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An Efficient Oxyfunctionalisation by Dimethyldioxirane of the Benzylethereal Carbon of Flavonoids; a General and Useful Way to Anthocyanidins

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Abstract: compounds with flavonoid structure were selectively oxyfunctionalised at the C-2 carbon atom by DMD. The reaction permitted a new route to flavylium salts. © 1997 Elsevier Science Ltd.

The reactivity of dimethyldioxirane (DMD) with benzylethers is a well-known process.[1] Recently we reported on the synthetic value of mild and efficient oxygen insertion on cyclic benzylethers (i.e. isocoumarins[2]) by DMD. In those cases no open chain products were observed. As a development of our studies, we report now an efficient chemo and regiospecific oxyfunctionalisation of the C-2 carbon of flavonoid structures.[3]


DMD

As depicted in Scheme 1, 2,4-*cis*-flavane-4-acetate **1**,[4] was oxidised by DMD at room temperature, affording the corresponding C-2 hydroxyderivative **2**[5] as the only product (63% yield). Under the same mild conditions, flavan-5,7,4'-triacetate **3**, easily obtained from natural naringenin by reduction with $NaBH_3CN$ and subsequent acetylation,[6] was oxidised by DMD in CH_2Cl_2 to give good yields (57 %) of the corresponding C-2 hydroxy derivative. The method is of interest as it shows opposite selectivity to that of other reagents that reportedly perform the oxyfunctionalisation on the C-4 benzylic carbon.[7]

The flavan-2-one **5**, instead, was only slowly oxidised and a low yield (27%) of the 2-hydroxy-flavan-4-one **6** was obtained, dehydration occurring under the reaction conditions to give **7** (14% yield) and **8** (10% yield) derived from a rearrangement of the epoxyderivative of **7**.[8] By treatment with silica

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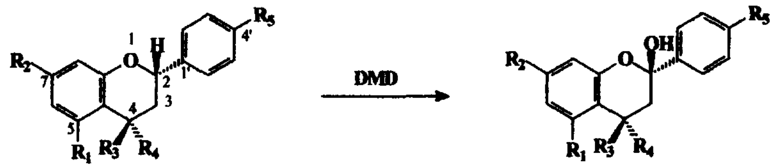
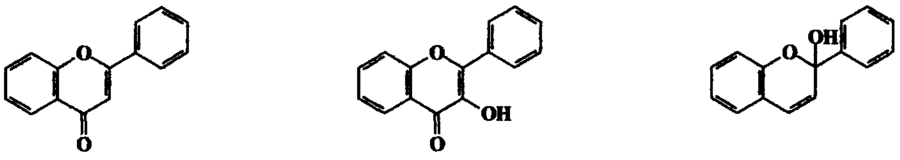
gel, **6** was converted completely to **7**. Other methods for the transformation of flavanones to flavones require the use of strong oxidants, as $Tl(AcO)_3$[9] or hypervalent iodine.[10]

Scheme 1. Hydroxylation of flavans and flavanones by DMD



1 R_1, R_2, R_3, R_5 = H R_4 = OAc	**2**
3 R_1, R_2, R_5 = OAc R_3, R_4 = H	**4**
5 R_1, R_2, R_5 = H R_3, R_4 = O	**6**

Figure 1.

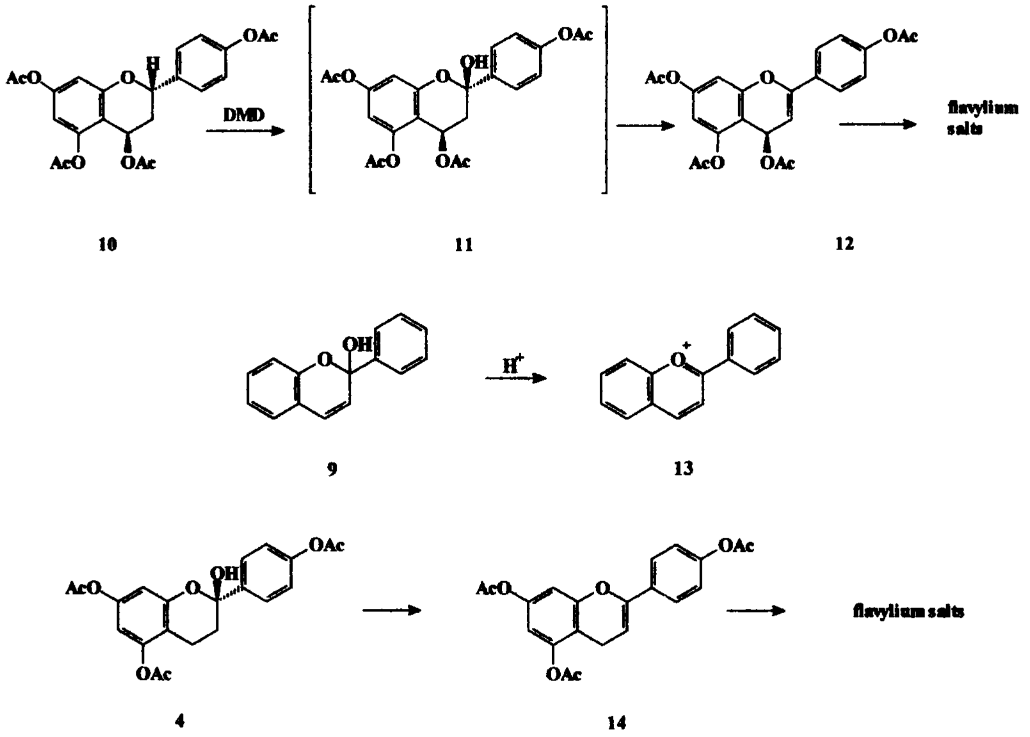


7 **8** **9**

The low reactivity of **5** confirms our previous observations about the deactivating effect, on the DMD reactivity, of a carbonyl function close to the reaction centre.[11] In the reported reactions no hydroxylation of the aromatic rings *via* a radical pathway was observed.

The reaction on 2,4-*trans*-flavan-4,5,7,4'-tetracetate **10** (Scheme 2), prepared by $NaBH_4$ reduction/acetylation transformation of naringenin,[12] gave directly the corresponding flav-2-ene **12** *via in situ* dehydration of the hydroxylated intermediate **11**. In this case **10**, carrying a 4-acetoxy group with the axial stereochemistry, lead, in the reaction conditions, to the dehydrated product. On the contrary compound **1**, with the 4-*equatorial*-acetoxy group not only was stable, but by further treatment of **2** with silica gel eliminated acetic acid to give **9** quantitatively.

Scheme 2. Approach to flavylium salts



Usually, C-2 hydroxyderivatives dehydrated with difficulty. In effect **4** was dehydrated only by the use of drastic conditions ($POCl_3$, 50°). The difference in behaviour between **1** and **10** could be ascribed to a hydrogen bond between the C-2 hydroxy group and the benzyletherеal oxygen, similarly to that reported for C-3 hydroxy groups.[13] When this bond is made weak by a steric interaction with an acetoxy group in the C-4 axial position, the dehydration is the preferred process.

The C-2 oxyfunctionalised products obtained in this way appear useful starting materials to access anthocyanidins, known to be colouring compounds. For example, **9** was easily transformed into the flavylium salt **13** by simple addition of a 37% solution of HCl in water, a procedure already known for chromenols.[14] Flavenes, such as **12** and **14**, are known to furnish the corresponding flavylium salts on treatment with mild oxidants.[15]

Our method appears of general value, since methods reported in literature work just for compounds carrying electrodonating groups on the aromatic rings, while DMD reacted also with substrates with no activated substituents. Moreover no selective oxyfunctionalisation of the C-2 carbon of flavonoids has been reported until now.

More work is in progress to transform commercially available flavanols and flavanones into biologically active flavenes, and to examine the effect exerted by different substituents on the aromatic rings, and work is also in progress to use the method to derivative isoflavans.

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