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BASE CATALYSED CYCLIZATION OF 1-(2'-HYDROXY-PHENYL)-2-YNONES : A NEW PATHWAY TO THE CHROMONE SKELETON.

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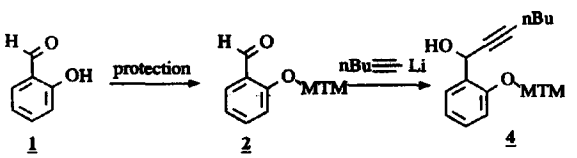
Summary : 2-n-Butyl chromone is synthesized by an efficient new method starting from salicylaldehyde. The key step uses cyclisation of an aromatic hydroxy-ynone. Some sensitive intermediates need to be protected as methylthiomethyl-ethers.

In a recent paper (1), we describe the cyclization of 6-hydroxy-2-ynols and ynoates as a efficient method for the synthesis of substituted 2-methylene tetrahydrofurans.

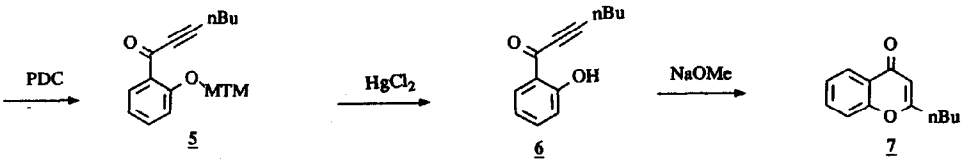
We now wish to describe the cyclization of 1-(2'-hydroxy-phenyl)-2 ynone as a new pathway to the chromone skeleton. This new method will probably be applied to the obtention of substitued derivatives of this kind of molecules.

The classical methods used for the synthesis of chromones and derivatives (2) always start from ortho-hydroxy acetophenones (3). Our own starting product is the most easier accessible salicylaldehyde 1. Substituted salicylaldehydes can also be obtained as commercial products.

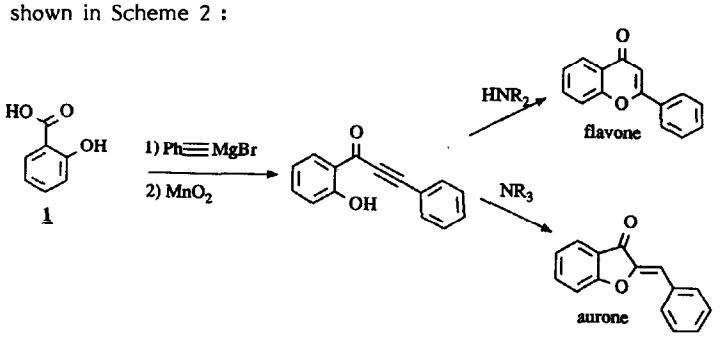
Salicyladehyde 1 was first protected as the methylthiomethyl ether 2 (4). Addition of an excess of lithium acetylide 3 (5) gave the expected alcohol 4 with a yield of 87 %. 4 was then oxidized into ynone 5 by means of an excess of pyridinum dichromate in methylene chloride (6). This last step worked with a yield of 75 %. Deprotection of the methylthiomethyl ether worked by refluxing ynone 5 with an excess of mercuric chloride in aqueous acetonitrile (4). This reaction performs quantitatively without any side reaction of mercuric chloride with the triple bond of the molecule. Hydroxy-ynone 6 is obtained as a yellow liquid. NMR and IR spectra of this molecule show a strong intromolecular hydrogen-bounding between the hydroxyl and carbonyl group. Cyclisation was finaly achieved by treating 6 with a catalytic amount of sodium methylate in anhydrous methanol. 2-n-Butyl-chromone 7 is obtained with an overall yield of 49% after five steps starting from salicylaldehyde 1 according to scheme 1.



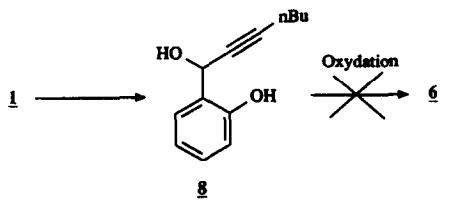
1 2 4



Flavones and aurones have been obtained by a similar approach by S.P. KORSHUNOV et al. (7) as shown in Scheme 2 :



However, their methodology cannot be applied to the synthesis of chromones. In fact, the diol 8 could easily be obtained by adding 2,5 equivalents of acetylide 3 on the unprotected salicylaldehyde 1 (Scheme 3). Diol 8, being very sensitive to heat and light, polymerisises rapidly and cannot be obtained as a pure compound. So, this product could not be directly oxidised into hydroxy-ynone 6 according to S.P. KORSONOV's method.



Intermediate protection of the sensitive intermediate 8 is absolutely necessary (Scheme 1).

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