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4-PHENYLSULPHINYL- AND 4-PHENYLSULPHONYL-COUMARINS AS 2π - COMPONENTS IN CYCLOADDITION REACTIONS.

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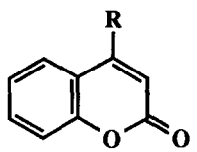
Abstract 4-Phenylsulphinyl - and 4-phenylsulphonyl-coumarins function as 2π-components in 1,3-dipolar cycloadditions to azomethine ylides generated by the Strecker Degradation, and in Diels-Alder reactions with 2,3-dimethylbutadiene. Thermal elimination of phenylsulphenic acid and aromatisation occurs in the cycloadduct derived from 4-phenylsuphinylcoumarin whilst cycloadducts from 4-phenylsulphonylcoumarin usually retain the phenylsulphonyl group and do not aromatise.

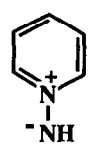
Coumarin (1a) typically exhibits low reactivity as a dienophile. Thus it fails to react with butadiene and isoprene and only reacts with 2,3-dimethylbutadiene under severe conditions (260°C, 40h) and in low yield (22%).[1] It's reactivity as a dipolarophile is mixed as judged by the yields obtained from 1,3-dipolar cycloaddition reactions with the azomethine imine (2)(28%)[2] and the nitrile imine (3)(63%).[3]



(1) a. R = H

b. R = SOPh

c. R = SO_2Ph

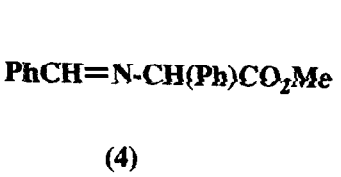


(2)

(3)

The abundance of naturally occurring coumanns[4] and their interesting physiological properties, e.g. aflatoxins,[5] angelicin,[6] warfarin and dicoumarol,[7] suggested an activated coumarin dienophile or dipolarophile would be synthetically useful. We therefore undertook the evaluation of (1b) and (1c). These compounds were prepared from 4-chlorocoumarin by reaction with thiophenol to give (1, R=SPh) followed by oxidation with 1 or 2 mole of 3-chloroperoxybenzoic acid to give (1b) and (1c) respectively. The sulphone has been reported previously.[8]

The benzylidene imine of phenylglycine methyl ester (4) failed to react with (1b) under conditions (xylene, 110°C) which are known to produce azomethine ylide (5) by 1,2-prototropy.[9] However, (1b) did react (DMF, 120°C, 24h) with the less stabilised azomethine ylide (6) formed *in situ* from phenyl glycine and benzaldehyde by condensation - decarboxylation.[10] The initial cycloadduct (7) eliminated phenylsulphenic acid under the reaction conditions and the resultant dihydropyrrole was aromatised to give (8) in 51% yield.



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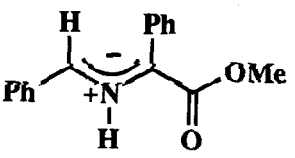

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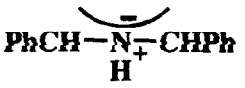

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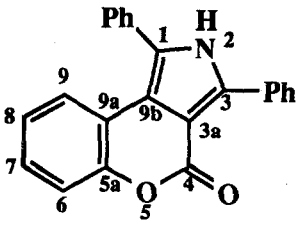

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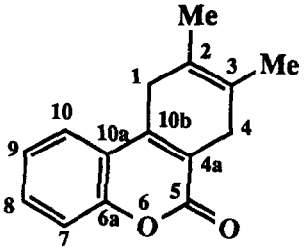

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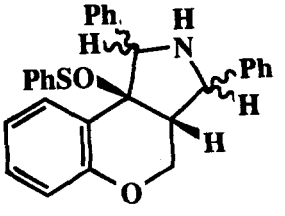

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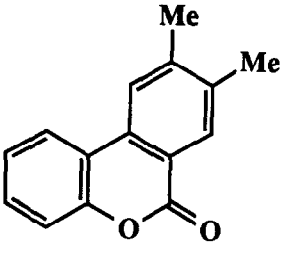

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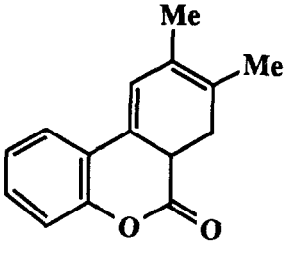
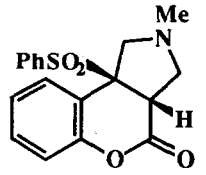


(11)

The sulphinyl coumarin (1b) reacts with 2,3-dimethylbutadiene under milder conditions (136°C, 36h) than coumarin itself, to give a ca. 2:1 mixture of (9) and (10). The presence of two triplets for the methylene groups at δ 3.1 and δ 3.3† together with two methyl singlets confirms structure (9) for the major product rather than (11). Efforts to separate (9) and (10) by thin-layer and column chromatography were unsuccessful. Hence the reaction mixture was oxidised with 2,3-dichloro - 5,6-dicyano - 1,4-benzoquinone to afford (10) in an overall yield of 74%.

The sulphonylcoumarin (1c) also failed to react with imine (4) on heating in toluene or xylene. However, (1c) reacts with a mixture of sarcosine and paraformaldehyde in boiling benzene to afford (13) in essentially quantitative yield. Thus (1c) traps the unstabilised azomethine ylide (14) generated in situ[11] to give (12) which subsequently eliminates phenylsulphinic acid regiospecifically to give (13).

An analogous reaction (DMF, 90°C, 1.5h) of (1c) with phenyl glycine and benzaldehyde occurred without loss of the phenylsulphonyl group and afforded a 4.4:1:3 mixture of (15), (16) and (17) in 80% combined yield. Chromatographic separation of the three isomers proved difficult and (15) and (17) were best separated by fractional crystallisation. The all-cis stereochemistry of 1-H, 3-H and 3a-H in (15) was assigned at the basis on n.O.e. data (see experimental). Assignment of relative



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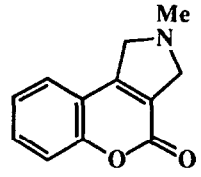

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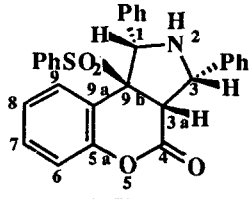

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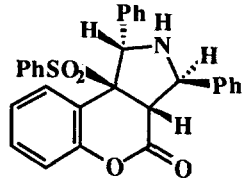

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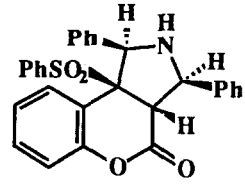

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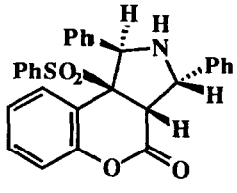

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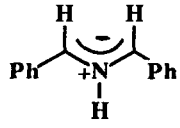

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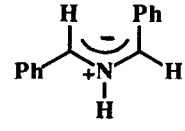

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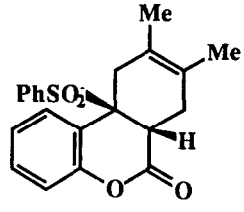

(21)

stereochemistry to (16) and (17) proved more difficult. The p.m.r. spectra of each isomer exhibited a singlet for 1-H whilst the 3-H and 3a-H appeared as mutually coupled doublets in both spectra. N.O.e experiments on both isomers showed that irradiation of the 1-H singlet resulted in enhancement of one of the doublet signals for the 3-H and 3a-H protons but not the other, thus ruling out structure (18). The chemical shifts of the 3-H and 3a-H protons in these two isomers are δ 4.62 and 4.15 and δ 4,27 and 4.20. The shielding effect of a cis-vicinal or a cis-1,3-phenyl substituent on the proton resonance signal in pyrrolidines is well established[12] whilst the $PhSO_2$ group would be expected to exert a deshielding effect on adjacent cis-protons. Thus the chemical shifts of the 3-H and 3a-H protons of the remaining two isomers accord with structure (16) for the isomer exhibiting proton signals at δ 4.62 and 4.15 and (17) for the isomer exhibiting signals at δ 4.27 and 4.20. Cycloadducts (15) and (17) are

derived from the syn-dipole (19) via endo- and exo- transition states respectively whilst (16) is derived from the anti-dipole (20).

The sulphonylcoumarin (1c) reacts with 2,3-butadiene in boiling benzene over 24h to afford the Diels-Alder adduct (21) in 72% yield. Thus there is the expected increase in dienophilic activity in going from (1a) to (1c).

Experimental General experimental details were as previously described.[9]

4-Phenylsulphinyl-2H-chromene-2-one (1b). 4-Phenylsulphenyl-2H-chromene-2-one (2.54g, 10mmol) was dissolved in methylene chloride (15ml) and the solution was cooled to 0°C. 3-Chloroperoxybenzoic acid (tech. grade 80-85%) (2.03g, 11.8mmol), dissolved in methylene chloride (25ml), was added dropwise with stirring over 0.5h and the reaction mixture was kept at room temperature for 15h. The mixture was then washed with 5% sodium bicarbonate (30ml), water (50ml), sodium bicarbonate (30ml), water (50ml), saturated brine (40ml) and water (2 x 50ml), and then dried (Na_2SO_4). The solvent was removed *in vacuo* to leave the crude product which was purified by flash chromatography eluting with 7:1 v/v toluene-ether, followed by crystallisation from ethanol to afford the product (1.86g, 69%), m.p. 154-156°C, as colourless prisms (found: C,66.5;H,3.8;S,11.9. $C_{15}H_{10}O_3S$ requires C,66.65; H,3.8;S,11.9%); ν_{max} 1715(CO),1050(SO),765 and 690 cm^{-1}; δ 7.27(1H, s, 3-H), 7.20-7.83 (9H, m, ArH); m/z (%) 270 (M^+, 24), 145(43) and 89(100).

1,3-Diphenylpyrrolo [3,4-c] chromene-4-one (8) A mixture of phenylsulphinyl-2H-chromene-2-one (1.62g, 6mmol), phenylglycine (0.907g, 6mmol) and benzaldehyde (0.637g, 6mmol) in DMF (30ml) was stirred and heated at 120°C for 24h. The reaction mixture was then poured over ice and the precipitated solid filtered, dissolved in chloroform (40ml), and washed with 2M sodium hydroxide (2 x 50ml), water (3 x 50ml) and dried (Na_2SO_4). The solvent was removed *in vacuo*, and the resulting gum triturated with ether to give the product as a cream solid (1.03g, 51%), which crystallised from benzene as colourless needles m.p. 272-275°C (found: C,81.65;H,4.5;N,4.25. $C_{23}H_{15}NO_2$ requires C,81.9;H,4.5;N,4.15%); ν_{max} 3350(NH), 1705 (CO), 765,755,740,705 and 700cm^{-1}; δ 6.97-7.87 (14H,m, ArH), 9.01 (1H, br s, 2-H); m/z(%) 337(M^+,100).

1,4-Dihydro-2,3-dimethyl-5H-benzo[c]chromene-5-one (9) and 2,3-dimethyl-5H-benzo[c]chromene-5-one (10). A mixture of 4-phenylsulphinyl-2H-chromene-2-one (1.62g, 6mmol) and 2,3-dimethylbuta-1,3-diene (1.452g, 17.7mmol) in xylene (8ml) was heated in a sealed tube at 136°C for 36h. The reaction mixture was then diluted with chloroform (60ml), washed with 5% sodium bicarbonate solution (2 x 75ml) and water (3 x 75ml) and dried (Na_2SO_4). The solvent was then removed *in vacuo* to yield the crude product in quantitative yield. The p.m.r. spectrum of the crude product showed it to be a 2:1 mixture of (9) and (10). Compound (9) was characterised only by it's p.m.r. δ 1.77 (3H, d, J 0.6Hz, Me), 1.80 (3H, d, J 0.67Hz, Me), 3.10 (2H, t, J 7Hz, CH_2), 3.31 (2H, t, J 7Hz, CH_2), 7.25-7.54 (4H, m, ArH).

The crude mixture of (9) and (10) was boiled in benzene (100ml) under reflux with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (2.27g, 10mmol) in an atmosphere of argon for 18h. Chloroform (70ml) was then added and the reaction mixture filtered. The filtrate was washed with water (3 x 150ml), 2M sodium hydroxide (2 x 100ml) and water (3 x 150ml) and dried (Na_2SO_4). The solvent was then removed *in vacuo* to leave the aromatised product (10) (996mg, 74%) as a nearly colourless solid,

which crystallised from ethyl acetate as colourless rods m.p. 177-179°C (Found: C,80.5;H,5.45; $C_{15}H_{12}0_2$ requires C,80.3;H,5.4%); ν_{max} 1715(CO) and 760cm^{-1}; δ 2.36 (3H, s, Me), 2.43 (3H, s, Me), 7.25-7.99 (4H, m, ArH), 7.80 (1H, s, 1-H), 8.08 (1H, s, 4-H); m/z(%) 224 (M^+, 100).

1,3-Dihydro-2-methyl-pyrrolo[3,4-c]chromene-4-one (13). A mixture of 4-phenylsulphonyl-2H-chromene-2-one (2.86g, 10mmol), sarcosine (14.24g, 0.16mmol) and paraformaldehyde (12g, 0.4mol) in boiling benzene (1.21) was stirred in a flask fitted with a Dean-Stark trap. Heating was continued for 3h. Chloroform was added (250ml), the reaction mixture filtered, and the filtrate evaporated *in vacuo*. The resulting crude product was dissolved in chloroform (400ml), and washed with 2M sodium hydroxide (2 x 300ml), and water (3 x 300ml), and dried (Na_2S0_4). The solvent was removed *in vacuo* to give the product as an off-white solid (1.97g, 98%), which crystallised from ethyl acetate as colourless needles m.p. 98-100°C (Found: C,71.7;H,5.5;N,7.0. $C_{12}H_{11}NO_2$ requires C,71.6;H,5.5;N,7.0%); ν_{max} 1715(CO), 770,750,730 and 715 cm^{-1}; δ 2.64 (3H, s, 2-Me), 3.97 (2H, t, J 4Hz, CH_2), 4.17 (2H, t, J 4Hz, CH_2), 7.25-7.56 (4H, m, ArH); m/z(%) 201(M^+, 100).

1,3,3a,9b-Tetrahydro-1,3-diphenyl-9b-phenylsulphonyl-pyrrolo[3,4-c]chroman-4-one (15)-(17). A mixture of 4-phenylsulphonyl-2H-chromene-2-one (2.86g, 10mmol), phenyl glycine (1.51g, 10mmol) and benzaldehyde (1.06g, 10mmol) in DMF (30ml) was stirred and heated at 90°C for 1.5h. The reaction mixture was then poured over crushed ice, and the colourless precipitate removed by filtration. This solid was dissolved in chloroform (60ml), and the solution was washed with water (2 x 100ml), dried (Na_2SO_4), and the solvent removed *in vacuo* to give the crude product (3.86g, 80%), whose p.m.r. spectrum showed it to comprise a 4.4:1:3 mixture of (15)-(17). Fractional crystallisation (benzene) gave pure (15). The mother liquor was evaporated to dryness, and the resulting solid was again crystallised from benzene. Three such cycles gave a mixture of isomers rich in (17). A further crystallisation produced large crystals, which proved to be pure (17). The resulting mother liquid was rich in (16) and p.m.r. data on (16) (including NOEDSY data) was obtained from this mixture.

1α,3α,3aα,9bα-Tetrahydro-1,3-diphenyl-9b-phenylsulphonyl-pyrrolo[3,4-c]chromene-4-one (15). Colourless needles (ethanol) m.p. 224-226°C (Found: C,72.6;H,4.8;N,3.0;S,6.65. $C_{29}H_{23}NO_4S$ requires C,72.3;H,4.8;N,2.9;S,6.7%); ν_{max} 3330(NH),17559(CO),1315 (sulphone), 1150(sulphone), 760,730,705 and 690 cm^{-1}; δ 4.54 (1H, d, J 11Hz, 3a-H), 5.08 (1H, d, J 11Hz, 3-H), 5.68 (1H, s, 1-H), 6.49-7.53 (19H, m, ArH), 7.70 (1H, br s, 2-H); ^{1}H NOEDSY (%): irradiation of 1-H caused enhancements of 3-H (6%), 3a-H (7), 2-H (10); irradiation of 3-H caused enhancements of 1-H (3), 3a-H (16); irradiation of 3a-H caused enhancements of 1-H (6) and 3-H (11); m/z (%) 340 (M-141,5) and 195(100).

1α,3β,3aα,9bα-Tetrahydro-1,3-diphenyl-9b-phenylsulphonyl-pyrrolo[3,4-c]chromene-4-one (16). Colourless prisms (benzene) m.p. 186-189°C (Found: C,72.1;H,5.0;N,2.8;S,6.9. $C_{29}H_{23}NO_4S$ requires C,72.3;H,4.8;N,2.9;S,6.7%); ν_{max}. 3350(NH),1760(CO),1300(sulphone),1145(sulphone),760,725,700, and 690 cm^{-1}; δ 4.15(1H, d, J 9Hz, 3a-H), 4.62(1H, d, J 9Hz, 3-H), 5.94(1H, s, 1-H), 6.77-7.55 (19H, m, ArH); ^{1}H NOEDSY(%); irradiation of 1-H caused enhancement of 3a-H (8); irradiation of 3-H did not cause enhancement of 1-H or 3a-H; irradiation of 3a-H caused enhancements of 1-H (5). m/z(%) 340(M^+,15), and 195(100).

1α,3α,3aβ,9bβ-Tetrahydro-1,3-diphenyl-9b-phenylsulphonyl-pyrrolo[3,4-c]chromene-4-one (17). δ 4.20(1H,

d, J 10Hz, 3a-H), 4.27(1H, d, J 10Hz, 3-H), 5.11(1H, s, 1-H), 6.71-8.13(19H, m, ArH); ^{1}H NOESDY(%): irradiation of 1-H caused enhancements of 3-H (7), ArH (20) and ArH (17).

1,4,4a,10b-Tetrahydro-2,3-dimethyl-10b-phenylsulphonyl-5H-benzo[c]chromene-5-one (21). A mixture of 4-phenylsulphonyl-2H-chromene-2-one (1.43g, 5mmol) and 2,3-dimethylbuta-1,3-diene (6ml) in benzene (30ml) was boiled under reflux for 24h. The reaction mixture was concentrated *in vacuo* to give a colourless solid which crystallised from benzene-light petroleum to give the product (1.33g, 72%) as colourless platelets m.p. 207-210°C (Found: C,68,6;H,5.6;S,8.6. $C_{21}H_{20}O_4S$ requires C,68.5;H,5.5;S,8.7%); ν_{max} 1760(CO), 1300 (sulphone), 1180 (sulphone), 770,760,720 and 690 cm^{-1}; δ 1.46(3H, s, Me), 1.66(3H, s, Me), 1.88-1.99(1H, br dd, 4-H), 2.34-2.43 (1H, br dd, 4-H), 2.80(2H, s, 1-H), 3.39(1H, dd, J 7 and 11Hz, 4a-H), 7.05-7.71(9H, m, ArH); m/z(%) 227(M^+, 100).

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