An Improved Synthesis of 3-Furoic Acid

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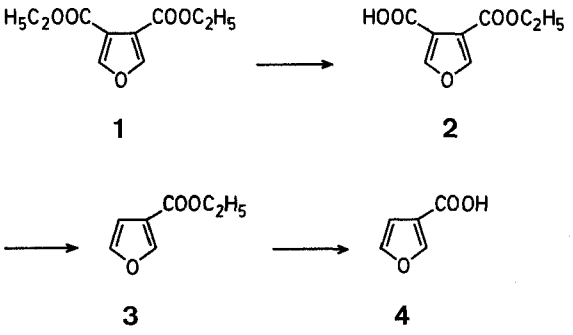
Although common in nature[1], 3-substituted furans are relatively inaccessible by synthesis. We recently sought a simple and inexpensive preparation of 3-furoic acid which was required for synthesis of certain toxic furanoterpenoids occurring in the sweet potato *(Ipomoea batatas)*[2,3,4]. 3-Furoic acid has historically been prepared by partial decarboxylation of polycarboxyfurans[5,6,7]. Galuszko and Wrobel reported an improved procedure[8] involving partial hydrolysis of diethyl furan-3,4-dicarboxylate (**1**) and decarboxylation of the resulting ester-acid (**2**) in quinaldine to give ethyl 3-furoate (**3**). Saponification gave **4** in an overall yield of 39%.



Diester **1** is commercially available making this an attractive process for preparation of **3** and **4**. We now report modifications of this procedure by which substantially higher yields have been obtained.

The partial hydrolysis of **1** to give **2** had been carried out by Galuszko and Wrobel under acidic conditions with a heterogeneous system. In our experience, control of hydrolysis was difficult and yields of **2** were often less than optimum. Alkaline hydrolysis employing an equivalent amount of sodium hydroxide gave more reproducible results and minimized formation of the corresponding diacid. A yield in excess of 80% was readily attained.

The use of quinaldine[8] in the decarboxylation of **2** appeared to offer no advantage; in fact, we experienced difficulty in freeing ester **3** from traces of quinaldine. A better yield of **3** was obtained when the reaction was carried out in the absence of solvent. Ester **3** was distilled from the molten reaction mixture as it was formed. Decarboxylation was effected in 96% yield. The final hydrolysis to form acid **4** was nearly quantitative giving an overall yield for conversion of **1** into **4** of 75%.

Melting points and boiling points are uncorrected. N.M.R. spectra were obtained using a Varian A-60 spectrometer with TMS as an internal standard. I.R. spectra were recorded using a Perkin Elmer model 337 spectrophotometer. U.V. spectra were obtained with a Bausch and Lomb model 505 spectrophotometer. Diethyl furan-3,4-dicarboxylate was obtained from Aldrich Chemical Company, Milwaukee, Wisconsin.

Furan-3,4-dicarboxylic Acid Monoethyl Ester (2):
A solution of diethyl furan-3,4-dicarboxylate (**1**; 81.0 g, 0.38 mol) in ethanol (1 l) in a 2000-ml flask was cooled to 0° in an ice/salt bath. A solution of sodium hydroxide (15.3 g, 0.38 mol) in water (60 ml) and ethanol (200 ml) was added rapidly with vigorous stirring. The mixture was allowed to stand at 0° for 5 hr. The flask containing the congealed mixture was fitted to a rotary evaporator and the ethanol removed. The solid residue was dissolved in water (500 ml) and the solution washed with ether (3 × 150 ml). The ether washings were combined, dried ($MgSO_4$), and concentrated to recover 8.8 g of unreacted **1**. The aqueous phase was acidified with 10 *N* hydrochloric acid (60 ml) and extracted with chloroform (3 × 350 ml). The extracts were combined and dried ($MgSO_4$), and the solvent removed to yield 60 g of a colorless solid product. N.M.R. analysis of crude **2** (methanol solution) showed that the product contained ~94% **2** and 6% of furan-3,4-dicarboxylic acid. However, the latter was of no consequence since in the succeeding step of the synthesis the diacid was effectively removed from the product. Thus, the yield of **2** was 81%. Recrystallization of a small sample from methanol gave pure **2**, m.p. 139–140° (Ref.[8], m.p. 136–137°).

I.R. (KBr): ν_{max} = 3115, 1720, 1625, 1525, 1430, 1310, 1205, 1065, 886, 760 cm^{-1}.

U.V. (methanol): λ_{max} = 206, (ε = 4460), 244 nm (3820).

N.M.R. (pyridine-d_5): δ = 0.49 (t, 3H), 3.58 (q, 2H), 7.62 (m, 2H), 15.00 (s, 1H).

Ethyl Furan-3-carboxylate (3):
A mixture of unrecrystallized **2** (94% purity, 60 g, 0.31 mol) and copper powder (60 g) was ground thoroughly in a mortar and placed in a 250-ml flask fitted with a distilling head and a condenser. The flask was heated with a burner at a rate such that **3** distilled as it was formed but without sublimation of the starting acid into the condenser. Heating was continued until a solid, non-volatile residue remained. The distillate was diluted with ether (100 ml), washed with sodium hydrogen carbonate solution, and dried ($MgSO_4$). The solvent was evaporated and the residue distilled to give colorless **3**; yield: 41.5 g (96%); b.p. 174–175°/760 mm; n_D^{25}: 1.4611 (Ref.[8], b.p. 170–176°; n_D^{25}: 1.4601). G.L.C. analysis (8′ × 3/8″ 15% UC-W98 on 80/100 Chrom Q; Varian model 1520-B) at 150° showed only a single peak.

I.R. (film): ν_{max} = 3135, 2970, 1720, 1580, 1500, 1310, 1165, 1080, 880, 765 cm^{-1}.

U.V. (methanol): λ_{max} = 209 (ε = 5580), 238 nm (3980).

N.M.R. (CCl_4): δ = 1.34 (t, 3H), 4.25 (q, 2H), 6.68 (m, 1H), 7.35 (m, 1H), 7.94 (m, 1H).

3-Furoic Acid (4):
A mixture of **3** (9.0 g, 0.064 mol), ethanol (15 ml), and 25% aqueous sodium hydroxide (25 ml) was refluxed for 1.5 hr. Water (20 ml) was added and the mixture agitated until all solid was dissolved. The solution was washed with ether (3 × 50 ml) and acidified with conc. hydrochloric acid (10 ml). The mixture was extracted with ether (5 × 50 ml). The extracts were dried ($MgSO_4$) and evaporated to give 6.9 g (96%) of **4**; m.p. 118–120°. One recrystallization from water gave product with m.p. 122–123° (Ref.[8], m.p. 118–120°).

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I.R. (KBr): $\nu_{max} = 1660$, 1560, 1500, 1430, 1305, 1185, 1000, 745 cm^{-1}.

U.V. (methanol): $\lambda_{max} = 210$ ($\varepsilon = 3960$), 237 nm (2750).

N.M.R. ($CDCl_3$): $\delta = 6.77$ (m, 1H), 7.42 (m, 1H), 8.10 (m, 1H), 10.18 (s, 1H).

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