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A New Synthesis of Coumarins

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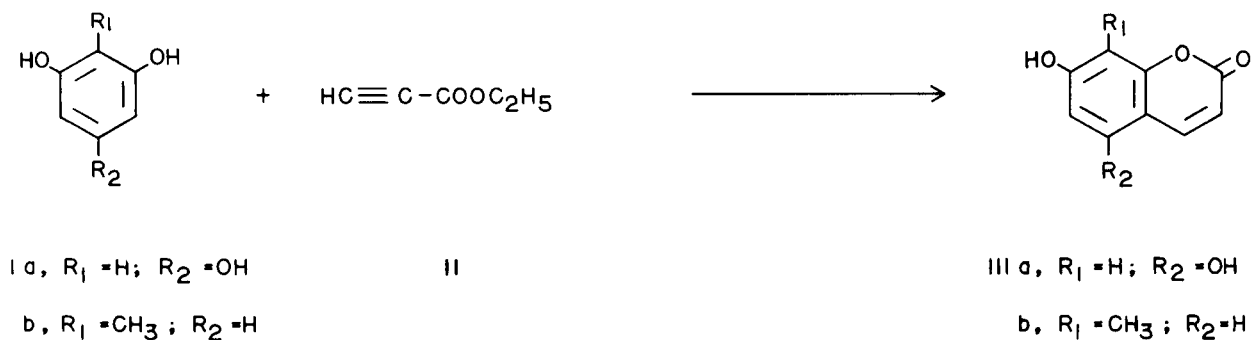
Coumarins bearing substituents in the 4-position or in both the 3- and 4-positions are readily obtained from reactive phenols *via* von Pechmann condensation with β -keto esters (1). No such effective, one-step method has been available for the conversion of polyhydric phenols to 3,4-unsubstituted coumarins. The von Pechmann condensation of phenols with malic acid in hot, concentrated sulfuric acid gives low yields of 3,4-unsubstituted coumarins (1), and sometimes fails completely, *e.g.*, with phloroglucinol (Ia) or its dimethyl ether (2). Thompson and Edee (3) found that *p*-cresol was converted to 6-methylcoumarin in 80% yield when they heated it with maleic or fumaric acid and 72% sulfuric acid. The application of this process to a polyhydric phenol has been studied by George (4), who reported that resorcinol, when heated with fumaric acid and concentrated sulfuric acid, was converted to 7-hydroxycoumarin (umbelliferone) in 70% yield. Attempts to duplicate George's results, including wide variation of reaction conditions, have failed to produce any 7-hydroxycoumarin. Similarly, no 8-methylumbelliferone (IIIb) was obtained when 2-methylresorcinol (Ib) was heated with maleic acid in 75% sulfuric acid. We conclude that condensation of polyhydric phenols with maleic or fumaric acid does not show promise as a method of coumarin synthesis.

In 1917, Fischer and Nouri (5) obtained 5,7-dihydroxy-4-phenylcoumarin from the zinc chloride-catalyzed condensation of phloroglucinol with ethyl phenylpropiolate. There have been no further applications of that reaction, nor has the use of other propiolate esters been reported. Base catalyzed

Michael addition of phenols to ethyl propiolate is, of course, a well known (6) step of a synthetic sequence leading to chromones. We wish to report that acid catalyzed condensation of ethyl propiolate (II) (7) with reactive phenols appears to be an effective method for the preparation of 3,4-unsubstituted coumarins.

For example, 5,7-dihydroxycoumarin (IIIa) was obtained in 89% yield from the condensation of phloroglucinol dihydrate (Ia) with ethyl propiolate (II), in the presence of zinc chloride. The dihydroxycoumarin was characterized by conversion to a diacetate in 83% yield. In an extension of the new process, we found that 2-methylresorcinol (Ib) also condenses with ethyl propiolate when heated with zinc chloride. Better results were obtained, however, when equimolar quantities of 2-methylresorcinol (Ib) and ethyl propiolate (II) were heated in 15% ethanolic sulfuric acid. 8-Methylumbelliferone (IIIb), m.p. 259.5-260.5° [reported (8): m.p. 258-259°], was obtained in 75% yield. The product was characterized by conversion to an acetate.

For comparison, it is interesting to note that Seshadri and Venkateswarlu (10) heated 2-methylresorcinol with malic acid in concentrated sulfuric acid to obtain a sample of 8-methylumbelliferone which melted 28° lower. They did not state the yield. Thus acid catalyzed condensation with ethyl propiolate appears to be a superior method for the introduction of an unsubstituted α -pyrone ring on a reactive phenol. Further studies of the scope of the new synthesis are in progress.



EXPERIMENTAL

5,7-Dihydroxycoumarin (IIIa).

A stirred mixture of 1.62 g. (0.010 mole) of phloroglucinol dihydrate (Ia), 1.47 g. (0.015 mole) of ethyl propiolate (II), and 1.36 g. (0.010 mole) of zinc chloride was heated on a steam bath for one hour. A flocculent precipitate formed during the reaction and, after addition of 5% aqueous hydrochloric acid to the cooled reaction mixture, 1.58 g. (89% yield) of a light tan solid, m.p. 280° dec., [reported (9): m.p. 250° dec.] were collected. It can be recrystallized from water to obtain yellow needles but there is no significant change in the decomposition temperature.

The diacetate, m.p. 139.5-141° [reported (2): m.p. 140°] was obtained in 83% yield when crude 5,7-dihydroxycoumarin was refluxed in acetic anhydride containing anhydrous sodium acetate.

8-Methylumbelliferone (IIIb).

A solution of 1.24 g. (0.010 mole) of 2-methylresorcinol (Ib), 0.98 g. (0.010 mole) of ethyl propiolate (II), and 1.5 ml. of concentrated sulfuric acid in 8.5 ml. of ethanol was refluxed for twenty-four hours and then diluted with 50 ml. of water. The resultant precipitate was recrystallized from ethanol to yield 1.32 g. (75% yield) of pink needles, m.p. 259.5-260.5° [reported (8): m.p. 258-259°]. Except for its pink color, which can be removed by filtration of an acetone solution through a column of activated charcoal, the substance was identical (mixed m.p., infrared spectra) with an authentic sample (8) of 8-methylumbelliferone.

Treatment of the pink needles with boiling acetic anhydride containing anhydrous sodium acetate gave the acetate, m.p. 129-131°, in 77% yield after recrystallization from water.

Anal. Calcd. for $C_{12}H_{10}O_4$: C, 66.05; H, 4.62. Found: C, 65.71; H, 4.34.

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