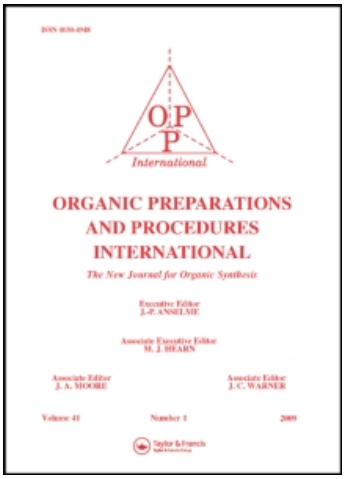

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IMPROVED SYNTHESIS OF A 2-ARYLBENZO[B]FURAN-3-CARBOXYLIC ACID

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EXPERIMENTAL SECTION

All melting points were determined in open capillary tubes and uncorrected. The IR spectra were recorded with a Hitachi 260-50 spectrometer. The ^1H NMR spectra were obtained on a Joel-PMX-60 spectrometer in $CDCl_3$ solution with TMS as the internal standard. Elemental analyses were performed with a Perkin-Elmer 240-C. Mass spectra were obtained from a Varian MAT112S unit using an ionization potential of 70eV and a directed inlet system.

Preparation of Mannich Bases (**1**). General Procedure.- To the aromatic amine (5 mmol) dissolved or suspended in 4-6 mL absolute ethanol, was added with stirring, the cyclic ketone (5 mmol) and the aromatic aldehyde (5 mmol). Conc. hydrochloric acid (0.2 mL) was then added with cooling in an ice-water bath. The mixture was stirred for 5-10 hrs at 0-20° (Table 1) and left standing overnight at 0°. The Mannich base **1** was collected and washed with 95% ethanol and 10% sodium bicarbonate respectively. The pure product was obtained by recrystallization from acetone and 95% ethanol (2:3).

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IMPROVED SYNTHESIS OF A 2-ARYLBENZO[b]FURAN-3-CARBOXYLIC ACID

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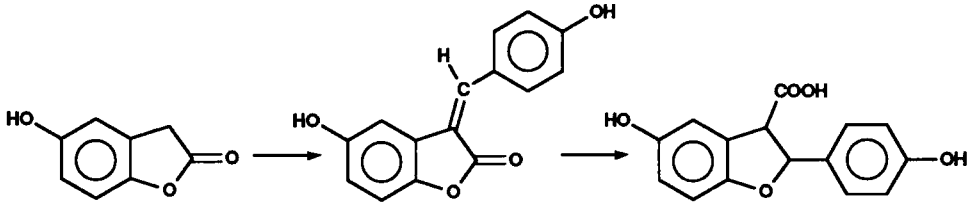
The stereospecific synthesis of (Z)-marginalin **2** through the pH controlled addition of *p*-hydroxybenzaldehyde to 5-hydroxy-2-coumaranone **1** has been reported.[1] This synthesis allowed the

determination of the (E)-configuration for the natural product isolated from the pygidial glands of the water-beetle *Dytiscus marginalis* by Schildknecht *et al.*[2] It was recently found[3] that treatment of (E) or (Z)-marginalin with sodium carbonate resulted in hydrolysis of the lactone ring followed by a slow rearrangement into the corresponding 2-phenylbenzo[b]furan-3-carboxylic acid (**3**).The overall yield of this two-step synthesis starting from 5-hydroxy-2-coumaranone (**1**) was 21%. The present publication reports a simpler method for the direct synthesis of the acid **3** in 60% yield.

In this procedure, 5-hydroxy-2-coumaranone (**1**) and *p*-hydroxybenzaldehyde were suspended in water followed by the addition of sodium hydroxide to pH 8; the reaction mixture was maintained for 24 hrs at 100° in a pressure-tight tube (the same result could be achieved by prolonged reflux under a stream of nitrogen). The phenolic character of both reagents resulted in the formation of a solution by heating. This was found to be the *sine qua non* condition for success of the reaction; for example, an attempted reaction with benzaldehyde proved unsuccessful (the addition of alcohols in order to facilitate the dissolution was avoided because this leads to alkoxylated secondary products[3]).

The resulting 5-hydroxy-2-(4'-hydroxyphenyl)-3-benzol[b]furan-3-carboxylic acid **3** was isolated by column chromatography on silica-gel and identified by its physico-chemical data (mp., e.i., MS, ^{1}H NMR, elemental analysis, properties of its methyl ester). The product **3** is highly fluorescent in the UV and is readily detected at the microgram level. This one-step method thus affords a very simple access to a substance which may be of biological interest (as a probable metabolite of marginalin) This reaction combines the Perkin condensation and rearrangement.[4,5]



1 **2** **3**

EXPERIMENTAL SECTION

Melting points were determined on a Kofler apparatus using a microscope and are corrected. The UV spectra were obtained from a Perkin Elmer Lambda-5 automatic spectrophotometer. The MS_1(electron impact) were determined on an AEI MS 50 apparatus and the ^{1}H NMR spectra on a Bruker 250 MHz spectrometer, ppm from zero TMS. The pressure-tight tube was a Sovirel pyrex screw-capped vessel 105x20 mm. Schleicher-Schüll SiO_2 fluorescent F254 plates 1 mm thickness were used for preparative TLC and the corresponding films for analytical control.

5-hydroxy-2-(4'-hydroxyphenyl)3-benzo[b]furancarboxylic Acid.(3).- In the optimum experiment, 5-hydroxy-2-coumaranone **1** (150 mg, 1 mM, Aldrich-Chemie) and *p*-hydroxybenzaldehyde (360 mg,

3 mM) were mixed in a 40 ml pressure-tight tube. Water was added (25 ml) and the pH of the suspension brought to 8 by the dropwise addition of a 2N NaOH solution. The mixture was progressively heated on the water bath with frequent shaking in order to achieve complete dissolution. The pressure-tight tube was then placed in an oven at 100° for 24 hrs and then brought back to room temp. The solution which was yellow due to the formation of marginalin at beginning, turned to brown and a precipitate appeared. A solution of 2N HCl was added (to pH 1) and the mixture was evaporated to dryness *in vacuo*, the residue being then extracted with methanol (10 ml x 2). This solution was adsorbed on 10 g SiO_2 and introduced on the top of a SiO_2 column chromatography prepared from 200 g (in ethyl acetate). This quantity had to be used because of tailing of the substance **3** on the chromatograph as observed by UV. Elution was carried out with ethyl acetate and monitored by TLC (fractions of 80 ml, SiO_2 films, ethyl acetate, UV observation at 366 nm with a Desaga lamp). The concentrated solutions containing **3** were collected and evaporated, giving 150.5 mg (60% from **1**). This substance is an off-white solid which does not redissolve easily in non-hydroxylated solvents but is pure enough for further purposes according to Rf, MS and mp. An analytical sample was crystallized from ethyl acetate, mp. 253-256° (dec.), new prisms formed from 230°.

UV (MeOH, nm, ε): λ 317 (1.8 x 10^4), 209 (3.8 x 10^4); MS, m/z, (%); 270, M^+, (20), 226, M-44, (100); ^1H NMR (DMSO-d_6): δ 6.77 and 6.22 (2d, 2 H each, J = 8 Hz, A_2B_2 system); 5.40, 5.65, 5.20 (dd, d, d, 1H each J (*ortho*) = 8 Hz, J (*meta*) = 3 Hz, ABX system).

Anal. Calcd. for $C_{15}H_{10}O_5$: C, 66.67; H, 3.72. Found: C, 66.78; H, 3.69

As mentioned earlier,[3] the methyl ester of **3** could not be obtained by reaction with diazomethane (this led to a mixture). It was prepared by refluxing (20 mg) of **3** in methanol (20 ml) containing sulfuric acid (0.2 ml of a 1 N solution). Although the esterification was incomplete after 6 hrs, the ester could be isolated in 47% yield by preparative TLC (SiO_2, ethyl acetate, UV observation) ; Rf 0.50, amorphous, MS, m/z, (%):284, M^+, (100), 253, M-31$^+$, (80), 226, M-58$^+$, (90).

Anal. Calcd.for $C_{16}H_{12}O_5$: C, 67.60; H, 4.26. Found; C, 67.57; H, 4.28.

These results are in agreement with the previously reported results[3] corresponding to the two-step synthesis of substance **3**.

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SYNTHESIS OF NOVEL TRIAZOLO[2,3-b]-1,3,4-THIADIAZOLIUM SALTS

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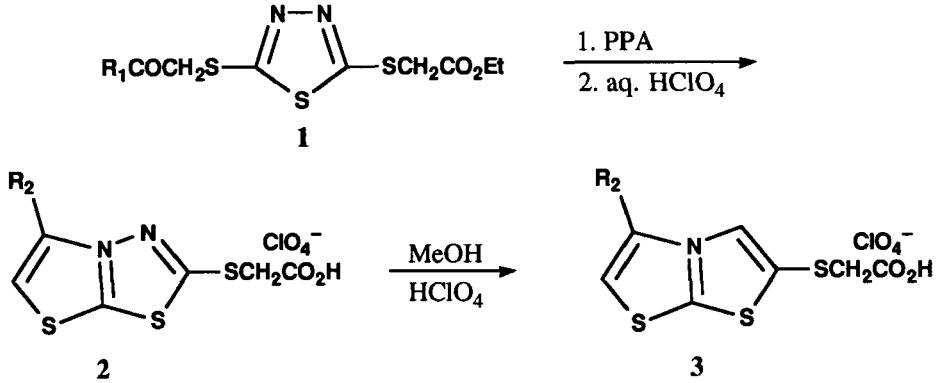
Thiazolo[2,3-b]-1,3,4-thiadiazolium salts have been prepared and studied as important synthetic intermediates of optically active heteroocines[1,2] and potential broad spectrum anthelmintics.[3] Recently, these heterocyclic quaternary salts have attracted much attention because of their importance as useful photographic development accelerators.[4,6] In continuation of our synthetic study on heterocyclic compounds as potential photographic development accelerators,[7] we now report the preparation of novel substituted thiazolo[2,3-b]-1,3,4-thiadiazolium salts **3**.

2-Ethoxycarbonylmethylthio-5-arylcarbonylmethylthio-1,3,4-thiadiazoles (**1**) are easily accessible products[7]and have been used as intermediates in the synthesis of photographic development-accelerator-releasing colorless couplers.[7] 2-Methoxycarbonylmethylthio-5-arylthiazolo[2,3-b]-1,3,4-thiadiazolium perchlorates (**3**) were obtained by the cyclodehydration of **1**



a) $R_1 = R_2 = C_6H_5$, b) $R_1 = R_2 = 4\text{-}BrC_6H_4$, c) $R_1 = R_2 = 4\text{-}ClC_6H_4$, d) $R_1 = R_2 = 4\text{-}MeC_6H_4$, e) R_1 $R_2 = 4\text{-}HOC_6H_4$, f) $R_1 = 4\text{-}MeOC_6H_4$, $R_2 = 4\text{-}HOC_6H_4$ g) $R_1 = 4\text{-}BuOC_6H_4$, $R_2 = 4\text{-}HOC_6H_4$