13.9 (q), 22.3 (t), 22.4 (t), 23.5 (t), 27.0 (t), 27.2 (t), 27.8 (t), 31.6 (t), 31.8 (t), 97.0 (d), 130.3 (s), 159.4 (s), 172.0 (s); exact mass *m/z* calcd for $C_{14}H_{24}O_3$ 240.17255, found 240.17325.

5-Hydroxy-3,4-diphenethyl-5*H*-furan-2-one (7b). A freshly made solution of $NaClO_2$ (0.600 g, 6.6 mmol) and $NaH_2PO_4 \cdot H_2O$ (0.600 g, 4.4 mmol) in water (6 mL) was added to a stirred solution of **7a** (34.0 mg, 0.123 mmol) in EtOH (6 mL). Stirring was continued for 4 h (mixture open to the air). At this stage, some **7a** remained (TLC, silica, 3:7 EtOAc−hexane). $NaClO_2$ (0.500 g, 5.53 mmol) and $NaH_2PO_4 \cdot H_2O$ (0.500 g, 3.62 mmol) were dissolved in H_2O (5 mL), and an aliquot (1 mL) of the freshly made solution was added to the reaction mixture. Stirring was continued for another 4 h. The yellow-colored solution was diluted with EtOAc (25 mL), and the aqueous layer was saturated with NaCl and extracted with EtOAc (4 × 15 m L). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (10 × 3 cm), using 3:7 EtOAc−hexane gave **7b** (34.3 mg, 90%): FTIR (CH_2Cl_2 cast) 3353, 1738 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.44−2.75 (m, 8 H), 3.26 (d, J = 8.4 Hz, 1 H), 5.79 (d, 8 Hz, 1 H), 7.07−7.31 (m, 10 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.7 (t), 27.7 (t), 33.3 (t), 33.5 (t), 97.2 (d), 126.3 (d), 126.6 (d), 128.2 (d), 128.5 (d), 128.6 (d), 128.7 (d), 129.7 (s), 140.1 (s), 140.8 (s), 159.2 (s), 171.9 (s); exact mass calcd for $C_{20}H_{20}O_3$ *m/z* 308.14124, found 308.14054.

Acetic Acid 4-Acetoxymethyl-5-hydroxy-2-oxo-2,5-dihydrofuran-3-ylmethyl Ester (8b). A freshly made solution of $NaClO_2$ (0.50 g, 5.53 mmol) and $NaH_2PO_4 \cdot H_2O$ (0.50 g, 3.6 mmol) in water (5 mL) was added to a stirred solution of **8a**[11] (17.8 mg, 0.083 mmol) in EtOH (5 mL). Stirring was continued for 12 h (mixture open to the air), and the yellow mixture was diluted with EtOAc (15 mL). Aqueous $NaHSO_3$ (1 M, 6 mL) was added, and the solution became colorless. The aqueous layer was saturated with NaCl and extracted with EtOAc (4 × 20 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (6 × 3 cm), using 5:7 EtOAc−hexane gave **8b**[12] (16.4 mg, 80%): FTIR ($CHCl_3$ cast) 3369, 1748 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.09 (s, 3 H), 2.12 (s, 3 H), 4.88−5.16 (m, 5 H), 6.09 (d, J = 8 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.5 (q), 20.6 (q), 55.4 (t), 57.4 (t), 96.9 (d), 127.3 (s), 157.1 (s), 169.7 (s), 170.6 (s), 170.7 (s); exact mass *m/z* calcd for $C_{10}H_{12}O_7$ 244.05830, found 244.05817.

3,4-Bis(benzyloxymethyl)-5-hydroxy-5*H*-furan-2-one (9b). A freshly made solution of $NaClO_2$ (0.50 g, 5.53 mmol) and $NaH_2PO_4 \cdot H_2O$ (0.50 g, 3.6 mmol) in water (5 mL) was added to a stirred solution of **9a**[13] (39.0 mg, 0.126 mmol) in EtOH (5 mL). Stirring was continued for 7.5 h (mixture open to the air). EtOAc (20 mL) was added to the yellow reaction mixture, and the aqueous layer was saturated with NaCl and extracted with EtOAc (4 × 20 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (10 × 3 cm), using 3:7 EtOAc−hexane, gave **9b** (34.0 mg, 79%): FTIR ($CHCl_3$ cast) 3354, 1766 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.43 (d, J = 7.5 Hz, 1 H), 4.33−4.64 (m, 8 H), 6.10 (d, J = 7.5 Hz, 1 H), 7.26−7.38 (m, 10 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 62.3 (t), 63.4 (t), 73.5 (t), 73.6 (t), 96.5 (d),

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127.9 (d), 128.0 (d), 128.2 (d), 128.5 (d), 128.6 (d), 137.0 (s), 137.5 (s), 157.8 (s), 170.0 (s); exact mass *m/z* calcd for $C_{20}H_{20}O_5$ 340.13107, found 340.13090.

3-Benzyl-5-hydroxy-4-phenyl-5*H*-furan-2-one (11b) and 4-Benzyl-5-hydroxy-3-phenyl-5*H*-furan-2-one (11c). A freshly made solution of $NaClO_2$ (0.20 g, 2.2 mmol) and $NaH_2PO_4 \cdot H_2O$ (0.20 g, 1.45 mmol) in water (2 mL) was added to a stirred solution of **11a** (30.3 mg, 0.129 mmol) in EtOH (2 mL). Stirring was continued for 4.5 h (mixture open to the air). EtOAc (20 mL) was added, and the aqueous layer was saturated with NaCl and extracted with EtOAc (4 × 15 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 × 46 cm), using 3:7 EtOAc−hexane, gave **11b** and **11c**[7] (ca 1:1, 24 mg, 69%).**Data for the more polar compound 11b:** FTIR (CH_2Cl_2 cast) 3358, 1738 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.67 (d, J = 8.5 Hz, 1 H), 3.88 (AB q, $\Delta\nu_{AB}$ = 39.6 Hz, J = 15.5 Hz), 6.45 (d, J = 8 Hz, 1 H), 7.22−7.55 (m, 10 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 30.1 (t), 97.2 (d), 126.7 (d), 128.3 (d), 128.3 (d), 128.7 (s), 128.8 (d), 129.0 (d), 130.3 (s), 130.4 (d), 137.1 (s), 156.0 (s), 171.8 (s); exact mass *m/z* calcd for $C_{17}H_{14}O_3$ 266.09430, found 266.09464. **Data for the less polar compound 11c:** FTIR ($CHCl_3$ cast) 3373, 1736 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.94 (AB q, $\Delta\nu_{AB}$ = 119.7 Hz, J = 15.2 Hz), 4.27 (br s, 1 H), 5.90 (d, J = 4.8 Hz, 1 H), 7.17−7.52 (m, 10 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 32.4 (t), 96.5 (d), 127.2 (d), 128.7 (d), 128.8 (d), 128.9 (s), 129.0 (d), 129.0 (d), 129.2 (d), 129.9 (s), 136.0 (s), 158.4 (s), 170.96 (s); exact mass *m/z* calcd for $C_{17}H_{14}O_3$ 266.09430, found 266.09445.

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Supporting Information Available: NMR spectra of new compounds and experimental details for the preparation of **5b**, 3,4-dipent-1-enylfuran, **6a**, 3,4-distyrylfuran, **7a**, **9b** (by photooxygenation), (*Z*)-3-benzyl-2-phenyl-2-butene-1,4-diol, **11a**, **11b** (by photooxygenation), and **11c** (by photooxygenation). This material is available free of charge via the Internet at http://pubs.acs.org.

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