SHORT PAPER

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Synthesis of 4-arylideneisochroman-1,3-dione under microwave irradiation†

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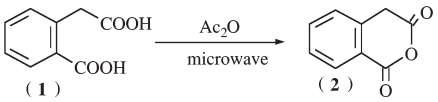
Homophthalic acid (**1**) and arylcarboxyaldehydes were condensed to form 4-arylideneisochroman-1,3-dione (**3**) in acetic anhydride in the presence of ammonium acetate under focused microwave irradiation. The stereochemistry of the products was determined by NMR and by X-ray diffraction of one isomer.

Keywords: isochromandione, microwave, NMR, X-ray diffraction

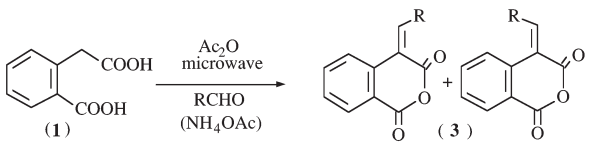
The chemistry of isochroman-1,3-dione (**2**) is poorly described in the literature.[1] However, we would expect a high carbon acidity for the methylene group of isochroman-1,3-dione (**2**) because the position of the methylene group can be compared to that of methylene in Meldrum's acid.

The microwave irradiation of homophthalic acid (**1**) in acetic anhydride lead to a mixture of isochroman-1,3-dione (**2**) and acetic acid (Scheme 1). Acetic anhydride acts as a water scavenger in a similar way to isopropenylacetate previously described.[2]



Scheme 1 Synthesis of isochroman-1,3-dione (**2**).

When an arylcarboxyaldehyde was added to homophthalic acid (**1**) in acetic anhydride under microwave irradiation, the Knoevenagel condensation[3] product (**3**) was formed. Better yields of 4-arylideneisochroman-1,3-dione (**3a–h**) were obtained when a catalytic amount of ammonium acetate was added to the mixture (Scheme 2).



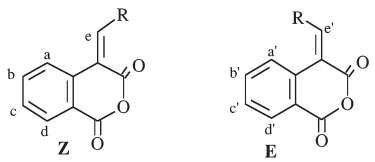
Scheme 2 One-pot reaction under microwave irradiation.

Products (**3a–h**) obtained are reported in Table 1.

Although some products were already known and the yields obtained were similar (50–90%), their spectral properties and their stereochemistries have not been previously described. The melting point of the mixture of isomeric products (**3a**, **3b**, **3h**) were comparable to the melting point found in the literature. We observed a marked difference for **3c** (180°C instead of 168°C). This could be due to a different ratio of *Z* and *E* isomers. All products showed an infrared absorption band characteristic of a lactone and gave correct elemental analysis (C, H).

The assignment of the stereochemistry was not straightforward and only one such study, by NMR was previously reported.[7] In our case, the correlation between NMR experiments (at 250 and 400 MHz: 1D, 2D ^{1}H-^{1}H, 2D ^{1}H-^{13}C, Overhauser studies) were needed to get the accurate stereochemistry of double bond. These results (especially the scalar coupling *J*) were also correlated to the result of molecular modeling studies.

The chemical shift, corresponding to the ethylenic proton, is for the compounds **3a–h** within the intervals 7.75 – 7.85 ppm or 8.05–8.40 ppm (Table 2, with the notation used on Scheme 3). Interestingly when a mixture of stereoisomers was present, the ethylenic protons were observed at a chemical shift within the two ranges.



Scheme 3 Stereoisomeric alkylidenisochromadiones (3).

Table 1 4-arylideneisochroman-1,3-dione (**3**).

No.	aldehyde	*Z*/*E*	Colour	M.P.(°C)	formula	lit.
3a	Anisaldehyde	30/70	Orange	145	$C_{17}H_{12}O_4$	5
3b	Piperonal	100/0	Orange	199	$C_{17}H_{10}O_5$	5,6
3c	Vanillin	100/0	Orange	180	$C_{17}H_{12}O_5$	5
3d	2,6-dichlorobenzaldehyde	50/50	Orange	165	$C_{16}H_8O_3Cl_2$	
3e	3,4-dichlorobenzaldehyde	34/66	White	193	$C_{16}H_8O_3Cl_2$	
3f	Mesitaldehyde	0/100	Orange	189	$C_{19}H_{16}O_3$	
3g	Ferrocenaldehyde	50/50	Black	>300	$C_{20}H_{14}O_3Fe$	
3h	Cinnamaldehyde	100/0	Yellow	226	$C_{18}H_{12}O_3$	5

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† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M)*.

Table 2 ^{1}H NMR and MS spectra of 4-arylideneisochroman-1,3-dione (**3**)

3a NMR ^{1}H (CDCl3, 400 MHz) : *E* isomer : 3.87, s, 3H, 3H$_h$'; 6.92, d, *J* = 8.9 Hz, 2H, 2H$_g$'; 7.46–7.56, m, 4H, 2Hf', H$_a$', H$_c$'; 7.81–7.86, m, 1H, H$_b$'; 8.12, s, 1H, H$_e$'; 8.18–8.23, m, 1H, H$_d$'.

3a NMR ^{1}H (CDCl$_3$, 400 MHz) : *Z* isomer : 3.89, s, 3H, 3H$_h$; 6.98, d, *J* = 8.9 Hz, 2H, 2H$_g$; 7.46–7.56, m, 1H, Hb; 7.75, ddd, *J* = 7.8 and *J* = 1.4 Hz, 1H, H$_c$; 7.81–7.86, m, 2H, H$_e$ and H$_a$; 7.96, d, *J* = 9.1 Hz, 2H, 2H$_f$; 8.18–8.23, m, 1H, Hd.

3a MS : 280 M+. (100); 252 M+. -CO (11); 237 M+ -CO-CH$_3$. (10); 193 M+. -CO$_2$ -CO (19); 165 (28).

3b NMR ^{1}H (CDCl$_3$, 400 MHz) : *Z* isomer : 6.09, s, 2H, CH$_2$; 6.90, d *J* = 8.2 Hz, 1H, H$_g$; 7.35, dd *J* = 8.0 Hz and *J* = 2.0 Hz, 1H, H$_f$; 7.55, ddd *J* = 8.1 Hz and *J* = 1.2 Hz, 1H, H$_c$; 7.65, d, *J* = 1.7 Hz, 1H, H$_h$; 7.77, ddd *J* = 8.2 Hz and *J* = 1.3 Hz, 1H, H$_b$; 7.80, d *J* =7.5 Hz, 1H, H$_a$, 7.78, s, 1H, H$_e$'; 8.23, dd *J* = 8.6 Hz and *J* = 1.1 Hz, 1H, H$_d$.

3b MS : 294 M+. (100); 266 M+. -CO (8); 250 M+. -CO$_2$ (7); 221 M+ -CO$_2$ -CO -H. (10); 192 M+. -CO -H$_2$CO -CO$_2$ (15); 165 (8).

3c NMR ^{1}H (CDCl$_3$, 250 MHz) : *Z* isomer : 3.9, s, 3H, 3H$_i$; 7.11, d *J* = 8.2 Hz, 1H, H$_g$; 7.32, dd *J* = 8.2 Hz and *J* = 2.2 Hz, 1H, H$_f$; 7.57, ddd *J* = 6.8 Hz and *J* = 1.5 Hz, 1H, H$_c$; 7.70, d *J* = 1.9 Hz, 1H, H$_h$; 7.74–7.84, m, 3H, H$_b$, H$_a$ and H$_e$; 8.23, dd, 1H, *J* = 7.8 Hz, H$_d$.

3c MS 296 M+. (12).

3d NMR ^{1}H (CDCl$_3$, 400 MHz) : *E* isomer : 7.08, d, *J* = 7.9 Hz, 1H, H$_a$'; 7.37–7.47, m, 4H, 2 H$_f$', H$_g$' and H$_c$'; 7.53, ddd, *J* = 1.19 Hz and *J* = 7.84 Hz, 1H, Hb'; 8.11, s, 1H, H$_e$'; 8.28, dd, 1H, *J* = 7.9 Hz and *J* = 1.4Hz, H$_d$'.

3d NMR ^{1}H (CDCl3, 400 MHz) : *Z* isomer : 7.29, ddd *J* = 8.0 Hz and *J* = 0.67 Hz, 1H, H$_g$; 7.37–7.47, m, 2H, 2 Hf; 7.66, ddd *J* = 7.5 Hz and *J* = 0.9 Hz, 1H, Hc; 7.84, ddd *J* = 7.6 Hz and *J* = 1.4 Hz, 1H, Hb; 7.85, s, 1H, He; 8.01, d *J* = 8.0 Hz, 1H, H$_a$; 8.31, dd, 1H, *J* = 7.9 Hz and *J* = 1.3 Hz, H$_d$.

3d MS : (chemical ionisation with acetonitrile) 319 MH+. (100); 283 M+-Cl. (13).

3e NMR ^{1}H (DMSO, 400 MHz) : *E* isomer : 7.65–7.75, m, 3H, H$_g$', H$_f$' and H$_c$'; 7.88, ddd *J* = 8.2 Hz and *J* = 1.3 Hz, 1H, H$_b$'; 8,01, d *J* = 1.7 Hz, 1H, H$_h$'; 8.12, dd *J* = 7.9 Hz and *J* = 1.2 Hz, 1H, H$_a$'; 8.20, d *J* = 8.0 Hz, 1H, H$_d$'; 8.32, s, 1H, He'.

3e *Z* isomer : 7.42, m, 1H, Hb; 7.49, dd *J* = 8.6 Hz and *J* = 1.8 Hz, 1H, Hf; 7.54–7.58, m, H$_c$ and H$_a$; 7.65–7.75, m, 1H, H$_g$; 7.83, d *J* = 1.5 Hz, 1H, H$_h$; 8.03, s, 1H, H$_e$; 8.09, m, 1H, H$_d$.

3f NMR ^{1}H (CDCl$_3$, 250 MHz) : *E* isomer : 2.10, s, 6H, o-CH$_3$; 2.35, s, 3H, p-CH$_3$; 6.95, s, 2H, H$_f$'; 7.13, dd (*J* = 7.79 Hz and *J* = 1.10 Hz), 1H, H$_a$'; 7.38, ddd (*J* = 7.43 Hz and 1.63 Hz), H$_b$'; 7.45, ddd (*J* = 7.40 Hz and 1.21 Hz), H$_c$'; 8.23, dd (*J* = 7.54 Hz and *J* = 1.69 Hz), 1H, H$_d$'; 8.39, s, 1H, H$_e$'.

3f MS : 292 M+. (72) ; 277 M+ CH$_3$. (100); 249 M+ -CO -CH$_3$. (36); 248 M+. -CO$_2$ (37); 246 (37); 233 M+ -CO$_2$ -CH$_3$. (17); 231 (34); 220 M+. -CO$_2$ -CO (20); 205 M+ -CO$_2$ -CO -CH$_3$. (20); 165 (6).

3g NMR ^{1}H (CDCl$_3$, 250 MHz) isomer *E* : 4.25, s, 5H, Hj'; 4.64, dd, 2H, H$_i$' and H$_g$'; 4.75, s, 1H, H$_h$'; 5.15, s, 1H, H$_f$'; 7.48, t, 1H, H$_c$'; 7.72, t, 1H, H$_b$'; 7,80, d, 1H, H$_a$'; 8.05, s, 1H, H$_e$'; 8.22, d, 1H, H$_d$'.

3g NMR ^{1}H (CDCl$_3$, 250 MHz) isomer *Z* : 4.25, s, 5H, Hj; 4.64, dd, 2H, H$_i$ and H$_g$; 4.75, st, 1H, H$_h$; 5.15, st, 1H, H$_f$; 7.45, t, 1H, H$_c$; 7,54, t, 1H, H$_b$; 7.81, s, 1H, H$_e$; 8,13, d, 1H, H$_a$; 8.19, d, 1H, H$_d$

3g MS : 358 M+. (100); 314 M+. -CO$_2$ (23); 293 M+ -C$_5$H$_5$. (15); 287 (10); 221 M+. -CO$_2$ -CO -C$_5$H$_5$. (12); 165 (14).

3h NMR ^{1}H (CDCl$_3$, 250 MHz) : *Z* isomer : 7.31, d, 1H, H$_g$ (^3J = 15.44 Hz); 7.40–7.43, m, 3H, 2Hi and Hj ; 7.50, ddd *J* = 8.0 Hz and *J* = 1.0 Hz, 1H, Hc ; 7.61–7.65, m, 2H, 2 H$_h$; 7.73, ddd *J* = 8.2 Hz and *J* = 1.4 Hz, 1H, H$_b$; 7.77, d, 1H, H$_e$ (^3J = 11.52 Hz); 7.84, d *J* = 7.9 Hz, 1H, H$_a$; 8.24, dd *J* = 7.9 Hz and *J* = 1.2 Hz, 1H, H$_d$; 8.47, dd, 1H, Hf (^3J = 15.44 and 11.52 Hz).

3h MS : 276 M+. (90); 275 M+-H. (84); 248 M+. -CO (68); 232 M+. -CO$_2$ (45); 231 M+.-CO$_2$ -H. (100); 204 M+. -CO$_2$ -CO (92); 202 M+. -CO$_2$ -C$_2$H$_4$ (44); 165 (3).

It was supposed that the compounds with the most deshielded proton He' (8.05–8.40 ppm) correspond to the *E* stereoisomer due to the proximity of the carbonyl function. This assumption was confirmed by the X-ray structure of compound **3f** (chemical shift for H$_e$'= 8.39 ppm), that indeed reveals the presence of a double bond with the stereochemistry E.

Secondly, nuclear Overhauser studies were performed in the case of **3b**. A good separation occurred between the two signals of He and Ha (benzene d$_6$, at 50°C) and we have shown that an NOE effect exists between them confirming the stereochemistry *Z* for **3b.**

Table 3 δ ethylenic protons (ppm) of *E* (He) and *Z* (He') stereoisomers

No.	*Z*	*E*
3a	7.81–7.86	8.12
3b	7.78	
3c	7.74–7.84	
3d	7.85	8.11
3e	8.03	8.32 (DMSO)
3f		8.39
3g	7.81	8.05
3h	7.77	

The structure of **3f** was solved by single crystal diffraction. The stereochemistry *E* of the double bond C4-C15 is clearly identified from the single crystal X-ray diffraction picture (Fig. 1). Interestingly, several bond angles are slightly different to the value usually observed. As an example, the angle C3–C4–C15 is 128.27 while the angle C15–C4–C16 is 114.54. The value of these angles could arise from the steric interaction between the mesityl group and the hydrogen atom borne by the carbon C15. Due to the small angle C15–C4–C16, the oxygen O2 is push away and consequently the angle O2–C16–C4 is rather large (125.77°). Also worthy of note is the dihedral angle C5–C3–C4–C15 (15.3°) which deviates from its expected value of 0° thus minimising the interaction between the mesityl group and the carbon C15.

The best conformers were produced using a MMFF molecular mechanic model, followed by an AM1 semi-empirical calculation to establish the equilibrium geometry of each conformer. Finally a single point calculation by *ab initio* 6-31G(*) Hartree-Fock method gave the lowest energy of each best conformer. We have measured the dihedral angle and intramolecular distance in these stable conformations. The diamagnetic anisotropy effect was determined according to the literature.[8]

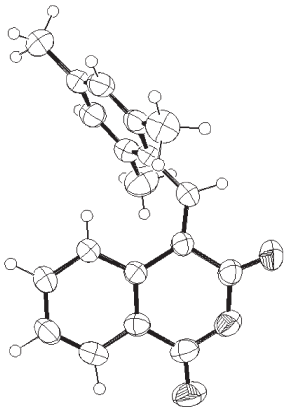

Fig. 1 ORTEP view of **3f**.

Conclusion

We have described a rapid and convenient synthesis of alkylidenisochromadione. Although some products were already known we have assigned, for the first time, the correct stereochemistry based on NMR analysis and one X-ray structure. These compounds could potentially be of interest for their biological properties and for their thermochromic properties.[9]

Experimental

Proton ^{1}H and ^{13}C NMR (reference from internal Me_4Si) were recorded on a Bruker AC 250 or 400 instrument from solution in $CDCl_3$. FT-IR spectra were recorded on a Perkin-Elmer 16 PC spectrometer. Microwave irradiations were carried out in a resonance cavity TE_{01} at 2450 MHz with a universal generator MES 73–800. Molecular modeling were performed using PC Plus Spartan (Wavefuntion Inc., 18401 Von Karman Ave, Suite 370, Irvine, CA 92612) on a 1 MHz Athlon PC computer. Mass spectra were recorded on a Varian Saturn 2000. Electronic ionization was used except **3d** (chemical ionization with acetonitrile).

Solvents were dried and degassed before use. Melting points (MP; °C) are uncorrected.

Typical experiment: with anisaldehyde: Homophthalic acid (0.36 g, 2×10^{-3} mol) in acetic anhydride (10 ml) was irradiated in an open Pyrex tube 8 mm diameter with focused microwaves (40 W or 100W) in resonance cavity TE_{01} at 2450 MHz with an universal generator MES 73-800 for 15 min. Anisaldehyde (0.272g, 2×10^{-3} mol) and ammonium acetate (7.7 mg, 10^{-4} mol) was added and the mixture was irradiated for 2 min (250W). The product was filtered off and re crystallised from ethanol (yield 75%).

Structure solution and refinement: The crystal structure was solved by direct methods using SHELX97 package.[10] All non-hydrogen atoms were refined anisotropically and the structure was refined by full matrix least-squares analysis (264 parameters) to a conventional R factor (all data) of 0.0957. The Goodness of fit (GOF) was 1.101. The all H atoms were placed *via* difference Fourier maps and refined with isotropic atomic displacement parameters.

Crystal data for compound **3f**: C_{19} H_{16} O_3 ; M = 292.34; Space group *P-1*, Triclinic ; a = 8.033(5), b = 8.281(3), c = 12.118(7) Å, α = 80.03(4), β = 88.46(5), γ = 69.87(4) ; U = 745.0(7) Å^3 , Z = 2 ; Mo K_α radiation (λ= 0.71073 Å), μ (Mo K_α) = 0.088 mm^{-1} ; Unique reflections = 3599.

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