2,3-Dihydro-1,4-dioxin in Organic Chemistry. Part X.[1] A new Synthesis of 3-Hydroxy-3-cyclobutene-1,2-dione (Semisquaric acid)

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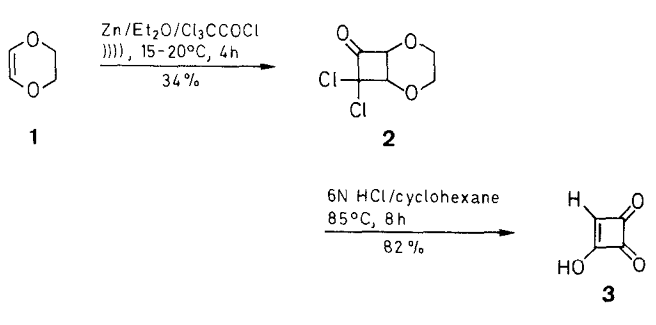
Cycloaddition of 2,3-dihydro-1,4-dioxin (**1**) to 1,1-dichloroketene, generated from zinc and trichloroacetyl chloride by sonication, leads to 7,7-dichloro-2,5-dioxabicyclo[4.2.0]octan-8-one (**2**) which upon acid hydrolysis affords semisquaric acid (3-hydroxy-3-cyclobutene-1,2-dione, **3**).

Semisquaric acid (3-hydroxy-3-cyclobutene-1,2-dione, **3**) is isolated as its potassium salt, which is trivially called moniliformin, from the maize mold *Fusarium moniliforme*. This compound and related derivatives show growth-regulating effects on plants and are toxic to mammals by selective inhibition of mitochondrial pyruvate and α-ketoglutarate oxidation.[2] Several synthetic routes to semisquaric acid have been described; they are mainly based on the formation of a hydrolyzable four-membered ring precursor via a [2 + 2] cycloaddition.[3] More recently, a synthesis of **3** starting from squaric acid has been reported.[4]

As part of our general interest in synthetic applications of 2,3-dihydro-1,4-dioxin (1,4-dioxene, **1**), we have examined the use of this electron-rich olefin in the formation of C–C bonds with simultaneous introduction of useful functional groups.[5] This communication describes a new method for the preparation of semisquaric acid based on a [2 + 2] cycloaddition of 2,3-dihydro-1,4-dioxin to dichloroketene.

In contrast to 3,4-dihydro-2*H*-pyran,[6] the reaction of 2,3-dihydro-1,4-dioxin with dichloroketene, generated by dehydrohalogenation of dichloroacetyl chloride with triethylamine, fails to give the expected cyclobutanone derivative **2**, instead an intractable mixture is formed. This result could be explained in terms of the low reactivity of **1** toward ketenes. Kinetic studies on the cycloaddition of enol ethers with diphenylketene had shown that 2,3-dihydro-1,4-dioxin is 2.2 times less reactive than 3,4-dihydro-2*H*-pyran.[7]

It was recently reported that cycloadditions of olefins with dichloroketene are accelerated by sonication.[8] We have successfully applied this procedure to the preparation of 7,7-dichloro-2,5-dioxabicyclo[4.2.0]octan-8-one (**2**). When a solution of trichloroacetyl chloride in dry diethyl ether is added slowly to a sonicated mixture of 2,3-dihydro-1,4-dioxin (**1**) and zinc powder in dry diethyl ether, the cycloadduct **2** is obtained in 34% yield. Acid hydrolysis of this compound is achieved by stirring **2** in cyclohexane in the presence of 6 N hydrochloric acid in a two-phase system at 85 °C for 8 h, and gives 3-hydroxy-3-cyclobutene-1,2-dione (**3**) in 82% yield after purification.



Although the yield of the first step is only modest, the present method offers the merits of being short, and using 2,3-dihydro-1,4-dioxin as an easily available non-toxic starting material.

2,3-Dihydro-1,4-dioxin was prepared according to the literature procedure.[10] Trichloroacetyl chloride was freshly distilled, and diethyl ether was dried over sodium under reflux. Ultrasonic waves were generated using a direct immersion horn (20W/cm3, Bioblock Vibracell 300 W). Unless otherwise stated, melting points were determined on a Reichert apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer spectrophotometer 399. NMR spectra were recorded on a Bruker W.P.200 spectrometer.

7,7-Dichloro-2,5-dioxabicyclo[4.2.0]octan-8-one (2):
To a dry, N_2-filled 250 mL four-necked round-bottom flask, fitted with a nitrogen inlet, pressure-equalising addition funnel and a thermometer, are added 2,3-dihydro-1,4-dioxin (4 mL, 47 mmol), dry Et_2O (75 mL) and Zn powder (2.5 g, 18 mmol). After prior sonication for 15 min, a solution of trichloroacetyl chloride (2 mL, 18 mmol) in dry Et_2O (30 mL) is added over a period of 4 h while maintaining sonication. The internal temperature is kept between 15–20 °C by application of an external ice bath. The mixture is filtered through Celite and the filtrate is washed with H_2O (30 mL), sat $NaHCO_3$ solution (3 x 30 mL) and brine (30 mL). After drying the solution ($MgSO_4$), the solvent and excess dioxene are removed to afford the cycloadduct **2**; yield: 1.2 g (34%); mp 86–87 °C (petroleum ether).

$C_6H_6Cl_2O_3$	calc.	C 36.57	H 3.07	O 24.36
(197.0)	found	36.50	3.18	24.52

IR (CCl_4): $\nu = 1920, 1280, 1190, 1160, 910\ cm^{-1}$.

^{1}H-NMR ($CDCl_3$/TMS): $\delta = 3.64$–3.76 (m, 4H), 4.34 (d, 1H, $J = 5$ Hz), 5.30 (d, 1H, $J = 5$ Hz).

^{13}C-NMR ($CDCl_3$/TMS): $\delta = 62.9$, 63.6 (C-2, C-3), 71.0 (C-5), 80.8 (C-8), 81.5 (C-7), 192.7 (C-6).

3-Hydroxy-3-cyclobutene-1,2-dione (Semisquaric Acid) (3):
A mixture of the adduct **2** (650 mg, 3.3 mmol), hexane (4 mL) and 6 N aq HCl (4 mL) is heated at 85 °C under vigorous stirring for 8 h. Continuous extraction of the product with Et_2O (30 mL) overnight followed by evaporation of the solvent leads to a solid residue which is washed with $CHCl_3$ (5 mL) to afford **3**; yield: 265 mg (82%); mp 142–146 °C (dec), [Lit.[4] mp 139–146 °C (dec)].

^{1}H-NMR (acetone-d_6): $\delta = 8.67$ (s, m), 11.59 (6s s, 1H, OH).

^{13}C-NMR (acetone-d_6): $\delta = 166.7$ (C-4), 199.0 (C-1, C-3), 202.9 (C-2).

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