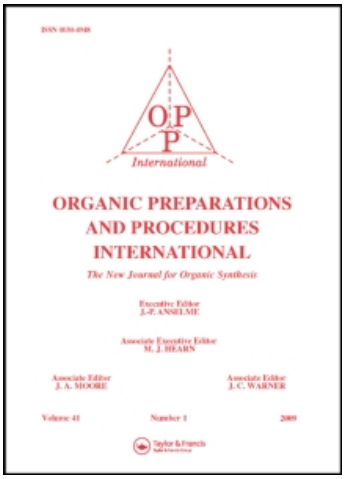

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AN IMPROVED SYNTHESIS OF ETHYL 4-HYDROXY-3-METHYLBENZOFURAN-2-CARBOXYLATE

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AN IMPROVED SYNTHESIS OF ETHYL 4-HYDROXY-3-METHYLBENZOFURAN-2-CARBOXYLATE

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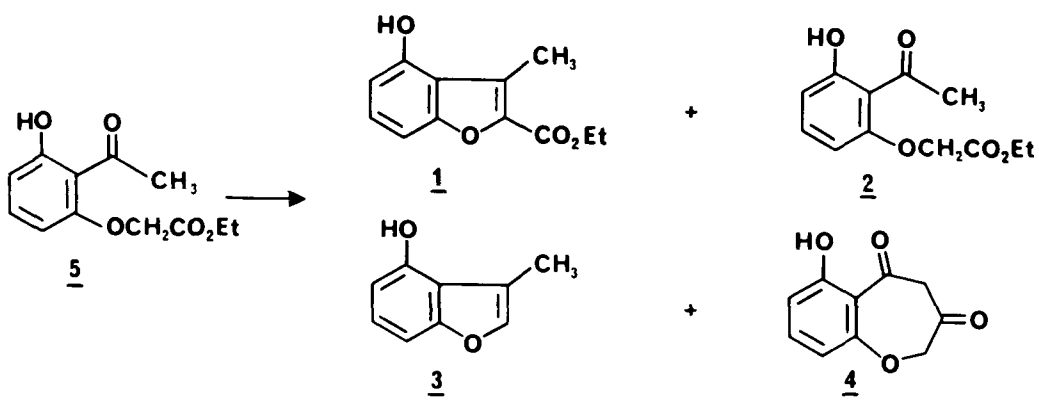
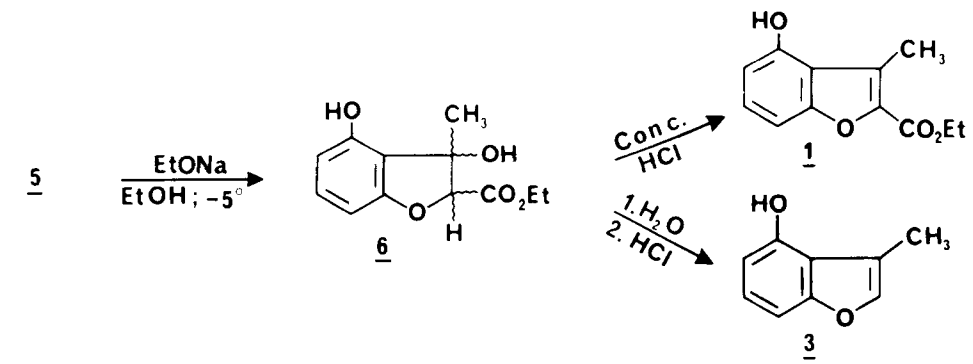
The known ethyl 4-hydroxy-3-methylbenzofuran-2-carboxylate (1) was originally prepared by cyclization of ethyl 2-acetyl-3-hydroxyphenoxyacetate (5) using sodium ethoxide in ethanol.[1] The 11% overall yield was found to be too low for large scale synthesis. Furthermore, the separation of 1 from 2-acetyl-3-hydroxyphenoxyacetic acid (2) and 4-hydroxy-3-methylbenzofuran (3) formed as by-products would present a serious problem on a large scale synthesis. Wasson et al.[2] succeeded in improving the yield to 31%. However, they obtained an additional by-product identified as 6-hydroxy-1-benzoxepin-3,5(2H,4H)-dione (4) in 4% yield; 4 was formed only when a phenolic hydroxyl group ortho to the acetyl was present. For these reasons, we reinvestigated this cyclization and now report an improved procedure for the preparation of 1.



Examination of this cyclization reaction under various temperature conditions led to the observation that ethyl 3-hydroxy-2-acetylphenoxy-acetate (5) in ethanol containing sodium ethoxide at -5° over a period of 18 hrs gave a more polar derivative. Based on its behavior on thin layer chromatography, this new material is presumed to be a mixture of the E,Z ethyl 3,4-dihydroxy-3-methyl-2,3-dihydrobenzofuran-2-carboxylate (6a and 6b) which was unstable; all attempts to isolate and characterize them were unsuccessful. Suzuki et al.[3] have also investigated this cyclization reaction of 4-substituted-2-acetylphenoxyacetic acids and were unable to isolate such intermediates. The properties of these intermediates (6a and 6b) were examined; this has allowed us to devise excellent syntheses for 1 and 3.



Treatment of the E,Z-mixture (6) with conc. hydrochloric acid causes dehydration to 1 in nearly quantitative yields. Under the basic conditions resulting from the addition of water, they can also be hydrolyzed to a mixture of sodium carboxylates (7a and 7b) which in turn decarboxylatre and dehydrate readily on acidification with dilute hydrochloric acid to give 3.

EXPERIMENTAL SECTION

Melting points were taken on a Thomas Hoover apparatus in open capillary tubes and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 267 grating spectrophotometer and were recorded as KBr disks unless otherwise noted. A Varian EM-390 spectrometer was used to record NMR

spectra in deuterochloroform unless otherwise indicated. Proton chemical shifts are relative to tetramethylsilane (TMS) as internal standard. All reactions were monitored routinely with the aid of thin layer chromatography (TLC) using precoated 0.25 mm silica gel GF plates, Analtech, visualizing them with sulfuric acid.

Ethyl 4-Hydroxy-3-methylbenzofuran-2-carboxylate (1).- To a sodium ethoxide solution, prepared by dissolving sodium (145 g, 6.3 moles) in anhydrous ethanol (10.6 L) under a nitrogen atmosphere and cooled to around -10°, was added with stirring ethyl 2-acetyl-3-hydroxyphenoxyacetate (5) (1 kg, 4.2 moles) over a period of 10 minutes. The solution was stirred for 18 hours while the temperature was maintained between 0 and 7°. The reaction mixture was then poured into a cold mixture of water (10 L), conc. hydrochloric acid (2.5 L) and ice (13 L). After stirring for 10 minutes, a saturated solution of sodium chloride (4 L) was added. The solid was collected, washed with water and air-dried to yield 940 g (98%) of 1. A sample recrystallized from ethanol had mp. 156-157°, lit.[2] mp. 157-159°.

4-Hydroxy-3-methylbenzofuran (3).- A 50 mL aliquot of the above reaction mixture was transferred to a separate flask and the temperature was maintained at about 0°. Water (10 mL) was then added and the hydrolysis was monitored by TLC. The mixture was then acidified with 1N hydrochloric acid (60 mL) and stirred for 15 minutes. The reaction mixture was extracted with ethyl acetate, washed with water, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was chromatographed on silica gel (elution with toluene) to afford 1.61 g (51%) of 3, mp. 110-112°, lit.[2] mp. 110-112°.

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IODIDE SALTS OF NITROGEN HETEROCYCLES BY BROMIDE-IODIDE EXCHANGE

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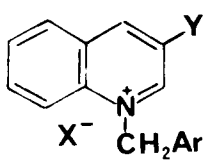
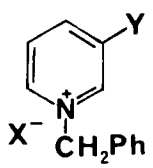
The choice of procedure for the preparation of 1-substituted benzyl-3-cyanoquinolinium iodides (2a-k) seems to be very limited.[1] We now report an ion exchange procedure in a specially chosen solvent mixture which optimizes the yields of iodide salts of nitrogen containing heterocyclic aromatic compounds.



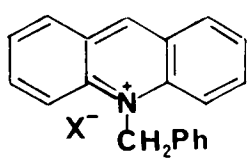
X: 1 = Br, 2 = I

Y: a-h = CN, i-j = $CONH_2$, k = H



X: 3 = Br, 4 = I

Y: a = $CONH_2$, b = H



X: 5 = Br
6 = I

Ar: a = C_6H_5, b = p-$CH_3C_6H_4$
c = p-FC_6H_4, d = m-FC_6H_4
e = p-BrC_6H_4, f = p-$CF_3C_6H_4$
g = m-$CF_3C_6H_4$, h = p-CNC_6H_4
i = C_6H_5, j = p-FC_6H_4, k = C_6H_5