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Oxyfunctionalisation of Activated Methylenes by Dimethyldioxirane: an Easy Conversion of Isochromans into Isocoumarins

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Abstract: the concerted activating effect of two groups allowed the oxidation of methylene carbons, otherwise almost inert, by dimethyldioxirane. The method permitted an easy oxidation of isochromanes to isocoumarins. © 1997 Elsevier Science Ltd.

The efficiency of dimethyldioxirane (DMD) to insert oxygen into tertiary C-H bonds has been widely reviewed in recent works,[1] as well as the activating effect exerted by alcoholic or ethereal oxygens on this process.[2]

We have recently investigated on the fine regioselective tuning of substituents in the selective oxidation of phenyl-alkyl glycols, showing a clear activation of *ortho* and *para* electron-donating groups in the oxidation of the benzyl carbinol.[3] Such activation was explained by a stabilising effect of the transition state in which a little positive charge is formed on the site of the reaction.

Studies on the oxidative cleavage of benzyl ethers suggested some concerted activation provided by phenyl ring and oxygen atom[4] on the oxidation of methylene groups.

Herein we report on the synthetic useful oxidation of doubly activated methylenes of isochromans and diphenylmethanes.

As reported in Table 1, isochroman **1** was readily oxidised, affording quantitatively isocoumarine **2**.

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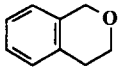
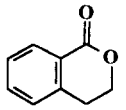
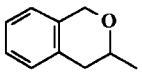
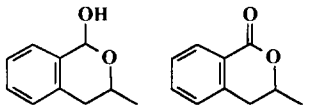
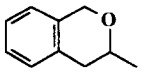
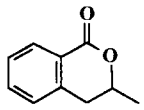
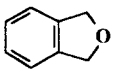
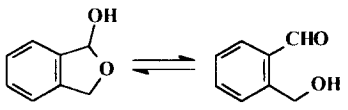
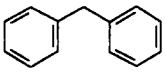
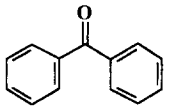
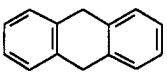
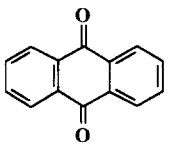
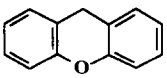
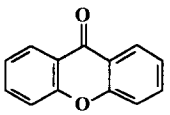
Table 1. Oxidation of benzylic methylenes by DMD[a]

substrate	DMD	react. time	products	yield [b]
 1	2 eq.	30 min.	 2	65-80%
 3	2 eq.	30 min.	 4 5	Quant. (7:3)
 3	3 eq.	60 min.	 5	Quant.
 6	1 eq.	10 min.	 7 8	80%
 9	2 eq.	24 h	 10	92%
 11	4 eq.	24 h	 12	87%
 13	2 eq.	8 h	 14	95%

a) Reactions were performed at rt. on 0.5 mmol scale, adding aliquots of a 0.08M solution of dimethyldioxirane in acetone to the substrate dissolved in CH_2Cl_2 if necessary, and monitored by TLC and GC.

b) Yields are of isolated products. The mixture of 7 and **8** was analysed by NMR[5] on crude and not further purified. The methyl ether of 7 was obtained in 62% yield after in situ derivatisation with methanol and BF_3 etherate and purification by flash chromatography.

At low conversions, the hemiketal could be isolated from the reaction mixture and identified as the product of the first step. Apparently, the further oxidation of the cyclic hemiketal is faster then the cleavage of the C-O bond, making the procedure noteworthy for the synthesis of isocoumarins, from the easily available substituted isochromanes.[6]

To our knowledge such transformation is usually performed by strong oxidants, such as, for example, SeO_2[7] and PCC[8], heterogeneous $KMnO_4/Al_2O_3$ system[9] or O_2/CO mixture in presence of Pd-Cu catalysts.[10]

Isocoumarins, isolated from a wide variety of microbial, plant and insect sources, display a wide range of biological activities as, for example, antifungals, phytotoxycs, plant growth regulators, diuretics, antihypertensives and antitumor agents.[11]

This general behaviour was confirmed in the case of 3-methylisochromane, with notable peculiar characteristics.

With high DMD/substrate ratios (>2:1) and 0.08M solutions of dimethyldioxirane, the reaction was complete in 30 min., leading to a mixture of 3,4-dihydro-3-methyl-H-2-benzopyran-1-ol **4** and methylisocoumarin **5** (7:3 ratio). With longer reaction time, the mixture converged quantitatively to **5**.

The result confirmed the chemoselectivity of the oxidation by DMD of benzylethereal methylenes vs. ethereal methines[4] and provides a good synthetic tool for an easy access to 3-alkyl substituted isocoumarins, since no open chain product was detected. This feature points out to the mildness of the process.

Comparing the fates of substrates **1** and **3**, we noted a clear deactivating effect of the methyl at C-3 on the reactivity of lactol **4**.

Moreover, the first oxidation process showed a marked diastereoselectivity, since the ^{1}H-NMR analysis of the crude suggested a ratio between the two diastereoisomers **4** of about 5:1.[12]

Worthy of note was the results obtained at different concentrations of DMD solutions.

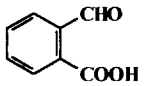
Working with diluted DMD solutions (0.04M) the lactone **5** was the only product detected (GC-MS), even with equimolar amounts of DMD and at low conversion.

This behaviour may be explained through a co-ordination between the OH of the lactol and an oxygen of DMD. Convincing experimental evidences in favour of directing effects exerted by hydroxyl both in epoxidations[13] and in alkyl C-H oxygen insertions[14] are reported in literature. Hydrogen bonding interactions between DMD and solvents were also invoked.[13a, 14]

Therefore, we may suppose the presence of a dynamic equilibrium between the lactol and DMD in their co-ordinated and free forms. When the lactol is bonded to DMD it is apparently less reactive. At high concentrations the lactol, once formed, spends more time as the co-ordinated species, thus resulting the main product observed.

Effects of different solvents on such oxidation are under investigation and will be material for a further paper.

For phthalan **6** the reaction, monitored by TLC, appeared to be complete in few minutes and the NMR analysis on the crude showed that the product was an inseparable mixture of **7** and **8**.[5] To characterise **7** fully, we derivatised it in situ, obtaining the methyl ether in an overall yield of 65%. An excess of DMD led to the further oxidation of **7** and **8** to give a mixture of products, probably due to radical processes. From the crude some amounts of **15** were recovered and characterised as the methyl ester derivative.



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Although some examples of oxyfunctionalisation of benzylic sites of certain polyaromatic compounds by dioxiranes are reported,[15] the oxidation of methylenes by DMD often gives results of little synthetic value.

The examples reported in Table 1 for compounds **9**, **11** and **13** show that the concerted activation effect of two phenyl rings is strong enough to make methylenes easily oxidable by DMD. For **10** and **12** the reaction proceeded quite slowly whereas **14** was oxidised in few hours, confirming an efficient activation of the process by an electron-donating group,[3] through the π system of the aromatic ring.

In these cases alcoholic intermediates were detected for low conversion but it was never possible to stop the reactions to the first step, since the oxidation of the benzyl alcohol moiety was a faster process.

In this work dimethyldioxirane has shown a good effectiveness and synthetic usefulness in the functionalisation of activated methylene moieties, providing an interesting and useful alternative to methods based on polluting transition metal oxidants. Since a number of natural compounds have the base structure of isocoumarins[11] or anthraquinones,[16] our major interest in this field is to exploit DMD potentialities for simple transformations of functionalised isochromanes and dihydroanthracenes to biologically active compounds, via processes with a low environmental impact.

EXPERIMENTAL

Starting materials were available by Aldrich Chimica and Fluka companies and were used without further purification. Compound **3** was prepared as reported in literature.[17]

DMD solutions in acetone were prepared as reported by Adam[18] and co-workers using oxone available by Fluka company.

All reactions were performed, in a typical procedure, by adding portions of a DMD solution to a stirred solution of substrate (0.1 mmol) at room temperature and stirring for the time required to the complete conversion of the substrate. Reactions were monitored by GC and product ratios were calculated by ^{1}H-NMR spectra of the crude, when necessary. GC-MS was performed on products that were not possible to purify for elementary analysis.

The work up of all the reactions consisted in evaporating the solvent in vacuum. When necessary, the reaction products were purified by flash chromatography eluting with a mixture of petroleum ether and ethyl acetate. When it was not possible to isolate the isomers by this way we characterised the products in mixture.

^{1}H-NMR spectra were recorded in deuterochloroform solution at 200 or 300 MHz and ^{13}C-NMR-^{1}H broad-band decoupled spectra were recorded in the same solvent at 75 MHz. Chemical shifts δ refer to the signal of tetramethylsilane. Coupling constants *J* were measured in Hz.

The reaction products **2**, **10**, **12** and **14** are commercially available and were characterised by comparison with authentic samples. Products **7** and **8** were characterised by comparing the NMR signals with that reported in literature.[5]

3,4-dihydro-3-methyl-H-2-benzopyran-1-ol (4): 200 mg of **3** were reacted at room temp. with 15 ml of a 0.08 M solution of DMD in acetone. After 30 min. the reaction was complete and the simple evaporation of the solvent in vacuum gave a mixture of the two diastereoisomers of **4** (70%) and **5** (30%), as resulted by NMR analysis on the crude. ^{1}H-NMR: δ ($CDCl_3$ and D_2O) main isomer: 1.35 (3H, d, J=6, CH_3), 2.65 (2H, d, J=6, C^4-H), 4.34 (1H, sx, J=6, C^3-H), 6.05 (1H, s, C^1-H); MS m^+/z (% rel. Int.): 164 (13.2), 163 (21.9), 120 (87.1), 119 (100), 91 (54.6); minor isomer: 1.37 (3H, d, J=6, CH_3), 2.7 (2H, d, J=9, C^4-H), 4.6-4.72 (2H, m, C^3-H), 5.92 (1H, s, C^1-H).

3-methyl-isocoumarin (5): (a) Using an excess of DMD **4** gave a quantitative amount of **5**. (b) A solution of 200 mg of **3** in 15 ml of acetone, were added of 15 ml of a 0.08 M solution of DMD in acetone. The reaction was monitored every 10 minutes by GC. The formation of **5** was observed since from the first analysis. After 2 h the reaction was complete. ^{1}H-NMR: δ ($CDCl_3$) 1.48 (3H, d, J=6, CH_3), 2.92 (2H, m, C^4-H), 4.63, 4.69 (1H, 2d, J=6, 10, C^3-H). ^{13}C-NMR: δ ($CDCl_3$) 20.8, 34.7, 75.1, 124.8, 127.2, 127.5, 130.1, 133.6, 139.0, 165.7. MS m^+/z (% rel. Int.):162 (14.7), 118 (100), 91 (10.2), 90 (34.4), 89 (11.6). Calc. for $C_{10}H_{10}O_2$ (162) C 74.06, H 6.21; found C 74.22, H 6.60.

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