

## Hydrogen Peroxide Oxygenation of Furan-2-carbaldehyde via an Easy, Green Method

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**ABSTRACT:** Derivatives of 2(*SH*)-furanone ( $\gamma$ -crotonolactone) are important intermediate synthetic products with a wide range of biological effects that have become widely used in the pharmaceutical industry, medicine, and veterinary medicine, in particular in the prevention and treatment of fish diseases. However, the environmental issue of obtaining these compounds while reducing the negative impact on the surrounding environment remains relevant. This article describes for the first time a method of  $\gamma$ -crotonolactone synthesis that is based on the concept of green chemistry. Synthesis is carried out under mild conditions using nontoxic reagents by furfural oxidation. For the first time, a mixture of hydrogen peroxide and acetic acid was used for the oxidation of furfural in a ratio of 1:0.05. A mixture of organic acids (succinic, maleic, fumaric, formic, and cinnamic acids), obtained as a byproduct in the synthesis of  $\gamma$ -crotonolactone, can be used as a highly effective, ecofriendly organic fertilizer or in a preparation with a stimulating effect.

**KEYWORDS:** furan-2-carbaldehyde, 2(*SH*)-furanone ( $\gamma$ -crotonolactone), green chemistry, hydrogen peroxide, acetic acid

### INTRODUCTION

The use of compounds of the furan series, namely, derivatives of 2(*SH*)-furanone ( $\gamma$ -crotonolactone or 2-butenolide), in synthetic organic chemistry and in the national economy have been known for a long time.<sup>1,2</sup> Compounds of this class are found in beer, kvass, fermented foods, and especially in contaminated feeds exposed to mold.<sup>3,4</sup> They attract considerable attention as growth regulators of plants,<sup>5</sup> substances that inhibit tumor growth in organisms, as they are inhibitors of cell metamorphosis,<sup>6</sup> and promoters of the growth of industrial fish cultures.<sup>7</sup> 2(*SH*)-Furanones are known as compounds with antifungal and antibacterial activities.<sup>8–10</sup>

Under the influence of  $\gamma$ -crotonolactone, the contents of thiol groups in the intestinal mucosa increase because of increased biosynthetic processes in the gut associated with increased secretion of specific enzymes. The experiments for the determination of the total proteolytic activity of fish intestine exposed to  $\gamma$ -crotonolactone demonstrate this very clearly. The total proteolytic activity, characterizing the number of enzymes in the intestinal mucosa, increases significantly (by 24%) in the second day and continues to remain at a high level for 3 days. On the 30th day, it grows up to 30%. It is noted that the proteolytic activity of the intestine continues to remain high even after the end of  $\gamma$ -crotonolactone addition to the feed. 2(*SH*)-Furanone does not have a negative effect on the fish body; on the contrary, this drug helps to suppress the growth of pathogenic microflora in the intestine.<sup>11,12</sup>

At the same time, formic, fumaric, maleic, succinic, and cinnamic acids as a product of the furfural oxidation are used in almost all fields of the industrial and food chemistry. Formic

acid and its salts are used in the feed industry, textile dyeing and finishing, food additives, grass silage, natural rubber, leather tanning, etc.<sup>13</sup> Fumaric acid is nontoxic and versatility reagent, that used in the resin industry, green chemistry as an eco-friendly catalyst, and in the food industry as a nutritional additive and acidulant.<sup>14</sup> Maleic acid is not so widespread like fumaric acid. Maleic acid is used for the production of maleinate resins, copolymers, and generally as a chemical precursor of fumaric acid and maleic anhydride.<sup>15</sup> Moreover, cinnamic acid and its derivatives are known as natural occurring products.<sup>16</sup> They were found in all green plants.<sup>17</sup> Cinnamic acids are also used in medicinal chemistry as a perspective objects with a different useful spectrum of activities.<sup>18</sup>

Another promising direction for the use of 2(*SH*)-furanone is fish breeding, which is particularly widespread in Central and Eastern Europe as well as in Asia. Drugs based on 2(*SH*)-furanone inhibit the development of cyanobacteria, which prevents fish death in ponds. In particular, there is a positive result from the use of drugs based on  $\gamma$ -crotonolactone and from the use of a mixture of the above-mentioned organic acids in the cultivation of fish in natural reservoirs and in recirculating aquaculture systems, which stimulate the development of a natural fodder base in fish-breeding ponds.<sup>19</sup> This allows the use of such drugs in the intensive cultivation of live feeds, in particular those of freshwater planktonic crustaceans such as daphniids. These organisms are widely used both in

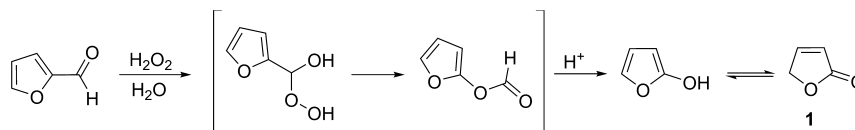
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## Scheme 1. Oxidation Mechanism of Furan-2-carbaldehyde



ornamental aquaculture and in the larviculture of many commercial fish species.<sup>20</sup>

Therefore, the aim of this study was to improve the synthesis of 2(*SH*)-furanone using nontoxic and environmentally friendly hydrogen peroxide oxygenation in the presence of a catalytic amount of acetic acid in water.

## MATERIALS AND METHODS

**Chemicals.** All analytical-grade chemicals were obtained from Sigma-Aldrich and were used without any further purification. Double-distilled water was used in this study.

**General Experimental Details.** All melting points were determined in open capillary tubes on a Boetius apparatus and are uncorrected. The <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra were recorded on a Bruker Avance DRX-500 spectrometer (500 MHz) in DMSO-*d*<sub>6</sub>; the chemical shifts were measured relative to tetramethylsilane. Mass spectra were recorded on an Agilent 1100 Series G1956B LC/MSD SL LCMS system using electrospray ionization at atmospheric pressure (70 eV). UV spectra were recorded on a SPECORD M 40 spectrophotometer. IR spectra were recorded on a SPECORD M 80 spectrophotometer in tablets with KBr. Elemental analysis was carried out on a PerkinElmer 2400 CHN analyzer. Separate determination was carried out using an HPP4001 liquid chromatograph with two serially coupled glass columns (150 × 3.3 mm) packed with the Separon SC-X C-18 adsorbent (0.6% acetic acid as the mobile phase, flow rate of 0.3 cm<sup>3</sup>/min). Monitoring of the reactions was performed by TLC on Silufol UV 254 plates.

**Oxidation of Furfural.** The oxidation reaction with hydrogen peroxide was carried out in a three-necked round-bottom glass flask equipped with a reflux condenser and a mechanical stirrer. The flask was loaded under stirring with the furfural (13.0 mL, 0.160 mol) and water (50 mL), and a mixture of 37.5% H<sub>2</sub>O<sub>2</sub> (14.7 mL, 0.192 mol) with acetic acid (0.55 mL, 0.0096 mol) was slowly added. The reaction mixture was kept under constant stirring for 24 h at a temperature below 60 °C.

After completion of the reaction, water was removed under reduced pressure. The light-yellow precipitate of organic acids was filtered off. 2(*SH*)-Furanone was obtained from the filtrate by vacuum distillation at 12 mmHg. The yield of 2(*SH*)-furanone was 71%.

**2(*SH*)-Furanone (1).** Colorless to slightly light-yellow liquid, bp 85–88 °C at 12 mmHg. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 4.88 (dd, <sup>4</sup>J = 2.2 Hz, <sup>3</sup>J = 1.7 Hz, 2H, 5-H), 6.10 (dt, <sup>4</sup>J = 2.2 Hz, <sup>3</sup>J = 5.8 Hz, 1H, 3-H), 7.58 (dt, <sup>4</sup>J = 1.7 Hz, <sup>3</sup>J = 5.8 Hz, 1H, 4-H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 71.9, 121.1, 152.2, 173.7. IR (KBr, cm<sup>-1</sup>): 1739, 1781 (C=O), 1053–1205 (–C–O–C–). Anal. calcd for C<sub>4</sub>H<sub>4</sub>O<sub>2</sub>: C, 57.14; H, 4.80. Found: C, 57.10; H, 4.71. MS (EI) *m/z* 85.11 [M + H]<sup>+</sup>.

The calculated and found data for succinic, maleic, fumaric, formic, and cinnamic acids were confirmed by the literary data.

## RESULTS AND DISCUSSION

Catalytic oxidation of furan-2-carbaldehyde (furfural) attracts the attention of many researchers. This aldehyde is derived from vegetable wastes<sup>21–23</sup> and is available on the market as a chemical reagent. The furfural molecule contains several reaction centers, which implies a wide variety of syntheses. Projects on the oxidation of furfural by molecular oxygen after photoinitiation<sup>24</sup> and in conditions of heterogeneous catalysis, including through the use of compounds of transitional and noble metals (Cu(OAc)<sub>2</sub>, Mn(OAc)<sub>2</sub>, Pd(OAc)<sub>2</sub>, AgOAc,

FeSO<sub>4</sub>, RuCl<sub>3</sub>, NiCl<sub>2</sub>, V<sub>2</sub>O<sub>5</sub>, Co(NO<sub>3</sub>)<sub>2</sub>, TiO<sub>2</sub>–ZrO<sub>2</sub>, and Pb(OAc)<sub>2</sub>) are well-known.<sup>25–34</sup> The oxidation of furfural with hydrogen peroxide in the presence of a photogenic iron catalyst in the form of a complex [FeCp(C<sub>6</sub>H<sub>5</sub>R)]PF<sub>6</sub> (R = H, Cl, or CH<sub>3</sub>) was also reported.<sup>35</sup> However, insufficient attention was paid to the homogeneous reactions of furfural with aqueous hydrogen peroxide in the works mentioned above.

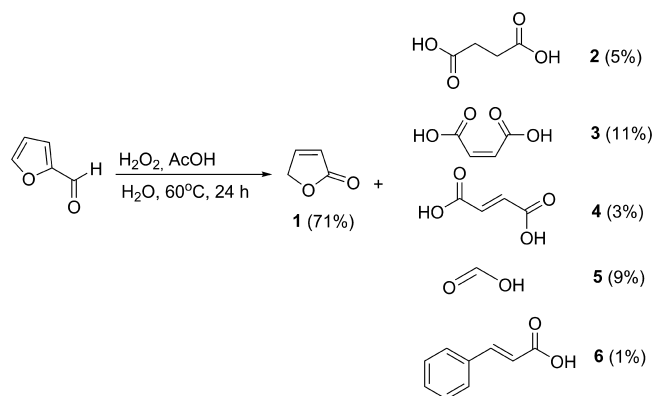
At the same time, it is known that in the process of furfural oxidation with hydrogen peroxide (Scheme 1), depending on the reaction conditions and the catalyst type, various reactive compounds are formed,<sup>36,37</sup> which provide the means for the implementation of various synthetic pathways on the basis of the reactions of furfural with aqueous H<sub>2</sub>O<sub>2</sub> and catalysts.

All of the methods given above are multistage and include the use of hard-to-reach and in some cases toxic materials, such as organic solvents (dichloroethane and chloroform) and complex salts of heavy and transition metals, such as Cu<sup>2+</sup>, Mn<sup>2+</sup>, Pd<sup>2+</sup>, Ag<sup>+</sup>, Ru<sup>3+</sup>, Ni<sup>2+</sup>, V<sup>5+</sup>, and Co<sup>2+</sup>, in the role of catalyst. These catalysts are expensive and have a negative impact on the environment.

Therefore, in this work, a method of  $\gamma$ -crotonolactone synthesis was designed on the basis of the concept of green chemistry; namely, the oxidation of furfural was carried out in an aqueous solution without the use of organic solvents, and for the first time, an aqueous solution of hydrogen peroxide was used in the role of an oxidizer with a small amount of acetic acid as a promoter of the reaction. Oxidation was carried out for 24 h with vigorous stirring and at a temperature below 60 °C. The process was controlled by UV spectroscopy (residual aldehyde) and TLC (acid formation). The compositions of the reaction products were determined by high-performance liquid chromatography (HPLC) using authentic samples. As a result, the target product,  $\gamma$ -crotonolactone (1), was obtained with a yield of ~71% and a light-yellow crystalline precipitate (Scheme 2).

Using HPLC, it was determined that the crystalline precipitate contained mainly a mixture of organic acids,

## Scheme 2. Oxidation of Furan-2-carbaldehyde with H<sub>2</sub>O<sub>2</sub> and Acetic Acid in Water



namely, succinic (2), maleic (3), fumaric (4), formic (5), and cinnamic acids (6). This mixture of organic acids can be used in agriculture as nontoxic, ecologically pure organic fertilizer.

Thus, using the concept of green chemistry,  $\gamma$ -crotonolactone, an important intermediate synthetic product with a wide range of biological effects, was synthesized by the oxidation of furfural under soft conditions and using nontoxic reagents. For the oxidation of furfural, a mixture of hydrogen peroxide and acetic acid was used in a ratio of 1:0.05 for the first time. The byproduct was a mixture of organic acids that can be used in the national economy as a highly effective, environmentally friendly organic fertilizer.

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### Notes

The authors declare no competing financial interest.

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