

Direct Formation of 4-Alkoxy Derivatives from 2,5-Dimethyl-4-hydroxy-3(2*H*)-furanone and Aliphatic Alcohols

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The reaction of 2,5-dimethyl-4-hydroxy-3(2*H*)-furanone (DHF) with aliphatic alcohols using a small amount of strong acid catalyst proceeded, in an analogous way to classical carboxylic acid ester formation, to give good yields of the 4-alkoxy derivatives. This raises the possibility that this type of ester-like formation might occur in foods that contain both DHF and alcohols. Odor threshold determinations of 4-alkoxy DHF derivatives from a number of common food alcohols including methanol, ethanol, butanol, 3-methylbutanol, and (*Z*)-3-hexenol showed them, however, to be relatively weak odorants.

Keywords: 2,5-Dimethyl-4-hydroxy-3(2*H*)-furanone; alkoxy derivatives; synthesis; odor thresholds

INTRODUCTION

2,5-Dimethyl-4-hydroxy-3(2*H*)-furanone (DHF) has been well established as an important aroma component of a number of fruits including pineapple (Rodin et al., 1965), strawberry (Re et al., 1973), and raspberry (Honkanen, 1980). The methoxy derivative, 2,5-dimethyl-4-methoxy-3(2*H*)-furanone (DMF), is also a known component of strawberries (Ito et al., 1990) and arctic bramble (Kalio, 1976). The method commonly used for the synthesis of DMF is the action of diazomethane on DHF (cf. Sen et al., 1991; Wilhalm et al., 1965).

We have been studying the importance of DHF to tomato flavor (Krammer et al., 1994; Buttery et al., 1995). Some tomato products contain appreciable amounts of (*Z*)-3-hexenol and 3-methylbutanol. If DHF could react directly with these alcohols under the mild acid conditions of the tomato then there is a possibility that alkoxy derivatives of these alcohols with DHF would be present. This study was undertaken to test whether such direct reaction was possible under normal (more vigorous) laboratory conditions. It was also undertaken to obtain spectral reference data and to evaluate the sensory significance of the most likely alkoxy compounds.

EXPERIMENTAL PROCEDURES

Synthesis of 2,5-Dimethyl-4-ethoxy-3(2*H*)-furanone. 2,5-Dimethyl-4-hydroxy-3(2*H*)-furanone (2.0 g) was added to anhydrous ethanol (120 mL) in a 250 mL round bottom flask. *p*-Toluenesulfonic acid (100 mg) was then added, a drying tube attached to the top of the reflux condenser, and the mixture refluxed for 6 h. The mixture was then cooled, shaken with solid NaHCO₃ (5 g), and filtered through a ca. 2 mm layer of NaHCO₃ to remove the acid catalyst. The ethanol was then removed under reduced pressure. The 2,5-dimethyl-4-ethoxy-3(2*H*)-furanone was purified by preparative gas chromatography (GC). The yield (determined by GC) based on the DHF was 80%.

Synthesis of 2,5-Dimethyl-4-methoxy-3(2*H*)-furanone. This was synthesized using essentially the same procedure as for the ethoxy compound except methanol was used instead of ethanol. The yield also was better than 80%.

Synthesis of 2,5-Dimethyl-4-butoxy-3(2*H*)-furanone. 2,5-Dimethyl-4-hydroxy-3(2*H*)-furanone (2.0 g) was added to 100 mL of butanol, 50 mL of benzene, and 100 mg of *p*-toluenesulfonic acid in a 250 mL round bottom flask. A Dean–Stark trap, containing ca. 10 g of 8 mesh anhydrous

CaSO₄, was attached to the flask. A drying tube was placed on top of the reflux condenser. The mixture was refluxed for 16 h and then allowed to cool. The *p*-toluenesulfonic acid was then removed with NaHCO₃ as above and the filtered solution concentrated under reduced pressure. The yield of 2,5-dimethyl-4-butoxy-3(2*H*)-furanone based on the DHF was 90%. The product was purified by preparative GC.

Synthesis of 2,5-Dimethyl-4-(3-methylbutoxy)-3(2*H*)-furanone and 2,5-Dimethyl-4-((*Z*)-3-hexenoxy)-3(2*H*)-furanone. These compounds were synthesized in a way similar to that of the butoxy compound using benzene with the Dean–Stark trap to remove water. The yields based on the original DHF were 50–60%.

Mass Spectra. These were obtained with a HP 5970 (mass detector) quadrupole mass spectrometer. The samples were introduced into the mass spectrometer using a HP 5890 gas chromatograph with a 60 m long by 0.25 mm i.d. fused silica capillary, wall coated with DB-1.

Nuclear Magnetic Resonance Spectra. These were measured in CDCl₃ with a Bruker ARX 400 spectrometer.

Infrared Absorption Spectra. These were measured neat as films between salt plates using a Perkin-Elmer Model 1600 FT-IR infrared spectrophotometer.

Materials. 2,5-Dimethyl-4-hydroxy-3(2*H*)-furanone and common alcohols were obtained from Aldrich Chemical Co., Milwaukee, WI. (*Z*)-3-Hexenol was obtained from Bedoukian Research, Inc., Danbury, CT. 2,5-Dimethyl-4-methoxy-3(2*H*)-furanone was obtained from Firmenich SA., Geneva, Switzerland.

Odor Threshold Determination. These were determined on samples purified by preparative GC in odor-free distilled water (pH 7) following procedures already described (e.g., Buttery et al., 1995). The number of experienced judges was 18–21. The solutions were presented to the judges in flexible Teflon bottles each fitted with a 6 cm long by 0.64 cm diameter Teflon tube through the bottle cap to facilitate transfer of the vapor to the judge's nose when the bottle was gently squeezed. Solutions were diluted by factors of 2 for each step in the judgment. For each concentration the judges were given two coded bottles, one containing the solution and the other odor-free water. The judge's task was to record which coded bottle possessed an odor. Probit analysis (a statistics program for drug dose tests) was used to determine the threshold point (taken where 75% of panelists give the correct judgment) and the 95% confidence intervals.

RESULTS AND DISCUSSION

The methods for the synthesis of esters from aliphatic alcohols and carboxylic acids have long been well

Table 1. Odor Thresholds of Alkoxy Derivatives of 2,5-Dimethyl-4-hydroxy-3(2*H*)-furanone in Water (pH 7)

compd	threshold in nL/L ^a (ppb)	95% confidence limits
2,5-dimethyl-4-methoxy-3(2 <i>H</i>)-furanone	3400	2000–6100
2,5-dimethyl-4-ethoxy-3(2 <i>H</i>)-furanone	2900	1600–16000
2,5-dimethyl-4-butoxy-3(2 <i>H</i>)-furanone	250	170–350
2,5-dimethyl-4-(3-methylbutoxy)-3(2 <i>H</i>)-furanone	900	600–1500
2,5-dimethyl-4-((<i>Z</i>)-3-hexenoxy)-3(2 <i>H</i>)-furanone	1900	1400–3700

^a 10⁻⁹ L of compound per L of water.

established. It was found that essentially the same methods were also successful if 2,5-dimethyl-4-hydroxy-3(2*H*)-furanone (DHF) was treated as a carboxylic acid. It was known that DHF has acidic properties, the -OH and C=O arrangement having some similarities to that of some other noncarboxylic acidic compounds such as ascorbic acid and tropolone. We had noted (Buttery et al., 1995) that a 2% water solution of DHF had a pH of 2.8, not very different from that of a 2% water solution of acetic acid (pH 2.7). Using a published procedure (Wilcox, 1984), titration with 0.5 N NaOH showed DHF to have a p*K*_a of ca. 8.2. This value shows DHF to be a weaker acid than aliphatic acids (p*K*_a = 4–5) but a stronger acid than phenol (p*K*_a = 9.9).

The yields of the DHF alkoxy derivatives were of the same order as generally found with carboxylic acid ester formation. The DHF seemed reasonably stable under the conditions of ester formation, although precautions were taken to use conditions so that the temperature remained below 100 °C by using benzene for the higher boiling alcohols. The benzene also functioned to remove water to a Dean–Stark trap.

2,5-Dimethyl-4-methoxy-3(2*H*)-furanone. The sample obtained from the reaction of methanol with DHF had mass spectra, GC retention index, and IR spectrum identical to those of an authentic commercial sample.

2,5-Dimethyl-4-ethoxy-3(2*H*)-furanone. This compound had a mass spectrum (intensities in parentheses) showing ions at 41 (5), 43 (100), 55 (9), 57 (54), 69 (5), 72 (15), 83 (2), 85 (58), 99 (2), 112 (2), 113 (3), 127 (1), 128 (15), 141 (2), 156 (48) M⁺; Kovats' GC retention index on DB-1, 1090; ¹H NMR spectrum δ 1.27, t, *J* = 7 Hz, 3H (CH₃CH₂-), 1.44, d, *J* = 7 Hz, 3H (CH₃- 2 position of the furanone ring), 2.19, d, *J* = 1 Hz, 3H (CH₃- at 5 position of the furanone ring), 4.07, m, 2H (CH₃CH₂O-), 4.40, q, *J* = 7 Hz, 1H (*H* at 2 position of the furanone ring); ¹³C NMR δ 198.5, 178.5, 135.3, 80.3, 67.6, 16.48, 15.3, 13.5; IR spectrum, major absorption bands at 2982, 1704, 1632, 1426, 1311, 1202, 1031, 998 cm⁻¹.

2,5-Dimethyl-3-butoxy-3(2*H*)-furanone. Mass spectrum showed ions at 39 (12), 41 (22), 43 (80), 55 (9), 57 (49), 69 (2), 72 (40), 85 (100), 99 (1), 110 (1), 128 (67), 141 (2), 184 (26) M⁺; Kovats' GC retention index on DB-1, 1260; ¹H NMR spectrum δ 0.94, t, *J* = 7 Hz, 3H (CH₃-CH₂CH₂-), 1.42, m, 2H (CH₃CH₂CH₂-), 1.43, d, *J* = 7 Hz, 3H (CH₃- at 2 position of the furanone ring), 1.62, m, 2H (CH₃CH₂CH₂CH₂-), 2.18, d, *J* = 1 Hz, 3H (CH₃- at 5 position of the furanone ring), 4.0, m, 2H (-CH₂CH₂O-), 4.4, q, *J* = 7 Hz, 1H (*H* at 2 position of the furanone ring); ¹³C NMR spectrum δ 198.5, 178.3, 135.7, 80.3, 71.8, 31.9, 18.9, 16.5, 13.8, 13.5; IR spectrum, major absorption bands at 2961, 1703, 1631, 1311, 1200, 1140, 1075, 1003 cm⁻¹.

2,5-Dimethyl-4-(3-methylbutoxy)-3(2*H*)-furanone. Mass spectrum showed ions at 41 (21), 43 (100), 55 (14), 57 (22), 71 (7), 72 (34), 83 (4), 85 (74), 111 (2), 128 (82), 129 (14), 141 (1), 155 (1), 198 (25) M⁺; Kovats'

GC retention index, 1305; ¹H NMR spectrum δ 0.93, d, *J* = 7 Hz, 6H (CH₃CH(CH₃)CH₂CH₂-), 1.43, d, *J* = 7 Hz, 3H (CH₃- at 2 position of the furanone ring), 1.54, q, *J* = 7 Hz, 2H (-CH₂CH₂O-), 1.76, hep, *J* = 7 Hz, 1H (CH₃CH(CH₃)CH₂CH₂-); 2.18, s, 3H (CH₃- at 5 position of the furanone ring), 4.04, m, 2H (-CH₂CH₂O-), 4.40, q, *J* = 7 Hz, 1H (*H* at 2 position of the furanone ring); ¹³C NMR spectrum δ 198.5, 178.2, 135.7, 80.3, 70.5, 38.6, 24.8, 22.55, 22.52, 16.5, 13.5; IR spectrum major absorption bands at 2958, 1703, 1631, 1426, 1311, 1199, 1005 cm⁻¹.

2,5-Dimethyl-4-((*Z*)-3-hexenoxy)-3(2*H*)-furanone. Mass spectrum showed ions at 41 (47), 43 (84), 55 (83), 57 (21), 67 (23), 72 (33), 83 (10), 85 (77), 128 (100), 129 (17), 167 (4), 210 (8) M⁺; Kovats' GC retention index on the DB-1 capillary, 1480; ¹H NMR spectrum δ 0.97, t, *J* = 7 Hz, 3H (CH₃CH₂CH=CH-), 1.43, d, *J* = 7 Hz, 3H (CH₃- at 2 position of the furanone ring), 2.06, p, *J* = 7 Hz, 2H (CH₃CH₂CH=CH-), 2.18, d, *J* = 1 Hz, 3H (CH₃- at 5 position of the furanone ring), 2.40, q, *J* = 7 Hz, 2H (-CH=CHCH₂CH₂-), 4.03, m, 2H (-CH₂CH₂O-), 4.40, q, *J* = 7 Hz, 1H (*H* at 2 position of the furanone ring), 5.36, m, 1H (-CH=CH-), 5.49, m, 1H (-CH=CH-); ¹³C NMR spectra δ 198.3, 178.3, 135.5, 134.2, 124.2, 80.4, 71.4, 28.0, 20.7, 16.5, 14.2, 13.5; IR spectra, major absorption bands at 2965, 1702, 1630, 1311, 1198, 1138, 1075, 1009 cm⁻¹.

Except for the methoxy compound these DHF alkoxy compounds do not seem to have been previously described in the literature. The spectral data are quite consistent with these structures. One other possible product from this type of reaction is the formation of ketals from the reaction of the alcohols with the C=O group in the 3-position of the furanone ring. Ketals of this type would have a considerably higher molecular weight and show quite different IR and NMR spectral data. No ketals were detected.

From this study the ease with which DHF reacts with alcohols raises the possibility that this type of alkoxy formation might occur in foods, where both are found, especially because of the acidic nature of many fruits and vegetables. Reactions that occur easily in the laboratory can also frequently be catalyzed by enzyme systems and such a pathway has been suggested by Kalio (1976) for formation of DMF from DHF in arctic bramble.

Odor Threshold Studies. Table 1 lists the odor thresholds determined for these compounds in odor-free distilled water (pH 7.0). They are all considerably weaker odorants than 2,5-dimethyl-4-hydroxy-3(2*H*)-furanone itself (threshold 60 mg/L at pH 7; Buttery et al., 1995). The most potent was the butoxy derivative with a threshold of 250 nL/L. The least potent was the well-known methoxy derivative with a threshold of 3400 nL/L. It might be noted that in other studies (Pyysalo et al., 1977) a threshold of 0.03 nL/L (ppb) had been reported for the methoxy derivative. Our data on the GC purified material is ca. 10⁵ times higher than this. Pyysalo et al. (1977) did not report that their sample

was purified by GC. Small concentrations of impurities can frequently lower the apparent thresholds of weak odorants significantly.

The methoxy compound has been reported as occurring in strawberries at a concentration as high as 18500 nL/L (Sanz et al., 1995) which is several times over its threshold and at that level it has a good probability of contributing to the odor and flavor. As the other alkoxy compounds have not yet been reported in fruits and vegetables, if they are present, they probably only occur at trace levels. With the high odor thresholds found it would seem that they have a very low probability of contributing to the odor and flavor of the food.

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