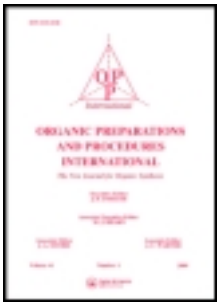

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THE ALKYLATION OF COUMARIN AT C-3 OF 4-HYDROXYCOUMARIN

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THE ALKYLATION OF COUMARIN AT C-3 OF 4-HYDROXYCOUMARIN‡

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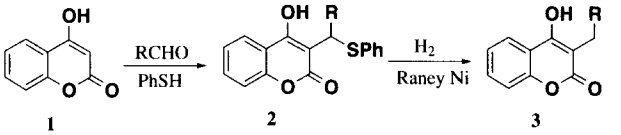
Several important natural compounds have an alkyl chain at C-3 on 4-hydroxycoumarin.[1] Compounds comprising 4-hydroxycoumarin nucleus are reported to have anthelmintic, hypnotic, insecticidal, antifungal activities and anticoagulant effect.[2] In an attempt to synthesize 3-geranyl-coumarin, which is one of the natural coumarins,[3] 4-hydroxycoumarin was treated with geranyl bromide in the presence of K_2CO_3, and the desired product was formed in low yield. Two major byproducts were the O-alkylated and 3-C alkylated compounds.[4] We have shown that the alkylation of the 4-hydroxycoumarin ambident anion in conjuction with a small counter ion led to O-alkylation, while in the presence of a larger counter ion, C-3 alkylated products were obtained as the main product.[5] Alkylation of 4-hydroxycoumarin (**1**) with reagents capable of forming stable carbonium ion intermediates yielded 3-alkylated products as well as O-alkylated products.[6,7]

In order to solve these problems, we have used a strategy similar to that already applied by Moreno-Manas and coworkers for the alkylation of 4-hydroxy-6-methyl-2-pyrone.[8,9] This paper describes the synthesis of aryl and heteroaryl [4-hydroxy-3-coumarinyl]phenylmercaptomethanes (**2**) and 3-alkyl-4-hydroxycoumarins (**3**) according to the following Scheme.

The reaction of **1** under typical Knoevenagel conditions led presumably to the quinone methide intermediate, which was then trapped by thiophenol giving rise the products of the general structure **2** in 51-89% yield as analytically pure compounds. Attempts to reduce **2b** to **3b** with different reducing agents, i.e. $NaBH_4$/MeOH, $NaBH_3CN/CH_3CO_2H$, $Na_2S_2O_4$ in aqueous EtOH as well as deactivated Raney-Ni according to the reported procedure,[9] were all unsuccessful. The hydrogenation of **2a** and **2b** in the presence of deactivated Raney-Ni catalyst afforded **3a** and **3b** in 75 and 85% yields, respectively.



1 2 3

a) R = H; b) R = C_6H_5; c) R = 4-MeO-C_6H_4; d) R = 4-Cl-C_6H_4; e) R = 3-NO_2-C_6H_4; f) R = 5-NO_2-furyl

EXPERIMENTAL SECTION

Mps are uncorrected and were determined on a Kofler-microheating stage. The IR spectra (KBr pellets) were recorded on a Perkin-Elmer M-377 spectrophotometer. ^1H NMR spectra were measured on a Perkin-Elmer R 12A spectrometer or on a Varian Unity 300 MHz instrument. EI mass spectra were recorded on a Hitachi Perkin-Elmer RMV-GL mass spectrometer.

General Procedure for Synthesis of 2.- To a stirred solution of aldehyde (12.5 mmol), thiophenol (37.5 mmol), acetic acid (0.5 mL), and pyridine (0.5 mL), was added dropwise a solution of 4-hydroxycoumarin (12.5 mmol) in ethanol (50 mL). The resulting mixture was refluxed for 48 hrs. Evaporation of ethanol under vacuum gave a solid which was dissolved in chloroform (50 mL). The resulting solution was washed with 0.1M hydrochloric acid and water, dried over sodium sulfate, evaporated and the residual solid was recrystallyzed from the appropriate solvent to afford **2**.

Compound 2a, 74% (from MeOH), mp. 163-165°, IR 1650 (C=O), 1620, 1590 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.99 (s, 1H, OH), 7.20-7.90 (m, 9H, arom.), 4.30 (s,2H, CH_2) ppm.

Anal. Calcd. for $C_{16}H_{12}O_3S$: C, 67.57; H, 4.25, Found: C, 67.85; H, 4.20

Compound 2b, 65% (from MeOH), mp159-161°, IR 1660 (C=O) 1610, 1595 (C=C arom.) cm^{-1}; ^1H NMR ($CDCl_3$): δ 11.2 (s, 1H, OH), 7.1-8.0 (m, 14H, arom.), 6.18 (s, 1H, CH) ppm; EIMS m/z (relative intensity) 360, (6), 251 (22), 250 (50), 249 (80), 221 (20), 110 (100), 84 (57).

Anal. Calcd. for $C_{22}H_{16}O_3S$: C, 73.29; H, 4.47. Found: C, 73.50; H, 4.51.

Compound 2c, 72% (from EtOH), mp. 148-150°, IR 1670 (C=O) 1620,1610 (C=C arom.) cm^{-1}; ^1H NMR ($CDCl_3$): δ 11.65 (s, 1H, OH), 6.9-8.0 (m, 13H, arom.), 6.3 (s, 1H, CH), 4.0 (s, 3H, CH_3) ppm.

Anal. Calcd. for $C_{23}H_{18}O_4S$: C, 70.73; H, 4.65. Found: C,71.05; H, 4.75

Compound 2d, 65% (from MeOH-Et_2O, 1:1), mp. 108-110°, IR 1645 (C=O) 1620, 1610 (C=C arom.) cm^{-1}; ^1H NMR ($CDCl_3$): δ 11.2 (s,1H, OH), 7.20-8.1 (m, 13H, arom.), 6.05 (s, 1H, CH) ppm.

Anal. Calcd. for $C_{22}H_{15}ClO_3S$: C, 66,89; H, 3.83. Found: C, 67.01, H, 3.80

Compound 2e, 89% (from EtOH), mp. 180-182°, IR 1660 (C=O), 1610, 1560 (C=C arom) cm^{-1}; ^1H NMR ($CDCl_3$): δ 11.0 (s, 1H, OH), 7.2-8.1 (m, 13H, arom), 5.8 (s, 1H, CH) ppm.

Anal. Calcd. for $C_{22}H_{15}NO_5S$: C, 65.15; H,3.37. Found: C, 64.95; H, 3.70

Compound 2f, 51% (from EtOH) mp. 250-252°, IR 1720 (C=O), 1605 (C=C arom.), 1480, 1365 (NO_2) cm^{-1}. ^1H NMR ($CDCl_3$): δ 11.5 (s, 1H, OH), 6.5-8.1 (m, 11H, arom.), 5.35 (s, 1H, CH) ppm.

Anal. Calcd. for $C_{20}H_{13}NO_6S$: C, 60.73; H, 3.31. Found: C, 60.51; H, 3.21

General Procedure for Synthesis of 3.- A suspension of Raney-Ni W-2 (15 mL) was boiled in acetone for 45 min.[9] The acetone was decanted and then ethanol (50 mL) was added to the Raney-Ni W-2. Compound **2** (1.5 mmol) was then added and the mixture was hydrogenated at room temperature and atmospheric pressure for 2 hrs. The reaction mixture was filtered through Celite and then filtrate was concentrated *in vacuo*. The solid residue was purified by chromatography on silica gel using a mixture benzene-acetone- acetic acid (8:1:1).

Compound 3a, 75%, mp. 229-231° (Lit. [10] mp. 230-231°), IR 1665 (C=O), 1610 C=C arom.) cm^{-1}; ^1H NMR (DMSO-d_6): δ 11.1 (s, 1H OH), 7.1-8.0 (m, 4H arom.), 2.1 (s, 3H, CH_3) ppm.

Compound 3b, 85%, mp. 202-204° (Lit. [10] mp. 204-206°), IR 1660 (C=O), 1615 (C=C arom.) cm^{-1}; ^1H NMR (DMSO-d_6): δ 11,2 (s, 1H, OH), 7.0-8.0 (m, 9H, arom.), 3.8 (s, 2H, CH_2) ppm; EIMS m/z (relative intensity) 252 (100), 223 (49), 147 (44), 121 (80), 120 (36) 91 (36), 77 (26).

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AN IMPROVED GENERAL METHOD FOR THE PREPARATION OF 4-ARYL SUBSTITUTED *bis*PYRAZOLO[3,4-b;4',3'-e]PYRIDINES

Submitted by (03/19/96)

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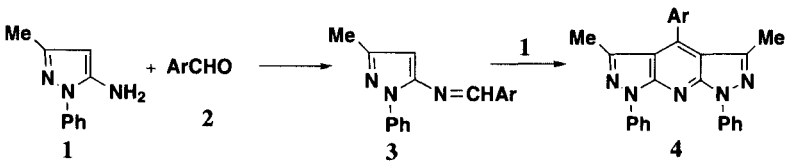
4-Aryl substituted *bis*pyrazolo[3,4-b:4',3'-e]pyridines (BPPs) as large conjugated π-systems are a class of compounds of potential use in photophysical processes such as photo-induced electron transfer reactions.[1] Moreover, a representative number of those derivatives show biological activities.[2] Despite the importance of these compounds, the methodologies available for their preparations are generally limited in scope,[2-7] give poor yields (30-40%) and present problems in purification of the products. The present work describes an improved general procedure for the preparation of a comprehensive series of 4-aryl-3,5-dimethyl-1,7-diphenyl-BPPs.



a) Ar = C_6H_5 **b**) Ar = 4-MeC_6H_4 **c**) Ar = 4-FC_6H_4 **d**) Ar = 4-ClC_6H_4
e) Ar = 4-BrC_6H_4 **f**) Ar = 4-$CF_3C_6H_4$ **g**) Ar = 4-$MeOC_6H_4$ **h**) Ar = 4-$Me_2NC_6H_4$
i) Ar = 4-$NO_2C_6H_4$ **j**) Ar = 4-CNC_6H_4 **k**) Ar = 4-$MeO_2CC_6H_4$ **l**) Ar = 2-BrC_6H_4
m) Ar = 2-furoyl **n**) Ar = 4-pyridyl

In our own experiments, we found ethanol to be a superior solvent to DMF. We also established that the use of a 10% excess of aldehyde led to desired BPPs in much higher yields. An alterna-