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A NEW SYNTHESIS OF 4-CHROMANONES

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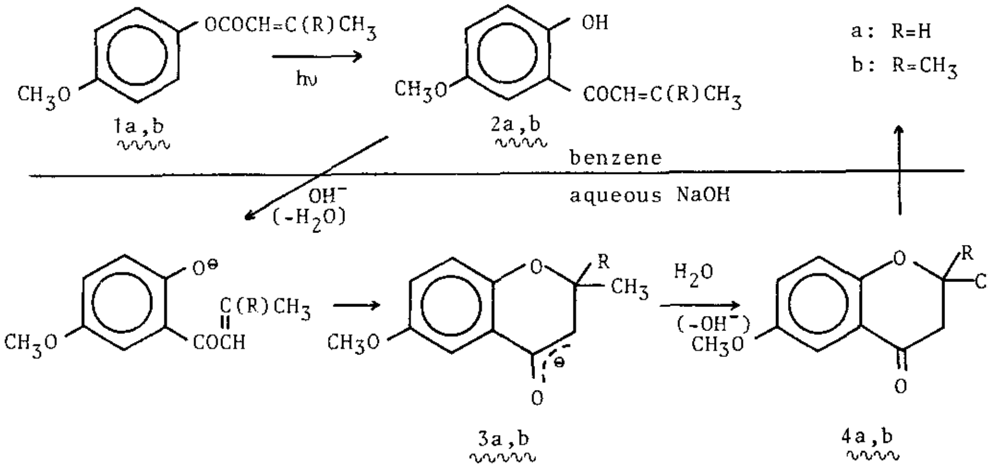
Abstract - Aryl esters of α,β-unsaturated carboxylic acids undergo photorearrangement, followed by basic cyclization, to give 4-chromanones. Reduction/dehydration of these compounds affords 2H-chromenes in excellent overall yields.

The discovery that precocenes are potent juvenile hormone inhibitors[1,2] has led to a renewed interest in the synthesis of the 2H-chromene unit. Among the most general approaches to this system are the treatment of coumarins with Grignard reagents, the rearrangement of aryl propargyl ethers, the cyclization of o-allylphenols and the condensation of phenols with α,β-unsaturated carbonyl compounds.[3,4] However, the development of economical and specific insecticides of this type depends on the availability of even more efficient and selective synthetic methods. We hereby report a new and elegant procedure which provides a direct route to 4-chromanones. As these compounds can be reduced to the corresponding alcohols, which in turn are easily dehydrated,[5,6] the procedure here described constitutes a useful alternative for the preparation of 2H-chromenes.

As a continuation of previous work directed to the photochemical synthesis of oxygen heterocycles,[7-10] we planned to check the prospects of a synthetic scheme based on the photo-Fries rearrangement[11,12] of substituted aryl acrylates. In a first stage, 1 g of the model ester **1a** (or **1b**) was irradiated in benzene (300 ml) with a medium pressure mercury lamp and a quartz immersion well. After 10 h, an equilibrium was reached in which only 25 % of the starting material (50 % in the case of **1b**) was present in the reaction mixture. The main products were **2a** (710 mg) or **2b** (460 mg), and the rest was unidentified polymer. Cyclization to **4** took place quantitatively by treatment with 10 % NaOH in a separate step.

Although the reaction was clean and easy to perform and the required conditions were mild as compared to the acid-catalyzed condensation of phenols with α,β-unsaturated acids,[13,14] the overall yields were only moderate, especially in the case of the dimethyl derivative **4b**. However, it is noteworthy that the dark reaction of *p*-methoxyphenol with β,β-dimethylacrylic acid in the presence of polyphosphoric acid gives only a 18 % of **4b**, apparently due to the lack of an activating substituent at the C-3 position of the phenolic nucleus.[5]

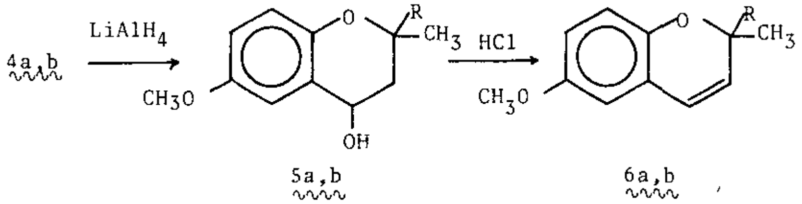
The fact that photochemical rearrangement of **1a,b** proceeds only to a limited extent can be probably attributed to the filtering action of *o*-hydroxyketones **2a,b**. This would be in accord with the intense UV-absorption of these products and their ability to dissipate the absorbed energy by an intramolecular proton transfer mechanism.[15,16] In order to circumvent this limitation we have modified the initial conditions, carrying out the irradiations in a two-phase system benzene/10 % aqueous NaOH. Operating in this way, chromanones were directly obtained in excellent yields (**4a**: 91 %, **4b**: 82 %).



A plausible explanation for this favourable change could be the following: removal of the photo-Fries products **2a,b** from the organic phase is efficiently accomplished by extraction with an alkaline solution, because of the acidity of phenolic hydroxyl groups. Subsequent base-promoted cyclization occurs in the aqueous phase, giving rise to enolates **3a,b**. After taking a proton from water, the resulting chromanones **4a,b** return finally to the organic phase.

As all possible impurities (*p*-methoxyphenol, carboxylic acids, etc.) tend to be retained in the alkaline solution, simple evaporation of the organic solvent gives the desired products in pure state.

Reduction of **4a,b** with excess lithium aluminium hydride resulted in the formation of chromanols **5a,b** and final dehydration with HCl afforded chromenes **6a,b** in 90 % yield from **4**.



In summary, the alternative now described is an efficient direct route of wide applicability to 2*H*-chromenes. It requires simple starting materials and easy manipulations. Further synthetic applications are currently being investigated.

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