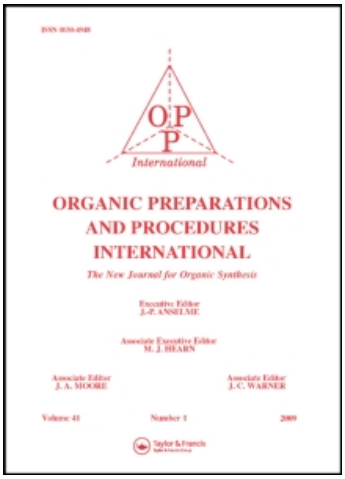

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A SIMPLE PROCEDURE FOR THE ALKYLATION OF 4-HYDROXYCOUMARINS AT C-3 POSITION

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A SIMPLE PROCEDURE FOR THE ALKYLATION OF 4-HYDROXYCOUMARINS AT C-3 POSITION

Submitted by (10/22/98)

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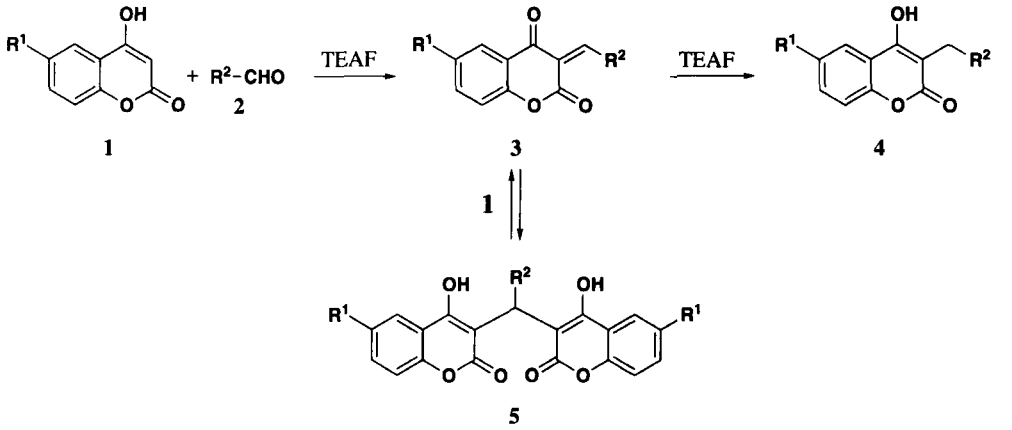
A number of pharmacologically interesting compounds contain the coumarin skeleton[1] and 4-hydroxycoumarins bearing a substituent at C-3 are particularly important compounds. The most significant biological activities are anticoagulation effect[1] and HIV protease inhibition.[2] The alkylation[3] of 4-hydroxycoumarin at C-3 position with alkyl halides is not selective, with O-alkylation being a competing reaction.[4] This explains why efforts have been devoted to produce 3-substituted 4-hydroxycoumarins from 4-hydroxycoumarins (**1**) and aldehydes, a reaction which, however, leads[5] to the Michael adducts **5** as the final products.[6] Treatment of these adducts **5** with 2 molar equivalent sodium cyanoborohydride at reflux in methanol for 42 h gave the desired 3-alkyl-4-hydroxycoumarins **4** and an equivalent amount of the 4-hydroxycoumarin. The method[6] requires two steps however, with long reaction times and the separation of **4** from **1** is tedious in some cases. The yields for 3-methyl- and 3-benzyl-4-hydroxycoumarin were 60 and 79%, respectively. Another recent two-step method[7] involves the reaction of an aldehyde, 4-hydroxycoumarin and thiophenol in the presence of catalytic amounts of pyridine and acetic acid in ethanol at reflux for 48 h. The isolated [4-hydroxy-3-coumarinyl]phenylmercaptomethane intermediates were hydrogenated over Raney-Ni catalyst in ethanol at room temperature for 2 hours. Details for both steps were given only for two compounds. The overall yield of 3-benzyl- and 3-methyl-4-hydroxycoumarin was 55%.

We now report a simple method for the production of 3-alkyl-4-hydroxycoumarins **4** in 60-83% yield. The coumarin **1** and aldehyde **2** were heated in a mixture of triethylamine and formic acid (2:5 molar ratio). The reaction was complete at 140-150° within 2 hours. This route is based on the reported reduction of 2-benzylidene-1,3-diketones (at 140-150°),[8] benzylidenebarbiturates (at 60-125°)[9]



and benzylidene-Meldrum's acids (at room temperature)[10] without any catalyst by using triethylammonium formate (TEAF) reagent with the composition of $(Et_3N)_2{\bullet}(HCO_2H)_5$. The procedures are simple, rapid and safe. The ratio of hydrogen in the evolved gas was no more than 0.1% investigated by mass spectrometer in the synthesis of **4b** (there is no reference to the evolution of hydrogen in the literature[8-10]). The reduction is specific for the double bond coupling to the C-2 position of 1,3-diones. The reaction gave good yields with benzaldehyde **2a** and its derivatives **2b-e** but in the case of isobutyraldehyde **2f** the yield was moderate. The reaction failed with cyclohexanone or propiophenone.

TABLE 1. Preparation of 3-Alkyl-4-hydroxycoumarins

Cmpd	R^1	R^2	Yield (%)	mp. (°C)	Cryst. solvent
4a	H	C_6H_5	77	204-206[a]	EtOH-H_2O
4b	H	3,4-$(OMe)_2C_6H_3$	83	200-202	$CHCl_3$
4c	H	2,4-$Cl_2C_6H_3$	68	261-263	*i*-PrOH
4d	H	3-OH-C_6H_4	72	166-167	MeOH-H_2O
4e	cyclohexyl	C_6H_5	80	208-210	EtOAc
4f	H	*i*-Pr	60	144-145	MeOH-H_2O

a) Lit.[11] mp. 204-206°

EXPERIMENTAL SECTION

Melting points are uncorrected and were determined on a Kofler instrument. ^1H NMR spectra were recorded on a Bruker WP- 200 SY spectrometer. IR spectra were obtained on a Perkin Elmer FT-IR instrument. The evolved gas was analyzed by Quadrupole Mass Spectrometer QGA-2 ATOMKI. Aldehydes, formic acid, triethylamine were purchased from Aldrich and E. Merck and were used without further purification. TEAF (about 100 mL) was prepared as follows: triethylamine (48.6 g, 67.2 mL, 0.48 mol) was added dropwise to formic acid (55.2 g, 45.3 mL, 1.20 mol) with cooling and stirring. 4-Hydroxycoumarin (mp. 210-212°) and 6-cyclohexyl-4-hydroxycoumarin (mp. 226-228°) were synthesized according to the literature method.[12]

TABLE 2. IR and ^{1}H NMR Spectra of 3-Alkyl-4-hydroxycoumarins

Cmpd	IR (CO) (cm^{-1})	^{1}H NMR	Elemental Analysis (Found) C	H
4a	1654	3.89 (s, 2H); 7.0-8.1 (m, 9H); 11.78 (s,1H)	76.18 (75.94)	4.79 (4.67)
4b	1647	3.67 (s, 3H); 3.70 (s, 3H); 3.80 (s, 2H); 6.6-8.8 (m, 7H); 11.60 (s, 1H)	69.22 (69.21)	5.16 (5.05)
4c	1655	3.91 (s, 2H); 7.0-8.1 (m, 7H); 11.80 (s, 1H)	59.84 (59.72)	3.14 (3.28)
4d	1666	3.83 (s, 2H); 6.5-8.1 (m, 8H); 9.25 (s, 1H); 11.60 (s, 1H);	71.64 (71.73)	4.51 (4.57)
4e	1654	1.0-2.8 (complex, 11H); 3.89 (s, 2H); 7.0-8.0 (m, 8H); 11.5 (s, 1H)	79.02 (78.81)	6.63 (6.81)
4f	1667	0.88 (d, 6H); 1.88 (q, 1H); 2.42 (d, 2H); 7.2-8.0 (m, 4H); 11.21 (s, 1H)	71.54 (71.39)	6.47 (6.61)

General Procedure.- An aldehyde (20 mmol) and a 4-hydroxycoumarin (20 mmol) were added to 20 mL of TEAF. The reaction mixture was stirred and heated to 140° and it was maintained between 140 and 150° for about 1.5 h (TLC; end or significant reduction of carbon dioxide evolution). The reaction mixture was allowed to cool to 50° then it was poured onto a mixture of ice and water (about 150 mL) and acidified to pH 2 with 6N HCl. The precipitated solid was collected, washed with water, then dried. The yields of the crude products were 90-98% and the products were crystallized from the appropriate solvent or a mixture of solvents (see Table 1).

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A ONE-STEP SYNTHESIS OF 1-HYDROXY-10-METHYL-9(10H)-ACRIDINONE

Submitted by Gary M. Coppola
(12/16/98)

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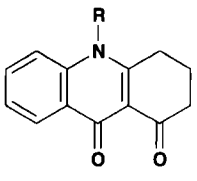
The yellow acridone alkaloid 1-hydroxy-10-methyl-9(10H)-acridinone (**4**) is found in a variety of plant species. It has been isolated from the roots of *Boenninghausenia albiflora*[1,2] and *Ruta chalepensis*[3] and also from callus cultures obtained from the meristematic cells of *Ruta graveolens*.[4] Two multistep systheses of **4** have been reported. The first is a five-step biomimetic approach involving the cyclization of an intermediate N-methylamino-2,6-dimethoxybenzophenone[5] (1.5% overall yield). The second, a four-step sequence starting from an acylmalonate, gives the product in 27% overall yield.[6]

We previously described a two-step synthesis of 10-alkyl-9-acridanones from the reaction of N-alkylisatoic anhydrides with the lithium enolate of 2-cyclohexen-1-one followed by aromatization of the intermediate 1,2-dihydroacridones.[7] It is also known that isatoic anhydrides react with the anions derived from β-ketoesters and β-diketones to form 3-carboalkoxy- or 3-acyl-4-quinolinones.[8,9] It was envisioned that a similar reaction of N-methylisatoic anhydride (**2**) with the sodium salt of cyclohexane-1,3-dione (**3**) would furnish the 1,9-acridinedione (**1**, R = CH_3). Subsequent substitution α to the 1-carbonyl by a suitable functional group (*e. g.* halogen or phenylselenide) would upon elimination, aromatize to produce the desired alkaloid **4**. N-Unsubstituted isatoic anhydrides have been reported to react with **3** at elevated temperature to produce **1** (R = H) in moderate yields.[10]



1

When the sodium salt of **3** was treated with N-methylisatoic anhydride (**2**) in DMF at 120° for 48 h, a single compound was isolated in 15% yield. The remainder of the reaction mixture was highly polar decomposition products. Analysis of this yellow solid it proved to be the aromatized acridone **4** not the acridinedione **1**. If the potassium salt of **3** (generated with KH in DMF) was used and the reaction heated at 110° for 18 h, the yield of **4** rose to 31%. When the potas-