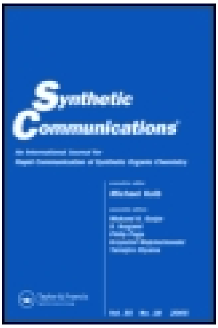

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A SHORT AND EFFICIENT SYNTHESIS OF 2-METHYLTETRAHYDROFURAN-3-ONE

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Abstract : 2-Methyltetrahydrofuran-3-one **(3)**, a volatile constituent of the aroma complex of roasted coffee, is efficiently prepared in satisfactory yield (55,2%) by oxidative hydroxylation of the 2-acetylbutyrolactone **(4)**.

Tetrahydrofuran-3-ones, while a comparatively simple functional array, are a somewhat rare class of compounds. Characteristic examples of natural products containing the above nucleus are the muscarine alkaloids[1], isolated from various poisonous mushrooms such as *Amanita muscaria,* the ascofuranone **(1)**, an antibiotic and hypolipidemic agent from *Ascochyta viciae*[2] and the chilenone A **(2)**, (Scheme 1) a secondary metabolite of the red marine algae *Laurencia chilensis*[3]. The simplest representative of this group of compounds, the 2-methyltetrahydrofuran-3-one **(3)**has been reported as one of the characteristic volatile constituents

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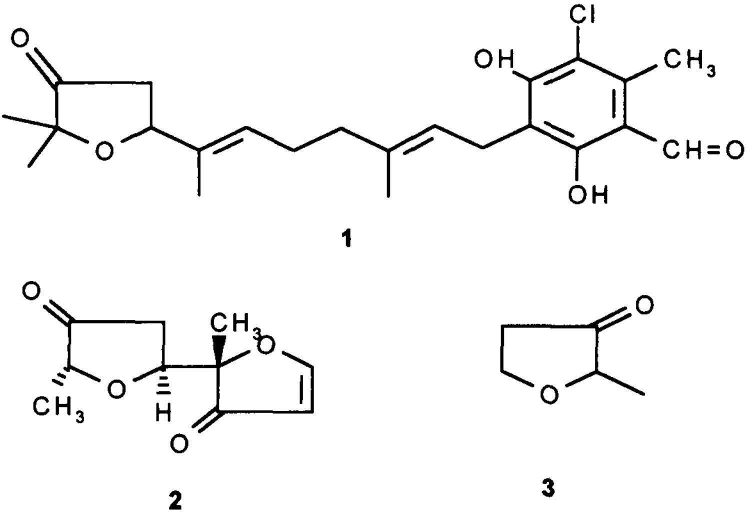
of the aroma complex of roasted coffee, from which it has been isolated[4]. It has.also been detected as a constituent of the beer and chips flavor[5], as well as a component in the Maillard reaction of different amino acids with fructose in cocoa butter-water[6].



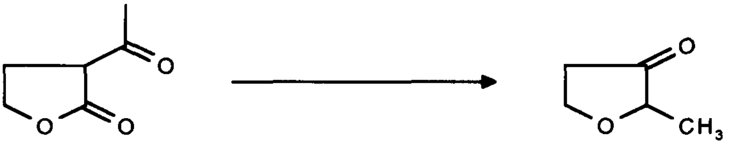
Scheme 1

The structure of **3** was elucidated by means of spectroscopic techniques and synthesis[4]. Several synthetic approaches to the construction of compound **3**, have appeared in the literature. Characteristic examples are: the alkoxyde treatment of the corresponding tetrahydrofuranic chlorhydrine[7] the hydration and cyclisation of an acetylenic diol[8], a reaction scheme based on the bisalkylation of the 1,3-dithiane[9] and the direct catalytic oxygenation of the 2-methyltetrahydrofurane in the presence of ruthenium complexes[10].

These methods suffer from the multistep sequence needed, the specific reagents used or the drastic conditions required and the low overall yield.

We report in this paper a short and efficient synthesis of 2-methyltetrahydrofuran-3-one **(3)**, by the oxidative hydroxylation of the 2-acetylbutyrolactone **(4)** a common and cheap starting material, using Oxone^R in a buffered aqueous solution keeping the pH constantly above 8,5.

In view of our interest in the synthesis of hydroxylated derivatives of butyrolactones, we tried the hydroxylation of 2-acetylbutyrolactone, by inorganic peracids as the potassium persulfate, the sodium perborate or the commercial Oxone^R, using one equivalent of reagent in each case. Quite unexpectedly, in every experiment with the above peracids, regardless to the conditions, a small amount of **3** was always produced. We started then a more careful study of the above reaction, in order to ameliorate the yield and develop a convenient procedure for the synthesis of **3**. The results of that study are summarized in Table 1.



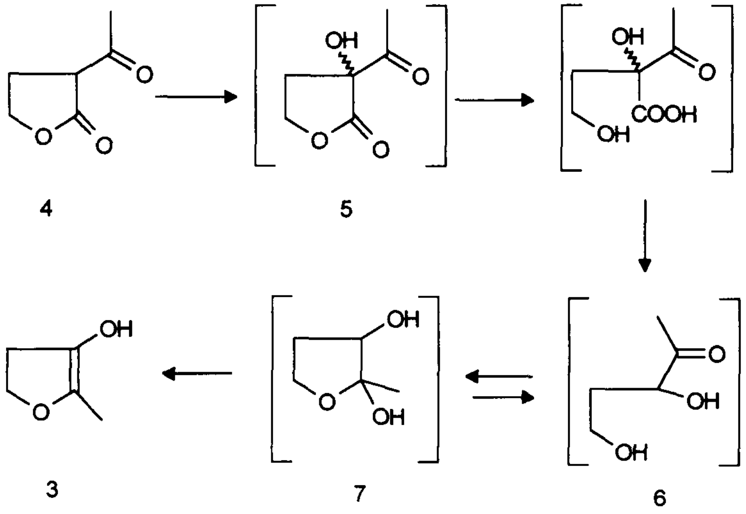
4 3

Table 1. Oxidations of 2-acetylbutyrolactone

Oxidant	Temperature °C	Reaction time Hours	Yield[a] %
Potassium persulfate	20-25	3	22,5
Potassium persulfate	50-55	2	15,0
Sodium perborate tetrahydrate	20-25	3	12,4
Oxone^R Potassiumperoxymonosulfate	20-25	3	55,2
Oxone^R	20-25	6	45,0
Oxone^R	50-55	3	25,7

[a] Yield of isolated product.

Although no systematic mechanistic studies have been done, we can reasonably assume that the formation of the 2-methyltetrahydrofuran-3-one (**3**), is the result of the hydroxylation of the 2-acetylbutyrolactone to the intermediate **5**, followed by the opening of the lactonic ring and the decarboxylation to the dihydroxyketone **6**. Formation of the hemiacetal **7** and subsequent dehydration leads to **3** , which is the tautomer of the 2-methyltetrahydrofuran-3-one (Scheme 2).



Scheme 2

In conclusion, Oxone^{R} has proven to be an efficient reagent, useful for the oxidative hydroxylation of the 2-acetylbutyrolactone (**4**) to the valuable 2-methyltetrahydrofuran-3-one (**3**). This process is readily applicable to large scale preparation, in view of the easy availability and low cost of the reagents and its operational simplicity, affording a sufficiently pure compound without any chromatographic separation.

Experimental : All solvents and reagents are commercially available and used as received. Potassium persulfate, sodium perborate, Oxone^R and the 2-acetylbutyrolactone are purchased from Sigma-Aldrich Chemie Gmbh (Germany). IR spectra were run on a Perkin Elmer 7200 FT-IR spectrophotometer in 5% CCl_4 solutions.^{13}C and ^1H NMR spectra were determined on a Varian Mercury 200 MHz spectrometer, using $CDCl_3$ as solvent and TMS as internal standard. Mass spectra were measured on a GC-MS Hewlett-Packard 5890-5970 system.

2-Methyltetrahydrofuran-3-one (3): To a solution of NaOH (80 g, 2,0 mol) and sodium tetraborate decahydrate (Borax) (85 g, 0,22 mol) in 800 ml of water at 20°C, the 2-acetylbutyrolactone **(5)** (128g, 1,0 mol) was added at once. Under vigorous stirring Oxone^R (387g, 1 equivalent of [O]) was added by portions of 20 g, in 2 hours, keeping the temperature below 25 °C. During the addition of Oxone^R the pH was constantly keeped above 8,5 by the addition of 20% aqueous solution of KOH. Stirring was continued for one more hour and then a 50% solution of H_2SO_4 was added slowly until pH 2,0. The crystalline solids were filtered and the clear solution was steam distilled, until 1,5 lit of yellow distillates are collected. The distillate was extracted by CH_2Cl_2 (3 X 250 ml). The organic phase was washed by a saturated solution of $NaHCO_3$, dried (Na_2SO_4) and concentrated under water pump vacuum. The resulting crude product was purified by distillation at normal pressure to afford pure **3**: (55,2 g , 55,2% yield, purity by GC 99,3 %), bp 138-140 °C at 760 mmHg (lit. [7], 137 °C at 740 mmHg); v_{max}/CCl_4 1765 cm^{-1} ; δ_H 1,21 (1H, d, J 7Hz), 2,40-2,47 (2H, m), 3,62-3,76 (1H, m), 3,91-4,05 (1H, m), 4,18-4,29 (1H, m); δ_C 15,36 (CH3), 36,34 (CH2), 63,97 (CH2), 75,96 (CH); m/z(%), 100 (M^+, 32), 72(55), 55(2), 45(42), 44(47), 43(100).

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