Synthesis of 1-(3′-Hydroxy-4′-methoxyphenyl)-1,2-butanedione

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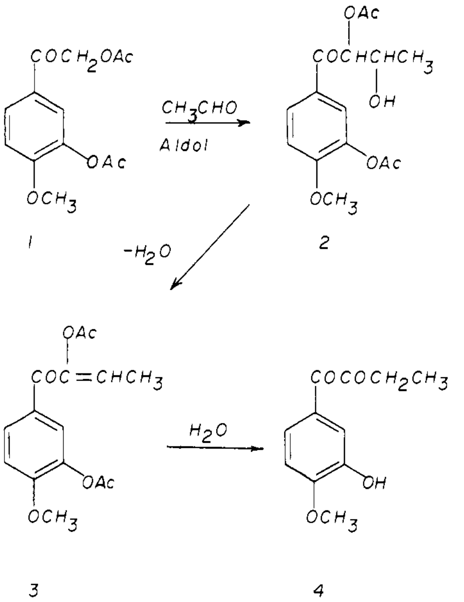
A new synthesis of the α-diketone system via an aldol condensation is described.

CONDENSATION of 2,3′-dihydroxy-4′-methoxyacetophenone diacetate (*4*) (1) with acetaldehyde furnished 1-(3′-hydroxy-4′-methoxyphenyl)-1,2-butanedione (4) in moderate yield. The utility of this method is shown by the fact that the standard oximination route to α-diketones (*3*) failed in this case. Attempts to hydrolyze 1-(3′-hydroxy-4′-methoxyphenyl)-1, 2-butanedione-2-oxime produced isovanillic acid (*5*) instead of the desired diketone via an abnormal Beckmann rearrangement (*1*). Although no further work is planned to develop this method, since the main synthetic objective has been accomplished, it is possible that the route may serve for the synthesis of other sensitive α-diketones. This report is being made, in part, to communicate this suggestion. The following sequence serves to rationalize this reaction:



Acid catalyzed aldol condensation of ketone 1 with acetaldehyde formed the carbon-carbon bond in the usual manner to give the expected β-ketol (2) as the first intermediate. The β-ketol thus produced underwent acid catalyzed β-elimination, typical of β-hydroxyketones, to yield an enol ester, intermediate 3. Enol esters hydrolyze with great ease under acid conditions similar to these. Hydrolysis of enol ester 3 yielded the enol form of diketone 4 which tautomerized to furnish diketone 4. Phenolic esters also hydrolyze easily, and the phenolic ester group was probably lost during the course of this reaction by the usual acid catalyzed route.

Diketone 4 shows the lemon-yellow color typical of α-diketones. The infrared spectrum of diketone 4 has a doublet in the 6-micron region characteristic of the symmetric-asymmetric stretch of an α-diketone grouping. Chemical evidence also supports the structural assignment. Treatment of diketone 4 with hydroxylamine furnished the 2-oxime, which proved identical to an authentic sample (*5*).

EXPERIMENTAL

Melting points were determined on a Kofler micro hot stage and are corrected. The infrared spectra were obtained in Nujol mulls on a Perkin-Elmer Infracord, Model 137.

1-(3′-Hydroxy-4′-methoxyphenyl) -1,2- butanedione (4). A solution of 263 mg. of 2,3′-dihydroxy-4′-methoxyacetophenone diacetate (*4*) (1), 44 mg. of acetaldehyde, and 1.35 ml. of concentrated hydrochloric acid in 10 ml. of glacial acetic acid was heated on the steam bath for 1½ hours. Solvent was removed and the residual oil was distilled at 160° to 170° C. at 10- to 15-microns. The deep yellow distillate was purified by thin-layer chromatography. Glass plates coated with a 1-mm. layer of silica gel HF were employed in the chromatography. The chromatograms were developed with a 20% solution of acetone in methylene chloride. Ether elution of the fastest moving yellow band yielded 166 mg. (81%) of diketone which slowly solidified. The diketone thus obtained crystallized from hexane as lemon yellow needles, m.p. 68° C. Anal. Calcd. for $C_{11}H_{12}O_4$: C, 63.5; H, 5.8. Found: C, 63.6; H, 5.8.

Treatment of diketone 4 with hydroxylamine hydrochloride and sodium acetate according to the method of Feigl (*2*) converted it into 1-(3′-hydroxy-4′-methoxyphenyl)-1,2-butanedione-2-oxime, m.p. 135° C. The oxime thus obtained did not depress the melting point of an authentic sample (*5*); also, the two oximes had identical infrared spectra. Anal. Calcd. for $C_{11}H_{13}NO_4$: C, 59.2; H, 5.87. Found: C, 59.4; H, 5.89.

LITERATURE CITED

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