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Aromatic ring hydroxylation of flavanones by dimethyldioxirane

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Abstract

The selective and efficient oxidation of flavanones with dimethyldioxirane (DMD) is reported. Aromatic rings carrying methoxy groups were selectively hydroxylated in neutral and acidic media. In the latter case inversion of chemoselectivity with respect to the benzylethereal position was observed. This behaviour was exploited to obtain polyhydroxylated flavanones, which are compounds with potential antioxidant and biological properties. © 2000 Elsevier Science Ltd. All rights reserved.

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Flavonoids are phenol derivatives present in substantial amounts (0.5–1.5%) in plants[1] in which they carry out important functions for their biochemistry and physiology.[2] These compounds contribute colour, flavour and processing characteristics important in many foods (vegetables, fruits) and in drinks (tea, wine). Food from common plants contain from traces up to several grams of flavonoids per kilogram fresh weight.[3] In particular, flavanones (2,3-dihydro-2-phenyl-4*H*-1-benzopyran-4-one derivatives) are present in the fruits of genus *Citrus*[4] and are present in wastes and residues obtained during the industrial processing of lemons.[5] Biological properties of flavonoids and their pharmaceutical potencies have been widely investigated and extensively reviewed during the past 30 years.[6] Recently it has been reported that their antioxidant activity, involving efficiency in capturing free radicals, is highly influenced by the presence of oxygenated groups (hydroxyls, methoxyls) on the aromatic rings; an *ortho*-dihydroxy system is of particular interest.[7]

Our group has been working for several years on selective oxidation of natural products by dimethyldioxirane (DMD).[8] This peroxide inserts oxygen into C–H bonds very efficiently and can discriminate between different sites in the same molecule. Selectivities are often as high as those that enzymes are

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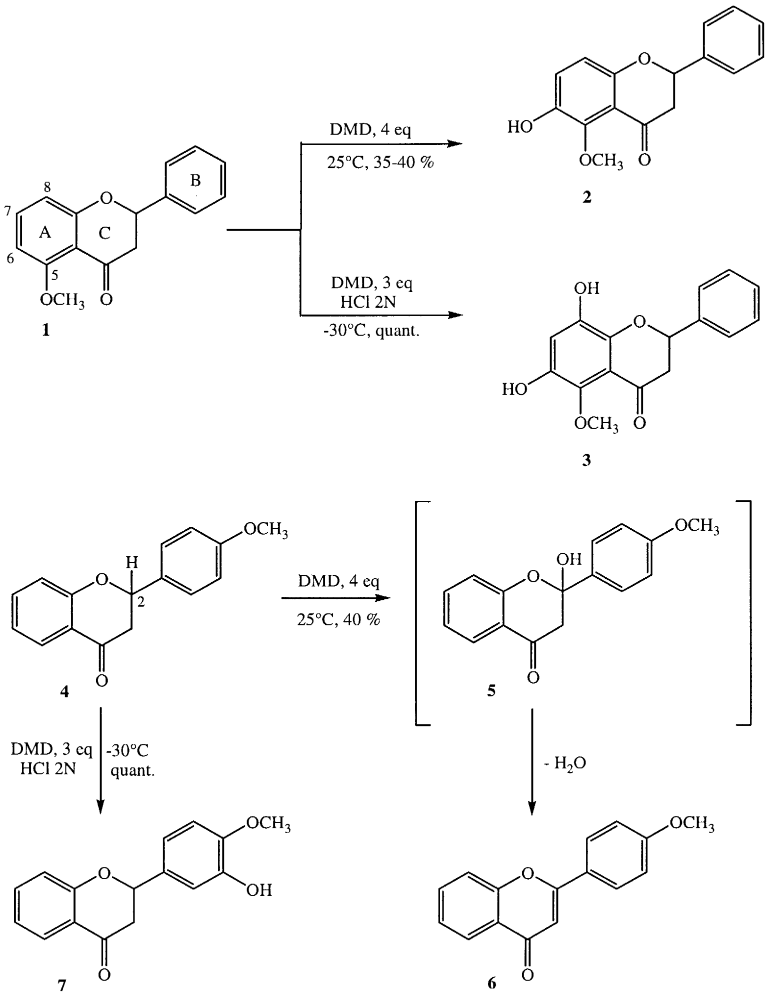
able to achieve. We planned to exploit such efficiencies and selectivities to perform transformations of readily available compounds to obtain more interesting products.

In a previous paper we reported on a new route to flavylium salts based on the high selectivity of DMD for the oxidation of benzyl ethereal carbons;[9] we now report efficient oxygen insertion into activated aromatic rings of flavanones, the regio- and chemoselectivity of the insertion strongly depends on the neutral or acidic reaction conditions.

The model compound considered first, 5-methoxyflavanone **1**, reacted with DMD to give, in satisfactory yield, a polar compound and spectroscopic analysis showed it to be the 6-hydroxy derivative **2** (Scheme 1).[10]

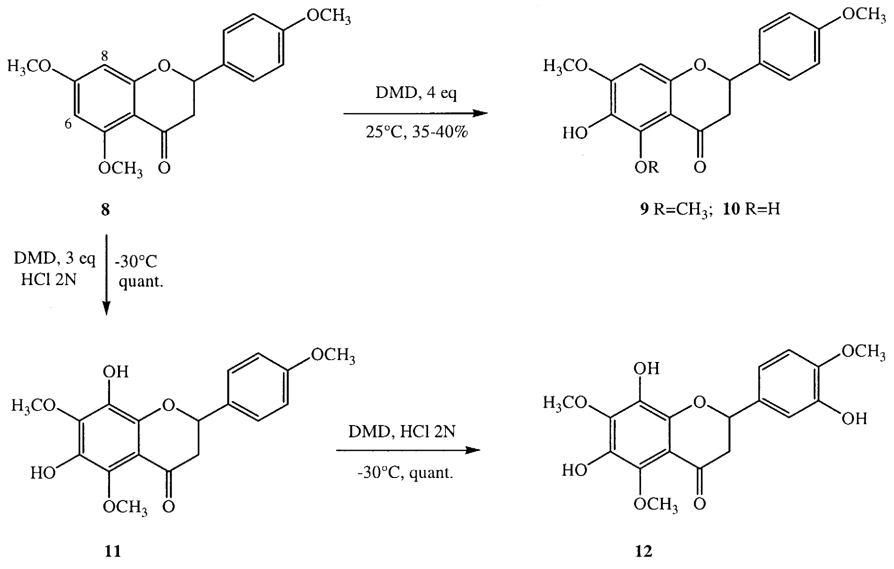


Scheme 1.

With the aim of making DMD more electrophilic and so more reactive towards aromatic centres, we performed the reactions in acidic medium, namely in a 2N solution of HCl. In this case the reaction took a different course with formation of the dihydroxylated product **3**[10] in almost quantitative yield. 4′-Methoxyflavanone **4** reacted with DMD, under neutral conditions, at the benzyl ethereal position,[9,11] but when the reaction was carried out under acidic conditions selective oxidation of the aromatic ring B occurred to give **7**.[12] This reaction was quantitative and occurred in a few minutes.

The inversion of chemoselectivity under neutral conditions is worthy of note: protonation of the benzopyranic oxygen probably caused deactivation of the C-2 position while protonated dimethyldioxirane was more electrophilic and was then able to carry out aromatic ring oxidation.

With more substituted flavanones such as **8**, DMD reacted under neutral conditions to give essentially two compounds (**9**[10], **10**[13]), one of which lacked a methyl substituent (Scheme 2). With a further equiv. of DMD **9** was quantitatively transformed into **10**, a most interesting and specific demethylation.



Scheme 2.

This reaction may occur via a radical process and the carbonyl group should play a determining role in favouring the process (e.g. via dipolar interaction with DMD). Under acidic conditions **10** was not produced, but after just one minute the reaction led to a quantitative yield of the C-6, C-8 dihydroxy derivative **11**.[12] On forcing the reaction further, functionalisation occurred on the ring B *ortho* to the methoxy group to give compound **12**.[12] Evidently in acidic media radical pathways were suppressed and cleavage of the O–O bond of DMD is favoured.

In summary, the utilisation of acid media in DMD oxidation reactions on flavanones allows their quantitative transformation into polyhydroxylated compounds.

Other authors[14] previously reported different behaviour in the acid-catalysed oxidation of methoxybenzenes by DMD, obtaining mainly *p*-benzoquinones. In our case a simple aromatic substitution occurs in which an electrophilic oxygen inserts on an highly activated carbon atom. In the light of their promising biological activity as antioxidants and anticancer agents, the method appears as a direct route to polyhydroxylated flavonoids starting from material largely available in nature, and more work is in progress to exploit its potential.

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10. Data obtained by ^{13}C NMR spectra allowed identification of the correct structure for **2**, **3** and **9** on the basis of NMR studies reported in the literature for flavonoids carrying methoxy groups on the A-ring. (Panichpol, K.; Waterman, P. G. *Phytochemistry* **1978**, *17*, 1363 and references cited therein). A methoxy substituent on an aromatic system lies in the plane of the ring. In this conformation there is the maximum overlap between the lone pair of the oxygen and the π-orbitals of the aromatic ring. The methyl carbon is then shielded by the conjugated electrons and chemical shifts occur between 55.0 and 56.5 ppm. When the methoxy group is between bulky substituents, this conformation is disfavoured, the oxygen is not fully conjugated with the aromatic ring and the methoxy carbon is deshielded to 59.5–63.6 ppm. This is the case with the C-5 methoxy carbon of **2**, **3** and **9** which occurs in the 61.0–61.7 ppm region.
11. Compound **6** was identified with data reported in literature (Adam, W.; Golsch, D.; Hadjiarapoglou, L.; Patonay, T. *J. Org. Chem*. **1991**, *56*, 7292).
12. Structures of compounds **7**, **11** and **12** were established by NMR spectroscopy.
13. A signal at 196 ppm in the ^{13}C NMR proved the structure of **10**; if the C-5 methyl had been removed in the other case the signal should be at 187 ppm.
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