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Synthesis of Oxo- and Thio-analogues of 2-Oxo-2*H*-chromen-7-yl Dimethylcarbamates

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ABSTRACT

A range of novel 2-oxo-2*H*-chromen-7-yl dimethylcarbamates was synthesized containing either an oxygen or sulphur atom in the α-position to the carbonyl or thiocarbonyl group of the amide moiety. The synthesis and spectroscopic data of these compounds are reported. Microwave synthesis was essential for the successful synthesis of some of the sulphur-containing carbamates. The synthesized compounds will be used in a subsequent study on the influence of the α-substituent on the amide rotational barrier.

KEY WORDS: rotational barrier, thiocarbamates

1. Introduction

Furocoumarins (psoralens) and their related coumarin derivatives, isopsoralens, are well recognized for their photochemotherapeutic activity.[1–3] For this reason, there has been much research performed to optimize and provide new routes for their synthesis.[2,4–7] Previous work in our group involved the development of a synthetic route toward derivatives of 7-oxo- and 7-thioisopsoralen derivatives substituted at the 5′ position, as potential DNA intercalators.[8] During this study, it was found that the 2-oxo-2*H*-chromen-7-yl dimethylcarbamate derivatives synthesized exhibited interesting and widely varying amide rotational isomerism.

The barriers to internal rotation in amides are a result of resonance between the nitrogen lone pair and the carbonyl group. This results in a partial double bond character in the C-N bond. This model, proposed by Pauling,[9] has been the subject of much contention and extensive research has been conducted to examine the actual influences and reason for this rotation. The bulk of research in this area has been conducted on small molecules such as dimethylformamide (DMF), dimethylacetamide (DMA), and their thio analogues. There is little literature, however, concerning larger molecules with additional substituents on the nitrogen and/or at the α-position to the carbonyl.[10,11]

With the intention to study this rotational optical isomerism further, a range of these compounds was synthesized to investigate the effect of an oxygen or sulphur substituent α to the amide carbonyl as illustrated in Fig. 1.

2. Results and Discussion

For carbamates (**3a–c**), the synthetic route is shown in Scheme 1. 7-Hydroxycoumarin (**1**) was treated with NaH and subsequently reacted with the relevant carbamoyl chloride (**2a–c**), to yield the 2-oxo-2*H*-chromen-7-yl dimethylcarbamates (**3a–c**) in 57–81 % yields.

In order to obtain analogues with sulphur at the α-position, as shown in Scheme 2, the prepared compound **3c** was subject to a Newman-Kwart-type rearrangement to form **3d**.

The Newman-Kwart rearrangement has been shown computationally by Jacobsen *et al.* to occur through a four-membered cyclic transition state in a concerted fashion (Scheme 3), which is consistent with earlier kinetic studies.[12–14] It has also been established by Jacobsen *et al.* that in order for this concerted process of C-O bond breaking and C-S bond formation in the transition state to occur, a π-system connected *via* oxygen to the thiocarbonyl moiety is essential. More recently a bimolecular transition state fitting these criteria has been proposed which is also a concerted process, but proceeds through an equivalent eight-membered ring, as shown in Fig. 2.[15] This transition state remains as yet uninvestigated.

Although this reaction is well-documented,[15–23] all attempts using conventional approaches failed to afford any product, yielding only charred remains. It has been reported that in some cases, decomposition occurs in the presence of atmospheric oxygen, before the rearrangement is able to take place.[23] In our case, a nitrogen atmosphere was applied to avoid this problem; however, it did not prevent decomposition. Compound **3d** was subsequently obtained, to our delight, in 89 % yield by use of microwave irradiation in the presence of a minimal volume of DMA. This result is attributed to non-thermal microwave effects. Interestingly, this result was obtained without the use of an inert atmosphere. Compound **3d** was subsequently used for both the rotational barrier investigations (which are currently under investigation) and as a starting material for **3e.**

In order to achieve the dithio analogues, it is necessary to cleave the carbamate group of compound **3d**, affording

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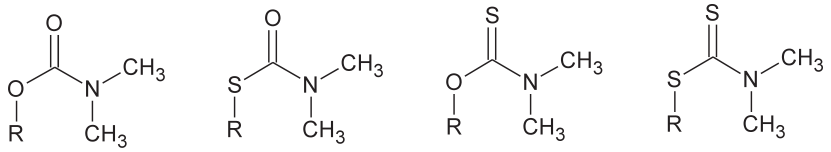
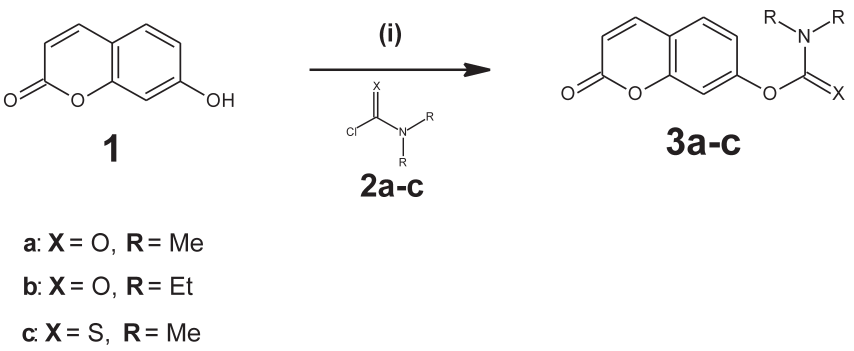
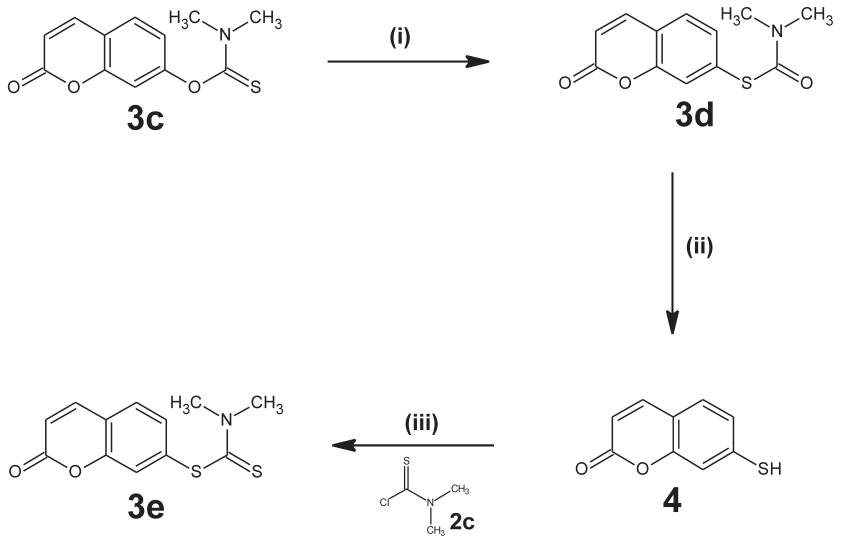


Figure 1 Structures of dimethylformamide analogues.



Scheme 1
(**i**) THF, NaH, then R_2NCXCl, 57–81 %



Scheme 2
(**i**) DMA, MW, 250 W, 260 °C, 89 %; (**ii**) KOH, MeOH, rf 7h, then HCl; (**iii**) THF, NaH, then $(CH_3)_2NCSCl$.

7-mercapto-2*H*-chromen-2-one (**4**). This can be subsequently treated with NaH and further reacted with *N,N*-dimethylthiocarbamoyl chloride, forming 2-oxo-2*H*-chromen-7-yl dimethylcarbamodithioate (**3e**). Unfortunately obtaining **3e** was not possible, as explained below.

Cleavage of the carbamate group to afford **4** can be achieved in two ways, by reflux under basic conditions[24] as described below or by reaction with $LiAlH_4$.[25] Both of these methods were performed and both were found to be unsuccessful, with recovery of the starting material only. The former mentioned method was attempted using both convection heating and microwave irradiation; to our surprise, the latter did not afford any product either.

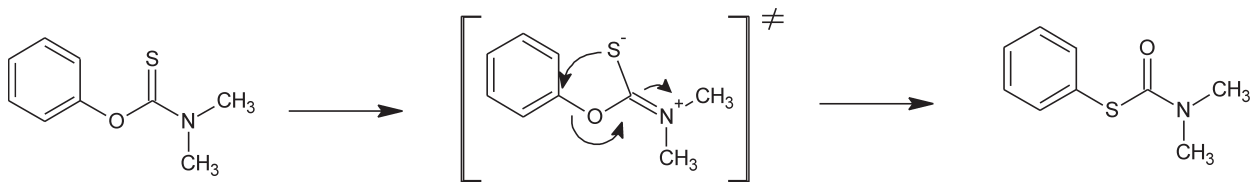
In summary, four of the five compounds required for further study were successfully synthesized (**3a**–**d**). Due to the inability to overcome the problem of cleaving the dimethylcarbamothioate group to yield **3e**, analogous phenolic compounds were synthesized as described in Scheme 4. Using this approach, the calculated barriers of **7a** and **7b** will be compared with those of their coumarin counterparts to determine whether the coumarin ring has a similar effect on C-N rotation as the phenyl ring and consequently whether these can be considered equivalent for potential comparison. If so, the data obtained for **7c** could be related to those of **3e**.

Phenol (**5**) was used as starting material for **7b,** the equivalent for **3c**. To obtain the equivalents for **3d** and **3e**, thiophenol (**6**) was used as a precursor. Compound **7c** could be prepared either by using *N,N*-dimethylcarbamoyl chloride with **6** or by Newman-Kwart rearrangement of **7b** under microwave irradiation.

The ^{1}H NMR spectra of these compounds show that the methyl peaks of the amide resonate as two separate peaks (see Fig. 3); however, in some cases these peaks are already partially (**3d** and **7a**) or completely (**7c**) coalesced at room temperature. This indicates a lower barrier to internal rotation.

The crystal structure of phenyl *N,N*-dimethylcarbamodithioate (**7c**) shows that the molecules pack in the $P2_1/c$ space group and are arranged perpendicular to one another (see Fig. 4).

As expected, the thioamide moiety is planar, indicating the



Scheme 3
Mechanism of the Newman-Kwart rearrangement.

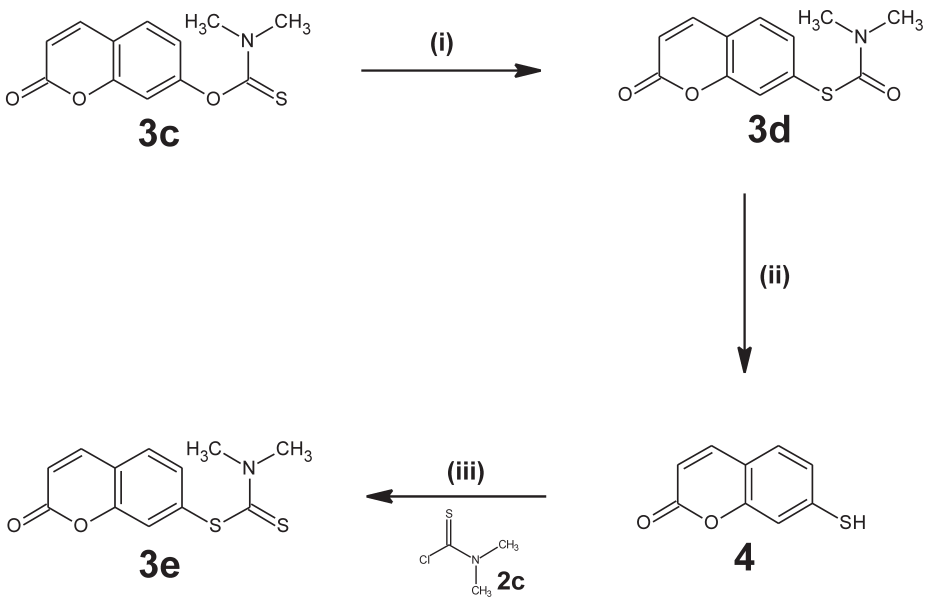
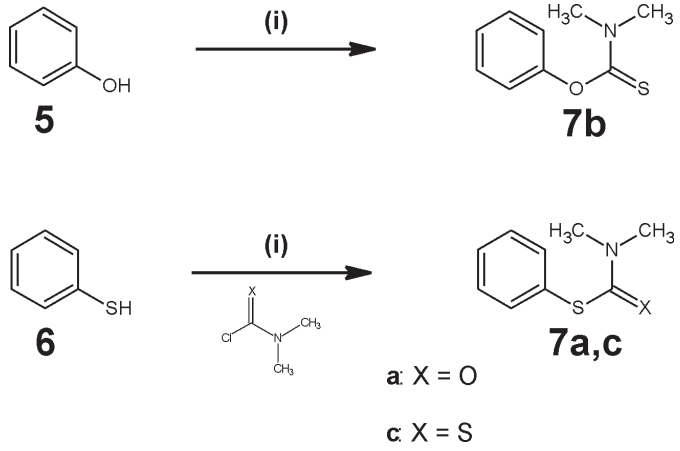


Figure 2 Proposed bimolecular transition state.[15]



Scheme 4
(**i**) THF, NaH, then $(CH_3)_2NCXCl$, 42–72 %.

resonance between the amine and thiocarbonyl. It is also observed to be rotated 88.6 ° out of the plane of the phenyl ring. Examination of the bond lengths also supports this ground state resonance; the C–N bond length is found to be 1.336 Å in the crystal structure, indicating it to be a partial double bond, the literature value for this being 1.34 Å.[26] Interestingly, the C=S bond length is found to be less than expected for partial resonance at 1.661 Å, compared with literature values of 1.82 Å (C–S) and 1.56 Å (C=S).[26]

One of the methods used to calculate the rotational barriers of these compounds is Exchange Spectroscopy (EXSY) NMR, a 2D NOESY method that makes use of the intensities of the relevant peaks to quantitate the magnetization exchange rates of the exchange equilibrium. This is achieved using the EXSYCalc program.[27] To do this, two spectra are required at mixing times of 0 and x (where x is large enough for the exchange process to occur). A representative example is shown in Fig. 5.

From the magnetization exchange rates, the rotational barrier is calculated using the Eyring equation,

$$\Delta G_{rot} = -RT \ln(k_1 h/k_b T) ,$$

where ΔG_{rot} is the Gibbs energy of rotation, R is the gas constant, T is the temperature, k_1 is the magnetization exchange rate, h is Planck's constant and k_b is Boltzmann's constant.

3. Conclusion

Four of the five coumarin analogues (**3a–d**) were successfully synthesized, however attempts to prepare the dithio derivative (**3e**) proved unsuccessful. To circumvent this problem, phenyl analogues (**7a–c**) were synthesized in order to obtain suitable analogues for further investigation by NMR spectroscopy and computational techniques obtained for C-N rotation in these

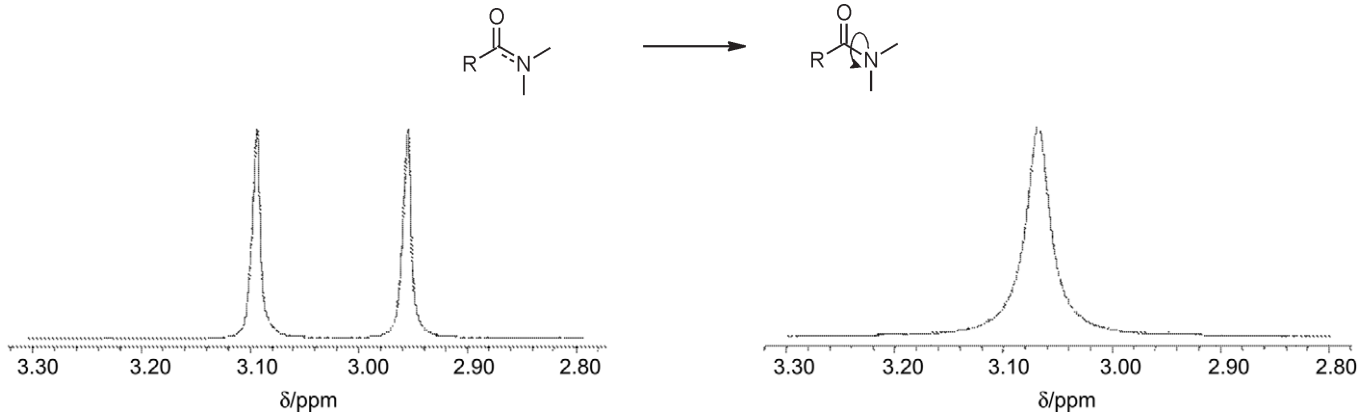


Figure 3 Coalescence of representative amide ^{1}H NMR signals with increasing temperature: left 303 K, right 344.5 K.

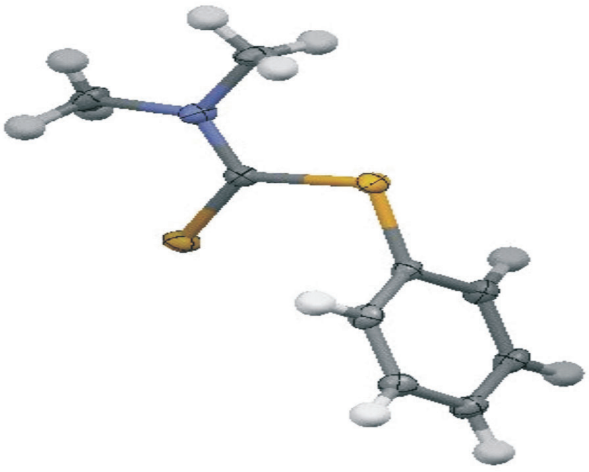


Figure 4 ORTEP model of crystal structure of compound **7c**.

simpler analogues (**7c** in particular). To the best of our knowledge, very little research has been conducted to date investigating the influence on the amide rotational barrier of substituents positioned α to the carbonyl group. Consequently we believe the synthesis of these compounds is important in order to shed light upon such processes, which forms part of an ongoing investigation.

4. Experimental

4.1. General

All NMR spectra were obtained from $CDCl_3$ or $C_2D_2Cl_4$ reference solutions using a Bruker (Karlsruhe, Germany) Avance 400 MHz spectrometer. ^{13}C spectra were obtained at 100 MHz.

Low-resolution mass spectra (electron impact) were obtained using a Thermofinnigan (Suwanee, GA, USA) trace GC coupled with a Polaris Q mass spectrometer. Infrared spectra were recorded with a Perkin-Elmer (Waltham, MA, USA) Spectrum One spectrometer as neat thin films or as nujol mulls. Melting points were recorded using a Kofler Hotstage melting point apparatus and are uncorrected. Radial chromatography was performed on a Harrison Research (Palo Alto, CA, USA) Chromatatron model 7924T using a 2 mm layer of Merck silica gel 7749. The solvent system was delivered by gravity flow. Microwave reactions were performed in a CEM Discovers (Matthews, NC, USA) Microwave System™. Tetrahydrofuran was distilled over sodium metal/benzophenone under a nitrogen atmosphere prior to use, and stored over 3 Å molecular sieves. Distilled hexane was used for all chromatography.

4.2. X-Ray Crystallography

Crystallographic measurements were made using a 3 kW Spellman X-ray generator (Oxford, UK) with a 3 kW ceramic X-ray tube and an Xcalibur 2 CCD diffractometer. The structure was solved using the SHELXS-97[28] program by direct methods. The structure was plotted using the program ORTEP.[29]

Crystal Data of Compound **7c**. $C_9H_{11}NS_2$, M = 197.31 g mol^{-1}, T = 100(2) K, λ = 0.71073 Å, a = 7.538(5), b = 8.989(5), c = 14.229(5) Å, α = 90.000(5), β = 90.959(5)°, γ = 90.000(5) °, V = 964.0(9) Å^3, space group $P2_1/c$, Z = 4, D_x = 1.359 mg m^{-3}, μ = 0.495 mm^{-1}, F(000) = 416. Crystal size 0.6 × 0.55 × 0.25 mm; θ range for data collection 3.82–34.11 °; index range –10<h<11, –13<k<13, –21<l<21; reflections collected 14 324; independent reflections 3567 [$R_{(int)}$ = 0.0538]; refinement method full-matrix least-squares on F^2; data/restraints/parameters 3567:0:153; goodness-of-fit on F^2 1.071; $R(F)$ [I>2ó(I)] = 0.0568; wR_2 = 0.1461; largest diff. peak and hole 1.721 and –0.986 e Å^{-3}.

4.3. Typical Synthesis of O-(2-oxo-2*H*-chromen-7-yl) *N,N*-dimethylcarbamothioate (3c)

NaH (0.093 g of an 80 % oil dispersion, 3.2 mmol) was added to a 100 mL round bottom flask under a dry nitrogen atmosphere. This was washed with a little THF to remove the oil. 7-Hydroxy-2*H*-chromen-2-one (0.50 g, 3.09 mmol) was then dissolved in dry THF (40 mL) in a round bottom flask and transferred *via* canula to the reaction vessel. This was allowed to stir at room temperature for 30 min until evolution of hydrogen gas had ceased. Dimethylthiocarbamoyl chloride (0.396 g, 3.2 mmol) was transferred *via* canula into the reaction as a solution in dry THF. The solution was then stirred at 60 °C for a further 30 min with a nitrogen-containing balloon to allow for increased pressure. The solution was then cooled and concentrated to 10 mL *in vacuo* after which it was poured over ice-water causing precipitation. This was filtered and recrystallized from ethanol to give the product as white crystals (0.636 g, 81 %), m.p. 182–183 °C (lit.[30] 156–157 °C).

^1H NMR (500 MHz, $C_2D_2Cl_4$) δ = 4.64 and 4.73 [2xs, 6H, N(C$\underline{H}_3$)$_2$], 7.68 (d, 1H , J = 9.52 Hz, H-3), 8.35 (dd, 1H, J = 2.22 and 8.30 Hz, H-8), 8.37 (d, 1H, J = 2.08 Hz, H-6), 8.79 (d, 1H,

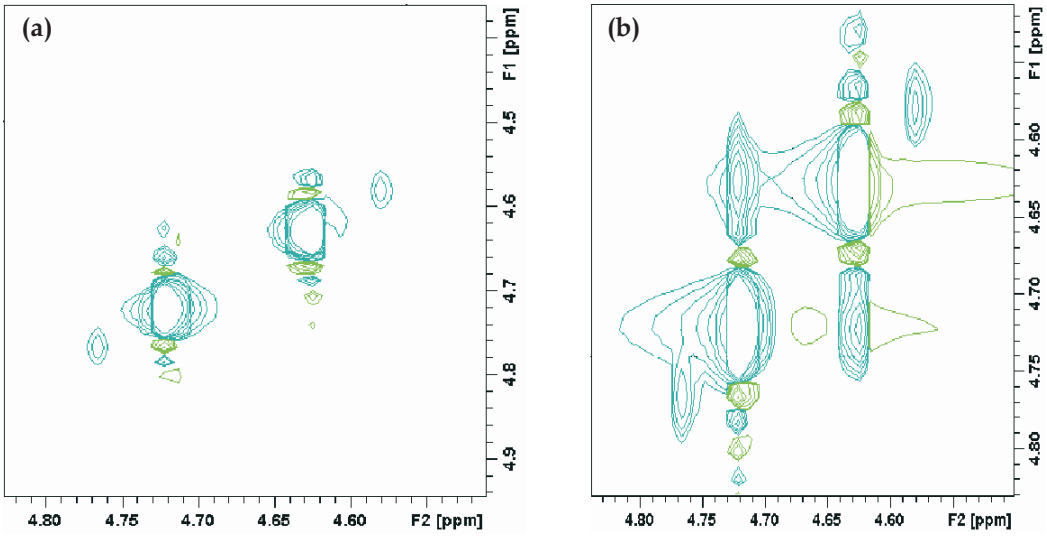


Figure 5 Partial ^1H 2D NOESY plots showing the two methyl peaks of a representative dimethylcarbamothioate group at mixing times of (**a**) 0 ms and (**b**) 1147 ms.

J = 8.32 Hz, H-5), 9.02 ppm (d, 1H, J = 9.56 Hz, H-4). ^{13}C NMR (100 MHz, $C_2D_2Cl_4$) δ = 40.4 and 44.8 [N(C$\underline{H}_3$)$_2$], 112.9 (C-8), 117.2 (C-2), 118.0 (C-4), 121.3 (C-6), 129.6 (C-5), 144.6 (C-3), 155.7 (C-9), 157.6 (C-1), 161.9 (C-7), 187.6 ppm (C-10). IR (neat): 2933, 1713, 1700, 1620, 1538, 1119, 839 cm^{-1}. MS (EIMS): *m/z* = 249 [M+] (5), 207 (2), 177 (6), 149 (7), 121 (9), 77 (6), 72 (100 %).

4.4. Attempted Synthesis of S-(2-oxo-2*H*-chromen-7-yl) *N,N*-dimethylcarbamothioate (6c)

O-(2-oxo-2*H*-chromen-7-yl) *N,N*-dimethylcarbamothioate (0.100 g, 0.40 mmol) was heated neat under nitrogen for 40 min at 240–260 °C. This was then cooled and an attempt to recrystallize from ethanol yielded only insoluble charred remains with 14 % starting material recovered. Attempts in refluxing solvent also failed, yielding the same insoluble remains with varying recovery of starting material.

4.5. Synthesis of S-(2-oxo-2*H*-chromen-7-yl) *N,N*-dimethylcarbamothioate (6c)

O-(2-oxo-2*H*-chromen-7-yl) *N,N*-dimethylcarbamothioate (64 mg, 0.26 mmol) was dissolved in 2 mL DMA in a microwave pressure tube and irradiated with 260 W for 40 min (cooling off). The solution was then cooled and 1 mL distilled water added, causing precipitation of the product as a pale orange solid. This was filtered and washed with cold water (2 × 6 mL aliquots) yielding 57 mg of the product (89 %), m.p. 179–184 °C (lit.[30] 180–183 °C).

^{1}H NMR (500 MHz, $C_2D_2Cl_4$) δ = 4.30 and 4.37 [2xs, 6H, N(CH$_3$)$_2$], 7.72 (d, 1H, J = 9.55 Hz, H-3), 8.71 (dd, 1H, J = 1.45 and 8.05 Hz, H-6), 8.76–8.79 (m, 2H, H-5 and H-8), 9.01 ppm (d, 1H, J = 9.45 Hz, H-4). ^{13}C NMR (100 MHz, $C_2D_2Cl_4$) δ = 30.8 (C-10), 117.0 (C-3), 118.8 (C-4a), 123.0 (C-8), 127.5 (C-5), 131.0 (C-6), 133.5 (C-7), 142.8 (C-4), 153.2 (C-8a), 160.1 (C-2), 165.0 ppm (C-9). IR (neat): 3051, 2928, 1717, 1664, 1601, 1392, 848 cm^{-1}. MS (EIMS): *m/z* = 249 [M+] (6), 207 (1), 177 (7), 149 (8), 121 (10), 77 (6), 72 (100 %).

4.6. Synthesis of 2-oxo-2*H*-chromen-7-yl *N,N*-dimethylcarbamate (3a)

Method was carried out as described for **3c** above. NaH (0.093 g of an 80 % oil dispersion, 3.2 mmol), 7-hydroxy-2*H*-chromen-2-one (0.50 g, 3.09 mmol), dimethylcarbamoyl chloride (0.342 g, 3.2 mmol). The remaining peach solid was purified by radial chromatography (1:2 ethyl acetate:hexane) to yield the product as white crystals (0.422 g, 57 %), m.p. 148–154 °C (lit.[30] 149–150 °C).

^{1}H NMR (500 MHz, $CDCl_3$) δ = 2.96 and 3.05 [2xs, 6H, N(C$\underline{H}_3$)$_2$], 6.30 (d, 1H, J = 9.65 Hz, H-3), 7.02 (dd, 1H, J = 2.20 and 8.44 Hz, H-6), 7.06 (d, 1H, J = 2.12 Hz, H-8), 7.38 (d, 1H, J = 8.44 Hz, H-5), 7.61 ppm (d, 1H, J = 9.52 Hz, H-4). ^{13}C NMR (100 MHz, $C_2D_2Cl_4$) δ = 36.5 and 36.8 [N(C$\underline{H}_3$)$_2$], 110.4 (C-8), 115.6 (C-3), 116.1 (C-4a), 118.6 (C-6), 128.3 (C-5), 142.9 (C-4), 153.8 (C-7), 154.2 (C-8a), 154.7 (N$\underline{C}$O), 160.6 ppm (C-2). MS (EIMS): *m/z* = 233 [M$^+$] (8), 133 (2), 105 (3), 77 (4), 72 (100), 51 (3 %).

4.7. Synthesis of 2-oxo-2*H*-chromen-7-yl *N,N*-diethylcarbamate (3b)

Method was carried out as described for **3c** above. NaH (0.093 g of an 80 % oil dispersion, 3.2 mmol), 7-hydroxy-2*H*-chromen-2-one (0.50 g, 3.09 mmol), diethylcarbamoyl chloride (0.434 g, 3.2 mmol). The product was obtained as a viscous mustard liquid, which could not be recrystallized or purified due to its tackiness.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.24 and 1.29 [2xt, 6H, J = 7.15 Hz, N(CH$_2$C$\underline{H}_3$)$_2$], 3.42 and 3.47 [2xq, 4H, J = 6.86 Hz, N(C$\underline{H}_2$CH$_3$)$_2$], 6.38 (d, 1H, J = 9.54 Hz, H-3), 7.12 (dd, 1H, J = 2.26 and 8.53 Hz, H-6), 7.15 (d, 1H, J = 2.26 Hz, H-8), 7.48 (d, 1H, J = 8.28 Hz, H-5), 7.70 ppm (d, 1H, J = 9.54 Hz, H-4). ^{13}C NMR (100 MHz, $C_2D_2Cl_4$) δ = 10.8 and 11.7 [N(CH$_2$C$\underline{H}_3$)$_2$], 39.6 and 39.9 [N(C$\underline{H}_2$CH$_3$)$_2$], 107.7 (C-8), 112.8 (C-3), 113.4 (C-4a), 116.2 (C-6), 125.9 (C-5), 140.8 (C-4), 115.6 (C-7), 115.9 (C-8a), 153.1 (N$\underline{C}$O), 158.3 ppm (C-2). MS (EIMS): *m/z* = 260 [M$^+$] (6), 134 (8), 100 (100), 72 (56), 44 (26 %).

4.8. Synthesis of *o*-phenol *N,N*-dimethylcarbamothioate

Method was carried out as described for **3c** above. NaH (0.147 g of an 80 % oil dispersion, 4.90 mmol), phenol (0.419 g, 4.45 mmol), dimethylthiocarbamoyl chloride (0.660 g, 5.34 mmol). The product was extracted with dichloromethane and purified by radial chromatography (1:2 ethyl acetate:hexane), to give 583 mg (72 %) as a yellow oil (lit.[30] m.p. 31–32 °C).

^{1}H NMR (500 MHz, $C_2D_2Cl_4$) δ = 3.31 and 3.43 [2xs, 6H, N(C$\underline{H}_3$)$_2$], 7.08 (2xd, 2H, J = 8.40 and 8.70 Hz, -O-C=C$\underline{H}$-CH=CH-), 7.26 (t, 1H, J = 7.42 Hz, -O-C=CH-CH=C$\underline{H}$-), 7.40 ppm (t, 2H, J = 7.95 Hz, -O-C=CH-C$\underline{H}$=CH-). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 38.7 and 43.2 [N(C$\underline{H}_3$)$_2$], 122.8 (O-C=C$\underline{H}$-CH=CH), 125.9 (O-C=CH-CH=C$\underline{H}$), 129.2 (O-C=CH-C$\underline{H}$=CH), 154.1 (O-C$\underline{=}$CH-CH=CH), 187.8 ppm [-O-(C$\underline{=}$S)-N]. IR (neat): 3340, 2940, 1781, 1535, 1395, 1206, 769, 691 cm^{-1}. MS (EIMS): *m/z* = 181 [M$^+$] (4), 180 (12), 88 (58), 72 (100 %).

4.9. Synthesis of S-phenyl *N,N*-dimethylcarbamothioate: Method 1

o-Phenol *N,N*-dimethylcarbamothioate (200 mg, 1.10 mmol) was dissolved in 2 mL DMA in a microwave pressure tube and irradiated with 260 W for 40 min (cooling off). The solution was then cooled and 1 mL distilled water added, causing deposition of the product as a dark orange oil. The DMA/water solution was decanted, to leave the oil product. Conversion was accomplished in 50 % yield by NMR.

4.10. Synthesis of S-phenyl *N,N*-dimethylcarbamothioate: Method 2

Method was carried out as described for **3c** above. Thiophenol (0.656 g, 5.95 mmol), NaH (0.157 g, 6.54 mmol), dimethylcarbamoyl chloride (0.735 g, 5.95 mmol). The product was extracted with dichloromethane and purified by radial chromatography (1:2 ethyl acetate:hexane) to give 679 mg (63 %) as a pale yellow oil, which solidified under vacuum, m.p. 41–42 °C (lit.[16] 43–44 °C).

^{1}H NMR (500 MHz, $CDCl_3$) δ = 4.32 [br. s, 6H, N(C$\underline{H}_3$)$_2$], 8.65–8.72 (m, 3H), 8.76–8.82 ppm (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 38.37 (N(C$\underline{H}_3$)$_2$), 130.17 (S-C$\underline{=}$CH-CH=CH), 130.3 (S-C=C$\underline{H}$-CH=CH), 130.5 (S-C=CH-CH=C$\underline{H}$), 137.1 (S-C=CH-C$\underline{H}$=CH), 168.0 ppm [S-(C$\underline{=}$O)-N]. IR (neat): 2974, 2885, 1455, 1380, 1090, 881 cm^{-1}. MS (EIMS): *m/z* = 180.9 [M$^+$] (6), 109 (7), 72.1 (100), 65.2 (6), 39.1 (3 %).

4.11. Synthesis of Phenyl *N,N*-dimethylcarbamodithioate

NaH (0.128 g of an 80 % oil dispersion, 4.26 mmol), thiophenol (0.427 g, 3.87 mmol), dimethylthiocarbamoyl chloride (0.574 g, 4.65 mmol). The product was extracted with dichloromethane and purified by radial chromatography (1:2 ethyl acetate:hexane), to give 321 mg (42 %) as a yellow solid, m.p. 88–92 °C (lit.[31] 93–94 °C).

^{1}H NMR (500 MHz, $CDCl_3$) δ = 3.52 and 3.57 [2xs, 6H, N(C$\underline{H}_3$)$_2$],

7.43–7.53 ppm (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 42.0 and 45.6 ($N(\underline{C}H_3)_2$), 129.1 (S-C=$\underline{C}$H-CH=CH), 130.0 (S-C=CH-CH=$\underline{C}$H), 131.8 (S-$\underline{C}$=CH-CH=CH), 136.9 (S-C=CH-$\underline{C}$H=CH), 197.6 ppm [S-($\underline{C}$=S)-N]. IR (neat): 3071, 1948, 1864, 1574, 1438, 1071, 738, 688 cm^{-1}. MS (EIMS): *m/z* = 197 [M+] (6), 196 (42), 88 (100 %).

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