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Model Studies for Damage to Nucleic Acids Mediated by Thiyl Radicals

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Abstract. *The ability of phenylthiovinyl radicals to abstract hydrogen from appropriately substituted carbon atoms has been studied as a model for the reactions of the deoxyribose units of DNA with similar radicals in vivo.*

Resistance to radiotherapy and chemotherapy is inherent in certain tumour cell lines. In recent investigations of causes of such resistance, Ozols et al.[1] have determined that the intracellular levels of glutathione are raised to many times the normal level. Glutathione has at least two potential modes for conferring resistance:(i) as a nucleophilic thiol, it can intercept anti-tumour agents which act by alkylating DNA, and (ii) glutathione can quench reactive radicals such as those formed by high energy radiation on human tissue. The glutathionyl radical so formed is very unreactive towards DNA.[2]

In view of the above findings, we wished to design systems which could overcome the resistance to radiotherapy by making use of the high concentrations of glutathionyl radicals present in such cells. The simplest design for such a reagent would feature an alkyne linked to DNA. As shown in Figure 1, addition of a glutathionyl radical to such an alkyne leads to a vinyl radical which would be expected to be capable of abstracting a hydrogen[3] from deoxyribose.

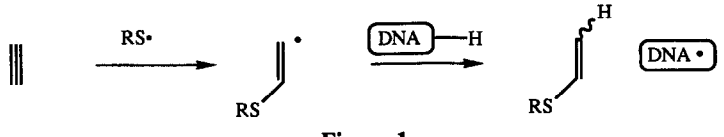


Figure 1

It is known that damage to DNA can be incurred as a result of abstraction of the 1', 4' or 5' hydrogens of a deoxyribose. Suitable abstracting agents are an hydroxyl radical[4] or a metal-bound oxyl radical[5] or the trigonal carbon radicals associated with such anti-tumour agents as neocarzinostatin, esperamicin and calicheamicin[6]. [The mechanism occasioned by removal of the 4' hydrogen is shown in Figure 2]. In each of the three cases, the reaction features formation of a stabilised radical on a carbon adjacent to oxygen. However, the hydrogen abstracting powers of β-thiovinyl radicals have not been studied in systems of this sort, and so we have now studied a number of substrates and the results form the subject of this paper.

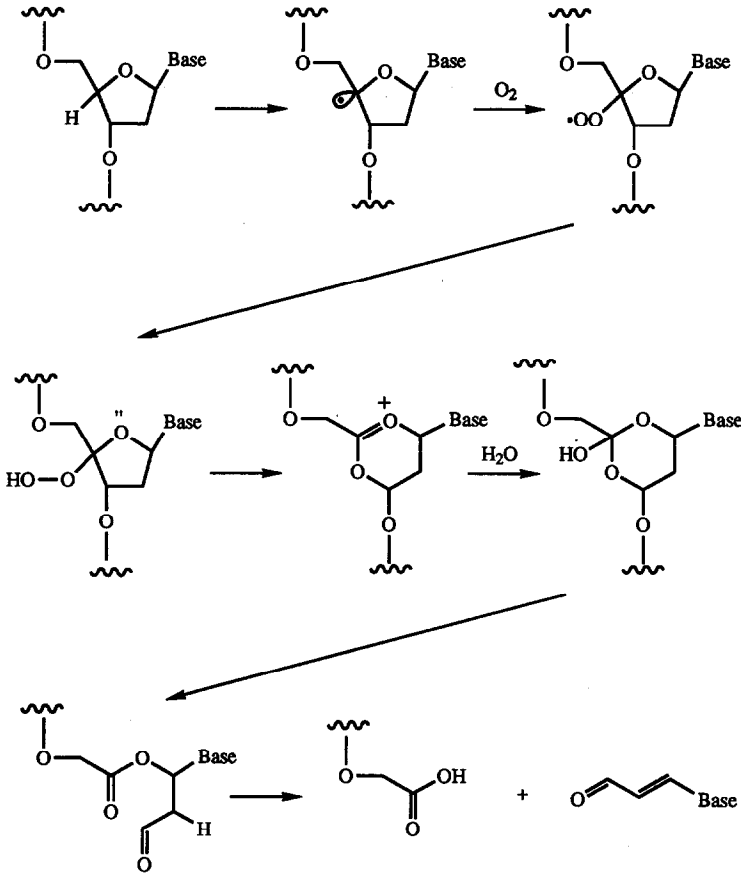
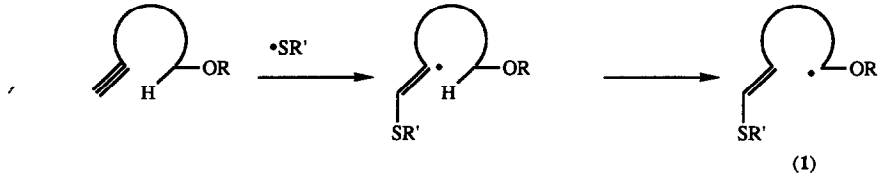


Figure 2

The general scheme planned for each of the substrates is shown in Figure 3. Addition of a thiyl radical to an alkyne leads to formation of a vinyl radical which is so placed as to favour abstraction of a particular



(1)

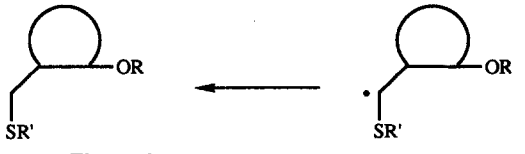
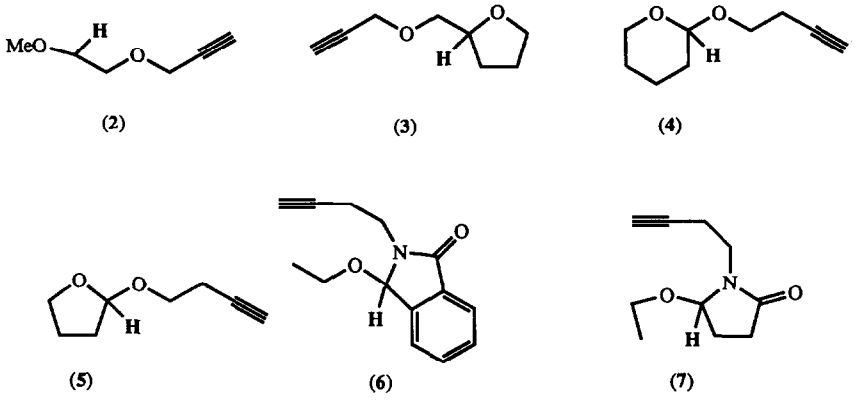


Figure 3

hydrogen; the radical produced (1), can add to the nearby alkene, and the isolation of such cyclic molecules would be one way to indicate the occurrence of the desired reaction. The model compounds synthesised are shown in Figure 4.

Thiyl radicals were easily generated from sun-lamp irradiation of phenyl disulphide; the reactions were performed in benzene. Benzene may not normally be thought of as being very similar to water, but these two solvents are two of the most inert to radical reactions.

Model Compounds



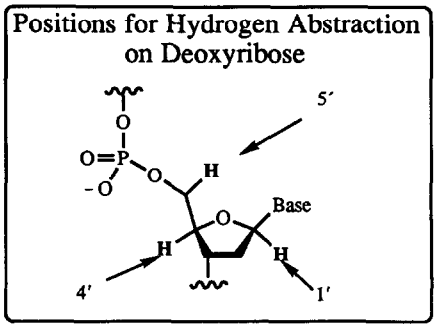


Figure 4

Compound (2) served as a model for removal of hydrogen from position 5' on deoxyribose, since in both cases the hydrogen is found on an acyclic carbon. Addition of phenylthiyl radicals to this molecule and to other molecules in this study led to complex product mixtures, and our product isolation from the crude reaction mixture for this experiment and for other related experiments was guided by nmr at each stage of the chromatographic purification. The products isolated from the reaction were (8), [as a mixture of E- and Z- isomers] and (9). The intramolecular reaction of vinyl radicals derived from alkynes with arenes to give products related to (9) has previously been observed but at very high (pyrolytic) temperatures[7]. The intermolecular equivalent where the intermediate radical attacks the benzene solvent is most surprising.

The cyclic ether (3) was next studied. Removal of the hydrogen shown in bold script would mimic 4'-hydrogen abstraction. The products isolated from the radical reaction, (10) and (11), were analogous to

those discussed above, but now the spiroether (12) was also seen. Complete purification of (12) proved impossible, so conversion of crude (12) to the corresponding sulphone (12a) was effected by treatment with oxone. This led to isolation of one diastereomer of the sulphone.

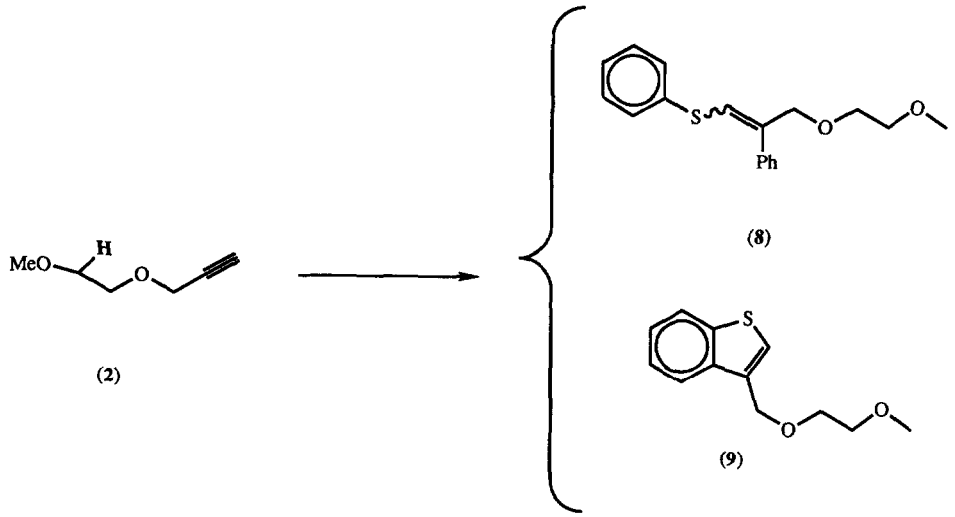


Figure 5

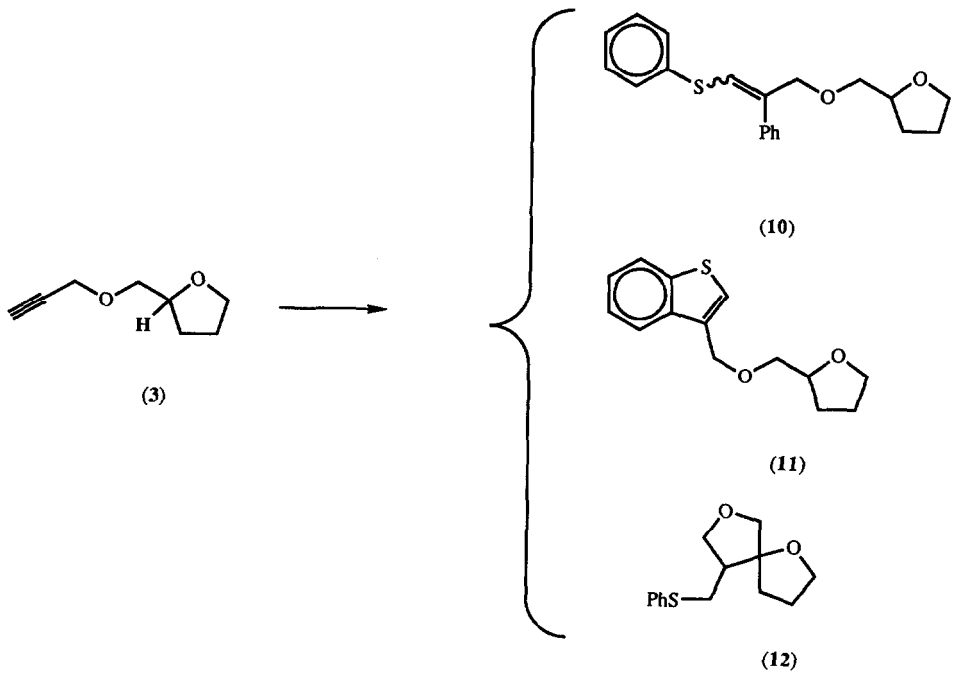


Figure 6

To model abstraction of the hydrogen atom at the 1' position on a deoxyribose, compounds (4) and (5) were initially studied[8]. At the 1' position, the hydrogen is linked to a carbon which is bonded to two heteroatoms; a radical resulting from abstraction of such a hydrogen should therefore be somewhat more stabilised than a radical at the 5' or 4'positions. Reaction of model (4) led to isolation of the spiroketal sulphide (13). The analogous sulphide (14) was formed from (5) but could not be completely purified from reaction of (5); however oxidation to the corresponding sulphone with oxone led to the corresponding sulphone (14a).

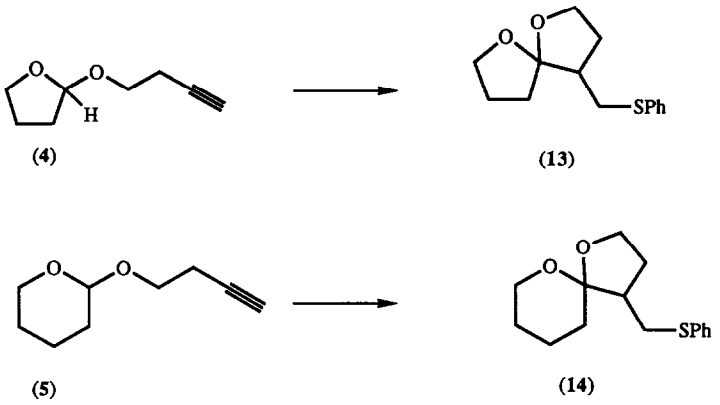
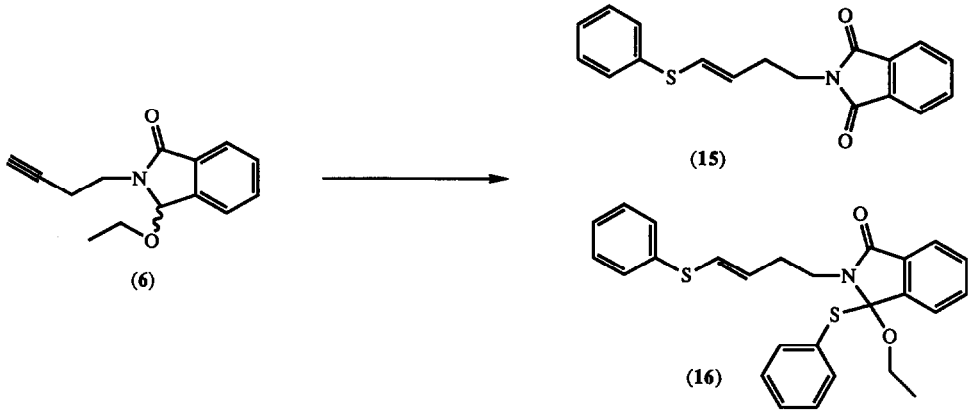


Figure 7

In attempts to produce closer models of the target 1'-hydrogen featuring adjacent oxygen and nitrogen rather than oxygen alone the compounds (6) and (7) were synthesised. The principal products resulting from substrate (6) were (15) and an unstable compound tentatively identified as (16). It was suspected that the imide, (15), had arisen from the orthothioamide (16) by hydrolysis during work-up, but it was not clear how the orthothioamide (16) had arisen. Thus it could have been formed by the desired hydrogen atom abstraction by a vinyl radical, and the product radical quenching by attack on diphenyl disulphide; alternatively, PhS• could have directly abstracted the hydrogen atom independently of any chemistry occurring at the alkyne. To check this point, the N-butyl substrate (17) was prepared and subjected to the same reaction conditions. No evidence of direct hydrogen atom abstraction by PhS• was seen, and only the starting compound, (17) was observed in the nmr spectrum of the crude reaction product.

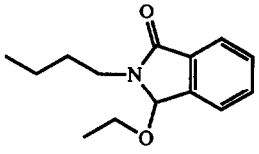
As a final model, the substrate (7) was prepared. This behaved in a most unexpected fashion, giving rise to the pyrrolidone (18) as a mixture of stereoisomers in 10% yield. The proton nmr spectrum of this mixture of diastereoisomers was complex; however, analysis of the ^{13}C nmr and analysis of the $^{13}C/^{1}H$ correlation spectrum proved instructive. Thus four carbon signals were present representing methyl carbons. Four CH carbon signals from 69.5 to 80.55 correlated with proton signals in the range 3.4 to 3.9 representing CH groups next to oxygen and four carbon CH signals from δ85.5 to 90.6 correlated with proton signals from 5.0 to 5.4 and represented N-CH-O signals. Four carbonyl carbon signals were also present from 173.6 to 174.9ppm. The reaction to form the seven-membered ring structures feature an initial hydrogen abstraction *via* an eight-membered transition state, followed by a seven *exo-trig* cyclisation. Plainly, unusual features govern the selectivities seen in this reaction. Examination of models

show that the observed hydrogen atom abstraction is easily achieved due to the extra rigidity imposed on the system by virtue of the lactam ring, and the anomeric effect. However, it is not easily explained why the analogous substrate (6) should have behaved so differently.



(6) (15) (16)

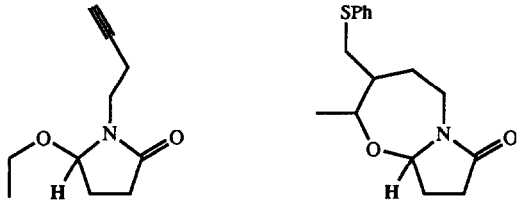
Figure 8



(17)

Figure 9

In summary, these studies show that the addition of thiyl radicals to alkynes produces vinyl radicals which are capable of hydrogen atom abstraction from tetrahydrofurans. The observed chemistry of the model systems is quite unexpectedly complex, and it is not yet clear if this results from intrinsic difficulties in the hydrogen abstraction chemistry or from other factors, for example related to the photocleavage of the disulphide. For DNA cleavage to be effected by the chemistry modelled here would not necessarily require high yielding reactions. Studies are now in progress to see if radiosensitisation can indeed be effected by this mechanism.



(7) (18)

Figure 10

Acknowledgments. We thank the SERC for support, and the SERC Mass Spectrometry service Swansea for performing accurate mass determinations on FAB spectra.

Experimental Section.

Melting points were carried out on a Kofler hot stage apparatus and are uncorrected. Microanalyses were determined using a Perkin-Elmer 240B elemental analyser. Infrared spectra were recorded on a Perkin-Elmer 1720 FTIR spectrometer. Ultraviolet spectra were recorded on a Philips PU8700 spectrometer in ethanol unless otherwise stated. ^{1}H nmr (^{13}C nmr) spectra were recorded at 90 MHz (23 MHz) on a Perkin-Elmer R32 (Jeol FX90Q), at 250 MHz (63 MHz) on a Bruker WM250, at 270 MHz (68 MHz) on a Jeol EX270 and at 400 MHz (100 MHz) on a Bruker AM400 spectrometer. $CDCl_3$ was used as solvent except where otherwise noted. Mass spectra were recorded on a VG Micromass 70E, an AEI MS902 spectrometer or at the SERC mass spectrometry unit at Swansea.

Solvents were dried and/or distilled before use. Tetrahydrofuran was distilled from sodium-benzophenone. Pyridine was distilled from calcium hydride. Benzene was dried over sodium wire. Chromatography was performed using Sorbsil C60 (May and Baker), Kieselgel 60 (Art 9385), Kieselgel HF254 silica gels or Brockman Grade 1 neutral alumina.

3-(2-methoxyethoxy)-1-propyne (2)

Tetrahydrofuran (200 ml) was added to washed sodium hydride (0.53 g of 60% suspension, 13.3 mmol; 1.5 eq) and then propargyl alcohol (0.76g, 0.8 ml, 13.3 mmol; 1.5 eq) was added dropwise. The solution was stirred at room temperature for 30 minutes, then 2-bromoethyl methyl ether (0.9 ml, 1.3 g, 9 mmol; 1.0 eq) was slowly added. The solution was stirred for twelve hours and then the solvent was evaporated and the resultant solid was washed with diethyl ether (300 ml). The organic solution was evaporated to give an oil which was chromatographed [20% ethyl acetate in 40/60 petrol, R_F 0.4,] to yield 3-(2-methoxyethoxy)-1-propyne (2) as a colourless volatile oil (140 mg, 14%); υ_{max} 3 260 (≡C-H), 2 116 (C≡C), 672 cm-1 (≡C-H); δ_H (250 MHz) 2.45 (1H, t, *J* 2.4 Hz), 3.40 (3H, s), 3.58 (2H, m), 3.70 (2H, m), 4.22 (2H, d, *J* 2.4 Hz); δ_C (22.5 MHz) 60.14 (t), 60.60 (q), 69.67 (t), 72.16 (t) , 75.74 (d), 79.38 (s).

Reaction of phenylthiyl radical with 3-(2-methoxyethoxy)-1-propyne

3-(2-methoxyethoxy)-1-propyne (2), (100 mg, 0.88 mmol; 1.0 eq) was dissolved in benzene (175 ml) and stirred under an argon atmosphere. The solution was then irradiated with uv light from a 300 W sun-lamp until reflux started. Phenyl disulphide (145 mg, 0.66 mmol; 1.5 eq) pre-dissolved in benzene (25 ml) was added dropwise over a period of 4 hours. After addition was complete, the solution was irradiated for a further hour and then the solution allowed to cool to room temperature. The solvent was then removed by rotary evaporation to yield a yellow oil. Tlc and nmr analysis of the complex mixture revealed complete conversion of the starting material. The mixture was then chromatographed [40/60 petrol→10% diethyl ether in 40/60 petrol] to yield the following compounds:

3-methoxyethoxy-1-phenylthio-2-phenylprop-1-ene (8) (24.6 mg, 9.3%) [100% dichloromethane, R_F 0.33] (2 geometric isomers, 1:3 by ^{1}H nmr) ; υ_{max} 3 057 (Ar-H), 1 679 cm^{-1} (C=C); λ_{max} 196 (ε 45 000 $dm^3\ mol^{-1}\ cm^{-1}$), 284 nm (15 000); δ_H (400 MHz, d^6-acetone, * denotes major isomer) 3.31 (3H*, s), 3.32 (3H, s), 3.53 to 3.56 (2H and 2H*, m), 3.68 to 3.70 (2H*, m), 4.42 (2H*, d, *J* 1.2 Hz), 4.67 (2H, s), 6.78 (1H*, t, *J* 1.2 Hz,), 6.94 (1H, s), 7.28 to 7.58 (10H and 10H*, m); δ_C (100 MHz, d^6-acetone, 58.68 (q), 69.21 (t), 69.90 (t), 69.97(t), 72.35 (t), 72.45 (t), 75.17 (t), 124.20 (d), 126.77 (d),

126.96 (d), 127.42 (d), 127.19 (d), 127.97 (d), 128.31 (d), 128.85 (d), 128.90 (d), 129.06 (d), 129.73 (d), 129.84 (d), 129.95 (d), 130.09 (d), 132.96 (s), 136.97 (s), 138.16 (s), 138.36 (s), 138.76 (s), 140.49 (s); m/z 300(M^+)(21%) 225 (39), 191 (21), 77 (6).;

3[2-methoxyethoxymethyl]benzo[b]-thiophene (9) [dichloromethane, R_F 0.30] (12.0 mg, 6.1%); (Found: M+, 222.0726. $C_{12}H_{14}O_2S$ requires 222.0714) υ_{max} 3 060 (Ar-H), 1 713 (C=C), 1 583 (Ar), 1 529 (Ar) cm^{-1}; λ_{max} 198 (ε 18 000 dm^3 mol^{-1} cm^{-1}), 228 (17 000), 258 (4 000), 289 (3 000), 298 nm (3 000); δ_H (400 MHz, d^6-acetone) 3.35 (3H, s), 3.57 to 3.59 (2H, m), 3.70 to 3.73 (2H, m), 4.86 (2H, d, *J* 1.0 Hz), 7.42 to 7.48 (3H, m, Ar), 7.96 to 8.00 (2H, m, Ar); m/z 222 (M^+, 86%), 147 (100), 134 (6), 133 (3), 77 (8), 59 (38).

2-[(2-Propynyloxy)methyl]-tetrahydrofuran (3)

Sodium hydride (2.85 g of 60% suspension in mineral oil, 72 mmol; 2.0 eq) was washed with dried tetrahydrofuran to remove the oil, and then dry tetrahydrofuran (150 ml) was added and cooled at -15°C. 2-Hydroxymethyl-tetrahydrofuran (3.46 ml, 3.65 g, 36.0 mmol; 1.0 eq) was added dropwise in over 15 minutes. The solution was stirred for a further 10 minutes, then propargyl bromide (4.4 ml, 5.8 g of an 80% solution, 39 mmol; 1.1 eq) was slowly added over a period of 3 hours. During addition the solution went dark brown. After three hours, water was very carefully added, the tetrahydrofuran removed by evaporation and the residue was extracted with ethyl acetate (250 ml) and water (400 ml). Chromatography [20% ethyl acetate in 40/60 petrol] yielded 2-[(2-propynyloxy)methyl]-tetrahydrofuran (3) as a volatile, pale yellow coloured oil [20% ethyl acetate in 40/60 petrol, R_F 0.30] (3.14 g, 63%); υ_{max} 3 290 (≡C-H), 2 114 (C≡C), 669 (≡C-H) cm^{-1}; m/z 71 $(C_4H_4O)^+$, 100%), δ_H (250 MHz, d^6-acetone) 1.62 to 1.68 (1H, m), 1.83 to 1.99 (3H, m), 2.96 (1H, t, *J* 2.3 Hz), 3.52 (2H, d, *J* 4.9 Hz), 3.69 (1H, m), 3.82 (1H, m), 4.00 (1H, m), 4.20 (2H, d, *J* 2.3 Hz); δ_C (22.5 MHz, d^6-acetone) 25.90 (t), 28.61 (t), 58.46 (t), 68.16 (t), 72.71 (t), 75.20 (d), 78.07 (d), 80.62 (s).

Reaction of phenylthiyl radical with 2-[(2-propynyloxy)methyl]-tetrahydrofuran (3).

To a flask containing dried benzene (200 ml) irradiated with a 300 W sun-lamp was added phenyl disulphide (3.12 g, 14.3 mmol; 2.0 molar eq) dissolved in benzene (25 ml) and 2-[(2-propynyloxy)methyl]-tetrahydrofuran (1 g, 7.2 mmol; 1.0 eq) dissolved in benzene (25 ml) over a period of 2 hours. After addition, the solution was stirred for a further 30 minutes with continual irradiation, and then analysed by tlc. Since all the alkyne had disappeared, the solution was allowed to cool. The benzene was then removed by rotary evaporation. Nmr analysis confirmed conversion of the starting material. The mixture was extracted with ethyl acetate (150 ml) and water (200 ml), and then chromatographed.

The following products were isolated:

2-[[(2-phenyl-3-phenylthio)-prop-2-enyloxy]methyl]-tetrahydrofuran (10) (18.4 mg, 0.8%); (Found: M^+, 326.1340. $C_{20}H_{22}O_2S$ requires 326.1340); υ_{max} 3 055 (Ar-H), 1 582 cm^{-1} (C=C) ; λ_{max} 198 (ε 23 052 dm^3 mol^{-1} cm^{-1}), 286 nm (7 313); δ_H (400 MHz) 1.53 to 1.63 (1H, m), 1.73 to 1.95 (3H), 3.52 (minor isomer, 2H, m), 3.53 (2H, m), 3.76 (1H, m), 3.85 (1H, m), 4.05 (1H, m), 4.40 (major isomer, 1H, dd, *J* 12.0, 1.1 Hz), 4.42 (major isomer, 1H, dd, *J* 12.0, 1.1 Hz), 4.65 (minor isomer, 1H, d, *J* 12.0 Hz, k), 4.69 (minor isomer, 1H, d, *J* 12.0 Hz), 6.63 (major isomer, 1H,broad s), 6.81 (minor isomer, 1H, s), 7.22 to 7.50 (10H, m); δ_C (100 MHz,) 25.90 (t), 28.34 (t), 28.43 (t), 68.57 (t), 69.26 (t), 72.58 (t), 72.80 (t), 75.41 (t), 78.07 (d), 124.88 (d), 126.27 (d), 126.98 (d), 127.12 (d), 127.55 (d), 127.65 (d), 127.97 (d), 128.35 (d), 128.53 (d), 128.64 (d), 129.28 (d), 129.42 (d), 129.80 (d), 129.87 (d), 136.20 (s), 136.48 (s), 136.60 (s), 137.10 (s), 137.89 (s), 140.0 (s); m/z 326(M^+)(11%), 85 (100).;

3-[(tetrahydro-2-furanylmethoxy)methyl]benzo[b]-thiophene. (11) (34.2 mg, 1.9%); (Found: M^+, 248.0859. $C_{14}H_{16}O_2S$ requires 248.0871); υ_{max} 3 072 (Ar-H), 1 581 (Ar), 1 527 cm^{-1} (Ar); λ_{max} 202 (ε 27 800 dm^3 mol^{-1} cm^{-1}), 228 (33 000), 259 (7 400), 289 (4 000), 298 nm (4 000); δ_H (400 MHz) 1.55 to 1.64 (1H, m), 1.79 to 1.96 (3H, m), 3.44 to 3.54 (2H, m), 3.74 to 3.79 (1H, m), 3.86 to 3.91 (1H, m), 4.03 to 4.11 (1H, m), 4.79 (1H, dd, *J* 11.5, 0.9 Hz), 4.85 (1H, dd, *J* 11.5, 0.9 Hz), 7.25 to 7.40 (3H, m), 7.86 (2H, m.); δ_C (100 MHz, d^6-acetone) 26.19 (t), 28.87 (t), 68.06 (t), 68.45 (t), 73.59 (t), 78.56 (d), 123.23 (d), 123.42 (d), 124.82 (d), 125.25 (d), 134.83 (s), 139.21 (s), 141.33 (s); m/z 248 (M^+, 27.5%), 147 (53.4), 85 (14.7), 71 (100).

Also isolated was slightly impure sulphide (12) which was oxidised to the sulphone (12a). However, the more efficient preparation of this molecule resulted from *in situ* oxidation as follows:

9-[phenylsulphonylmethyl]-1,7-dioxaspiro-[4,4]-nonane (12a)

2-[(1-Methyl-2-propynyl)oxy]-tetrahydrofuran (3) (1.0 g, 7.0 mmol; 1.0 eq) was dissolved in dry benzene (200 ml) and irradiated with uv light from a 300 W sun-lamp. Slow addition of phenyl disulphide (3.12 g, 14 mmol; 4.0 eq) in dry benzene (50 ml) was carried out by means of a syringe pump over five hours, followed by a further half hour irradiation. The solvent was then removed by rotary evaporation to yield a brown oil. To this was added oxone (43.9 g; 20.0 eq) and stirred in methanol (200 ml) for four hours at 0°C. A further portion of oxone (20 g) was then added and the solution stirred for a further 2 hours at room temperature. The mixture was partitioned between diethyl ether and water, the organic layer then dried (magnesium sulphate) and concentrated to give a brown solid. The mixture was chromatographed [100% 40/60 petrol→100% diethyl ether→100% methanol]. Repeated chromtography [diethyl ether, then [50% ethyl acetate in toluene then 10% diethyl ether in toluene gave 9-[phenylsulphonylmethyl]-1,7-dioxaspiro-[4,4]-nonane (12a), (3.4 mg, 0.17%); υ_{max} 3 064 (Ar-H), 1 586 (Ar), 1 307 (SO_2), 1 147 cm^{-1} (SO_2); δ_H (400 MHz, d^6-acetone) 1.78 to 2.00 (4H, m), 2.42 to 2.50 (1H, m), 3.20 (1H, dd, *J* 14.5, 10.6 Hz), 3.45 (1H, dd, *J* 14.5, 2.7 Hz), 3.57 (1H, d, *J* 9.1 Hz), 3.58 (1H, dd, *J* 9.0, 9.0 Hz), 3.64 (1H, d, *J* 9.1 Hz), 3.75 (2H, m), 4.01 (1H, dd, *J* 9.0, 9.0 Hz), 7.66 to 7.71 (2H, m), 7.72 to 7.80 (1H, m), 7.94 to 8.00 (2H, m); δ_C (100 MHz, d^6-acetone) 26.53 (t), 32.71 (t), 42.81 (d), 54.97 (t), 68.60 (t), 72.91 (t), 77.93 (t), 90.24 (s), 128.80 (d), 130.31(d), 134.65 (d), 140.90 (s); m/z 283 ($M+H^+$,38%), 141 (90), 111 (53), 71 (14).

2-[(3-Butynyl)oxy]-tetrahydrofuran (4)

3-Butyn-1-ol (0.54 ml, 0.50 g, 7.1 mmol; 1.0 eq) and 2,3-dihydrofuran (0.54 ml, 0.50 g, 7.1 mmol; 1.0 eq) were both added to a catalytic amount of pyridinium *p*-toluene sulphonate in dichloromethane (25 ml) at 0°C and stirred for 12 hours. The solution was then evaporated to dryness and partitioned between ethyl acetate (150 ml) and water (200 ml). Tlc analysis [20% ethyl acetate in 40/60 petrol] showed one major spot [R_F0.44] and two minor impurities [R_F 0.23 and 0.10]. Purification by chromatography [20% diethyl ether in 40/60 petrol] yielded 2-[(3-butynyl)oxy]-tetrahydrofuran (4) [20% ethyl acetate in 40/60 petrol, R_F 0.45,] (592 mg, 59%); υ_{max} 3 292 (≡C-H), 2 121 (C≡C), 1 097 (O-C-O), 1 042 (O-C-O), 643 cm^{-1} (≡C-H); δ_H (250 MHz) 1.78 to 2.05 (5H, m), 2.46 (2H, td, *J* 7.0, 2.7 Hz), 3.35 (1H, dt, *J* 9.9, 7.0 Hz), 3.76 (1H, dt, *J* 9.9, 7.0 Hz), 3.82 to 3.96 (2H, m), 5.16 (1H; m); δ_C (22.5 MHz) 18.98 (t), 23.40 (t), 32.34 (t), 65.27 (t), 66.79 (t), 69.17 (d), 81.42 (s), 103.85 (d); m/z 140 (M^+, 0.3%), 101 (28.8), 71 (100), 53 (63).

4-[(Phenylthio)methyl]-1,6-dioxaspiro[4.4]nonane (13)

To a flask irradiated by uv light (from a 300 W sun-lamp) containing dried benzene (125 ml) was

separately added solutions of phenyl disulphide (3.12 g, 14.3 mmol; 2.0 molar eq) in benzene (25 ml) and 2-[(3-butynyl)oxy]-tetrahydrofuran (1.0 g, 7.2 mmol, 1.0 eq) in benzene (25 ml) over a period of three hours. After addition, the irradiation was continued for a further half hour. After cooling to room temperature, the solvent was removed by rotary evaporation and the mixture was analysed by tlc [20% ethyl acetate in 40/60 petrol] which indicated a complex mixture. This was chromatographed [0→100% diethyl ether in hexane] to give the desired compound as a mixture of two diastereoisomers (3:1 ratio by ^{1}H nmr) [20% ethyl acetate in 40/60 petrol, R_F 0.24]. This mixture was then purified by HPLC [dichloromethane, flow rate 3 ml min^{-1}, retention time 32 minutes] to yield 4-[(phenylthio)methyl]-1,6-dioxaspiro[4.4]nonane (13) (21 mg, 1.2%); (Found: *[M+H]*$^+$, 251.1106. $C_{14}H_{19}O_2S$ requires 251.1106); υ_{max} 3 058 (Ar-H), 1 583 (Ar), 1 090 (O-C-O), 1 023 (O-C-O);δ_H (400 MHz, d^6-acetone) 1.84 to 2.03 (5H, m), 2.16 to 2.25 (1H, m), 2.27 to 2.33 (1H, m), 2.71 (1H, dd, *J* 12.7, 10.5 Hz), 3.24 (1H, dd, *J* 12.7, 4.5 Hz), 3.73 to 3.85 (4H, m), 7.20 (1H, tt, *J* 7.4, 1.3 Hz), 7.32 (2H, m), 7.38 (2H, m); δ_C (100 MHz, d^6-acetone) 24.81 (t), 30.69 (t), 31.81(t), 36.06 (t), 45.55 (d), 64.97 (t), 66.72 (t), 116.58 (s), 126.79 (d), 129.85 (s), 137.35 (s); m/z 251 (*[M+H]*$^+$, 54%), 142 (33), 141 (100).

2-(3-butynyloxy)tetrahydro-2H-pyran (5)

3-butyn-1-ol (2.3 ml, 2.1 g, 30 mmol; 1 eq), 3,4-dihydro-2H-pyran (3.3 ml, 3.0 g, 30 mmol; 1 eq) and pyridinium *p*-toluene sulphonate (30 mg, 120 mm; 0.004 eq) were dissolved in dichloromethane (50 ml) at 0°C and stirred for 10 hours. The reaction mixture was then washed with water (150 ml), dried (magnesium sulphate), concentrated and purified by chromatography [20% diethyl ether in 40/60 petrol] to yield 2-(3-butynyloxy)tetrahydro-2H-pyran (5) as a colourless oil [R_F 0.53] (3.8 g, 82%); (Found: M$^+$, 154.0963. $C_9H_{14}O_2$ requires 154.0994); υ_{max} 3 295 (≡C-H), 2 121 (C≡C), 1 137 (O-C-O), 1 123 (O-C-O), 640 cm^{-1} (≡C-H); δ_H (250 MHz) 1.50 to 1.86 (6H, m), 1.98 (1H, t, *J* 2.7 Hz), 2.51 (2H, td, *J* 7.0, 2.7 Hz), 3.52 (1H, m), 3.56 (1H, dt, *J* 9.7, 7.0 Hz), 3.85 (1H, dt, *J* 9.7, 7.0 Hz), 3.89 (1H, m), 4.66 (1H, t, *J* 3.4 Hz); δ_C (22.5 MHz) 19.39 (t), 19.98 (t), 25.51 (t), 30.55 (t), 61.97 (t), 65.54 (t), 69.28 (d), 81.36 (s), 88.64 (d); m/z 154 (*M*$^+$, 0.4%), 153 (2.7), 85 (100), 57 (7.0), 53 (58.4).

4-[(Phenylsulphonyl)methyl]-1,6-dioxaspiro[4.5]decane (14a)

Phenyl disulphide (142 mg, 0.71 mmol; 1.0 eq) and 2-(3-butynyloxy)-tetrahydro-2H-pyran (100 mg, 0.71 mmol; 1.0 eq) were dissolved in benzene (50 ml) and irradiated with uv light over a 3 hour period by a 300 W sun-lamp. Tlc analysis [20% ethyl acetate in 40/60 petrol] of the crude mixture showed many product spots, and that all the starting material had disappeared. Nmr analysis showed the expected AB pattern for the CH_2 α to the sulphur in the extremely complex spectrum. The mixture was chromatographed [0→100% diethyl ether in 40/60 petrol, followed by 0→100% diethyl ether in dichloromethane], finally yielding 4-[(phenylthio)methyl]-1,6-dioxaspiro[4.5]decane (14) almost pure as a single isomer [20% ethyl acetate in 40/60 petrol, R_F 0.66] (15.5 mg). This was then oxidized to the sulphone using Oxone (0.36 g, 0.6 mmol; 10.0 eq) in methanol (10 ml, 0°C). Evaporation of the solution, followed by partitioning between ethyl acetate and water and finally purification by chromatography [diethyl ether] yielded 4-[(phenylsulphonyl)methyl]-1,6-dioxaspiro[4.5]decane (14a) [50% diethyl ether in 40/60 petrol, R_F 0.13,] (2.6 mg, 3% overall); (Found: *[M+H]*$^+$, 297.1161. $C_{15}H_{21}O_4S$ requires 297.1161); υ_{max} 3 064 (Ar-H), 1 586 (Ar), 1 307 (SO_2), 1 147 cm^{-1} (SO_2); δ_H (400 MHz) 1.46 to 1.70 (6H, m), 1.70 to 1.93 (1H, m), 2.22 (2H, m), 3.14 (1H, dd, *J* 11.7, 7.8 Hz), 3.22 (1H, dd, *J* 11.7, 2.6 Hz), 3.48 (1H, m), 3.72 (1H, m), 3.85 (2H, m), 7.58 (2H, t, *J* 8.4 Hz),

7.67 (1H, t, *J* 8.4 Hz), 7.93 (2H, d, *J* 8.4 Hz); δ_C (100 MHz) 19.84 (t), 25.10 (t), 29.86 (t), 31.21 (t), 42.28 (d), 57.40 (t), 61.16 (t), 65.79 (t), 104.86 (s), 127.89 (d), 129.32 (d), 135.69 (d), 140.1 (s); m/z 297 (24%), 156 (13), 155 (100).

3-butynyl *p*-toluenesulphonate

p-Toluenesulphonyl chloride (7.6 g, 40 mmol; 1.5 eq) and 3-butyn-1-ol (2 ml, 1.9 g, 26 mmol; 1.0 eq) were added to pyridine (20 ml, 0°C) and stirred for 3 hours. The solution was then evaporated, the residue dissolved in diethyl ether, extracted with 2M hydrochloric acid and washed with sodium carbonate solution. The solution was dried (magnesium sulphate), the solvent evaporated and the residue chromatographed [20% ethyl acetate in 40/60 petrol, R_F 0.22,] to yield 3-butynyl p-toluenesulphonate as a colourless oil (4.4 g, 75%); (Found: M^+, 224.0519. $C_{11}H_{12}SO_3$ requires 224.0507); (Found: C, 58.81; H, 5.4. $C_{11}H_{12}SO_3$ requires C, 58.91; H, 5.4); υ_{max} 3 293 (≡C-H), 3 067 (Ar-H), 2 125 (C≡C), 1 599 (Ar), 1 496 (Ar), 1 359 (SO_2-O), 1 190 cm^{-1} (SO_2-O); λ_{max} 199 (ε 13 200 dm^3 mol^{-1} cm^{-1}), 226 (11 400), 262 (800), 273 nm (705); δ_H (250 MHz, d^6-acetone) 2.47 (1H, t, *J* 2.7 Hz), 2.49 (3H, s), 2.65 (2H, td, *J* 6.4, 2.7 Hz), 4.17 (2H, t, *J* 6.4 Hz), 7.52 (2H, m), 7.88 (2H, m); δ_C (100 MHz, d^6-acetone) 19.14 (t), 20.95 (q), 68.32 (t), 71.28 (d), 79.37 (s), 128.07 (d), 130.25 (d), 133.34 (s), 145.37 (s); m/z 224 (M^+, 19.37%), 185 (94.26), 172 (77.92), 91 (100).

N-(But-3-ynyl)-phthalimide

Potassium phthalimide (2.48 g, 13.4 mmol; 2.0 eq) and 3-butynyl *p*-toluenesulphonate (1.5 g, 6.7 mmol; 1.0 eq) were dissolved in dimethyl formamide and heated for 2 hours at 80°C. Tlc analysis [20% ethyl acetate in 40/60 petrol] showed complete disappearance of the starting material. The mixture was poured into water (150 ml) and extracted with diethyl ether, dried (magnesium sulphate) and then purified by chromatography [20% ethyl acetate in 40/60 petrol, R_F 0.30] to yield N-(3-butynyl)-phthalimide as a white crystalline solid (671 mg, 50%); m.p. 136.5 to 137.5°C; (Found: M^+, 199.0632. $C_{12}H_9NO_2$ requires 199.0633); (Found: C, 72.35; H, 4.5; N, 7.2. $C_{12}H_9NO_2$ requires C, 72.35; H, 4.6; N, 7.0%); υ_{max} (KBr) 3 257 (≡C-H), 1 768 (C=O), 1 724 cm^{-1} (C=O); λ_{max} 193 (ε 9 400 dm^3 mol^{-1} cm^{-1}), 219 (19 500), 294 nm (800); δ_H (400 MHz) 1.97 (1H, br s), 2.62 (2H, td, *J* 7.1, 2.3 Hz), 3.89 (2H, t, *J* 7.1 Hz), 7.72 to 7.74 (2H, m), 7.85 to 7.94 (2H, m); δ_C (100 MHz) 18.35 (t), 36.53 (t), 70.27 (d), 80.28 (s), 123.37 (d), 131.98 (s), 134.05 (d), 166.03 (s); m/z 199 (M^+, 45.5%), 160 (100), 132 (2.3), 77 (35.0).

2-(3-Butynyl)-3-ethoxy-2,3-dihydro-1H-isoindol-1-one (6)

N-(3-Butynyl)-phthalimide (500 mg, 2.5 mmol; 1.0 eq) was dissolved in ethanol (50 ml) and cooled to 0°C. Sodium borohydride (95 mg, 2.5 mmol; 4.0 eq) was then added and the solution stirred for one hour before being allowed to warm to room temperature over two hours. The solution was then acidified with 2M hydrochloric acid in ethanol and then evaporated to give a solid residue which was partitioned between water (200 ml) and diethyl ether (150 ml). The organic layer was dried (magnesium sulphate), evaporated and then purified by chromatography [30% diethyl ether in 40/60 petrol] to yield 2-(3-butynyl)-3-ethoxy-1-H-isoindol-1-one (6) as a clear oil [20% ethyl acetate in 40/60 petrol, R_F 0.35,] (556 mg, 95.8%); (Found: M^+, 229.1112. $C_{14}H_{15}NO_2$ requires 229.1103); υ_{max} 3 294 (≡C-H), 3 054 (Ar-H), 2 120 (C≡C), 1 705 (C=O), 1 601 cm^{-1} (Ar); λ_{max} 229 (ε 11 600 dm^3 mol^{-1} cm^{-1}), 246 nm (7 024); δ_H (400 MHz) 1.15 (3H, t, *J* 7.0 Hz), 1.99 (1H, t, *J* 2.6 Hz), 2.51 to 2.70 (2H, m), 2.99 to 3.06 (1H, m), 3.15 to 3.22 (1H, m), 3.47 to 3.54 (1H, m), 3.91 to 3.98 (1H, m), 6.08 (1H, s), 7.50 to 7.61 (3H,

m), 7.83 (1H, d, *J* 7.4 Hz); δ_C (100 MHz) 15.09 (q), 18.33 (t), 38.33 (t), 57.93 (t), 70.06 (d), 81.48 (s), 86.57 (d), 123.40 (d), 123.52 (d), 129.86 (d), 132.08 (d), 132.64 (s), 141.18 (s), 167.59 (s); m/z 229 (M^+, 15%), 200 (4.78), 190 (84), 185 (7), 184 (35), 146 (100), 145 (7), 77 (24), 76 (7).

Reaction of phenylthiyl radical with 2-(3-butynyl)-3-ethoxy-2,3-dihydro-1H-isoindol-1-one (6)

2-(3-Butynyl)-3-ethoxy-2,3-dihydro-1H-isoindole-1-one (6) (500 mg, 2.5 mmol; 1.0 eq) was dissolved in dry benzene (175 ml) and irradiated with uv light from a 300 W sun-lamp. When reflux started, phenyl disulphide (550 mg, 2.5 mmol; 2.0 eq) dissolved in benzene (25 ml) was added dropwise over a period of 6 hours. After addition was complete, the solution was irradiated for a further 30 minutes and then (when cool) evaporated to dryness. The residue was then chromatographed to give the following products:

2-(4-phenylthio-but-3-enyl)-2,3-dihydro-1H-isoindole-1,3-dione (15) [30% dichloromethane in toluene, R_F 0.12] (19.3 mg, 2.5%); (Found: M^+, 309.0826. $C_{18}H_{15}NO_2S$ requires 309.0823); υ_{max} 3 056 (Ar-H), 1 772 (C=O), 1 713 (C=O), 1 615 (C=C), 1 583 (Ar), 1 520 cm^{-1} (Ar); λ_{max} 194.1 (1.322 absorbance units), 219 (1.455), 241 (0.578), 266 nm (0.358); δ_H (250 MHz, d^6-acetone) 2.59 to 2.75 (2H, m), 3.81 to 3.93 (2H, m), 5.92 to 6.04 (1H, m), 6.28 to 6.39 (1H, m), 7.14 to 7.40 (5H, m), 7.80 to 8.01 (4H, m); m/z 309 (M^+, 23%), 199 (44).

3-ethoxy-3-phenylthio-2-(4-phenylthio-but-3-enyl)-2,3-dihydro-1H-isoindol-1-one (16) [50% dichloromethane in toluene, R_F 0.1] (13.5 mg, 1.2%); υ_{max} 3 058 (Ar-H) 1 713 (C=O), 1 616 (Ar), 1 582 cm-1 (Ar) ;λ_{max}195, 200, 218, 240, 265 nm; δ_H (400 MHz) 1.18 to 1.25 (3H, m), 2.53 to 2.79 (2H, m), 3.16 to 3.28 (2H, m), 3.71 to 3.86 (2H, m), 5.79 to 6.04 (1H, m), 6.18 to 6.35 (1H, m), 7.00 to 7.87 (14H, m).

N-butyl-phthalimide

Potassium phthalimide (4.55 g, 25 mmol; 1.0 eq) and 1-iodobutane (5.6 ml, 8.9 g, 50 mmol; 2.0 eq) were heated in dry dimethyl formamide at 55°C overnight. Tlc analysis [20% ethyl acetate in 40/60 petrol] showed one major compound [R_F 0.6], so the solution was allowed to cool to room temperature. The mixture was then poured into water (100 ml) and extracted with diethyl ether (75 ml). The organic layer was then dried (magnesium sulphate), evaporated and then purified by chromatography [20% diethyl ether in 40/60 petrol] to give N-butyl-phthalimide as a crystalline solid (2.26 g, 45%); m.p. 33 to 34°C; (Found: C, 70.99; H, 6.6; N, 7.1. $C_{12}H_{13}NO_2$ requires C, 70.92; H, 6.5, N, 6.9%); υ_{max} 3 061 (Ar-H), 1 773 (C=O), 1 718 (C=O), 1 616 cm^{-1} (Ar); λ_{max} 220 (21 100 dm^3 mol^{-1} cm^{-1}), 241 (5 800), 292 nm (960); δ_H (250 MHz) 0.95 (3H, t, *J* 7.3 Hz), 1.30 to 1.45 (2H, m), 1.64 to 1.72 (2H, m), 3.69 (2H, t, *J* 7.3 Hz), 7.69 to 7.75 (2H, m), 7.80 to 7.86 (2H, m); δ_C (67.8 MHz) 13.62 (q), 20.06 (t), 30.62 (t), 37.79 (t), 123.13 (d), 132.17 (s), 133.82 (d), 168.46 (s); m/z 203 (M^+, 29%), 174 (8), 161 (40), 160 (100), 133 (5).

2-butyl-3-ethoxy-2,3-dihydro-1H-isoindole-1-one (17)

N-Butylphthalimide (1 g, 5 mmol; 1.0 eq) was dissolved in ethanol (100 ml) and cooled to 0°C. Sodium borohydride (750 mg, 20 mmol; 4.0 eq) was added and the solution stirred for one hour before being allowed to warm to room temperature over two hours. The solution was acidified with 2M hydrochloric acid in ethanol and evaporated to give an oily residue which was partitioned between water and diethyl ether. The organic layer was dried (magnesium sulphate), evaporated and then purified by column chromatography [30% diethyl ether in 40/60 petrol] to yield 2-butyl-3-ethoxy-2,3-dihydro-1H-

isoindol-1-one (17) as a clear oil (446 mg, 39%); (Found: M^+, 233.1405. $C_{14}H_{19}NO_2$ requires 233.1416); υ_{max} 1 705 (C=O), 1 617 cm^{-1} (Ar); λ_{max} 197 (ε 4 145 dm^3 mol^{-1} cm^{-1}), 249 nm (472); δ_H (400 MHz, d^6-acetone) 0.96 (3H, t, *J* 5.4 Hz), 1.12 (3H t, *J* 7.0 Hz), 1.38 (2H, m), 1.67 (2H, m), 3.08 (1H, m), 3.2 to 3.3 (2H, m), 3.71 (1H, dt, *J*13.6, 7.7 Hz), 5.95 (1H, s), 7.2 to 7.5 (4H, m); δ_C (100 MHz, d^6-acetone) 14.04 (q), 15.48 (q), 20.89 (t), 31.04 (t), 39.83 (t), 58.90 (t), 86.68 (d), 123.54 (d), 124.43 (d), 130.52 (d), 132.6 (d), 133.99 (s), 142.72 (s), 167.42 (s); m/z 233 (M^+, 5.36%), 204 (66), 188 (61), 147 (18), 146 (100), 133 (50), 77 (20), 76 (5).

1-(3-butynyl)-2,5-pyrrolidinedione

Triphenylphosphine (5.25 g, 20 mmol; 1.0 eq), succinimide (2.4 g, 24 mmol; 1.2 eq) and butynol (1.5 ml, 20 mol; 1.0 eq) were dissolved in tetrahydrofuran and cooled to -5°C in a salt/ice bath. Diethyl azodicarboxylate (3 ml, 3.5 g, 20 mmol, 1.0 eq) was added dropwise in over a period of 20 minutes and the whole solution was left to stir for twelve hours. The solution was then evaporated to dryness to leave a yellowish solid. This was dissolved in dichloromethane and washed with 2M sodium hydroxide solution, then 2M hydrochloric acid, followed by a saturated solution of sodium bicarbonate and finally with brine. The solution was dried (magnesium sulphate) and evaporated to yield a colourless solid. This was chromatographed [diethyl ether] to yield 1-(3-butynyl)-2,5-pyrrolidinedione as a colourless oil [R_F 0.4] (2.59 g, 86%); (Found: M^+, 151.0663. $C_8H_9NO_2$ requires 151.0633); (Found: C, 63.36; H, 6.2. $C_8H_9NO_2$ requires C, 63.57; H, 6.0); υ_{max} 3 274 (≡C-H), 2 120 (C≡C), 1 776 (C=O), 1 704 cm^{-1} (C=O); λ_{max} 197 nm (dm^3 mol^{-1} cm^{-1}); δ_H (80 MHz) 1.97 (1H, t, *J* 2.7 Hz), 2.52 (2H, td, *J* 7.0, 2.7 Hz), 2.73 (4H, s), 3.70 (2H, t, *J* 7.0 Hz); δ_C (68 MHz) 17.34 (t), 28.10 (t), 37.11 (t), 70.22 (d), 70.05 (s), 176.91 (s); m/z 152 (9%), 151 (M^+, 83), 150 (7), 112 (43), 67 (69).

1-(3-butynyl)-5-ethoxy-2-pyrrolidinone (7)

1-(3-Butynyl)-2,5-pyrrolidinedione (1.8 g, 11.9 mmol; 1.0 eq) was dissolved in ethanol (200 ml) and cooled to 0°C. Sodium borohydride (2 g, 66 mmol; 5.6 eq) was then added, and the solution kept at -5°C for five hours. During the 5 hours, 1 drop of 2M hydrochloric acid in ethanol was added every 15 minutes. The solution was then acidified (pH 3.0) with 2M hydrochloric acid in ethanol and stirred at -5°C for another hour before being neutralised with 2% potassium hydroxide in ethanol and evaporated to dryness to yield a colourless solid. This solid was then washed with dichloromethane, which was evaporated to yield a slightly coloured oil. The oil was then chromatographed [100% diethyl ether, R_F 0.2,] to yield 1-(3-butynyl)-5-ethoxy-2-pyrrolidinone (7) as a colourless oil (0.86 g, 40%); (Found: C, 65.94; H, 8.5; N, 7.7. $C_{10}H_{15}NO_2$ requires C, 66.27; H, 8.3; N, 7.7); υ_{max} 3 249 (≡C-H), 2 119 (C≡C), 1 696 cm^{-1} (C=O); δ_H (250 MHz) 1.24 (3H, t, *J* 7.0 Hz), 2.00 (1H, t, *J* 2.7 Hz), 2.11 to 2.61 (6H, m), 3.30 to 3.43 (1H, m), 3.49 (2H, m), 3.58 to 3.69 (1H, m), 5.12 (1H, m); δ_C (22.5 MHz) 15.00 (q), 17.60 (t), 24.70 (t), 28.44 (t), 39.22 (t), 61.48 (t), 69.61 (d), 81.31 (s), 89.38 (d), 174.49 (s); m/z 181 (M^+, 5%), 142 (14), 136 (56), 98 (100), 68 (53), 67 (2).

Reaction of phenylthiyl radical with 1-(3-butyl)-5-ethoxy-2-pyrrolidinone (7).

1-(3-Butyl)-5-ethoxy-2-pyrrolidinone (750 mg, 4.14 mmol;1.0 eq) was dissolved in benzene (200 ml) and irradiated with uv light from a 300 W sun-lamp. When reflux began, phenyl disulphide (1.8 g, 8.18 mmol; 4.0 eq) dissolved in benzene (25 ml) was added dropwise over a period of 5 hours. After addition was complete, irradiation was continued for a further hour and then ceased. After the solution cooled, the solvent was removed by evaporation to yield a dark red coloured oil. Analysis by tlc and ^1H

nmr both indicated complete conversion of starting material. The oil was then chromatographed [100% dichloromethane→100% diethyl ether→100% methanol] to give 5 impure fractions. Only one compound, 7-pyrrolido[2,1-b]-2-methyl-3-(phenylthiomethyl)-2,3,4,5 tetrahydro-[1,3]oxazepine (18) [80% ethyl acetate in toluene, R_F 0.2] was eventually purified as a colourless oil (4 diastereoisomers; 4.7 : 3.0 : 1.2 : 1.0 by ^{13}C nmr). (115.3 mg, 9.5%); (Found: M^+, 291.1296. $C_{16}H_{21}NO_2S$ requires 291.1293); υ_{max} 3 057 (Ar-H), 1 688 (C=O), 1 583 (Ar), 1 481 cm^{-1} (Ar); λ_{max} 196, 255 nm; δ_H (400 MHz) 1.20-1.28 (3H, overlapping doublets), 1.6-4.1(10H, overlapping multiplets), 5.0-5.3 (1H, overlapping multiplets), 7.1-7.4 (5H, ArH); δ_C (100 MHz) 19.25 (q), 19.48 (q), 19.73 (q), 20.71 (q), 25.51 (t), 25.78 (t), 26.84 (t), 26.97 (t), 27.82 (t), 28.66 (t), 29.12 (t), 29.51 (t), 29.62 (t), 30.04 (t), 30.12 (t), 31.35 (t), 37.10 (t), 37.74 (t), 38.17 (t), 38.30 (t), 40.03 (t), 41.22 (t), 42.05 (d), 42.26 (d), 45.23 (d), 47.67 (d), 69.26 (d), 72.78 (d), 80.21 (d), 80.55 (d), 85.50 (d), 87.61 (d), 89.89 (d), 90.59 (d), 126.21 (d), 126.28 (d), 126.32 (d), 126.55 (d), 129.03 (d), 129.07 (d), 129.12 (d), 129.41 (d), 129.52 (d), 129.58 (d), 129.85 (d), 136.10 (s), 136.34 (s), 173.82 (s), 173.91 (s), 174.17 (s), 174.96 (s); m/z 291 (M^+, 8%), 182 (36), 138 (100), 109 (8).

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