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Ring Contraction of Sulfenamides Derived from Thiochroman-4-ones

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Abstract: Thiochroman-4-ones and chroman-4-ones react with an excess of thionyl chloride to give the α-chlorosulfenyl chlorides (2) which form sulfenamides (3) when treated with secondary amines. On hydrolysis, (3) undergo a ring contraction to give benzo[*b*]thiophen-3-ones (4).

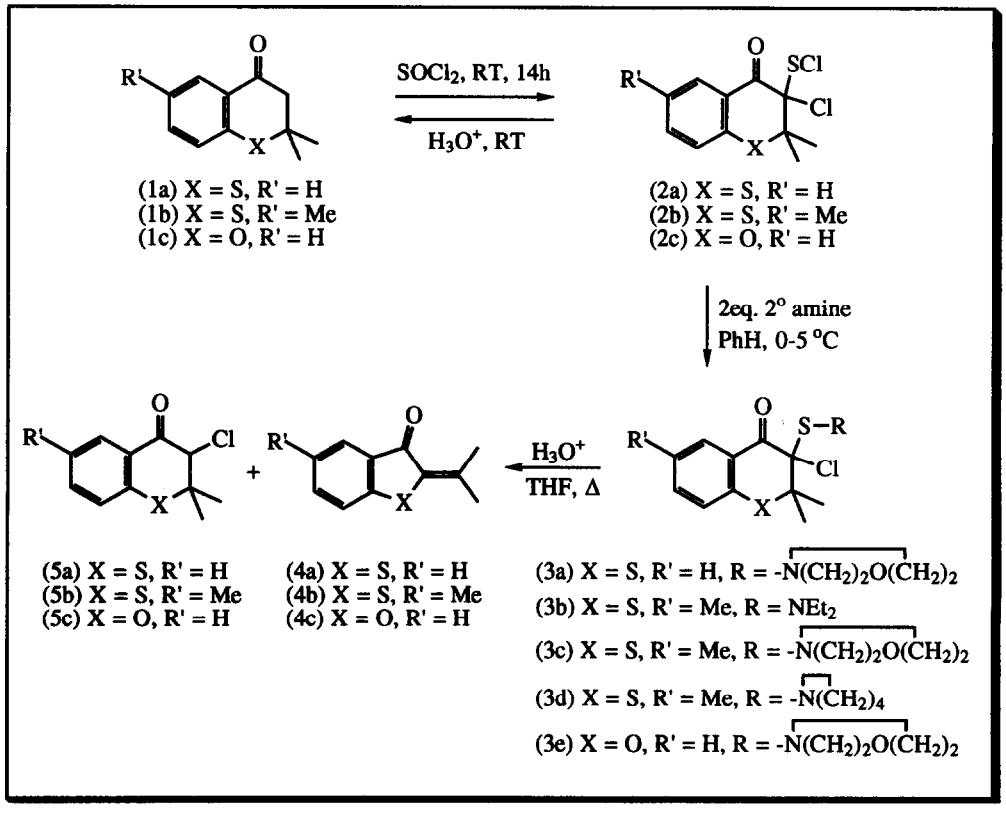
INTRODUCTION

As part of our study of condensed heterocycles containing a thiochroman unit,[1] we required a facile synthesis of thiochroman-3,4-diones, a so far unexplored aspect of thiochroman chemistry.[2] A survey of the literature indicated that the acidic hydrolysis of α-chlorosulfenamides, available from the pyridine catalysed reaction of thionyl chloride with α-methylene ketones[3] and addition of a secondary amine to the α-chlorosulfenyl chloride,[4] gave 1,2-diketones in good yield.[5] This route appeared attractive and we now report our initial results on its application to some oxygen and sulfur heterocycles.

RESULTS AND DISCUSSION

Stirring a solution of a 2,2-disubstituted thiochroman-4-one (1) overnight in an excess of thionyl chloride gave, on removal of the unreacted $SOCl_2$, the α-chlorosulfenyl chlorides (2) in high yield, without the need for the pyridine catalyst.[2]

The ^1H and ^{13}C NMR spectra of these compounds are markedly different from those of the thiochromanones.[6] The unsymmetrical substitution at C-3 confers diastereotopic properties on the geminal methyl groups which now appear as individual signals shifted slightly downfield at ~δ 1.6 and δ 1.8. Of course the signals for the C-3 methylene protons are absent. The most noticeable feature in the ^{13}C NMR spectra of the α-chlorosulfenyl chlorides is the considerable downfield shift of the C-3 signal, which now absorbs in the range δ 92-93 as a consequence of the presence of the two electronegative substituents. In comparison, C-3 in thiochromanones absorbs typically at ~ δ 50.[7]



Although the α-chlorosulfenyl chlorides (2) are hydrolysed to thiochromanones under acidic conditions, on treatment with two equivalents of a secondary amine in cold benzene the sulfenamides (3) are formed in excellent yield.

The ^1H and ^{13}C NMR spectra of these compounds closely resemble those of the starting α-chlorosulfenyl chlorides, though with the obvious presence of signals associated with the amine functionality. These latter signals were poorly resolved in all examples (3a-e). Figure 1 displays the partial ^1H NMR spectra of (3b) at different temperatures. At -20 °C, a complex multiplet results for each of the NCH_2

protons and the terminal methyl groups each afford a triplet. It is possible that this resolution is a consequence of restricted rotation of the diethylamino function. On warming, these signals collapse into broad peaks which on further warming (55 °C) begin to sharpen, as an averaged proton environment is now observed. Ultimately, a quartet and a triplet is expected for the diethylamino function, but we were unable to record the spectrum at a sufficiently high temperature to achieve this behaviour in $CDCl_3$. Attempts to observe this phenomenon by recording the spectrum in DMSO-d_6 at 90 °C resulted in the decomposition of the sample.

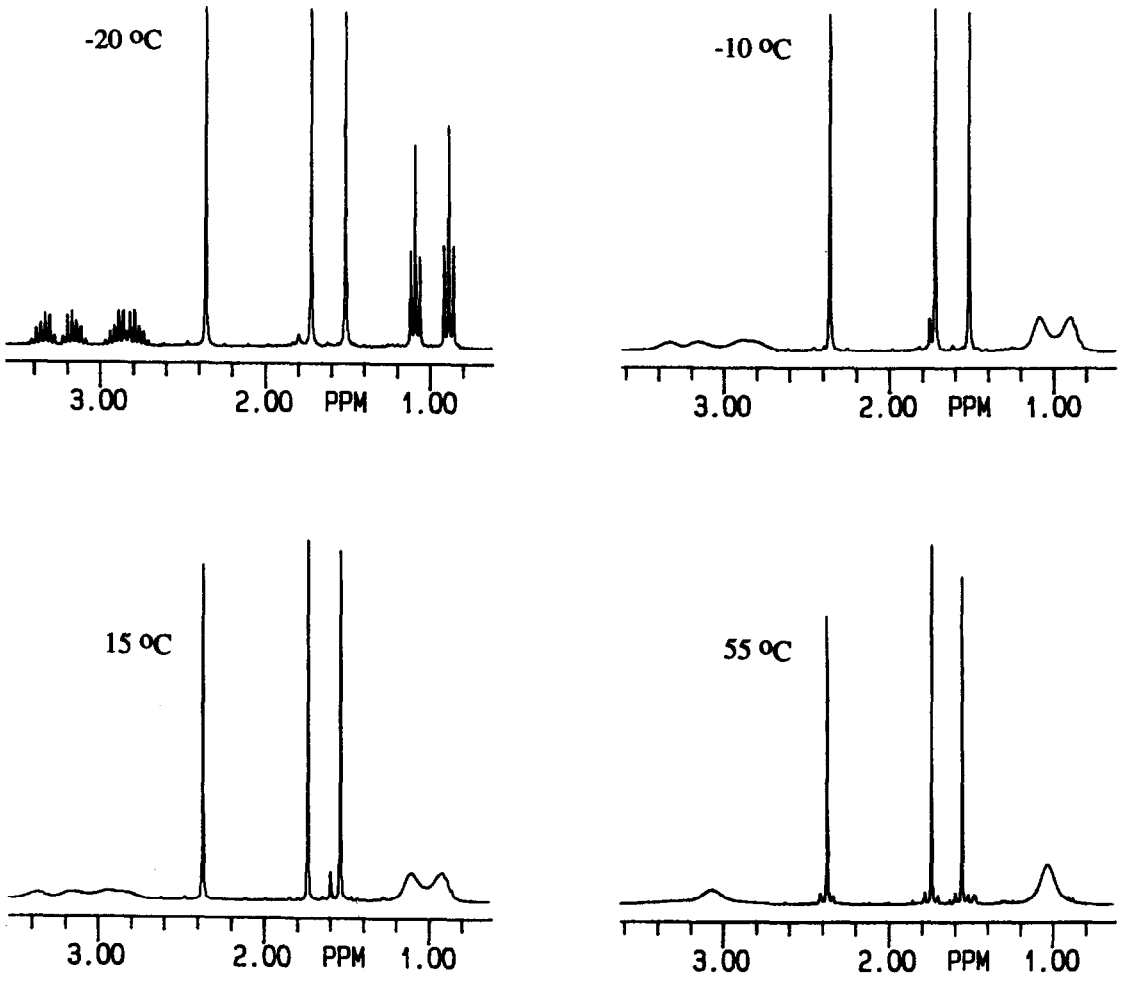


Figure 1 Partial ^1H NMR Spectra of (3b) at Different Temperatures.

When the sulfenamide (3a) was hydrolysed by refluxing with dilute HCl in THF, two products resulted which were separated by elution of the reaction mixture from silica. The least polar fraction was identified as 2,3-dihydro-2-isopropylidenebenzo[*b*]thiophene-3-one (4a) (69%) from its physical characteristics[8] and from its ^{1}H NMR spectrum which displayed methyl signals at δ 2.15 and δ 2.52, shifted downfield through conjugation with the carbonyl function. The infrared spectrum displayed a carbonyl stretching band at 1659 cm^{-1}, typical of an α,β-unsaturated carbonyl group. The more polar minor fraction was characterised as 3-chloro-2,2-dimethyl thiochroman-4-one (5a). The methyl groups of this compound are non-equivalent and absorb at δ 1.47 and δ 1.58 in the ^{1}H NMR spectrum and H-3 appears as a singlet at δ 4.76, shifted downfield by its proximity to the electron withdrawing substituents. This chemical shift compares favourably with that of H-3 (δ 4.90) in 3-bromothiochroman-4-one.[9] No thiochroman-3,4-dione was detected in the reaction mixture. Similar behaviour was shown by (3c) under identical conditions to those used for (3a), affording the benzo[*b*]thiophene-3-one (4b) (62%) and the chlorothiochroman-4-one (5b) (δ 4.75 for H-3). The hydrolysis of (3b) and (3d), in which only the amide function differs, gave identical reaction products to those obtained from (3c).

The α-chloroketones (5a and b) may be intermediate in the formation of the ring contracted product. Indeed, the alkaline hydrolysis of 3-chloro-2-methylthiochroman-4-one has been shown to afford 2-acetyl-2,3-dihydrobenzo[*b*]thiophene-3-one.[10] Additionally, the ring contraction of thiochromans with a suitably disposed 3-substituent *via* the intermediacy of a thiiranium cation has been documented.[11]

The sulfenamide (3e) derived from 2,2-dimethylchroman-4-one by identical procedures to those described for the sulfur analogues, gave the 3-chlorochroman-4-one (5c) and 2,2-dimethylchroman-4-one (1c) on hydrolysis. No comparable ring contracted product (4c) was observed, presumably because of the inability of the smaller oxygen heteroatom to provide anchimeric assistance in the expulsion of the 3-chloro substituent.

It is noteworthy that the melting point of (5c) is 20 °C lower than that reported in the literature.[12] However, ^{1}H and ^{13}C NMR spectra not only support the structure but also closely resemble those of various 3-bromo-2,2-dimethylchroman-4-ones prepared by bromination of the chromanone[13] and of several 2,2-disubstituted 3-chlorochroman-4-ones obtained by oxidation of the corresponding 3-chlorochroman-4-ols.[14] Furthermore, the identity of the compound was confirmed by high resolution electron impact mass spectrometry.

CONCLUSIONS

Thiochroman-4-ones react readily with thionyl chloride to give 3-chloro-3-chlorosulfenyl thiochroman-4-ones, subsequent treatment with a secondary amine affording 3-chloro-3-sulfenamidothiochroman-4-ones in excellent yield. The hydrolysis of these sulfenamides fails to produce a thiochroman-3,4-dione, instead forming a 3-chlorothiochroman-4-one and in particular affording a viable route to 2-alkylidenebenzo[*b*]thiophene-3-ones.

EXPERIMENTAL

Melting points were determined in capillary tubes and are uncorrected. Infrared spectra were recorded on a Mattson-Polaris Fourier Transform spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker WM250 instrument for solutions in $CDCl_3$; coupling constants are given in Hz. Flash chromatographic separations were performed on Crossfields Sorbsil C60 silica gel (M.P.D. 60Å, 40-60μ, activated) according to the published procedure.[15]

Conversion of Thiochroman-4-ones and Chroman-4-ones into their 3-Chloro-3-chlorosulfenyl Derivatives (1).

The ketone (10 mmol) was dissolved in thionyl chloride (100 mmol) and the solution kept overnight (14h) at room temperature. Removal of the excess thionyl chloride afforded a dark brown oil which crystallised on standing. Treatment with charcoal (Norit A) and recrystallisation from hexane and ethyl acetate afforded the following compounds.

3-Chloro-3-chlorosulfenyl-2,2-dimethylthiochroman-4-one (**2a**) (82%) as bright yellow crystals; m.p. 144.0-145.0 °C; υ_{max}/(Nujol) cm^{-1} 1705; δ_H 1.63 (3H, s, 2-Me), 1.85 (3H, s, 2-Me), 7.21-7.51 (3H, m, Ar-H), 8.31 (1H, dd, *J* 8.0, 1.5, 5-H); δ_C 24.7, 26.1, 52.3, 92.0, 126.7, 127.4, 128.6, 131.5, 133.8, 136.7, 180.3 (Found: C, 45.0; H, 3.4; Cl, 24.2; S, 21.6. $C_{11}H_{10}Cl_2OS_2$ requires C, 45.0; H, 3.4; Cl, 24.2; S, 21.8%).

3-Chloro-3-chlorosulfenyl-2,2,6-trimethylthiochroman-4-one (**2b**) (93%) as bright yellow crystals; m.p. 131.5-133.0 °C; υ_{max}/(Nujol) cm^{-1} 1695; δ_H 1.59 (3H, s, 2-Me), 1.83 (3H, s, 2-Me), 2.38 (3H, s, 6-Me), 7.12 (1H, d, *J* 8.0, 8-H), 7.29 (1H, dd, *J* 8.0, 1.2, 7-H), 8.11 (1H, d, *J* 1.2, 5-H); δ_C 20.8, 24.6, 26.1, 52.3, 92.3, 127.4, 128.4, 131.6, 133.3, 134.8, 136.9, 180.4 (Found: C, 47.2; H, 3.9; Cl, 22.9; S, 20.6. $C_{12}H_{12}Cl_2OS_2$ requires C, 46.9; H, 3.9; Cl, 23.1; S, 20.9%).

3-Chloro-3-chlorosulfenyl-2,2-dimethylchroman-4-one (**2c**) (88%) as bright yellow crystals; m.p. 84.5-85.5 °C; υ_{max}/Nujol cm^{-1} 1707; δ_H 1.51 (3H, s, 2-Me), 1.76 (3H, s, 2-Me), 6.96 (1H, dd, *J* 8.1, 1.2, 8-H), 7.11 (1H, m, 6-H), 7.56 (1H, m, 7-H), 7.99 (1H, dd, *J* 8.0, 1.2, 5-H); δ_C 22.5, 24.3, 85.8, 86.8, 118.0, 118.3, 122.4, 128.6, 136.6, 157.1, 180.2 (Found C, 47.7; H, 3.6; Cl, 25.4, S, 11.4. $C_{11}H_{10}Cl_2O_2S$ requires C, 47.7; H, 3.6; Cl, 25.6, S, 11.6%).

Preparation of 3-Chloro-3-sulfenamide Derivatives (3) of Thiochroman-4-ones and Chroman-4-ones.

A solution of the secondary amine (10 mmol) in dry benzene (10 cm^3) was added dropwise over a period of 5 minutes to a vigorously stirred solution of the 3-chloro-3-sulfenyl derivative (5 mmol) in benzene (30 cm^3) cooled to 5 °C. The resulting viscous solution was allowed to warm to room temperature and was then filtered through a celite pad, which was then washed well with benzene. Removal of the benzene gave the crude products which were recrystallised as below.

3-Chloro-2,2-dimethyl-3-(morpholinosulfenyl)thiochroman-4-one (**3a**) (99%) as pale yellow crystals from hexane; m.p. 128.0-129.0 °C; υ_{max}/(Nujol) cm^{-1} 1680; δ_H 1.54 (3H, s, 2-Me), 1.70 (3H, s, 2-Me), 2.95 (4H, bm, $(CH_2)_2N$), 3.57 (4H, bm, $(CH_2)_2O$), 7.15-7.45 (3H, m, Ar-H), 8.22 (1H, dd, *J* 8.0, 1.2, 5-H); δ_C 25.1, 25.3, 50.7, 57.5, 67.8, 95.2, 125.5, 126.8, 129.0, 130.5, 133.3, 138.2, 183.8 (Found: C, 52.6; H, 5.5; Cl, 10.3; N, 4.1; S, 18.8. $C_{15}H_{18}ClNO_2S_2$ requires C, 52.4; H, 5.3; Cl, 10.3; N, 4.1; S, 18.7%).

3-Chloro-3-(diethylaminosulfenyl)-2,2,6-trimethylthiochroman-4-one (**3b**) (78%) as pale yellow crystals from light petroleum (b.p. 30-40 °C); m.p. 78.0-79.0 °C; υ_{max}/(Nujol) cm^{-1} 1687; δ_H 0.92 (3H, bm, CH_3CH_2N), 1.10 (3H, bm, CH_3CH_2N), 1.54 (3H, s, 2-Me), 1.73 (3H, s, 2-Me), 2.37 (3H, s, 6-Me), 2.80 (1H, bm, CH_3CH_2N), 2.87 (1H, bm, CH_3CH_2N), 3.16 (1H, bm, CH_3CH_2N), 3.34 (1H, bm, CH_3CH_2N), 7.05 (1H, d, *J* 8.1, 8-H), 7.22 (1H, dd, *J* 8.0, 1.0, 7-H), 8.05 (1H, d, *J* 1.2, 5-H); δ_C 14.2, 20.8, 25.1, 25.4, 42.1, 50.9, 51.1, 52.8, 95.7, 126.7, 128.9, 130.8, 134.3, 134.7, 135.3, 184.9 (Found: C, 55.9; H, 6.5; Cl, 10.2; N, 4.1; S, 18.6. $C_{16}H_{20}ClNOS_2$ requires C, 55.9; H, 6.5; Cl, 10.3; N, 4.1; S, 18.6%).

3-Chloro-3-(morpholinosulphenyl)-2,2,6-trimethylthiochroman-4-one (**3c**) (91%) as pale yellow crystals from hexane and ethyl acetate; m.p. 138.0-140.5 °C; υ_{max}/(Nujol) cm^{-1} 1682; δ_H 1.53 (3H, s, 2-Me), 1.70 (3H, s, 2-Me), 2.37 (3H, s, 6-Me), 3.00 (4H, bm, $(CH_2)_2N$), 3.59 (4H, bm, $(CH_2)_2O$), 7.07 (1H, d, *J* 8.1, 8-H), 7.24 (1H, dd, *J* 8.0, 1.1, 7-H), 8.04 (1H, d, *J* 1.0, 5-H); δ_C 20.8, 25.1, 25.3, 50.7, 57.1, 67.8, 95.5, 126.8, 128.8, 130.7, 134.5, 134.8, 135.5, 184.0 (Found: C, 53.7; H, 5.6; Cl, 10.2; N, 3.9; S, 17.9. $C_{16}H_{20}ClNO_2S_2$ requires C, 53.7; H, 5.6; Cl, 9.9; N, 3.9; S, 17.9%).

3-Chloro-3-(pyrrolidinosulphenyl)-2,2,6-trimethylthiochroman-4-one (**3d**) (92%) as pale yellow crystals from light petroleum (b.p. 30-40 °C); m.p. 109.0-110.5 °C; υ_{max}/(Nujol) cm^{-1} 1681; δ_H 1.52 (3H, s, 2-Me), 1.78 (7H, bm, s, 2-Me, $(CH_2)_2$), 2.36 (3H, s, 6-Me) 3.09 (4H, bm, $(CH_2)_2N$), 7.04 (1H, d, *J* 8.0, 8-H), 7.23 (1H, dd, *J* 8.0, 1.4, 7-H) 8.05 (1H, d, *J* 1.3, 5-H); δ_C 20.8, 25.2, 25.3, 26.3, 50.8, 55.7, 96.0, 126.7, 128.9, 130.8, 134.3, 134.8, 135.2, 185.3 (Found: C, 56.3; H, 5.9; Cl, 10.5; N, 4.1; S, 18.6. $C_{16}H_{20}ClNOS_2$ requires C, 56.2; H, 5.9; Cl, 10.4; N, 4.1; S, 18.7%).

3-Chloro-2,2-dimethyl-3-(morpholinosulfenyl)chroman-4-one (**3e**) (93%) as colourless crystals from light petroleum (b.p. 40-60 °C) and hexane; m.p. 107.5-109.0 °C; υ_{max}/(Nujol) cm^{-1} 1695; δ_H 1.45 (3H, s, 2-Me), 1.73 (3H, s, 2-Me), 2.93 (4H, bm, $-N(CH_2)_2-$), 3.51 (4H, bm, $-O(CH_2)_2-$), 6.93 (1H, dd, *J* 8.0, 1.1, 8-H), 7.06 (1H, m, 6-H), 7.51 (1H, m, 7-H), 7.96 (1H, dd, *J* 8.2, 1.3, 5-H); δ_C 21.7, 23.9, 56.9 (broad, 2 x C), 67.7 (2 x C), 85.0, 88.5, 118.0, 119.7, 121.7, 127.7, 136.0, 157.5, 183.7 (Found: C, 55.1; H, 5.6; Cl, 11.0; N, 4.4; S, 9.7. $C_{15}H_{18}ClNO_3S$ requires C, 55.0; H, 5.6; Cl, 10.8; N, 4.3; S, 9.8%).

Acidic Hydrolysis of the α-Chlorosulfenamides (3).

A vigorously stirred solution of (**3**) (3 mmol) in THF (20 cm^3), water (8 cm^3) and conc. HCl (8 cm^3) was refluxed until tlc examination of the reaction mixture indicated that no starting material remained (1.5h). The cooled solution was diluted with water (200 cm^3) and extracted with ethyl acetate (3 x 50 cm^3). Removal of the solvent from the dried (Na_2SO_4) extracts gave a dark orange oil which was eluted from silica gel with 15% ethyl acetate in hexane to give two fractions:

(**3a**) Gave Fraction 1. *2,3-Dihydro-2-isopropylidenebenzo[b]thiophen-3-one* (**4a**) (69%) from light petroleum (b.p. 30-40 °C); m.p. 103.0-104.5 °C [lit. m.p. 103-105 °C[8]]; υ_{max}/(Nujol) cm^{-1} 1687; δ_H 2.15 (3H, s, Me), 2.52 (3H, s, Me), 7.20 (1H, m, Ar-H), 7.43 (1H, d, *J* 7.8, Ar-H), 7.51 (1H, m, Ar-H), 7.82 (1H, d, *J* 7.7, Ar-H); and Fraction 2. *3-Chloro-2,2-dimethylthiochroman-4-one* (**5a**) (19%) from light petroleum (b.p. 40-60 °C) and ethyl acetate; m.p. 74.5-75.5 °C; υ_{max}/(Nujol) cm^{-1} 1686; δ_H 1.47 (3H, s, 2-Me), 1.58 (3H, s, 2-Me), 4.76 (1H, s, 3-H), 7.20-7.24 (2H, m, Ar-H), 7.41 (1H, m, Ar-H), 8.11 (1H, dd, *J* 8.6, 1.8, 5-H). (Found C, 58.1; H, 4.8; Cl, 15.6; S, 14.3. $C_{11}H_{11}ClOS$ requires C, 58.3; H, 4.9; Cl, 15.6; S, 14.1%).

(**3c**) Gave Fraction 1. *2,3-Dihydro-2-isopropylidene-5-methylbenzo[b]thiophen-3-one* (**4b**) (62%) from light petroleum (b.p. 30-40 °C); m.p. 96.5-98.0 °C; υ_{max}/(Nujol) cm^{-1} 1684; δ_H 2.13 (3H, s, Me), 2.38 (3H, s, 5-Me), 2.52 (3H, s, Me), 7.33 (2H, m, Ar-H), 7.63 (1H, d, *J* 1.2, 4-H) (Found C, 70.5; H, 5.9; S, 15.6. $C_{12}H_{12}OS$ requires C, 70.6; H, 5.9; S, 15.7%); and Fraction 2. *3-Chloro-2,2,6-trimethylthiochroman-4-one* (**5b**) (28%) from light petroleum (b.p. 60-80 °C) and ethyl acetate; m.p. 85.0-86.0 °C; υ_{max}/(Nujol) cm^{-1} 1688; δ_H 1.47 (3H, s, 2-Me), 1.57 (3H, s, 2-Me), 2.35 (3H, s, 6-Me), 4.75 (1H, s, 3-H), 7.13 (1H, d, *J* 8.1, 8-H), 7.28 (1H, dd, *J* 8.0, 1.4, 7-H), 7.94 (1H, d, *J* 1.4, 5-H). (Found C, 60.0; H, 5.4;Cl, 14.9; S, 13.2. $C_{12}H_{13}ClOS$ requires C, 59.9; H, 5.5;Cl, 14.7; S, 13.3%).

(**3e**) Gave Fraction 1. *3-Chloro-2,2-dimethylchroman-4-one* (**5c**) (17%) as colourless crystals from light petroleum (b.p. 40-60 °C); m.p. 37.5-39.0 °C [lit. m.p. 57-58 °C[12]]; υ_{max}/(Nujol) cm^{-1} 1695; δ_H 1.53 (3H, s, 2-Me), 1.56 (3H, s, 2-Me), 4.40 (1H, s, 3-H), 6.97 (1H. dd, *J* 8.0, 1.2, 8-H), 7.04 (1H, m, 6-H), 7.52 (1H, m, 7-H), 7.90 (1H, dd, *J* 8.0, 1.3, 5-H); δ_C 22.1, 24.8, 64.6, 81.3, 118.2, 118.4, 121.5, 127.6, 136.6, 158.6, 186.1 (Found M^+, 210.0448; C, 62.8; H, 5.2; Cl, 16.8. $C_{11}H_{11}ClO_2$ requires M^+, 210.0447(6); C, 62.7; H, 5.3; Cl, 16.8%); and Fraction 2. 2,2-dimethylchroman-4-one (**2c**) (56%) as colourless crystals from hexane and ethyl

acetate; m.p. 88.0-88.5 °C [lit. m.p. 88-89 °C[16]]; δ_H 1.46 (6H, s, 2-Me), 2.73 (2H, s, 3-H), 6.97 (2H, m, 8-H, 6-H), 7.47 (1H, m, 7-H), 7.87 (1H, dd, *J* 8.1, 1.4, 5-H).

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