

# Unusual Friedel-Crafts Reactions. 3 (1). Synthesis of 2,4-Diethoxychromans and Their Conversion into Benzopyrylium Perchlorates

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By a coordinated reaction of phenols (I) and malonaldehyde-bis-(diethylacetal) (II) at ambient temperature, under unusual Friedel-Crafts conditions, a class of new compounds, 2,4-diethoxychromans (IV) has been synthesized. Subsequent treatment of IV in acetic acid with 70% perchloric acid produces 1-benzopyrylium perchlorates (V).

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As a result of our studies in the metal-assisted reactions of the phenolic nucleus with a variety of alkylating agents, we have found a general method for the selective attack at the *ortho* position to the phenoxy group (2).

When a metal phenolate is treated with an electrophile in poorly solvating media, an oriented complex is formed, providing a circumstance favorable for the *ortho*-site specific attack within the coordination sphere of the metal ion (3).

The use of a metal phenolate coupled with a Lewis acid greatly improved our reaction and we were able to obtain selective aromatic electrophilic substitutions under unusual Friedel-Crafts conditions (1,4).

In addition to these results, we have found that chrom-3-enes and chromans could be synthesized in one-step and high yields when the reaction was performed with electrophiles containing two reactive centres such as  $\alpha,\beta$ -un-

saturated carbonyl compounds (5) and isoprenoid dienes (6). This method seems to us a convenient procedure for

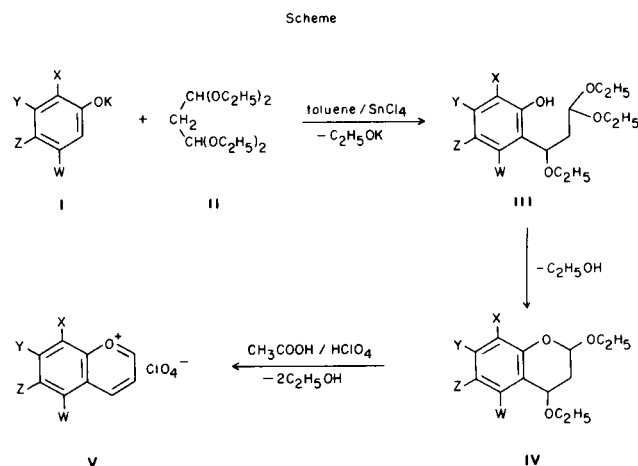


Table I

Synthesis of 2,4-Diethoxychromans (IVa-g)

Product	X	Y	Z	W	Yield (a) (%)	bp (°C)/torr (n <sub>D</sub> <sup>16</sup> )	Molecular formula	Analyses (%)	
								Calcd./Found	C
IVa	H	H	H	H	52 (93)	162-164/16 (1.5145)	C <sub>13</sub> H <sub>18</sub> O <sub>3</sub> (222.27)	70.24 70.14	8.16 8.40
IVb	CH <sub>3</sub>	H	H	H	55 (92)	178-180/16 (1.5151)	C <sub>14</sub> H <sub>20</sub> O <sub>3</sub> (236.30)	71.16 71.23	8.53 8.64
IVc	CH <sub>3</sub>	CH <sub>3</sub>	H	H	58 (90)	175-178/16 (1.5192)	C <sub>15</sub> H <sub>22</sub> O <sub>3</sub> (250.33)	71.97 71.80	8.86 8.96
IVd	C(CH <sub>3</sub> ) <sub>3</sub>	H	H	H	55 (90)	186-188/16 (1.5083)	C <sub>17</sub> H <sub>26</sub> O <sub>3</sub> (278.38)	73.34 73.14	9.41 9.60
IVe	H	H	OCH <sub>3</sub>	H	60 (89)	184-185/16 (1.5082)	C <sub>14</sub> H <sub>20</sub> O <sub>4</sub> (252.30)	66.64 66.68	7.99 8.05
IVf	H	H	Cl	H	38 (95)	oil (1.5231)	C <sub>13</sub> H <sub>17</sub> ClO <sub>3</sub> (256.72)	60.82 60.91	6.67 (b) 6.90
IVg	H	H	-(CH=CH) <sub>2</sub> -		58 (92)	viscous oil (1.5775)	C <sub>17</sub> H <sub>20</sub> O <sub>3</sub> (272.33)	74.97 75.06	7.40 7.60

(a) Actual yield of pure isolated compounds. Values in parentheses refer to yield based on unrecovered starting phenol. (b) Cl, Calcd. 13.81; Found 14.01%.

the synthesis of a large number of oxygen heterocycles.

By analogy with our above-mentioned results we also report here a method of access to 2,4-diethoxychromans (IV) by reaction of potassium phenolates (I) with malonal-

dehyde-bis-(diethylacetal) (II) in the presence of a stoichiometric amount of tin(IV)chloride in dry toluene at ambient temperature.

Table II

## Synthesis of 1-Benzopyrylium Perchlorates (Va-e)

Product	X	Y	Z	W	Yield (a) (%)	mp (b) (°C)	Appearance (c)	Formula	Analyses (%)		
									Calcd./Found	C	H
Va	H	H	H	H	98	195-198 (d)	pale yellow	C <sub>9</sub> H <sub>7</sub> ClO <sub>5</sub> (230.60)	46.87 46.90	3.05 3.36	15.37 15.49
Vb	CH <sub>3</sub>	H	H	H	95	134-136	orange	C <sub>10</sub> H <sub>9</sub> ClO <sub>5</sub> (244.63)	49.09 48.86	3.71 3.64	14.49 14.23
Vc	H	H	OCH <sub>3</sub>	H	99	170-174	yellow-ochre	C <sub>10</sub> H <sub>9</sub> ClO <sub>6</sub> (260.63)	46.07 46.40	3.48 3.14	13.60 13.52
Vd	H	H	Cl	H	93	176-179	golden yellow	C <sub>9</sub> H <sub>6</sub> Cl <sub>2</sub> O <sub>5</sub> (265.05)	40.78 41.09	2.28 2.38	26.75 26.36
Ve	H	H	-(CH=CH) <sub>2</sub>		100	198-200 (e)	golden yellow	C <sub>13</sub> H <sub>7</sub> ClO <sub>5</sub> (280.66)	55.63 55.41	3.23 3.15	12.63 12.43

(a) Actual yield of pure isolated products. (b) All compounds decompose with melt. (c) Microcrystalline solids. (d) Lit. 8f, mp 196-198°. (e) Lit. 8a, mp 200° dec.

Table III

## Spectroscopic Data of 2,4-Diethoxychromans (IVa-g)

Product	m/e (relative intensities %)	IR (film) ν (cm <sup>-1</sup> )	UV (C <sub>2</sub> H <sub>5</sub> OH) λ max (nm) (log ε)	<sup>1</sup> H NMR (deuteriochloroform) δ (ppm)
IVa	77 (25), 91 (25), 103 (17), 107 (23), 121 (91), 131 (100), 147 (26), 176 (34), 222 (6)	2980, 1490, 1460, 1228, 760	316 (3.87), 274 (3.36), 279 (3.33)	1.23 (t, 6H, OCH <sub>2</sub> CH <sub>3</sub> , J = 7.5 Hz); 2.13 (bt, 2H, CH <sub>2</sub> , J = 5.5 Hz); 3.35-4.25 (m, 4H, OCH <sub>2</sub> CH <sub>3</sub> ); 4.52 (t, 1H, C <sub>4</sub> -H, J = 5.8 Hz); 5.24 (t, 1H, C <sub>2</sub> -H, J = 4.5 Hz); 6.57-7.43 (m, 4H aromatic).
IVb	77 (16), 91 (16), 136 (78), 145 (100), 164 (43), 190 (44), 236 (17)	2980, 1470, 1200, 780, 742	217 (3.58), 276 (2.99), 280 (2.99)	1.22 (t, 6H, OCH <sub>2</sub> CH <sub>3</sub> , J = 7 Hz); 2.10 (t, 2H, CH <sub>2</sub> , J = 5.5 Hz); 2.20 (s, 3H, CH <sub>3</sub> ); 3.33-4.16 (m, 4H, OCH <sub>2</sub> CH <sub>3</sub> ); 4.48 (t, 1H, C <sub>4</sub> -H, J = 5.5 Hz); 5.28 (t, 1H, C <sub>2</sub> -H, J = 5.0 Hz); 6.59-7.26 (m, 3H aromatic).
IVc	91 (15), 103 (22), 135 (27), 149 (54), 150 (52), 159 (100), 204 (31), 250 (16)	2980, 1458, 1255, 809	217 (4.09), 274 (3.35), 282 (3.35)	1.18 (t, 3H, OCH <sub>2</sub> CH <sub>3</sub> , J = 7 Hz); 1.22 (t, 3H, OCH <sub>2</sub> CH <sub>3</sub> , J = 7 Hz); 2.12 (s, 3H, CH <sub>3</sub> ); 2.20 (s, 3H, CH <sub>3</sub> ); 1.90-2.30 (m, 2H, CH <sub>2</sub> ); 3.30-4.16 (m, 4H, OCH <sub>2</sub> CH <sub>3</sub> ); 4.43 (t, 1H, C <sub>4</sub> -H, J = 6 Hz); 5.26 (dd, 1H, C <sub>2</sub> -H); 6.53-7.10 (m, 2H aromatic).
IVd	135 (50), 177 (100), 187 (88), 233 (36), 278 (7)	2980, 1440, 1230, 750	217 (3.88), 269 (3.18), 274 (3.16)	1.21 (t, 3H, OCH <sub>2</sub> CH <sub>3</sub> , J = 7 Hz); 1.24 (t, 3H, OCH <sub>2</sub> CH <sub>3</sub> , J = 7 Hz); 1.36 (s, 9H, C(CH <sub>3</sub> ) <sub>3</sub> ); 1.90-2.46 (m, 2H, CH <sub>2</sub> ); 3.30-4.23 (m, 4H, OCH <sub>2</sub> CH <sub>3</sub> ); 4.43 (t, 1H, C <sub>4</sub> -H, J = 5 Hz); 5.25 (dd, 1H, C <sub>2</sub> -H); 6.56-7.33 (m, 3H aromatic).
IVe	91 (9), 137 (27), 152 (65), 161 (100), 180 (19), 206 (29), 252 (10)	2980, 1495, 1205, 818	218 (3.90), 224 (3.89), 293 (3.51)	1.15 (t, 3H, OCH <sub>2</sub> CH <sub>3</sub> , J = 7 Hz); 1.21 (t, 3H, OCH <sub>2</sub> CH <sub>3</sub> , J = 7 Hz); 1.93-2.26 (m, 2H, CH <sub>2</sub> ); 3.23-4.03 (m, 4H, OCH <sub>2</sub> CH <sub>3</sub> ); 3.70 (s, 3H, OCH <sub>3</sub> ); 4.50 (bt, 1H, C <sub>4</sub> -H, J = 6 Hz); 5.15 (dd, 1H, C <sub>2</sub> -H); 6.53-6.90 (m, 3H aromatic).
IVf	91 (16), 103 (71), 156 (100), 165 (100), 210 (48), 256 (13)	2980, 1480, 1260, 820	227 (4.01), 284 (3.31), 290 (3.25)	1.20 (t, 3H, OCH <sub>2</sub> CH <sub>3</sub> , J = 7 Hz); 1.26 (t, 3H, OCH <sub>2</sub> CH <sub>3</sub> , J = 7 Hz); 1.70-2.50 (m, 2H, CH <sub>2</sub> ); 3.26-4.06 (m, 4H, OCH <sub>2</sub> CH <sub>3</sub> ); 4.50 (dd, 1H, C <sub>4</sub> -H); 5.22 (dd, 1H, C <sub>2</sub> -H); 6.53-7.33 (m, 3H aromatic).
IVg	103 (11), 115 (19), 144 (19), 151 (50), 181 (100), 200 (30), 226 (18), 272 (29)	2980, 1250, 901, 826	288 (4.35), 265 (3.67), 275 (3.72), 287 (3.60), 317 (3.30), 331 (3.35)	1.25 (t, 3H, OCH <sub>2</sub> CH <sub>3</sub> , J = 7 Hz); 1.28 (t, 3H, OCH <sub>2</sub> CH <sub>3</sub> , J = 7 Hz); 1.64-2.70 (m, 2H, CH <sub>2</sub> ); 3.23-4.30 (m, 4H, OCH <sub>2</sub> CH <sub>3</sub> ); 4.87 (t, 1H, C <sub>4</sub> -H, J = 3.5 Hz); 5.28 (dd, 1H, C <sub>2</sub> -H); 6.86-7.90 (m, 6H aromatic).

Table IV  
Spectroscopic Data of 1-Benzopyrylium Perchlorates (Va-e)

Product	m/e (M <sup>+</sup> )	IR (nujol) $\nu$ (cm <sup>-1</sup> )	UV (70% HClO <sub>4</sub> ) $\lambda$ max (nm) (log $\epsilon$ )	<sup>1</sup> H NMR (CF <sub>3</sub> COOH) $\delta$ (ppm)
Va	131	1628, 1520, 1085, 840, 778	241 (4.28), 326 (4.13), 349 (3.53)	8.1-8.7 (m, 5H aromatic); 9.6-9.9 (m, 2H, H-2 and H-4).
Vb	145	1623, 1525, 1092, 845, 760	250 (4.31), 329 (4.04), 373 (3.40)	2.91 (s, 3H, CH <sub>3</sub> ); 7.8-8.5 (m, 4H aromatic); 9.5-9.9 (m, 2H H-2 and H-4).
Vc	161	1600, 1520, 1295, 1238, 1085, 875	245 (4.06), 259 (4.08), 336 (4.06), 395 (3.38)	4.18 (s, 3H, OCH <sub>3</sub> ); 7.5-8.4 (m, 4H aromatic); 9.5-9.7 (m, 2H, H-2 and H-4).
Vd	165, 167(a)	1612, 1520, 1106, 875	245 (4.25), 320 (4.17), 367 (3.40)	6.5-7.4 (m, 4H aromatic); 8.6-9.7 (m, 2H, H-2 and H-4).
Ve	181	1650, 1521, 1095, 890	285 (4.20), 395 (4.01)	7.5-8.7 (m, 7H aromatic); 9.4-9.9 (m, 2H, H-2 and H-4).

(a) Peak ratio, 167:165 = 2.87.

It seems that the reaction starts with an *ortho*-site specific attack on the phenol ring giving the intermediate III that has a tendency to cyclize under reaction conditions to generate the 2,4-diethoxychromans (IV) in moderately good yield with high selectivity.

We obtained the 2,4-diethoxychromans (IV) as a mixture of two stereoisomers separable by both tlc and high resolution techniques. The isomer ratio as obtained by glc (integrated peak area ratio, see Experimental) is greater than or equal to 95:5 in all cases, indicating that the reaction is also diastereoselective (7).

Compounds IV represent a class of chromans with an hitherto unknown substitution on the heterocyclic ring and may be regarded as potential benzopyrylium salts. In fact, compounds V were obtained in quantitative yield from IV by treatment with 70% perchloric acid, in acetic acid, at room temperature (8).

The generality of the synthesis was investigated by extending the reactions to various phenols. The method appears to be of broad applicability, but it should be noted that the reaction does not occur with phenols bearing strong electron-withdrawing substituents such as cyano- and nitro-groups and with polyhydric phenols.

Significant spectroscopic data of all 2,4-diethoxychromans (IV) and benzopyrylium perchlorates (V) are collected in Tables III and IV.

#### EXPERIMENTAL

All chemicals were reagent grade and were used without further purification. All bp and mp were determined on a Büchi apparatus and were uncorrected. Ir spectra (film or nujol) with a Perkin-Elmer 298 spectrometer. Uv spectra for solutions in 95% ethanol were measured using a Cary 17 spectrometer. <sup>1</sup>H-nmr spectra were obtained with a Varian

XL-100 instrument. Chemical shifts are expressed in ppm with respect to TMS. Mass spectra were determined on a Varian MAT CH5 spectrometer using direct insertion probe (70 eV). All microanalyses were performed by Istituto di Chimica Farmaceutica dell'Università di Parma, Italy.

Tlc experiments were carried out on Merck silica gel GF 254 plates using 9:1 (v/v) hexane/ethyl acetate mixture as eluent.

Glc analyses were performed with a Dani 3900 instrument using a SE 52 (20 m x 3 mm) pyrex capillary column.

A Perkin-Elmer Sigma 10 chromatography data station was used for quantitation.

#### 2,4-Diethoxychroman (IVa). Typical Procedure.

To a suspension of potassium phenolate [prepared *in situ* from phenol (0.94 g, 10 mmoles) and potassium pellets (0.39 g, 10 mmoles) in anhydrous toluene (50 ml)] was added a solution of tin(IV)chloride (2.59 g, 10 mmoles) in toluene (10 ml). The slurry was heated under reflux with stirring for 15 minutes, while a stream of dry nitrogen was passed. The resulting yellow suspension was cooled to room temperature and a solution of malonaldehyde-bis-(diethylacetal) (II, 2.2 g, 10 mmoles) in toluene (10 ml) was added. The reaction mixture was stirred for 12 hours at room temperature, then quenched with 10% aqueous hydrochloric acid solution (40 ml) and extracted with diethyl ether. After drying (sodium sulfate) the solvent was removed under reduced pressure and the residual oil chromatographed on silica gel (hexane/ethyl acetate 9:1 v/v) to give pure 2,4-diethoxychroman (IVa). The yield was 1.15 g (52% on phenol), bp 162-164° at 16 torr,  $n_D^{20}$  1.5145.

All the 2,4-diethoxychromans listed in Table I were prepared in a similar way.

#### Compounds IVa-f.

These are mixtures of *cis* and *trans* stereoisomers. The isomer ratio obtained from the integrated chromatograms (peak area ratio) are: IVa, 95:5; IVb, 94:6; IVc, 97:3; IVd, 96:4; IVe, 98:2; IVf, 95:5.

#### 1-Benzopyrylium Perchlorate (Va). Typical Procedure.

A stream of dry nitrogen was bubbled into a solution of 2,4-diethoxychroman (IVa, 2.22 g, 10 mmoles) in acetic acid (100 ml) for 15 minutes. Then 10 ml of 70% perchloric acid were added and the clear colorless solution was allowed to stand at room temperature for 5 hours under nitrogen. Anhydrous diethylether (200 ml) was added to precipitate the benzopyrylium perchlorate (Va) as a pale yellow powder

that was filtered with suction under nitrogen; yield 2.2 g (98%), mp 195-198° dec.

All the 1-benzopyrylium perchlorates listed in Table II were prepared in a similar way.

These salts are notoriously air and moisture-sensitive compounds, but in the solid state they can be stored in a refrigerator under nitrogen for several weeks without appreciable decomposition.

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