Pergamon

Tetrahedron 55 (1999) 14719–14728

TETRAHEDRON

Oxidation of 3-Arylisochromans by Dimethyldioxirane. An Easy Route to Substituted 3-Arylisocoumarins.

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Received 5 August 1999; revised 24 September 1999; accepted 7 October 1999

Abstract: The selective oxidation of the two different benzylethereal position of 3-arylisochromans by dimethyldioxirane as a function of different substituents on the, aromatic rings was studied. The easy oxidation of these compounds was exploited for a new easy access to substituted 3-arylisocoumarins.

Keywords: dioxirane, isocoumarins, oxidation

INTRODUCTION AND RESULTS

Isocoumarins and 3,4-dihydroisocoumarins, isolated from a wide variety of microbial, plant and insect sources, display a wide range of biological activities as, for example, antifungals, phytotoxics, plant growth regulators, diuretics, antihypertensives and anticancer agents.[1] Synthesis of new derivatives and improvements of known procedures are, therefore, of great interest.

We recently reported a simple and general method[2] to prepare 3-substituted isochromans, from readily available substrates. In particular, 3-allyl and 3-arylisochromans, endowed with either electron withdrawing or electron releasing groups, were prepared (yields ranging between 80 and 95%) starting from readily available diaryl diols.[3]

In order to develop a general methodology for direct access to isocoumarins and dihydroisocoumarins from such easily prepared isochromans, we tested 3-aryl and 3-allylisochromans upon oxidation by isolated Dimethyldioxirane (DMD).

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0040-4020/99/$ - see front matter
PII: S0040-4020(99)00917-5

3-Arylisochromans also appear to be good probes for providing mechanistic insights into DMD oxidation.

From a purely electronic view, the higher nucleophilicity of the tertiary C^3 position of 3-phenylisochroman over the secondary C^1 carbon should be expected. Indeed, a good oxidizability of tertiary benzylethereal positions in lignan compounds has been recently reported.[4]

On the other hand, 3-arylisochromans appear to be conformational folded, with the aryl moiety facing the C^1-H bond. Conformational studies on flavanoic structures show that such a conformation lies in an energy minimum (Fig. 1).[5]

Fig. 1

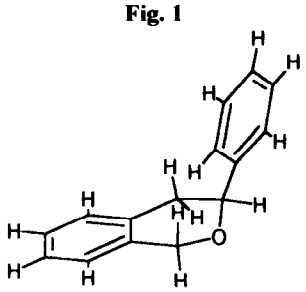
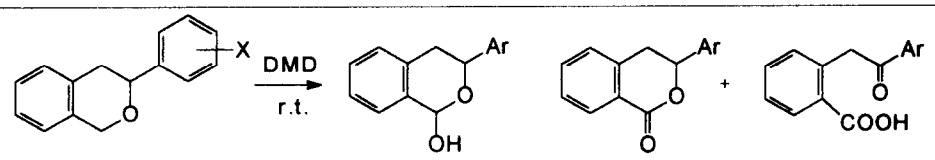


Table 1. Oxidation of 3-arylisochromans by DMD.



1 **2** **3** **4**

Entry[a]	substr.	X	DMD	React.time (h)	conv%	2	3	4
1	**1a**	**H**	1	6	75	59[b]	16	-
2	**1a**	**H**	3	12	>95	-	56[c]	34
3	**1b**	**4'-OCH_3**	1	4	65	19[d]	32[d]	-
4	**1b**	**4'-OCH_3**	3	10	>95	-	30	65
5	**1c**	**4'-NO_2**	1	12	63	38	25	-
6	**1c**	**4'-NO_2**	3	18	>95	-	68	17
7	**1d**	**3'-F**	1	8	60	46	14	-
8	**1d**	**3'-F**	3	8	>95	-	45	34
9	**1e**	**4'-F**	1	12	60	52	8	-
10	**1e**	**4'-F**	3	8	>95	-	58	25
11	**1f**	**3'-OCH_3**	3	5	90	-	56	34
12	**1f**	**3'-OCH_3**	5	12	>95	-	-	70

a) For entries **1**, **3**, **5**, **7**, **9**, the product ratios were determined by ^1H NMR of the reaction mixture. For entries **2**, **4**, **6**, **8**, **10**, yields are those of isolated product.
b) Diasteroisomeric ratio 10:1.
c) This product lead quantitatively to oxoacid when treated with an excess of DMD.
d) Together with 14% of oxoaldehyde **5**

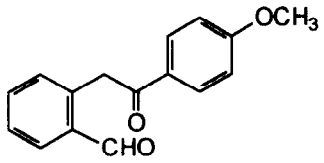
Moreover, a stabilisation of the positive charge on C^1 by the π electrons of the C^3 aryl group was already invoked in studies on acid catalysed nucleophilic substitution reactions[6] on those structures.

Since the high sensitivity of DMD to small changes in the geometrical environment of the active site is well known, we could imagine a similar stabilisation of the partial positive charge on C^1, which would emerge from the dioxirane approach on that site in a concerted mechanism. The results we obtained on the oxidation of substituted 3-arylisochromans (Table 1) support this hypothesis.

Indeed, treating 3-phenylisochromane with 1 eq. of DMD acetone solution at room temperature we obtained a 10:1 mixture of the diasteromeric 1-hydroxy-3-phenylisochromans as the main product (78% of the reacted substrate) and small amount of 3-phenyl-3,4-dihydroisocoumarin (entry 1). The same chemical behaviour was noted for isochromans bearing electron withdrawing groups on the C^3-aryl ring (entries 5,7 and 9), the only difference being a lower conversion of the substrate.

For 3-(4-methoxyphenyl)isochromane, we also found a small amount of open chain oxoaldehyde **5** (Fig. 2) in the reaction mixture. All these results show that, despite the more nucleophilic character of C^3 than C^1, the latter is the first site to be oxidised by DMD.

Fig. 2



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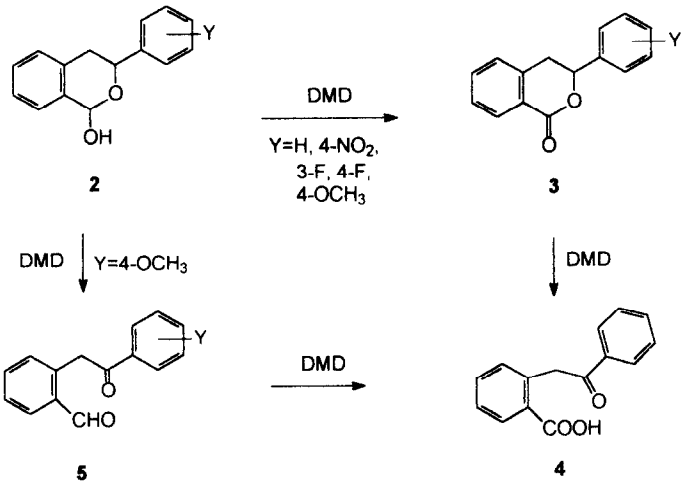
DISCUSSION

We did not find any product, which could be derived from a single oxidation of C^3. The oxoaldehyde **5** should be formed by oxidation at C^3 of the hemiacetal **2** (entry 3) and *in situ* ring opening. In this respect, we noticed a competition for DMD between tertiary benzylethereal C^3 and tertiary benzylhemiacetalic C^1 of 1-hydroxy-3-(4-methoxyphenyl)isochromane, but never between the former and secondary benzylethereal C^1 of 3-phenylisochromans. This experimental evidence can hardly be explained by simple electronic arguments. Instead, in a concerted oxidation mechanism we can imagine a transition state in which the incoming partial positive charge on C^1 is stabilised by the π electrons of the C^3 aryl ring, thus making C^1 the most reactive position toward DMD. The high diastereoselectivity of the monooxidation of 3-phenylisochroman supports this hypothesis, since such interaction probably works differently for the two C^1-H bonds, making one transition state highly favoured.[7]

Working with 3 eq. of DMD, we obtained in all cases quantitative conversion of substrate and a mixture of 3,4-dihydroisocoumarin **3** and oxoacid **4** in different ratios. We usually obtained 45-68% of isolated 3,4-dihydroisocoumarins as main products. Only 3-(4-methoxyphenyl) isochromane gave rise to oxoacid in 70% isolated yield. We also noted that isolated 3,4-dihydroisocoumarin **3** was completely transformed to oxoacid **4** when treated with an excess of DMD (Scheme 1).

These results support the hypothesis of two competitive oxidation pathways for the common hemiacetal **2**, depending on the substitution on the 3-aryl ring.

Scheme 1.



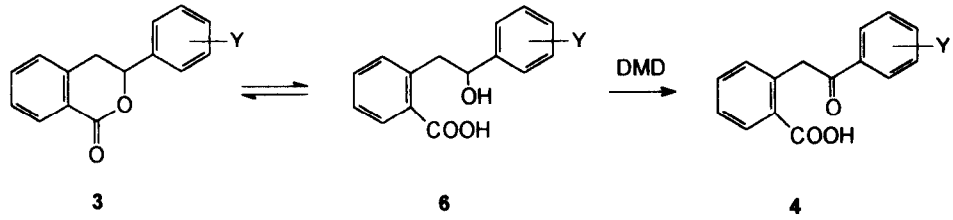
With unsubstituted or electron withdrawing group substituted aryl rings, 3,4-dihydroisocoumarin was the only observed product of the second oxidation and it was partially overoxidised by DMD to oxoacid. With methoxy-substituted phenyl ring, the C^3 competes with C^1 for DMD in the second oxidation. The overoxidation of both oxoaldehyde and 3,4-dihydroisocoumarin led to oxoacid.[8]

Concerning the oxidation of 3,4-dihydroisocoumarin **3**, the well known low reactivity of benzylester carbon centres suggests a lactyl ring opening prior to the oxidation of benzyl site (Scheme 2).

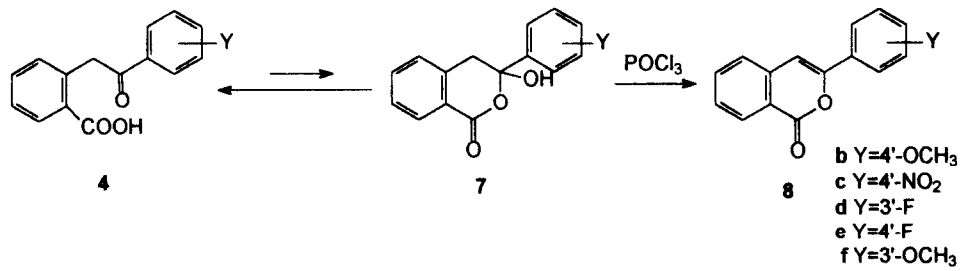
Nevertheless, we proved the existence of an equilibrium process between oxoacid **4** and 3-hydroxy-4-hydroisocoumarin, by treating **4** with $POCl_3$, which irreversibly afforded 3-arylisocoumarin (Scheme 3).

This last reaction was of general value and allowed us to quantitatively prepare various substituted 3-arylisocoumarins, endowed either with electron releasing or electron withdrawing groups. The reaction sequence DMD/$POCl_3$, pyridine was successfully used by us to synthesise the methylether of the Omalicine aglycone **8f** in 60% overall yield, starting from phthalan and 3-methoxybenzaldehyde.

Scheme 2.



Scheme 3.



EXPERIMENTAL

General methods.

^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian XL 300 and Varian Gemini 200 spectrometers in $CDCl_3$ as the solvent, if not specified. All chemical shifts are reported in parts per million against internal tetramethylsilane. Coupling constants *J* were measured in Hz. All reactions were monitored by TLC (Merck F254) or GC. GC analyses were performed on a HP 5880A chromatograph equipped with a OV 101 capillary column and a flame ionisation detector. GC-MS analyses were performed on a HP 5890 chromatograph and HP 5971 as mass detector. Silica gel Merck (200-400 mesh) was used for flash chromatography. DMD solutions were prepared as reported by Adam[9] and co-workers using Oxone available from Fluka. IR spectra were recorded in $CHCl_3$ solution, unless otherwise indicated.

All oxidations with Dimethyldioxirane were performed, in a typical procedure, by adding portions of a DMD solution to a stirred solution of substrate (0.1 mmol) in CH_2Cl_2 at room temperature. The work up of all the reactions consisted in evaporating the solvent in vacuum. When the isolation of the products was not possible by chromatography, we characterised them in the mixture.

The isochromans **1a**[3], **1b**, **1c**, **1d**, **1e** and **1f** were synthesised by our previously reported method.[2]

3-(4'-Methoxyphenyl)isochromane (1b). Oil. IR ν_{max}: 2940-2850 (br), 1602, 1500, 1475 cm^{-1}. ^1H NMR 2.9 (dd., 1H, $^2J_{HH}$=15, $^3J_{HH}$=4), 3.12 (dd., 1H, $^2J_{HH}$=15, $^3J_{HH}$=12), 3.85 (s, 3H, OCH_3), 4.71 (dd, 1H, $^3J_{HH}$=12, $^3J_{HH}$=4,), 5.03 (s, 2H,), 6.95 (d., 2H, $^3J_{HH}$=8) 7.05-7.30 (m, 4H), 7.40 (d., 2H, $^3J_{HH}$=8); ^{13}C NMR – 35.9, 55.2, 68.6, 76.4, 113.8, 124.1, 126.0, 126.4, 127.2, 128.7, 133.5, 134.7, 139.0, 160.0. Anal Calcd for $C_{16}H_{16}O_2$: C 79.97; H 6.71. Found C 79.8; H 6.5.

3-(4'-Nitrophenyl)isochromane (1c). Oil. IR ν_{max}: 2935, 3820, 1600, 1534, 1383 cm^{-1}. ^1H NMR 2.98 (d., 1H, $^3J_{HH}$=8.0), 3.01 (d., 1H, $^3J_{HH}$=5.5), 4.85 (dd., 1H, $^3J_{HH}$=5.5, $^3J_{HH}$=8.0), 5.05 (s, 2H,), 7.05-7.30 (m, 4H), 7.65 (d, 2H, $^3J_{HH}$=7.0), 8.25 (d, 2H, $^3J_{HH}$=7.0); ^{13}C NMR, -36.0, 68.5, 75.6, 123.6, 124.2, 125.4, 125.5, 126.8, 128.7, 132.4, 134.0, 147.2, 149.5. Anal. Calcd. for $C_{15}H_{13}NO_3$: C 70.58; H 5.13; N 5.49. Found: C 70.2; H 5.4; N 5.2.

3-(4'-Fluorophenyl)isochromane (1d). Oil. IR ν_{max}: 2940, 2905, 2840, 1605, 1380, 1284 cm^{-1}. ^1H NMR 3.00 (d., 1H, $^3J_{HH}$=4.5), 3.02 (d., 1H, $^3J_{HH}$=11.5), 4.7 (dd., 1H, $^3J_{HH}$=11.5, $^3J_{HH}$=4.5), 5.02 (s, 2H), 7.00-7.25 (m, 6H) 7.40-7.50 (m, 2H); ^{13}C NMR -36.1, 69.7, 76.2, 115.0 (d, $^2J_{CF}$=21.5), 124.2, 126.9 (d, $^3J_{CF}$=7.5), 127.5, 127.8, 128.7, 134.0, 135.5, 163.0 (d, $^1J_{CF}$=245.0). Anal. Calcd. for $C_{15}H_{13}FO$: C 78.93; H 5.74. Found: C 78.7; H 5.5.

3-(3'-Fluorophenyl)isochromane (1e). Oil. IR ν_{max}: 2950-2700 (br), 1595, 1502, 1380, 1269 cm^{-1}. ^1H NMR 3.01 (d., 1H, $^3J_{HH}$=4.5), 3.05 (d., 1H, $^3J_{HH}$=9.5), 4.75 (dd., 1H, $^3J_{HH}$=9.5, $^3J_{HH}$=4.5), 5.03 (s, 2H), 7.00-7.50 (m, 8H); ^{13}C NMR 35.3, 68.5, 76.0, 112.8 (d., $^2J_{CF}$=21.5), 114.3 (d., $^2J_{CF}$=21.5), 121.3 (d., $^4J_{CF}$=3.0), 124.1, 125.2, 125.4 (d., $^3J_{CF}$=8.0), 128.7, 129.8 (d., $^3J_{CF}$=8.0), 132.9, 134.2, 164.5 (d., $^1J_{CF}$=245.0). Anal. Calcd. for $C_{15}H_{13}FO$: C 78.93; H 5.74. Found: C 78.7; H 5.5.

3-(3'-Methoxyphenyl)isochromane (1f). Oil. IR ν_{max}: 3005, 2940, 1607, 1500, 1462 cm^{-1}. ^1H NMR 3.01 (dd, 1H, $^2J_{HH}$=14.5, $^3J_{HH}$=5.0), 3.15 (dd, 1H, $^2J_{HH}$=14.5, $^3J_{HH}$=10.0), 3.87 (s, 3H), 4.75 (dd, 1H, $^3J_{HH}$=10.0, $^3J_{HH}$=5.0), 5.05 (s, 2H), 6.90 (dt, 1H, $^3J_{HH}$=8.0, $^4J_{HH}$=2.5), 7.05-7.40 (m, 7H); ^{13}C NMR 36.0, 55.1, 68.6, 76.6, 111.1, 113.2, 118.1, 124.1, 126.1, 126.4, 128.7, 129.4, 133.4, 134.4, 143.7, 158.7. Anal. Calcd. for $C_{16}H_{16}O_2$: C 79.97; H 6.71. Found: C 79.7; H 6.6.

3,4-Dihydro-3-phenyl-*H*-2-benzopyran-1-ol (2a). With 1 eq. of DMD solution in acetone, after 6h at room temperature, 78% of **1a** was converted giving a mixture of **2a** (61%) and **3a** (17%), as indicated by NMR analysis on the crude material. ^1H NMR main product: 2.9-3.4 (m, 2H,), 5.3 (dd., 1H, $^3J_{HH}$=4.5, $^3J_{HH}$=9.0), 6.2 (s, 1H), 7.8 (m, 9H).

3,4-Dihydro-3-(4'-methoxyphenyl)-*H*-2-benzopyran-1-ol (2b). With 1 eq. of DMD solution in acetone, after 4h at room temperature, 65% of **1b** was converted giving a mixture of **2b** (19%) and **3b** (32%) and **5** (14%) as indicated by NMR analysis on the crude material. ^1H NMR of **2b**; 2.8-3.3 (m, 2H), 3.9 (s, 3H), 5.2 (dd., $^3J_{HH}$=9.0, $^3J_{HH}$=4.5).

2-[2-Oxo-2-(4'-methoxyphenyl)ethyl] benzaldehyde (5). ^1H NMR characteristic signals 3.9 (s, 3H),

4.7 (s, 2H), 6.95 (d, 2H, $^3J_{HH}$=11.5), 7.30 (d, 1H, $^3J_{HH}$=10.0), 7.50-7.65 (m, 2H), 7.85 (d, 1H, $^3J_{HH}$=10.0) 8.07 (d, 2H, $^3J_{HH}$=10.0), 10.20 (s, 1H).

3,4-Dihydro-3-phenylisocoumarine (3a) and **2-(2-oxo-2-phenylethyl)benzoic acid (4a)**. With 3 eq. of DMD solution in acetone, after 12h at room temperature, **1a** was completely converted to a mixture of **3a** and **4a**, in 56% and 34% isolated yield, respectively. **(3a).** Oil. IR ν_{max}: 3010-2850 (br), 1737, 1606, 1498 cm^{-1}. ^{1}H NMR 3.12 (dd, 1H, $^2J_{HH}$=11.5, $^3J_{HH}$=5.0), 3.35 (dd, 1H, $^2J_{HH}$=11.5, $^3J_{HH}$=10.0), 5.57 (dd., 1H, $^3J_{HH}$=5.0, $^3J_{HH}$=10.0), 7.20-7.60 (m, 8H), 8.18 (d, $^3J_{HH}$=5.0); ^{13}C NMR 35.4, 79.9, 124.9, 127.2, 127.8, 128.1, 128.5, 128.6, 130.2, 133.9, 138.4, 138.8, 164.7. Anal Calcd. for $C_{15}H_{12}O_2$; C 80.34, H 5.39. Found: C 80.5, H 5.2. **(4a).** Oil. IR ν_{max}(neat): 3430, 3050, 1717, 1690, 1410, 1270 cm^{-1}. ^{1}H NMR (DMSO d_6) 4.7 (s, 2H, CH_2), 7.10-8.18 (m, 9H), ^{13}C NMR (DMSO d_6) 44.9, 119.8, 126.0, 127.3, 128.7, 130.2, 130.7, 131.3, 133.0, 134.7 135.1, 170.7, 197.4. Anal. Calcd. for $C_{15}H_{12}O_3$: C 74.99, H 5.03. Found: C 75.1, H 4.9.

3,4-Dihydro-3-(4'-methoxyphenyl)isocoumarine (3b) and **2-[2-oxo-2-(4'-methoxyphenyl) ethyl] benzoic acid (4b)**. With 3 eq. of DMD solution in acetone, after 10h at room temperature, **1b** was completely converted to a mixture of **3b** and **4b**, in 30% and 65% isolated yield, respectively. **(3b)** Oil. IR ν_{max}: 2930, 2860, 1735, 1606, 1518, 1269 cm^{-1}. ^{1}H NMR 3.10 (dd, 1H, $^2J_{HH}$=18.0, $^3J_{HH}$=4.5), 3.35 (dd, 1H, $^2J_{HH}$=18.0, $^3J_{HH}$=11.5), 3.82 (s, 3H), 5.5 (dd., 1H, $^3J_{HH}$=11.5, $^3J_{HH}$=4.5), 6.93 (d, 2H, $^3J_{HH}$=8.0), 7.28 (d, 1H, $^3J_{HH}$=7.0), 7.39 (d, 2H, $^3J_{HH}$=8.0), 7.42 (dt, 1H, $^3J_{HH}$=7.0, $^4J_{HH}$=2.5), 7.54 (dt, 1H, $^3J_{HH}$=9.0, $^4J_{HH}$=4.5), 8.15 (dd, 1H, $^3J_{HH}$=7.0, $^4J_{HH}$=2.5), ^{13}C NMR 35.4, 55.3, 79.8, 114.0, 125.1, 127.3, 127.6, 127.8, 130.4 130.6, 133.8, 139.0, 159.8, 165.5. Anal Calcd. for $C_{16}H_{14}O_3$: C 75.57, H 5.55. Found: C 75.5, H 5.5. **(4b)**. Oil. IR ν_{max}(neat): 3430, 3002, 1719, 1685, 1410 cm^{-1}. ^{1}H NMR (DMSO d_6) 3.9 (s, 3H,), 4.8 (s, 2H), 7.05 (d, 2H, $^3J_{HH}$=6.0), 7.35 (d, 1H, $^3J_{HH}$=5.0), 7.40 (t, 1H, $^3J_{HH}$=5.5), 7.55 (t, 1H, $^3J_{HH}$=5.5), 8.0 (d, 1 $^3J_{HH}$=5.5), 8.06 (d, 2H, $^3J_{HH}$=7.0); ^{13}C NMR (DMSO d_6) 45.0, 55.9, 114.5, 127.6, 131.1, 131.2, 131.4, 131.7, 132.5, 132.8, 133.6, 139.0, 164.3, 168.5, 195.8. Anal. Calcd. for $C_{16}H_{14}O_4$: C 71.10, H 5.22. Found: C 71.0, H 5.2.

3,4-Dihydro-3-(4'-nitrophenyl)-*H*-2-benzopyran-1-ol (2c). With 1 eq. of DMD solution in acetone, after 12h at room temperature, 63% of **1c** was converted giving a mixture of **2c** (38%) and **3c** (22%) as indicated by NMR analysis on the crude material. ^{1}H NMR of **2c** ; 2.92-3.41 (m, 2H), 5.30 (dd., 1H, $^3J_{HH}$=4, $^3J_{HH}$=9), 6.24 (s, 1H), 7.05-8.20 (m, 9H).

3,4-dihydro-3-(4'-nitrophenyl)isocoumarine (3c) and **2-[2-oxo-2-(4'-nitrophenyl)ethyl] benzoic acid (4c)**. With 3 eq. of DMD solution in acetone, after 18h at room temperature, **1c** was completely converted giving **3c** (68%) and **4c** (17%). **(3c)**. Oil. IR ν_{max}: 2990-2800 (br), 1722, 1610, 1522, 1390 cm^{-1}. ^{1}H NMR 3.05 (dd, 1H, $^2J_{HH}$=11.0, $^3J_{HH}$=4.5), 3.15 (dd, 1H, $^2J_{HH}$=11.0, $^3J_{HH}$=10.0), 5.50 (dd. 1H, $^3J_{HH}$=10.0, $^3J_{HH}$=4.5, CH), 7.15 (d, 1H, $^3J_{HH}$=6.0), 7.30 (t, 1, $^3J_{HH}$=6.0), 7.45 (t, 1H, $^3J_{HH}$=6.0), 7.52 (d, 2H, $^3J_{HH}$=6.0), 8.00 (d, 1H, $^3J_{HH}$=6.0), 8.13 (d, 2H, $^3J_{HH}$=6.0); ^{13}C NMR 35.5, 78.5, 124.0, 124.7, 126.8, 127.4, 128.3, 130. 6, 134.3, 138.0, 145.5, 164.7. Anal. Calcd. for $C_{15}H_{11}NO_4$; C 66.91, H 4.12, N 5.20. Found C 66.8, H 4.1, N

5.0. **(4c)**. Oil. IR ν_{max}: 3005, 2840, 1715, 1520, 1358 cm^{-1}. ^1H NMR 4.75 (s, 2H), 7.20-8.20 (m, 8H). ^{13}C NMR 44.9, 119.6, 125.5, 126.2, 128.6, 130.8, 130.9, 134.8, 136.6, 149.4, 170.7, 197.4. Anal. Calcd. for $C_{15}H_{11}NO_5$; C 63.16, H 3.89, N 4.91. Found: C 62.9, H 3.7, N 4.8.

3,4-Dihydro-3-(3'-fluorophenyl)-*H*-2-benzopyran-1-ol (2d). With 1 eq. of DMD solution in acetone, after 8h at room temperature, 60% of **1d** was converted giving a mixture of **2d** (46%) and **3d** (14%) as indicated by NMR analysis on the crude material. ^1H NMR of **2d**: 2.94-3.20 (m., 2H,), 5.25 (dd., 1H, $^3J_{HH}$=9.0, $^3J_{HH}$=4.5), 6.23 (s., 1H), 7.05-7.65 (m., 8H, CH_{ar}).

3,4-Dihydro-3-(3'-fluorophenyl)isocoumarine (3d) and **2-[2-oxo-2-(3'-fluorophenyl)ethyl] benzoic acid (4d)**. With 3 eq. of DMD solution in acetone, after 8h at room temperature, **1d** was completely converted giving **3d** (41%) and **4d** (34%). **(3d)**. Oil. IR ν_{max}: 2930, 2845, 1728, 1614, 1593, 1272 cm^{-1}. ^1H NMR 3.17-3.30 (m., 2H), 5.60 (dd., 1H, $^3J_{HH}$=10.0, $^3J_{HH}$=4.5), 7.00-7.70 (m., 7H), 8.2 (d, 1H, $^3J_{HH}$=7.5); ^{13}C NMR 35.5, 79.0, 113.1 (d, $^2J_{CF}$=22.0), 115.5 (d., $^2J_{CF}$=22.0), 121.6, 127.3, 127.8, 130.2, 130.4, 130.5, 134.0, 138.5, 163.0 (d., $^1J_{CF}$=245.0), 165.3. Anal. Calcd. for $C_{15}H_{11}FO_2$: C 74.37, H 4.58. Found: C 74.4, H 4.7. **(4d)**. Oil. IR ν_{max}: 2935, 2845, 1720, 1616, 1595, 1499, 1294 cm^{-1}. ^1H NMR 4.7 (s., 2H), 7.20-7.70 (m., 6H), 7.85 (d, 1H, $^3J_{HH}$=7.5), 8.15 (d, 1H, $^3J_{HH}$=7.5). ^{13}C NMR 45.0, 114.8 (d., $^2J_{CF}$=22.0), 119.9 (d., $^2J_{CF}$=22.0), 123.8 (d, $^4J_{CF}$=3.5), 127.5, 128.2 (d, $^3J_{CF}$=7.5), 130.2 (d, $^3J_{CF}$=7.5), 132.0, 132.7, 133.3, 137.2, 162.8 (d., $^1J_{CF}$=245.0), 171.6, 196.1. Anal. Calcd. for $C_{15}H_{11}FO_3$: C 69.76, H 4.29. Found: C 69.5, H 4.6.

3,4-dihydro-3-(4'-fluorophenyl)-*H*-2-benzopyran-1-ol (2e). With 1 eq. of DMD solution in acetone, after 12h at room temperature, 60% of **1e** was converted giving a mixture of **2e** (51.6%) and **3e** (8.4%) as indicated by NMR analysis on the crude material. ^1H NMR of **2e**: 2.92-3.32 (m., 2H), 5.25 (dd., 1H, $^3J_{HH}$=10.0, $^3J_{HH}$=4.5), 6.22 (s., 1H), 6.95-7.82 (m., 8H).

3,4-dihydro-3-(4'-fluorophenyl)isocoumarine (3e) and **2-[2-oxo-2-(4'-fluorophenyl)ethyl] benzoic acid (4e)**. With 3 eq. of DMD solution in acetone, after 8h at room temperature, **1e** was completely converted giving **3e** (58%) and **4e** (25%). **(3e)**. Oil. IR ν_{max}: 2930, 2855, 1722, 1609, 1379, 1202 cm^{-1}. ^1H NMR 3.11 (dd, 1H, $^2J_{HH}$=15.0, $^3J_{HH}$=4.5), 3.31 (dd, 1H, $^2J_{HH}$=15.0, $^3J_{HH}$=11.5), 5.52 (dd., 1H, $^3J_{HH}$=11.5, $^3J_{HH}$=4.0), 7.10 (t, 2H, $^3J_{HH}$=7.0), 7.29 (d, $^3J_{HH}$=7.0), 7.43 (m, 3H), 7.58 (t, 1H, $^3J_{HH}$=7.0), 8.15 (d, 1H, $^3J_{HH}$=7.0); ^{13}C NMR 35.7, 79.5, 115.5 (d., $^2J_{CF}$=22.0), 125.0, 127.8, 128.0, 128.2 (d, $^3J_{CF}$=8.5), 131.1, 134.2, 139.4, 163.0 (d., $^1J_{CF}$=245.0), 164.0. Anal. Calcd. for $C_{15}H_{11}FO_2$: C 74.37, H 4.58. Found: C 74.2, H 4.5. **(4e)**. Oil. IR ν_{max}: 2930, 2865, 1715, 1610, 1215 cm^{-1}. ^1H NMR 4.85 (s., 2H), 7.22-8.20 (m., 8H). ^{13}C NMR 45.4, 116.2 (d., $^2J_{CF}$=22.0), 127.8, 131.6, 131.7 (d, $^3J_{CF}$=8.5), 131.8, 133.0, 133.6, 133.7, 166.3 (d., $^1J_{CF}$=245.0), 168.4, 196.0. Anal. Calcd. for $C_{15}H_{11}FO_3$: C 69.76, H 4.29. Found: C 69.6, H 4.1.

3,4-Dihydro-3-(3'-methoxyphenyl)isocoumarine (3f) and **2-[2-oxo-2-(3'-methoxyphenyl) ethyl] benzoic acid (4f)**. With 3 eq. of DMD solution in acetone, after 5h at room temperature, **1f** was completely converted giving **3f** (56%) and **4f** (34%). **(3f)**. Oil. IR ν_{max}: 3000-2855 (br), 1715, 1607, 1495, 1466, 1284

cm^{-1}. ^{1}H NMR 3.10 (dd, 1H, $^2J_{HH}$=13.5, $^3J_{HH}$=4.5), 3.33 (dd, 1H, $^2J_{HH}$=13.5, $^3J_{HH}$=11.0), 5.52 (dd, $^3J_{HH}$=11.0, $^3J_{HH}$=4.5), 6.9 (d, 1H, $^3J_{HH}$=6.0), 7.05 (bs, 2H), 7.25-7.35 (m, 2H), 7.45 (t, 1H, $^3J_{HH}$=6.0), 7.55 (t, 1H, $^3J_{HH}$=6.0), 8.15 (d, 1H, $^3J_{HH}$=6.0); ^{13}C NMR 35.8, 55.3, 79.8, 111.6, 114.2, 118.3, 125.1, 127.3, 127.8, 129.7, 130.4, 133.9, 138.9, 140.1, 159.8, 185.3. Anal. Calcd. for $C_{16}H_{14}O_3$: C 75.57, H 5.55. Found: C 75.9, H 5.5.

(4f). Oil. IR ν_{max}: 3005-2855 (br), 1710, 1295 cm^{-1}. ^{1}H NMR 3.95 (s, 3H), 4.70 (s, 2H), 7.12 (dd, 1H, $^3J_{HH}$=6.0, $^4J_{HH}$=2.5), 7.25 (d, 1H, $^3J_{HH}$=6.0), 7.35-7.55 (m, 4H), 7.65 (d, 1H, $^3J_{HH}$=6.0) 8.11 (d, $^3J_{HH}$=6.0); ^{13}C NMR 45.0, 55.4, 112.3, 119.6, 120.8, 127.3, 128.1, 129.5, 131.8, 132.6, 133.1, 137.5, 138.6, 159.7, 171.2, 197.2. Anal. Calcd. for $C_{16}H_{14}O_4$: C 71.10, H 5.22. Found: C 70.9, H 5.4.

General procedure for the synthesis of 3-arylisocoumarins (8b-f). To a stirred solution of oxoacid **4** (1 mmol) and 2 ml of pyridine at 0°C, 0.5 ml of $POCl_3$ were added dropwise. The reaction mixture was allowed to stand at room temperature and monitored by TLC. The mixture was diluted with ice water, extracted with diethylether, washed with HCl 10%, brine and dried over Na_2SO_4. All products were obtained in almost quantitative yield.

3-(4'-Methoxyphenyl)isocoumarine (8b). Oil. IR ν_{max}: 3035, 2970, 1730, 1633, 1600, 1512, 1290 cm^{-1}. ^{1}H NMR 3.85 (s, 3H), 6.81 (s, 1H), 6.95 (d, 2H, $^3J_{HH}$=9.0), 7.4-7.5 (m, 2H), 7.68 (t, 1H, $^3J_{HH}$=8.0), 7.80 (d, 2H, $^3J_{HH}$=9.0), 8.25 (d, 1H, $^3J_{HH}$=8.0); ^{13}C NMR 55.3, 100.2, 114.2, 120.1, 124.4, 125.7, 126.7, 127.6, 129.6, 134.8, 157.8, 153.6, 151.0, 152.5. Anal. Calcd. for $C_{16}H_{12}O_3$: C 76.18, H 4.79. Found: C 76.4, H 4.7.

3-(4'-Nitrophenyl)isocoumarine (8c). Oil. IR ν_{max}: 1725, 1610, 1518, 1430, 1385 cm^{-1}. ^{1}H NMR 6.84 (s, 1H), 7.30-7.80 (m, 7H), 8.22 (d, 1H, $^3J_{HH}$=5.5). Anal. Calcd. for $C_{15}H_9NO_4$: C 67.42, H 3.39, N 5.24. Found: C 67.2, H 3.2, N 4.9.

3-(3'-Fluorophenyl)isocoumarine (8d). Oil. IR ν_{max}: 1727, 1615, 1590, 1268 cm^{-1}. ^{1}H NMR 6.97 (s, 1H), 7.65 (ddt, 1H, *J*=8.0, 4.5, 2.0), 7.39-7.80 (m, 6H), 8.33 (m, 1H). ^{13}C NMR 103.1, 112.7 (d, $^2J_{CF}$=24.5), 117.3 (d, $^2J_{CF}$=24.5), 121.3 (d, $^4J_{CF}$=3.0), 125.7, 126.0, 126.6, 129.1, 129.3, 130.2, 130.9 (d, $^3J_{CF}$=8.0), 135.5, 137.6, 152.8 (d, $^3J_{CF}$=8.0), 162.4, 163.5 (d, $^1J_{CF}$=245.0). Anal. Calcd. for $C_{15}H_9FO_2$: C 75.00, H 3.78. Found: C 75.3, H 3.8.

3-(4'-Fluorophenyl)isocoumarine (8e). Oil. IR ν_{max}: 1723, 1612, 1205 cm^{-1}. ^{1}H NMR 6.9 (s, 1H), 7.1-7.92 (m, 7H), 8.3 (m, 1H). ^{13}C NMR 101.5, 115.9 (d, $^2J_{CF}$=22.0),, 116 120.3, 125.7, 127.1, 127.3, 128.13 (d, $^3J_{CF}$=6.5), 129.7, 134.9, 137.4, 163.7 ($^1J_{CF}$=245.0), 152.7, 162.5. Anal. Calcd. for $C_{15}H_9FO_2$: C 75.00, H 3.78. Found C 74.8, H 3.9.

3-(3'-Methoxyphenyl)isocoumarine (8f). Oil. IR ν_{max}: 1722, 1605, 1500, 1280 cm^{-1}. ^{1}H NMR 3.85 (s, 3H), 6.90 (s, 1H), 6.92 (broad, 1H), 7.3-7.5 (m, 5H), 7.70 (t, 1H, $^3J_{HH}$=8.0), 8.28 (d, 1H, $^3J_{HH}$=8.0). ^{13}C NMR 55.4, 102.0, 110.4, 115.8, 117.6, 120.4, 125.9, 128.1, 129.5, 129.7, 133.2, 134.8, 137.3, 153.3, 159.9, 162.2. Anal. Calcd. for $C_{16}H_{12}O_3$: C 76.18, H 4.79. Found: C 76.0, H 5.1.

Acknowledgements: we are grateful to "Consorzio I.N.C.A.- Venezia" to have supported this research with a grant.

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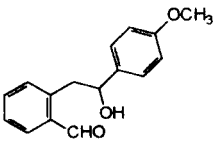
7. Due to the lability of hemiacetals **2**, we could not isolate and fully characterise them. Studies are in progress to trap them without losing configurational relationships between C^1 and C^3.
8. The oxidation of C^3 leads to the pyranyl ring opening. We could not, therefore, be sure whether the oxidation concerned the hemiacetal or the open chain hydroxyaldehyde



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