Radical Cyclisation in Heterocycle Synthesis. Part 1.[1] Sulfanyl Radical Addition–Cyclisation of Dienylamides for Lactam Synthesis

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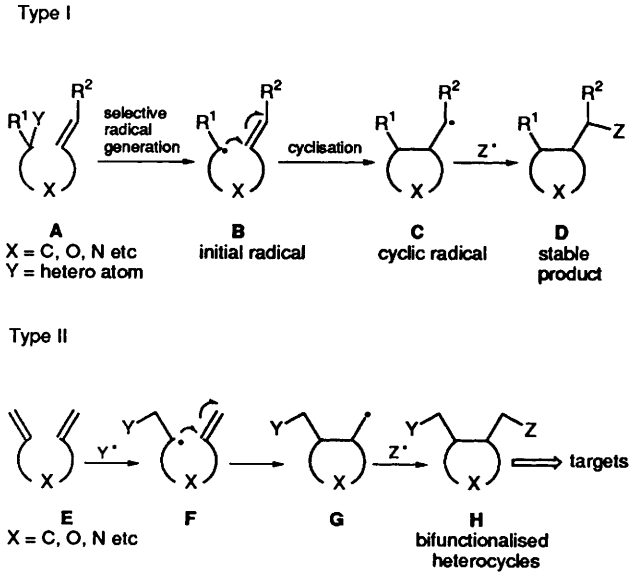
A new method for the synthesis of five- to eight-membered lactams by sulfanyl radical mediated addition–cyclisation of dienylamides is described. The sulfanyl radical addition–cyclisation of the dienylamide **1** was systematically investigated under four different conditions and was found to give the cyclised lactams **2–6** in 54–79% yield. The stereo- and regio-selectivity of sulfanyl radical addition–cyclisation was established from the preferential formation of the *trans*-cyclised lactam **3** and also from the substituent effects in the cyclisation of the dienylamides **11–18**. The sulfanyl radical mediated addition–cyclisation was successfully applied to the construction of the six- and eight-membered lactams **28a, b**.

Among the three chemical species, *i.e.* cations, anions and radicals, radicals have recently drawn the attention of synthetic chemists due to their high stereo- and regio-selectivity in radical cyclisations and also their potential utility in the synthesis of both carbocyclic and heterocyclic compounds.[2]

Radical cyclisations can be classified into two types, based on the structures of the radical initiators (Scheme 1). Type I radical



Scheme 1

cyclisations proceed by the formation of a carbon centred radical **B** generated by the homolytic cleavage of a carbon–heteroatom bond, such as C–X, C–S, C–Se, *etc.* The resulting radical **B** adds to the intramolecular multiple bond, generating the exocyclic radical **C**, which is then trapped to form the cyclised product **D**. Alternatively, the type II radical cyclisation[3] is defined as one in which the carbon centred radical **F** is generated by the addition of a radical **Y*** to an olefin, and this then undergoes the corresponding cyclisation process.

Type II radical addition–cyclisations[3] have at least three advantages over their type I counterparts: (*a*) the starting substrates **E**, which possess two double bonds, are readily synthesized; (*b*) the radical source **Y** and the radical trapping agent **Z** are also readily available and can be chosen depending on the structure of target molecules, and (*c*) the cyclised products **H** are bifunctionalised and thus regarded as useful key intermediates for further target molecules.

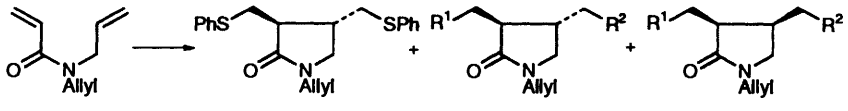
In a continuation of our study on the nucleophilic addition reaction of thiols,[4] we investigated the sulfanyl radical addition–cyclisation of dienylamides as a new development in the synthesis of lactams. To our knowledge, there are only two papers[3b,c] published on the sulfanyl radical-initiated addition–cyclisation of dienes that had been applied to the synthesis of bifunctionalised cyclopentanones, although the details of the reaction which are essential for its application to organic synthesis, such as the isolation of products and their yields, were not described.

In order to establish a new synthetic method for the construction of nitrogen-containing heterocycles by the use of a sulfanyl radical,[5] we employed the dienylamides as a substrate with two different double bonds; one that was in conjugation with the amide group and the other that was isolated. The radical addition–cyclisation to these amides would concomitantly form two carbon–sulfur bonds and one carbon–carbon bond. We therefore investigated the stereo- and regio-selectivity of the sulfanyl radical-initiated addition–cyclisation of dienylamides and in particular, we concentrated on the following points: (*a*) the regiochemistry of the addition of a phenylsulfanyl radical to either the unsaturated amide group or to the isolated double bond; (*b*) the mode of cyclisation, either 5-*exo-trig* or 6-*endo-trig*, and (*c*) the stereochemistry of the products.

Results and Discussion

Sulfanyl Radical Addition–Cyclisation of N,N-*Diallylacrylamide.*—In order to investigate the generality of the sulfanyl radical addition–cyclisation, we chose *N,N*-diallylacrylamide **1**[6] as the substrate and the mixture of diphenyl disulfide and benzenethiol as the sulfanyl radical source. The amide **1** possesses two types of double bond and was thus the most suitable substrate for the present study. Dissociation energies of diphenyl disulfide and benzenethiol are reported[7] to be 20–26 and 82 kcal mol^{-1}, respectively.

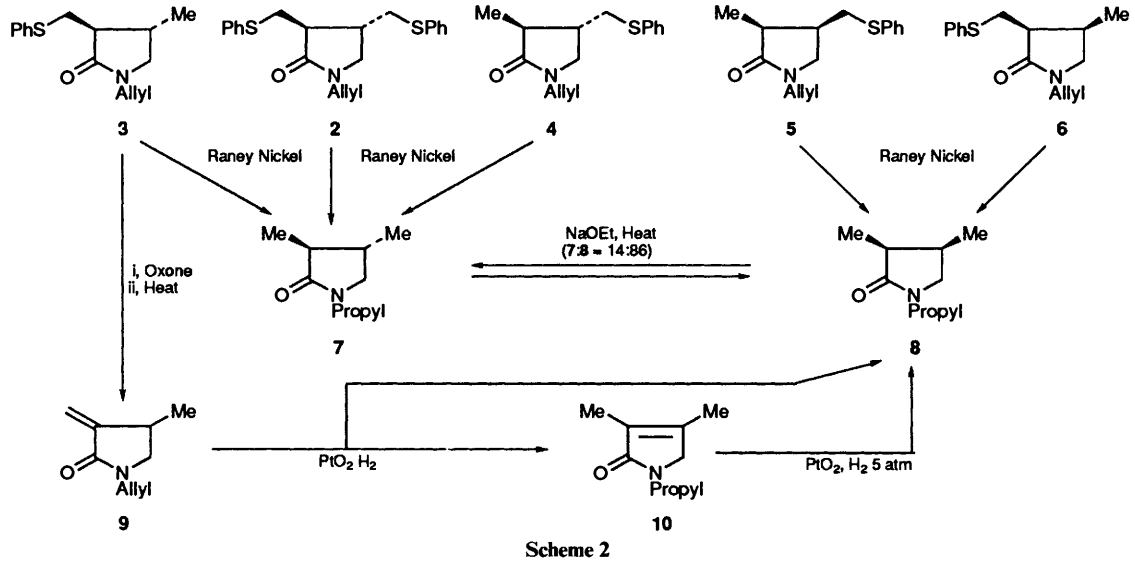
We applied four different sets of conditions (Methods A–D, see the Experimental section) to the amide **1**, and the results are summarised in Table 1. The photochemical reactions were performed by irradiating a solution of the amide **1** in benzene with light from a high pressure mercury lamp that had passed through a Pyrex filter. In the absence of diphenyl disulfide, the starting amide **1** was recovered completely. However, in the presence of 1 equiv. of diphenyl disulfide (Method A), the radical cyclisation of the amide **1** proceeded smoothly to yield the four cyclised lactams **2–5** in 54% combined yield, with the



1 2 3 R^1 = PhS, R^2 = H 4 R^1 = H, R^2 = PhS 5 R^1 = H, R^2 = PhS 6 R^1 = PhS, R^2 = H

Table 1 Sulfanyl radical addition–cyclisation of *N*,*N*-diallylacrylamide **1**

Entry	Method	Time (h)	Total yield (%)	Product ratio 2 : 3 : 4 : 5 : 6
1	A: *hν*, $(PhS)_2$	4	54	35 57 4 4 —
2	B: *hν*, $(PhS)_2$–PhSH	3	79	— 72 14 14 —
3	C: *hν*, PhSH	2	66	— 82 6 12 —
4	D: heat, PhSH–AIBN	1	76	— 58 14 14 14



Scheme 2

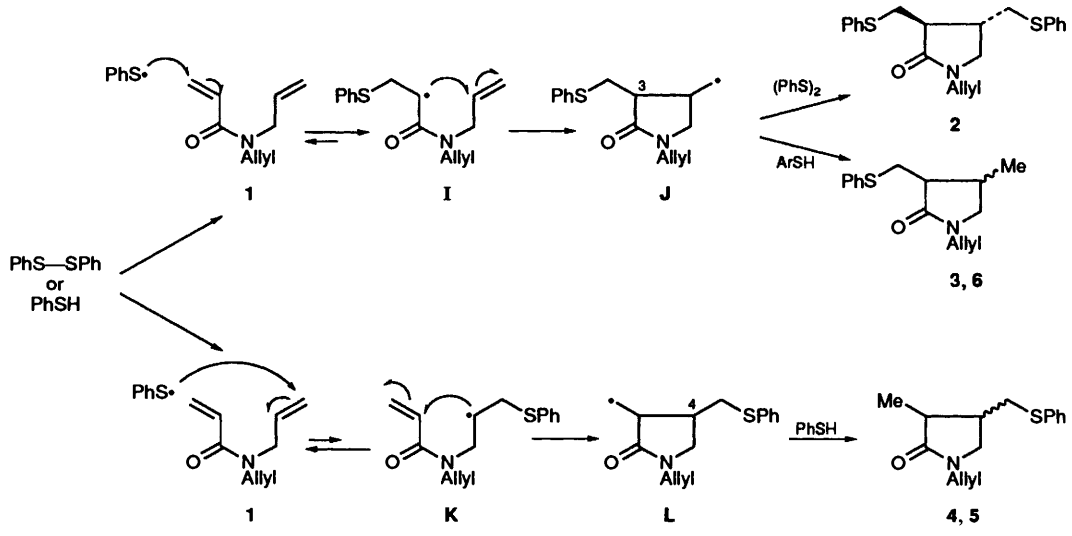
preferential formation of the lactam **3**. Upon irradiation in the presence of diphenyl disulfide and benzenethiol (Method B), the amide **1** gave three lactams **3**–**5** in 79% combined yields, with no formation of the lactam **2**. Irradiation in the presence of benzenethiol (Method C) **1** gave almost the same result as for Method B.

The amide **1** also afforded the cyclised lactams under thermal conditions. A benzene solution of the amide **1** was heated under reflux in the presence of benzenethiol and azoisobutyronitrile (AIBN) (Method D). The products were a mixture of the four lactams **3**–**6**, in 76% combined yield.

As shown in Table 1 the bis(phenylsulfanylmethyl) substituted lactam **2** was isolated only from the reaction under Method A where benzenethiol had not been used. The predominant formation of mono(phenylsulfanylmethyl) substituted lactam **3** is explained as a result of the radical cyclisation followed by hydrogen atom abstraction from benzenethiol. The *trans*-lactams **2**–**4** were obtained as the main products. The cyclisation expected to occur from the reaction between the two allyl groups in the amide **1** was not observed under the reaction conditions studied.

Structure Determination of the Cyclised Lactams.—The stereochemistry of all the products **2**–**6** was firmly established from their spectral data and their chemical conversions (Scheme 2). The lactam **2** showed a molecular ion peak at *m*/*z* 369, an IR absorption at 1678 cm^{-1} (five membered NCO) and ^1H NMR peaks at δ 7.37–7.26 (m, Ph × 2), 3.58 (dd, *J* 13 and 3), 3.48 (dd, *J* 13 and 4), 2.96 (dd, *J* 13 and 8), 2.82 (dd, *J* 13 and 9) ($PhSCH_2$ × 2), 2.60–2.54 (m, 3- and 4-H). Similarly, the lactams **3**–**6** showed the following characteristic spectra [*m*/*z* 261 (M^+), 1680–1677 cm^{-1} (NCO); δ 1.22–1.06 (d, *J* 7.5–6, CH*Me*)] which established their molecular structures without defining the relationships between the two chiral centres. The positions of the two substituents (methyl and phenyl sulfanylmethyl) in the lactams **3**–**6** were established from the COSY NMR spectra. Additionally, the chemical conversions into the authentic samples firmly established the stereostructures as follows. The three sulfides **2**–**4** were reduced with Raney nickel (W-2) to give the identical 3,4-dimethyl-*N*-propyl lactam **7** in good yield. Similarly, the sulfides **5** and **6** were converted into the dimethyl lactam **8**, a stereoisomer of compound **7**. Previously, Ikeda and co-workers[8] reported that upon treatment with sodium ethoxide in ethanol *cis*-3,4-dimethylpyrrolidin-2-ones were readily isomerised into the corresponding stable *trans*-isomers.

When the lactam **7** was treated with sodium ethoxide in refluxing ethanol, it was recovered unchanged, whilst the lactam **8** was converted into a 14:86 mixture of the two lactams **7** and **8**. The authentic *cis*-lactam **8** was prepared by the catalytic hydrogenation of the unsaturated lactams **9** and **10**[9] which were readily prepared from the lactam **3** *via* the oxidative elimination of the phenyl sulfanyl group followed by the isomerisation of the olefin **9** to **10** during the hydrogenation over platinum dioxide. Catalytic hydrogenation of the unsaturated lactams **9** and **10** also gave lactam **8**. A combination of the chemical isomerisation of the lactam **8** to the lactam **7** and spectral comparison of the authentic *cis*-lactam **8** with the two



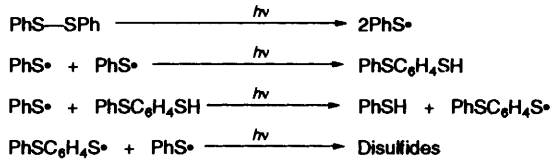
Scheme 3

lactams **7** and **8** firmly established that the lactams **2**–**4** were the *trans*-isomers while the lactams **5** and **6** were *cis*-isomers.

Plausible Reaction Pathway of Sulfanyl Radical Addition–Cyclisation.—The sulfanyl radical addition–cyclisation of the amide **1** can be summarised as follows: (*a*) the *trans*-3-phenylsulfanylmethyl lactam **3** was obtained as a major product, irrespective of the reaction conditions employed; (*b*) the *trans*-isomers **2**–**4** were formed in preference to the *cis*-isomers **5** and **6**; (*c*) no cyclisation between the two allyl groups was observed. Therefore, we have proposed a plausible reaction pathway which is shown in Scheme 3. The phenylsulfanyl radical, formed from the mixture of diphenyl disulfide and benzenethiol under either photochemical or thermal conditions, would prefer to attack the acryloyl group rather than allyl group (**1** ⟶ **I**). This is because the phenylsulfanyl radical is known to exhibit reactivity which is between a nucleophilic and an electrophilic radical[10] and thus its SOMO is expected to interact better with a lower energy LUMO, such as an electron deficient olefin from an acryloyl group. Another possible explanation for the preferred formation of the radical **I** over **K** is as follows. Sulfanyl radical additions to olefins are known[11] to be rapid and reversible. The resultant radical **I**, stabilised by an adjacent carbonyl group, is more stable than the radical **K**. Thus, the equilibrium between **1** and **I** favours the radical **I** whilst the equilibrium between **1** and **K** favours the starting amide **1**.

The radical cyclisation of **I** then undergoes a 5-*exo*-*trig*-cyclisation to form the radical **J**, which can then react with either diphenyl disulfide or benzenethiol to afford the final products **2**, **3** or **6**. There is also a minor reaction pathway *via* a cyclic radical **K**, which is formed by the addition of the phenyl sulfanyl radical to the allyl group in compound **1**.

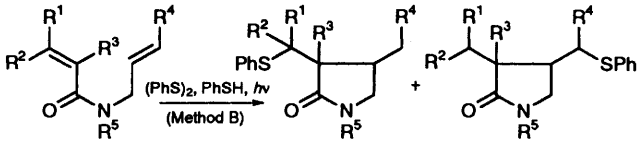
The fact that the mono(phenylsulfanylmethyl) lactams **3**, **4** and **5** were the major products, even in the absence of a thiol (Method A), can be explained by the reduction of the cyclised radicals **J** and **L** by benzenesulfanyl derivatives that can be formed *in situ* upon irradiation of diphenyl disulfide. Schaafsma *et al.*[12] have reported that upon irradiation, diphenyl disulfide undergoes a series of complex reactions, such as radical dissociation, substitution and recombination reactions, to give a variety of sulfur containing compounds (Scheme 4). The reaction pathway leading to the preferred formation of the *trans*-lactams **2**–**4**, can be explained in terms of the steric repulsion between the two substituents at the 3- and 4-positions of the cyclised radical intermediates **J** and **L**. Ikeda

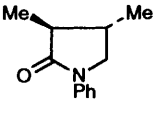


Scheme 4

and coworkers[8,13] have also reported that *trans*-lactams are preferentially formed in the carbamoylmethyl radical cyclisation of α-bromo amides.

Substituent Effect of the Sulfanyl Radical Addition–Cyclisation.—The substituent effect of the sulfanyl radical addition–cyclisation under the conditions described in Method B was then investigated in order to establish the generality of the cyclisation. The substrates were prepared by acylation of the corresponding amines and the results of the sulfanyl radical addition–cyclisation are summarised in Table 2.





The *N*-unsubstituted amide **11**[14] was completely recovered, due to the stable zig-zag conformation that makes it unsuitable for cyclisation[15] (entry 1), whilst the *N*-phenyl amide **12** underwent slow cyclisation to give the 3-(phenylsulfanylmethyl)-lactam **19**. The amides **13**–**15** with no substituent at the β-position of the unsaturated amide group gave mainly the lactams **20**–**22**, which possess the phenylsulfanylmethyl group at the 3-position (entries 4–6). The presence of a substituent α to the unsaturated amide **13** did not influence the radical cyclisation (entry 4). Alternatively, the presence of a substituent at the β-position in the amides **16** and **17** influenced dramatically the regioselectivity of the addition of the phenylsulfanyl radical, resulting in the exclusive formation of the 4-

Table 2 Substituent effect in the sulfanyl radical addition–cyclisation

Entry	Substrate	R^1	R^2	R^3	R^4	R^5	Product, yield (%) (*cis*:*trans*)	Product, yield (%) (*cis*:*trans*)
1	**11**[14]	H	H	Me	H	H	no cyclisation	
2	**12**	H	H	H	H	Ph	**19**, 15 (*t*)	—
3	**1**	H	H	H	H	Allyl	**3**, 57 (*t*)	**4**, **5**, 22 (1:1)
4	**13**	H	H	Me	H	Allyl	**20**, 89 (1:1)[a]	**23**, 2
5	**14**	H	H	H	Me	Bn	**21**, 75 (19:56)	—
6	**15**	H	H	H	Ph	Bn	**22**, 82 (8:74)	—
7	**16**	Me	Me	H	H	Allyl	—	**24**, 37 (24:13)
8	**17**	Me	H	H	H	Allyl	—	**25**, 68 (47:21)
9	**18**	Me	H	H	Me	Bn	no cyclisation	

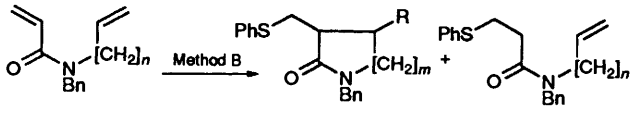
[a] The lactam **20** was formed as an inseparable mixture of two stereoisomers. The ratio was deduced from the ^{1}H NMR spectrum of the mixture.

Table 3 Sulfanyl radical addition–cyclisation of amides **27a–d**

Entry	Substrate (*n*)	Time (*h*)	Product yield (%) **28** (*cis*:*trans*)	**29**
1	**27a** (2)	5	*m* = 2, R = Me 87 (65:22)	—
2	**27b** (3)	9	*m* = 4, R = H 19	26
3	**27c** (4)	4	—	38
4	**27d** (6)	4	—	63

phenylsulfanylmethyl lactams **24** and **25** (entries 7 and 8). In the case of the amide **18**, which has two substituents at the terminals of both olefins, no cyclisation was observed (entry 9). The stereochemistry of all the products, except compound **20**, was established by both spectral data and chemical reactions. The lactam **19** was desulfurised to the known[8] *trans*-3,4-dimethyl-1-phenylpyrrolidin-2-one (**26**) upon treatment with Raney nickel (W-2). The lactam **20** existed as a 1:1 mixture of two inseparable stereoisomers. In the case of the lactams **21** and **22**, the *cis*-lactams exhibited the relevant coupling between the signals for the 3- and 4-hydrogens in the COSY spectra. The stereochemistry of the lactams **24** and **25** was readily deduced from the base catalysed isomerisation of the *cis*-isomers to the corresponding stable *trans*-lactams.[8]

Scope and Limitations.—In order to establish the generality of the sulfanyl radical addition–cyclisation, we also investigated the reactions of the *N*-ω-alkenylamides **27a–d**. The sulfanyl radical addition–cyclisation of the amides **27a–d** by method B was investigated and the results are summarised in Table 3. The



27a–d **28ab** **29a–d**

N-butenyl amide **27a** underwent a 6-*exo*-*trig* cyclisation to give a 3:1 mixture of the *cis*- and *trans*-six-membered lactams **28a**, which was separated and characterised by ^{1}H NMR spectra combined with NOESY spectra. NOEs were observed between the 4-Me and 5-H_{eq}, 4-Me and 6-H_{ax} and the 3-H_{ax} and 5-H_{ax} in the *cis*-**28a**.

The *N*-pentenylamide **27b** underwent an 8-*endo*-*trig*[16] cyclisation to give the eight-membered lactam **28b** in addition to the adduct **29b**. However, two amides **27c**, **d** with a longer carbon chain underwent no cyclisation, but instead addition of benzenethiol to the acryloyl group to give the adducts **29c**, **d** as the products.

In conclusion, we have found a new synthetic method for the formation of five- to eight-membered lactams *via* the sulfanyl radical addition–cyclisation of the dienylamides. Applications of this radical cyclisation to the synthesis of alkaloids and related heterocyclic compounds are in progress in our laboratory.

Experimental

^{1}H NMR spectra were measured using JEOL PMX-60 Si (60 MHz), Varian XL-200 (200 MHz) and VXR-500 (500 MHz) instruments for solutions in deuteriochloroform, unless otherwise stated (tetramethylsilane was used as the internal reference); *J* values are given in Hz. IR spectra were measured with a Hitachi 270-30 machine for solutions in chloroform, unless otherwise stated and mass spectra were taken with a Hitachi M-80 spectrometer. M.p.s were determined with a Kofler-type hot-stage apparatus and are uncorrected. All reactions were performed under nitrogen and extracts from the reaction mixtures were washed with water, dried (Na_2SO_4) and evaporated under reduced pressure. TLC was performed on precoated silica gel $60F_{254}$ (0.25 mm thick, Merck) and preparative TLC (PLC) on precoated silica gel $60F_{254}$ (0.5 mm thick, Merck), with UV detection at 254 and 300 nm. Medium-pressure column chromatography (MPLC) was undertaken on a 530-4-10V apparatus (Yamazen) with Lobar größe B (310-25, Lichroprep Si60, Merck) as column absorbent. For flash column chromatography, Merck Kieselgel 60 (230-400 mesh) was used. All products described in this paper were found to be homogeneous by TLC, MPLC and ^{1}H NMR spectra.

N,N-*Diallylacrylamide* **1**.—A solution of acryloyl chloride (900 mg, 10 mmol) in benzene (10 cm^3) was added at 0 °C to a stirred solution of diallylamine (970 mg, 10 mmol) and triethylamine (1.5 cm^3, 11 mmol) in benzene (20 cm^3). The mixture was stirred at 0 °C for 30 min and then filtered to remove the triethylamine hydrochloride. The filtrate was condensed under reduced pressure and the residue was purified by MPLC [methylene dichloride–ethyl acetate (20:1)] and distilled to afford the title amide **1** (1.5 g, 99%) as a colourless oil, b.p. 125 °C/5 mmHg (lit.,[6] 64 °C/0.05 mmHg); ν_{max}/cm^{-1} 1644 (NCO) and 1612 (C=C); δ_H(200 MHz) 6.61–6.33 (2 H),

5.94–5.67 (3 H) and 5.30–5.13 (4 H) (each m, olefinic H) and 4.20–3.90 (4 H, m, NCH_2 × 2) (Found: M^+, 151.1014. $C_9H_{13}NO$ requires *M*, 151.0995).

Sulfanyl Radical Addition–Cyclisation of the Amide **1**.—(*a*) Method A. A solution of the amide **1** (2 mmol) and diphenyl disulfide (2 mmol) in benzene (200 cm^3) was irradiated with a high-pressure (100 W) mercury lamp through a Pyrex filter (Eikosha, Osaka, Japan, PIH-100) at 5–10 °C for 4 h. The solvent was then evaporated to give a residue, which was purified by MPLC [methylene dichloride–ethyl acetate (20 : 1)] to afford the products **2–5** as shown in Table 1.

(*b*) Method B. A solution of a mixture of the amide **1** (2 mmol), diphenyl disulfide (2 mmol) and benzenethiol (2 mmol) in benzene (200 cm^3) was irradiated at 5–10 °C for 3 h and the crude product was purified as described in method A.

(*c*) Method C. A solution of a mixture of the amide **1** (2 mmol) and benzenethiol (2 mmol) in benzene (200 cm^3) was irradiated at 5–10 °C for 2 h and the crude product was purified as described in method A.

(*d*) Method D. A solution of benzenethiol (1 mmol) and AIBN [azo(isobutyronitrile)] (0.5 mmol) in benzene (5 cm^3) was slowly added *via* a syringe pump, to a stirred refluxing solution of the amide **1** (1 mmol) in benzene (10 cm^3) over a period of 30 min. The solvent was then evaporated and the residue was purified as described in method A.

trans-1-*Allyl*-3,4-*bis*[(*phenylsulfanyl*)*methyl*]*pyrrolidin*-2-*one* **2**. A yellow oil, b.p. 200–220 °C/5 mmHg; ν_{max}/cm^{-1} 1678 (NCO); δ_H(500 MHz) 7.37–7.26 (10 H, m, Ph × 2), 5.70 (1 H) and 5.36–5.12 (2 H) (each m, olefinic H), 3.87 (2 H, br d, *J* 6, $NCH_2CH{=}CH_2$), 3.58 (1 H, dd, *J* 13 and 3, PhSC*H*), 3.50 (1 H, dd, *J* 10 and 9, 5-H), 3.48 (1 H, dd, *J* 13 and 4, PhSC*H*), 3.14 (1 H, dd, *J* 10 and 6, 5-H), 2.96 (1 H, dd, *J* 13 and 8, PhSC*H*), 2.82 (1 H, dd, *J* 13 and 9, PhSC*H*) and 2.60–2.54 (2 H, m, 3- and 4-H) (Found: M^+, 369.1221. $C_{21}H_{23}NOS_2$ requires *M*, 369.1220).

trans-1-*Allyl*-4-*methyl*-3-[(*phenylsulfanyl*)*methyl*]*pyrrolidin*-2-*one* **3**. A colourless oil, b.p. 165–170 °C/6 mmHg; ν_{max}/cm^{-1} 1678 (NCO); δ_H(500 MHz) 7.44–7.18 (5 H, m Ph), 5.73 (1 H) and 5.26–5.15 (2 H) (each m, olefinic H), 3.90 (2 H, m, $NCH_2CH{=}CH_2$), 3.55 (1 H, dd, *J* 13 and 4, PhSC*H*), 3.42 (1 H, dd, *J* 10 and 8, 5-H), 3.02 (1 H, dd, *J* 13 and 8, PhSC*H*), 2.86 (1 H, dd, *J* 10 and 7, 5-H), 2.40–2.32 (2 H, m, 3- and 4-H) and 1.18 (3 H, d, *J* 6, Me) (Found: M^+, 261.1170. $C_{15}H_{19}NOS$ requires *M*, 261.1186) (Found: C, 68.8; H, 7.3; N, 5.2. $C_{15}H_{19}NOS$ requires C, 68.9; H, 7.3; N, 5.4%).

trans-1-*Allyl*-3-*methyl*-4-[(*phenylsulfanyl*)*methyl*]*pyrrolidin*-2-*one* **4**. A colourless oil; b.p. 160–165 °C/5 mmHg; ν_{max}/cm^{-1} 1680 (NCO); δ_H(500 MHz) 7.36–7.20 (5 H, m, Ph), 5.69 (1 H) and 5.20–5.15 (2 H) (each m, olefinic H), 3.93–3.82 (2 H, m, $NCH_2CH{=}CH_2$), 3.45 (1 H, dd, *J* 10 and 8, 5-H), 3.23 (1 H, dd, *J* 13 and 5, PhSC*H*), 3.06 (1 H, dd, *J* 10 and 7.5, 5-H), 2.89 (1 H, dd, *J* 13 and 9, PhSC*H*), 2.29 (1 H, br quint, *J* 7.5, 3-H), 2.16 (1 H, ddtd, *J* 9, 8, 7.5 and 5, 4-H) and 1.22 (3 H, d, *J* 7, Me) (Found: M^+, 261.1193. $C_{15}H_{19}NOS$ requires *M*, 261.1186).

cis-1-*Allyl*-3-*methyl*-4-[(*phenylsulfanyl*)*methyl*]*pyrrolidin*-2-*one* **5**. A colourless oil, b.p. 160–170 °C/6 mmHg; ν_{max}/cm^{-1} 1678 (NCO); δ_H(500 MHz) 7.36–7.21 (5 H, m, Ph), 5.69 (1 H) and 5.20–5.14 (2 H) (each m, olefinic H), 3.87 (2 H, br d, *J* 6, $NCH_2CH{=}CH_2$), 3.39 (1 H, dd, *J* 10 and 7, 5-H), 3.21 (1 H, dd, *J* 10 and 6, 5-H), 3.10 (1 H, dd, *J* 13 and 5, PhSC*H*), 2.76 (1 H, dd, *J* 13 and 10, PhSC*H*), 2.64 (1 H, quint, *J* 7.5, 3-H), 2.58 (1 H, m, 4-H) and 1.16 (3 H, d, *J* 7.5, Me) (Found: M^+, 261.1170. $C_{15}H_{19}NOS$ requires *M*, 261.1186).

cis-1-*Allyl*-4-*methyl*-3-[(*phenylsulfanyl*)*methyl*]*pyrrolidin*-2-*one* **6**. A colourless oil, b.p. 150–165 °C/5 mmHg; ν_{max}/cm^{-1} 1677 (NCO); δ_H(200 MHz) 7.50–7.14 (5 H, m, Ph), 5.70 (1 H) and 5.32–5.12 (2 H) (each m, olefinic H), 4.00 and 3.80 (each 1 H, br dd, *J* 15 and 6, $NCH_2CH{=}CH_2$), 3.56 (1 H, dd, *J* 12 and 2.5, PhSC*H*), 3.44 (1 H, dd, *J* 10 and 6, 5-H), 3.00–2.50 (4 H, m, PhSC*H*, 5-H, 4-H and 3-H) and 1.06 (3 H, d, *J* 7, Me) (Found: M^+, 261.1182. $C_{15}H_{19}NOS$ requires *M*, 261.1186).

Desulfurisation of the Sulfides **2–6**.—A mixture of the sulfides **2–6** (0.08 mmol) and Raney nickel (W-2) (1 cm^3) in ethanol (15 cm^3) was vigorously stirred under reflux for 1 h. The catalyst was then removed by filtration and the filtrate was condensed to give a residue which was purified by PLC [methylene dichloride–ethyl acetate (1 : 1)] to afford the *N*-propyllactam **7** or **8** (65–68%) as a colourless oil.

trans-3,4-*Dimethyl*-1-*propylpyrrolidin*-2-*one* **7**. A viscous oil, ν_{max}/cm^{-1} 1672 (NCO); δ_H(200 MHz) 3.38 (1 H, dd, *J* 10 and 7.5, 5-H), 3.28 and 3.20 (each 1 H, dt, *J* 13 and 7, NCH_2Et), 2.90 (1 H, br t, *J* 9, 5-H), 1.98 (2 H, m, 3- and 4-H), 1.54 (2 H, br sext, *J* 7, NCH_2CH_2Me), 1.18 and 1.13 (each 3 H, d, *J* 6.5, Me × 2) and 0.89 (3 H, t, *J* 7.5, NCH_2CH_2Me) (Found: M^+, 155.1323. $C_9H_{17}NO$ requires *M*, 155.1309).

cis-3,4-*Dimethyl*-1-*propylpyrrolidin*-2-*one* **8**. A viscous oil, ν_{max}/cm^{-1} 1664 (NCO); δ_H(200 MHz) 3.42 (1 H, dd, *J* 10 and 7, 5-H), 3.28 (1 H, dt, *J* 13 and 7.5, NCH_2Et), 3.18 (1 H, dt, *J* 13 and 7.5, CH_2Et), 2.91 (1 H, dd, *J* 10 and 5, 5-H), 2.50 (2 H, m, 3- and 4-H), 1.54 (2 H, sext, *J* 7.5, NCH_2CH_2Me), 1.08 (3 H, d, *J* 7, Me), 0.98 (3 H, d, *J* 6.5, Me) and 0.89 (3 H, t, *J* 7.5, NCH_2CH_2Me) (Found: M^+, 155.1291. $C_9H_{17}NO$ requires *M*, 155.1309).

1-*Allyl*-4-*methyl*-3-*methylidenepyrrolidin*-2-*one* **9**.—An aqueous solution (2 cm^3) of Oxone (115 mg, 0.38 mmol) was added to an ice-cooled solution of the lactam **3** (100 mg, 0.38 mmol) in methanol (10 cm^3). After stirring for 30 min at this temp., the mixture was extracted with methylene dichloride. The extract was then washed, dried and evaporated. The residue was dissolved in toluene (10 cm^3) and the solution was refluxed for 1 h. Evaporation of the solvent gave a residue which was purified by PLC [methylene dichloride–ethyl acetate (1 : 1)] to afford the lactam **9** (29 mg, 51%) as a pale yellow oil; ν_{max}/cm^{-1} 1680 (NCO) and 1658 (C=C); δ_H(200 MHz) 5.98 and 5.29 (each 1 H, d, *J* 3, $3\text{-}CH_2$), 5.82–5.62 (1 H) and 5.24–5.11 (2 H) (each m, olefinic H), 3.97 (2 H, dd, *J* 6 and 1, $NCH_2CH{=}CH_2$), 3.49 (1 H) and 2.94–2.82 (2 H) (each m, 4-H and $5\text{-}H_2$) and 1.19 (3 H, d, *J* 7, Me) (Found: M^+, 151.1004. $C_9H_{13}NO$ requires *M*, 151.0996).

Catalytic Hydrogenation of the Lactam **9**.—A solution of the lactam **9** (29 mg, 0.19 mmol) in methanol (10 cm^3) was hydrogenated in the presence of Adam's catalyst (platinum dioxide) (5 mg) under a hydrogen atmosphere for 30 min. Usual work up and purification of the crude product by PLC [methylene dichloride–ethyl acetate (1 : 1)] gave *compound* **8** (11 mg, 38%) and 3,4-*dimethyl*-1-*propyl*-2,5-*dihydro*-1H-*pyrrol*-2-*one* **10** (9 mg, 32%) both as a pale yellow oil. The lactam **8** was identical with the sample prepared from the *cis*-lactams **5** and **6** upon comparison of their IR and ^1H NMR spectra. Furthermore, hydrogenation of the lactam **10** (40 mg, 0.26 mmol) in the presence of platinum dioxide (20 mg) in methanol (50 cm^3) under 5 atm pressure of hydrogen for 4 days gave the saturated lactam **8** (4 mg, 10%), with recovery of the starting lactam **10** (25 mg).

3,4-*Dimethyl*-1-*propyl*-2,5-*dihydro*-1H-*pyrrol*-2-*one* **10**. A viscous oil, ν_{max}/cm^{-1} 1666 (NCO); δ_H(200 MHz) 3.74 (2 H, br s, $5\text{-}H_2$), 3.40 (2 H, t, *J* 7, NCH_2Et), 1.96 (3 H, br s, 3-Me), 1.80 (3 H, d, *J* 1, 4-Me), 1.59 (2 H, m, NCH_2CH_2Me) and 0.98 (3 H, t, *J* 7, NCH_2CH_2Me).

Isomerisation of the Two Lactams **7** *and* **8**.—According to the literature procedure,[8] sodium (25 mg, 1.09 mmol) was dissolved

in anhydrous ethanol (30 cm^3) and an aliquot of the resulting solution (1 cm^3) was diluted to 2 cm^3 by the addition of further ethanol (1 cm^3). To this solution the lactam **8** (6 mg, 0.04 mmol) was added. The resulting solution was refluxed for 2.5 h and then diluted with aqueous ammonium chloride and finally extracted with methylene dichloride. The extract was washed, dried and evaporated. The ^1H NMR spectrum of the residue showed that the product consisted of an 86 : 14 mixture of the *cis*-**8** and *trans*-**7** lactams. Under the same reaction conditions, the *trans*-lactam **7** was recovered quantitatively.

The Amides **12–17**.—(*a*) The amides **12**, **13**, **16** and **17** were prepared by acylation of the appropriate secondary amines with the corresponding acid chlorides in the presence of triethylamine in benzene in 90–98% yield, after distillation of the crude products.

N-*Allyl*-N-*phenylacrylamide* **12** (98%). A colourless oil, b.p. 135 °C/6 mmHg; ν_{max}/cm^{-1} 1648 (NCO) and 1612 (C=C); δ_H(60 MHz) 7.45–7.00 (5 H, m, Ph), 6.56–5.50 (3 H) and 5.30–4.85 (3 H) (each m, olefinic H) and 4.40 (2 H, d-like, *J* 7, NCH_2) (Found: M^+, 187.0989. $C_{12}H_{13}NO$ requires *M*, 187.0996).

N,N-*Diallylmethacrylamide* **13** (91%). A colourless oil, b.p. 120 °C/5 mmHg; ν_{max}/cm^{-1} 1642 (NCO) and 1616 (C=C); δ_H(60 MHz) 6.20–5.47 (2 H) and 5.47–4.90 (6 H) (each m, olefinic H), 4.00 (4 H, br d, *J* 6, NCH_2 × 2) and 2.00 (3 H, s-like, Me) (Found: M^+, 165.1151. $C_{10}H_{15}NO$ requires *M*, 165.1152).

N,N-*Diallyl*-3-*methylcrotonamide* **16** (98%). A colourless oil, b.p. 165–170 °C/5 mmHg; ν_{max}/cm^{-1} 1644 (NCO) and 1614 (C=C); δ_H(200 MHz) 5.95–5.68 (3 H) and 5.31–5.09 (4 H) (each m, olefinic H), 3.98 (4 H, m, NCH_2 × 2) and 1.97 and 1.83 (each 3 H, d, *J* 1.5, Me × 2) (Found: M^+, 179.1317. $C_{11}H_{17}NO$ requires *M*, 179.1309).

(E)-N,N-*Diallylcrotonamide* **17** (90%). A colourless oil, b.p. 120 °C/5 mmHg; ν_{max}/cm^{-1} 1660 (NCO) and 1610 (C=C); δ_H(60 MHz) 6.97 (1 H, dq, *J* 15 and 7, 3-H), 6.30–4.90 (7 H, m, olefinic H), 3.97 (4 H, br s, NCH_2 × 2) and 1.80 (3 H, dd, *J* 7 and 1.5, Me) (Found: M^+, 165.1145. $C_{10}H_{15}NO$ requires *M*, 165.1152).

(*b*) The amides **14**, **15** and **18** were prepared by alkylation of benzylamine with the appropriate alkyl halides (crotyl bromide for compounds **14** and **18** and cinnamyl bromide in compound **15**) followed by acylation with the corresponding acid chlorides in the presence of triethylamine in benzene in 40–58% yield, after purification by MPLC of the crude products.

(E)-N-*Benzyl*-N-*but*-2-*enylacrylamide* **14**. {47%, MPLC [ethyl acetate–hexane (1 : 1)]} as a colourless oil; ν_{max}/cm^{-1} 1644 (NCO) and 1612 (C=C); δ_H(200 MHz) 7.21 (5 H, s-like, Ph), 6.56–6.40 (2 H) and 5.79–5.40 (3 H) (each m, olefinic H), 4.53 (2 H, br s, NCH_2Ph), 4.08–3.73 (2 H, m, NCH_2) and 1.66 (3 H, d, *J* 5, Me) (Found: M^+, 215.1321. $C_{14}H_{17}NO$ requires *M*, 215.1309).

(E)-N-*Benzyl*-N-(3-*phenylallyl*)*acrylamide* **15**. {40%, MPLC [ethyl acetate–hexane (1 : 1)]} as a colourless oil; ν_{max}/cm^{-1} 1644 (NCO) and 1614 (C=C); δ_H(200 MHz) 7.23 (10 H, s, Ph × 2), 6.83–6.33 (4 H) and 5.83–5.56 (1 H) (each m, olefinic H), 4.69 (2 H, br s, NCH_2Ph) and 4.30–4.00 (2 H, m, NCH_2) (Found: M^+, 277.1474. $C_{19}H_{19}NO$ requires *M*, 277.1466).

(E,E)-N-*Benzyl*-N-*but*-2-*enylcrotonamide* **18**. {58%, MPLC [ethyl acetate–hexane (1 : 2)]} as a colourless oil; ν_{max}/cm^{-1} 1660 (NCO) and 1606 (C=C); δ_H(200 MHz) 7.20 (5 H, br s, Ph), 6.90 (1 H, dq, *J* 15 and 7, 3-H), 6.27 (1 H, br d, *J* 15, 2-H), 5.50 (2 H, m, olefinic H), 4.57 (2 H, br s, NCH_2Ph), 3.87 (2 H, m, NCH_2), 1.90 (3 H, d-like, *J* 7, Me) and 1.67 (3 H, d-like, *J* 6, Me) (Found: M^+, 229.1467. $C_{15}H_{19}NO$ requires *M*, 229.1466).

Sulfanyl Radical Addition–Cyclisation of the Amides **12–17**.—The amides **12–17** were subjected to a sulfanyl radical mediated addition–cyclisation as described in method B to give the products **19–25** as shown in Table 2. Two amides **11** and **18** were recovered.

trans-4-*Methyl*-1-*phenyl*-3-(*phenylsulfanylmethyl*)*pyrrolidin*-2-*one* **19**. A colourless oil, b.p. 220–230 °C/6 mmHg; ν_{max}/cm^{-1} 1678 (NCO); δ_H(500 MHz) 7.14–6.62 (10 H, m, Ph × 2), 3.89 (1 H, dd, *J* 9.5 and 7.5, 5-H), 3.59 (1 H, dd, *J* 13 and 3.5, PhSC*H*), 3.38 (1 H, dd, *J* 9.5 and 7.5, 5-H), 3.14 (1 H, dd, *J* 13 and 8, PhSC*H*), 2.53 (1 H, td, *J* 8 and 3.5, 3-H), 2.48 (1 H, br sept, *J* 7.5, 4-H) and 1.27 (3 H, d, *J* 7, Me) (Found: M^+, 297.1159. $C_{18}H_{19}NOS$ requires *M*, 297.1185).

1-*Allyl*-3,4-*dimethyl*-3-(*phenylsulfanylmethyl*)*pyrrolidin*-2-*one* **20** (cis-**20** : trans-**20** = 1 : 1). A colourless oil, b.p. 165–170 °C/6 mmHg; ν_{max}/cm^{-1} 1678 (NCO); δ_H(200 MHz) 7.50–7.12 (5 H, m, Ph), 5.74 (1 H, m, C*H*=CH_2), 5.30–5.16 (2 H, m, CH=CH_2), 3.92 (2 H, dt, *J* 6 and 1, NCH_2CH=CH_2), 3.40 (1/2 H, dd, *J* 10 and 8, 5-H), 3.35 (1/2 H, dd, *J* 10 and 8.5, 5-H), 3.26 (1/2 H, d, *J* 13, PhSC*H*), 3.18 (1/2 H, d, *J* 13, PhSC*H*), 3.16 (1/2 H, d, *J* 12, PhSC*H*), 3.10 (1/2 H, d, *J* 12, PhSC*H*), 3.04 (1/2 H, dd, *J* 10 and 7, 5-H), 2.86 (1/2 H, dd, *J* 10 and 9, 5-H), 2.56 (1/2 H, br sext, *J* 7, 4-H), 2.24 (1/2 H, br sext, *J* 7, 4-H), 1.27 (3/2 H, s, 3-Me), 1.09 (3/2 H, s, 3-Me), 1.17 (3/2 H, d, *J* 7, 4-Me) and 1.02 (3/2 H, d, *J* 7, 4-Me) (Found: M^+, 275.1343 $C_{16}H_{21}NOS$ requires *M*, 275.1342).

1-*Allyl*-3,3-*dimethyl*-4-(*phenylsulfanylmethyl*)*pyrrolidin*-2-*one* **23**. A colourless oil, b.p. 160–170 °C/5 mmHg; ν_{max}/cm^{-1} 1678 (NCO); δ_H(200 MHz) 7.42–7.24 (5 H, m, Ph), 5.72 (1 H, m, NCH_2C*H*=CH_2), 5.30–5.14 (2 H, m, NCH_2CH=CH_2), 3.91 (2 H, dt, *J* 6 and 1, NCH_2CH=CH_2), 3.47 (1 H, dd, *J* 10 and 8, 5-H), 3.20 (1 H, dd, *J* 13 and 4.5, PhSC*H*), 3.05 (1 H, dd, *J* 10 and 9, 5-H), 2.81 (1 H, dd, *J* 13 and 11, PhSC*H*), 2.28 (1 H, m, 4-H), 1.20 (3 H, s, Me) and 1.05 (3 H, s, Me) (Found: M^+, 275.1356. $C_{16}H_{21}NOS$ requires *M*, 275.1342).

1-*Benzyl*-4-*ethyl*-3-(*phenylsulfanylmethyl*)*pyrrolidin*-2-*one* **21**. *trans*-**21**: A yellow oil; ν_{max}/cm^{-1} 1678 (NCO); δ_H(500 MHz) 7.41–7.22 (10 H, m, Ph × 2), 4.49 and 4.40 (2 H, ABq, *J* 14, NCH_2Ph), 3.52 (1 H, dd, *J* 13 and 4, PhSC*H*), 3.33 (1 H, dd, *J* 10 and 8, 5-H), 3.09 (1 H, dd, *J* 13 and 8, PhSC*H*), 2.82 (1 H, dd, *J* 10 and 6.5, 5-H), 2.47 (1 H, br td, *J* 8 and 5, 3-H), 2.18 (1 H, m, 4-H), 1.70 (1 H, dqd, *J* 16, 7 and 5, C*H*Me), 1.32 (1 H, ddq, *J* 16, 9 and 7, C*H*Me) and 0.82 (3 H, t, *J* 7, Me) (Found: M^+, 325.1498. $C_{20}H_{23}NOS$ requires *M*, 325.1498).

cis-**21**: A yellow oil; ν_{max}/cm^{-1} 1676 (NCO); δ_H(500 MHz) 7.40–7.19 (10 H, m, Ph × 2), 4.47 and 4.40 (2 H, ABq, *J* 14, NCH_2Ph), 3.52 (1 H, dd, *J* 13 and 4, PhSC*H*), 3.23 (1 H, dd, *J* 10 and 6.5, 5-H), 2.98 (1 H, dd, *J* 10 and 3, 5-H), 2.96 (1 H, dd, *J* 13 and 10.5, PhSC*H*), 2.81 (1 H, ddd, *J* 10.5, 7 and 4, 3-H), 2.31 (1 H, br dtt, *J* 11, 7 and 4, 4-H), 1.63 (1 H, dqd, *J* 13.5, 7 and 4, C*H*Me), 1.18 (1 H, ddq, *J* 13.5, 11 and 7, C*H*Me) and 0.83 (3 H, t, *J* 7, Me) (Found: M^+, 325.1499. $C_{20}H_{23}NOS$ requires *M*, 325.1498).

1,4-*Dibenzyl*-3-(*phenylsulfanylmethyl*)*pyrrolidin*-2-*one* **22**. *trans*-**22**: A colourless oil; ν_{max}/cm^{-1} 1678 (NCO); δ_H(500 MHz) 7.37–6.96 (15 H, m, Ph × 3), 4.43 and 4.39 (2 H, ABq, *J* 15, NCH_2Ph), 3.42 (1 H, dd, *J* 13 and 3, PhSC*H*), 3.15 (1 H, dd, *J* 10 and 8, 5-H), 3.12 (1 H, dd, *J* 13 and 7, PhSC*H*), 2.98 (1 H, dd, *J* 13.5 and 5, C*H*Ph), 2.88 (1 H, dd, *J* 10 and 6, 5-H), 2.65–2.56 (2 H, m, 3- and 4-H) and 2.51 (1 H, dd, *J* 13.5 and 9, C*H*Ph) (Found: M^+, 387.1653. $C_{25}H_{25}NOS$ requires *M*, 387.1654) (Found: C, 77.3; H, 6.5; N, 3.4. $C_{25}H_{25}NOS$ requires C, 77.5; H, 6.5; N, 3.6%).

cis-**22**: A colourless oil; ν_{max}/cm^{-1} 1678 (NCO); δ_H(500 MHz) 7.45–6.76 (15 H, m, Ph × 3), 4.71 and 4.14 (2 H, ABq, *J* 14, NCH_2Ph), 3.65 (1 H, dd, *J* 13 and 3.5, PhSC*H*), 3.02 (1 H, br dd, *J* 10 and 5, 5-H), 3.00 (1 H, dd, *J* 13 and 11, PhSC*H*), 2.95 (1 H, br dd, *J* 13 and 3.5, C*H*Ph), 2.89 (1 H, br ddd, *J* 11, 7 and 4, 4-H), 2.85 (1 H, dd, *J* 10 and 2, 5-H), 2.69–2.62 (1 H, m, 3-H) and 2.09 (1 H, br t, *J* 13, C*H*Ph) (Found: M^+, 387.1639. $C_{25}H_{25}NOS$ requires *M*, 387.1654).

1-*Allyl*-3-*isopropyl*-4-(*phenylsulfanylmethyl*)*pyrrolidin*-2-*one* **24**. *trans*-**24**: A colourless oil, b.p. 150–160 °C/5 mmHg; ν_{max}/cm^{-1} 1672 (NCO); δ_H(500 MHz) 7.36–7.22 (5 H, m, Ph), 5.70 (1 H, m, NCH$_2$C*H*=CH$_2$), 5.20–5.15 (2 H, m, NCH$_2$-CH=C*H*$_2$), 3.95 (1 H, ddt, *J* 15, 6 and 1, NC*H*$_2$CH=CH$_2$), 3.81 (1 H, dd, *J* 15 and 6.5, NC*H*$_2$CH=CH$_2$), 3.44 (1 H, dd, *J* 10 and 8, 5-H), 3.13 (1 H, dd, *J* 13 and 5, PhSC*H*), 3.12 (1 H, dd, *J* 10 and 4, 5-H), 2.87 (1 H, dd, *J* 13 and 9, PhSC*H*), 2.34 (1 H, m, 4-H), 2.26 (1 H, br t, *J* 4, 3-H), 2.21 (1 H, m, Me$_2$C*H*) and 0.96 and 0.85 (each 3 H, d, *J* 7, Me × 2) (Found: M$^+$, 289.1498. $C_{17}H_{23}NOS$ requires *M*, 289.1498).

cis-**24**: A colourless oil, b.p. 150–160 °C/5 mmHg; ν_{max}/cm^{-1} 1674 (NCO); δ_H(500 MHz) 7.37–7.23 (5 H, m, Ph), 5.68 (1 H, m, NCH$_2$C*H*=CH$_2$), 5.20–5.15 (2 H, m, NCH$_2$CH=C*H*$_2$), 3.93 (1 H, ddt, *J* 15, 6 and 1, NC*H*$_2$CH=CH$_2$), 3.81 (1 H, br dd, *J* 15 and 6.5, NC*H*$_2$CH=CH$_2$), 3.34 (1 H, dd, *J* 10 and 7, 5-H), 3.22 (1 H, dd, *J* 10 and 6, 5-H), 3.17 (1 H, dd, *J* 13 and 5, PhSC*H*), 2.79 (1 H, dd, *J* 13 and 10.5, PhSC*H*), 2.58 (1 H, m, 4-H), 2.31 (1 H, dd, *J* 8 and 6, 3-H), 2.03 (1 H, br oct, *J* 6.5, Me$_2$C*H*) and 1.07 and 1.06 (each 3 H, d, *J* 7, Me × 2) (Found: M$^+$, 289.1496 $C_{17}H_{23}NOS$ requires *M*, 289.1498).

1-*Allyl*-3-*ethyl*-4-(*phenylsulfanylmethyl*)*pyrrolidin*-2-*one* **25**. *trans*-**25**: A colourless oil, b.p. 160–170 °C/5 mmHg; ν_{max}/cm^{-1} 1676 (NCO); δ_H(200 MHz) 7.42–7.23 (5 H, m, Ph), 5.72 (1 H) and 5.30–5.10 (2 H) (each m, olefinic H), 3.92 (2 H, m, NC*H*$_2$CH=CH$_2$), 3.50 (1 H, dd, *J* 10 and 8, 5-H), 3.21 (1 H, dd, *J* 13 and 5, PhSC*H*), 3.12 (1 H, dd, *J* 10 and 6, 5-H), 2.90 (1 H, dd, *J* 13 and 9, PhSC*H*), 2.40–2.20 (2 H, m, 3- and 4-H), 1.94–1.48 (2 H, m, MeC*H*$_2$) and 0.94 (3 H, t, *J* 7, Me) (Found: C, 69.9; H, 7.7; N, 5.0; M$^+$, 275.1347 $C_{16}H_{21}NOS$ requires C, 69.8; H, 7.7; N, 5.1%; *M*, 275.1343).

cis-**25**: A colourless oil, b.p. 150–160 °C/5 mmHg; ν_{max}/cm^{-1} 1674 (NCO); δ_H(500 MHz) 7.36–7.22 (5 H, m, Ph), 5.68 (1 H) and 5.19–5.14 (2 H) (each m, olefinic H), 3.92–3.81 (2 H, m, NC*H*$_2$CH=CH$_2$), 3.35 (1 H, dd, *J* 10 and 6.5, 5-H), 3.30 (1 H, dd, *J* 10 and 4, 5-H), 3.12 (1 H, dd, *J* 13 and 4, PhSC*H*), 2.68 (1 H, dd, *J* 13 and 11, PhSC*H*), 2.55 (1 H, m, 4-H), 2.42 (1 H, td, *J* 8 and 6, 3-H), 1.80 and 1.53 (each 1 H, m, MeC*H*$_2$) and 1.02 (3 H, t, *J* 7.5, Me) (Found: C, 70.0; H, 7.6; N, 5.0; M$^+$, 275.1357. $C_{16}H_{21}NOS$ requires C, 69.8; H, 7.7; N, 5.1%; *M*, 275.1343).

trans-3,4-*Dimethyl*-1-*phenylpyrrolidin*-2-*one* **26**.—According to the procedure described for the desulfurisation of compound **3**, treatment of the pyrrolidinone **19** with Raney Nickel followed by purification by the literature procedure[8] gave the dimethyllactam **26** (50%) as colourless crystals, m.p. 100–101 °C (lit.,[8] 94–96 °C), which exhibited IR and ^{1}H NMR spectra which were identical with those of the authentic sample; ν_{max}/cm^{-1} 1688 (NCO); δ_H(60 MHz) 7.63–6.96 (5 H, m, Ph), 3.79 (1 H, dd, *J* 10 and 7, 5-H), 3.33 (1 H, t, *J* 10, 5-H), 2.30–2.00 (2 H, m, 3- and 4-H), 1.24 (3 H, d, *J* 6, 3- or 4-Me) and 1.20 (3 H, d, *J* 6, 3- or 4-Me) (Found: M$^+$, 189.1168. $C_{12}H_{15}NO$ requires *M*, 189.1152).

Isomerisation of the Lactams **24** *and* **25**.—According to the procedure described in the isomerisation of the *cis*-lactam **8**, the *cis*-lactams **24** and **25** were readily converted into the corresponding *trans*-isomers [*trans*-**24** (99%) and *trans*-**25** (99%)] after refluxing in ethanolic sodium ethoxide for 2.5–4.5 h. Alternatively, the *trans*-lactams (*trans*-**24** and *trans*-**25**) were completely recovered under identical reaction conditions.

Preparation and subsequent Sulfanyl Radical Addition–Cyclisation of the Amides **27a–d**.—The appropriate alkenyl bromides (10 mmol) (but-3-enyl bromide, pent-4-enyl bromide, hex-5-enyl bromide or oct-7-enyl bromide) were added dropwise to a solution of benzylamine (3.2 g, 30 mmol) in benzene (20 cm^3) under ice-cooling. After stirring at 80–90 °C for 6 h, the mixture was diluted with benzene and washed with 10% aqueous sodium hydroxide and then water. The extract was then dried and evaporated. The residue was distilled to give the secondary amines which were subsequently acylated according to the procedure described in the preparation of the amides **1**. The amides **27a–d** were then subjected to sulfanyl radical addition–cyclisation (as described in method B) to afford the products **28** and **29** as shown in Table 3.

N-*Benzyl*-N-*but*-3-*enylacrylamide* **27a**. A colourless oil, b.p. 180–190 °C/5 mmHg; ν_{max}/cm^{-1} 1644 (NCO) and 1610 (C=C); δ_H(60 MHz) 7.23 (5 H, s, Ph), 6.43, 5.70 and 5.00 (each 2 H, m, olefinic H), 4.60 (2 H, br s, NC*H*$_2$Ph), 3.40 (2 H, m, NC*H*$_2$CH$_2$) and 2.37 (2 H, m, CH$_2$C*H*$_2$CH=CH$_2$) (Found: M$^+$, 215.1311. $C_{14}H_{17}NO$ requires *M*, 215.1309).

N-*Benzyl*-N-*pent*-4-*enylacrylamide* **27b**. A colourless oil, b.p. 190–200 °C/5 mmHg; ν_{max}/cm^{-1} 1644 (NCO) and 1610 (C=C); δ_H(60 MHz) 7.20 (5 H, s, Ph), 6.57–5.40 (4 H) and 5.30–4.57 (2 H) (each m, olefinic H), 4.63 (2 H, br s, NC*H*$_2$Ph), 3.37 (2 H, m, NC*H*$_2$CH$_2$), 2.67–1.47 (4 H, m, CH$_2$ × 2) (Found: M$^+$, 229.1449. $C_{15}H_{19}NO$ requires *M*, 229.1465).

N-*Benzyl*-N-*hex*-5-*enylacrylamide* **27c**. A colourless oil, b.p. 200–210 °C/5 mmHg; ν_{max}/cm^{-1} 1642 (NCO) and 1610 (C=C); δ_H(60 MHz) 7.20 (5 H, s, Ph), 6.59–5.42 (4 H, m, olefinic H), 5.10–4.76 (2 H, m, olefinic H), 4.59 (2 H, s, NC*H*$_2$Ph), 3.50–3.10 (2 H, m, NC*H*$_2$CH$_2$), 2.13–1.23 [6 H, m (CH$_2$)$_3$] (Found: M$^+$, 243.1611. $C_{16}H_{21}NO$ requires *M*, 243.1621).

N-*Benzyl*-N-*oct*-7-*enylacrylamide* **27d**. A colourless oil; ν_{max}/cm^{-1} 1642 (NCO) and 1612 (C=C); δ_H(60 MHz) 7.17 (5 H, s, Ph), 6.56–5.50 (4 H) and 5.07–4.73 (2 H) (each m, olefinic H), 4.60 (2 H, s, NC*H*$_2$Ph), 3.50–3.12 (2 H, m, NC*H*$_2$CH$_2$), 2.09–1.00 [10 H, m (CH$_2$)$_5$] (Found: M$^+$, 271.1921. $C_{18}H_{25}NO$ requires *M*, 271.1934).

1-*Benzyl*-4-*methyl*-3-(*phenylsulfanylmethyl*)*piperidin*-2-*one* **28a**. *trans*-**28a**: A colourless oil, b.p. 190–200 °C/5 mmHg; ν_{max}/cm^{-1} 1630 (NCO); δ_H(200 MHz) 7.52–7.20 (10 H, m, Ph), 4.63 (2 H, s, NC*H*$_2$Ph), 3.66 (1 H, dd, *J* 13 and 5, PhSC*H*), 3.44 (1 H, dd, *J* 13 and 4, PhSC*H*), 3.36–3.10 (2 H, m, 6-H$_2$), 2.44 (1 H, ddd, *J* 9, 5 and 4, 3-H), 2.40–2.10 (1 H, m, 4-H), 1.82 (1 H, br dq, *J* 13 and 4, 5-H$_{eq}$), 1.50 (1 H, dddd, *J* 13, 11, 9 and 6, 5-H$_{ax}$), 1.02 (3 H, d, *J* 7, Me) (Found: M$^+$, 325.1494. $C_{20}H_{23}NOS$ requires *M*, 325.1498).

cis-**28a**: A colourless oil, b.p. 190–200 °C/5 mmHg; ν_{max}/cm^{-1} 1628 (NCO); δ_H(500 MHz) 7.40–7.14 (10 H, m, Ph), 4.59 and 4.55 (2 H, ABq, *J* 14, NC*H*$_2$Ph), 3.92 (1 H, dd, *J* 13.5 and 4.5, PhSC*H*), 3.25 (1 H, br td, *J* 12 and 5.5, 6-H$_{ax}$), 3.15 (1 H, ddd, *J* 12.5, 6.5 and 3, 6-H$_{eq}$), 2.87 (1 H, dd, *J* 13.5 and 11, PhSC*H*), 2.65 (1 H, dt, *J* 11 and 4.5, 3-H), 2.49 (1 H, br qt, *J* 7 and 4, 4-H), 1.88 (1 H, dddd, *J* 13, 11, 6.5 and 4, 5-H$_{ax}$), 1.72 (1 H, m, 5-H$_{eq}$), 0.93 (3 H, d, *J* 7, Me) (Found: M$^+$, 325.1501. $C_{20}H_{23}NOS$ requires *M*, 325.1498).

1-*Benzyl*-3-(*phenylsulfanylmethyl*)*azocan*-2-*one* **28b**. A colourless oil, b.p. 220–230 °C/5 mmHg; ν_{max}/cm^{-1} 1632(NCO); δ_H(200 MHz) 7.42–7.20 (10 H, m, Ph), 5.33 (1 H, br d, *J* 15, NC*H*$_2$Ph), 3.98 (1 H, d, *J* 15, NC*H*$_2$Ph), 3.48 (1 H, dd, *J* 12 and 8, PhSC*H*), 3.56–3.34 (1 H, m, 8-H), 3.20–3.00 (2 H, m, 3- and 8-H), 3.00 (1 H, dd, *J* 12 and 5, PhSC*H*) and 1.90–1.30 (8 H, m, 4-, 5-, 6- and 7-H$_2$) (Found: M$^+$, 339.1648. $C_{21}H_{25}NOS$ requires *M*, 339.1655).

N-*Benzyl*-N-*pent*-4-*enyl*-3-(*phenylsulfanylmethyl*)*propion-amide* **29b**. A colourless oil; ν_{max}/cm^{-1} 1638 (NCO); δ_H(200 MHz) 7.46–7.08 (10 H, m, Ph × 2), 6.08–5.92 (1 H) and 5.90–5.60 (2 H) (each m, olefinic H), 4.64 (6/5 H, s, NC*H*$_2$Ph), 4.49 (4/5 H, s, NC*H*$_2$Ph), 3.48–3.02 (4 H), 2.80–2.58 (2 H) and 2.12–1.82 (2 H) (each m, 2-H$_2$, 3-H$_2$, NCH$_2$ and C*H*$_2$CH=CH$_2$) and 1.72–1.48 (2 H, m, CH$_2$) (Found: M$^+$, 339.1648. $C_{21}H_{25}NOS$ requires *M*, 339.1655). The ^{1}H NMR spectrum shows the existence of two rotational isomers in $CDCl_3$ solution.

N-*Benzyl*-N-*hex*-5-*enyl*-3-(*phenylsulfanylmethyl*)*propion-*

amide **29c**. A colourless oil; ν_{max}/cm^{-1} 1638 (NCO); δ_H(200 MHz) 7.44–7.09 (10 H, m, Ph × 2), 5.86–5.62 (1 H) and 5.06–4.98 (2 H) (each m, olefinic H), 4.64 (10/9H, s, NCH_2Ph), 4.48 (8/9 H, s, NCH_2Ph), 3.46–3.00 (4 H), 2.78–2.58 (2 H) and 2.12–1.86 (2 H) (each m, 2-H_2, 3-H_2, NCH_2 and $CH_2CH{=}CH_2$), 1.61–1.21 [4 H, m, $(CH_2)_2$] (Found: M^+, 353.1793. $C_{22}H_{27}NOS$ requires *M*, 353.1812). The ^1H NMR spectrum shows the existence of two rotational isomers in $CDCl_3$ solution.

N-*Benzyl*-N-*oct*-7-*enyl*-3-(*phenylsulfanylmethyl*)*propion-amide* **29d**. A colourless oil; ν_{max}/cm^{-1} 1636 (NCO); δ_H(200 MHz) 7.41–7.06 (10 H, m, Ph × 2), 5.90–5.68 (1 H) and 5.60–4.88 (2 H) (each m, olefinic H), 4.62 (7/6 H, br s, NCH_2Ph), 4.46 (5/6 H, br s, NCH_2Ph), 3.42–3.00 (4 H), 2.78–2.54 (2 H) and 2.10–1.80 (2 H) (each m, 2-H_2, 3-H_2, NCH_2 and $CH_2CH{=}CH_2$), 1.56–1.10 [8 H, m, $(CH_2)_4$] (Found: M^+, 381.2130. $C_{24}H_{31}NOS$ requires *M*, 381.2124). The ^1H NMR spectrum shows the existence of two rotational isomers in $CDCl_3$ solution.

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References

1 Preliminary communication: T. Naito, Y. Honda, O. Miyata and I. Ninomiya, *Heterocycles*, 1991, **32**, 2319.

2 For reviews of radical cyclisations see: (*a*) B. Giese, *Radicals in Organic Synthesis: Formation of Carbon–Carbon Bonds*, Pergamon Press, Inc., New York, 1986; (*b*) D. P. Curran, *Synthesis*, 1988, 417 and 489; (*c*) T. V. RajanBabu, *Acc. Chem. Res.*, 1991, **24**, 139; (*d*) C. P. Jasperse, D. P. Curran and T. L. Fevig, *Chem. Rev.*, 1991, **91**, 1237; (*e*) W. Smadja, *Synlett*, 1994, 1.

3 For Type II radical addition–cyclisation *via* the route involving the addition of a sulfanyl and related sulfonyl radicals see: sulfanyl radical: (*a*) C. A. Broka and D. E. C. Reichert, *Tetrahedron Lett.*, 1987, **28**, 1503; (*b*) M. E. Kuehne and R. E. Damon, *J. Org. Chem.*, 1977, **42**, 1825; (*c*) M. E. Kuehne and W. H. Parsons, *J. Org. Chem.*, 1977, **42**, 3408; (*d*) A. Padwa, H. Nimmesgern and G. S. K. Wong, *J. Org. Chem.*, 1985, **50**, 5620; (*e*) Y. Ichinose, K. Wakamatsu, K. Nozaki, J.-L. Birbaum, K. Oshima and K. Uchimoto, *Chem. Lett.*, 1987, 1647. Sulfonyl radical: (*f*) R. Nougier, C. Lesueur, E. De Riggi, M. P. Bertrand and A. Virgili, *Tetrahedron Lett.*, 1990, **31**, 3451; (*g*) I. De Riggi, J.-M. Surzur, M. P. Bertrand, A. Archavlis and R. Faure, *Tetrahedron*, 1990, **46**, 5285; (*h*) I. De Riggi, R. Nouguier, J. M. Surzur, C. Lesueur, M. P. Bertrand, C. Jaime and A. Virgili, *Bull. Soc. Chim. Fr.*, 1993, **130**, 229; (*i*) C.-P. Chuang, *Tetrahedron*, 1991, **47**, 5425; (*j*) C.-P. Chuang, *Synth. Commun.*, 1992, **22**, 3151; (*k*) C.-P. Chuang, *Tetrahedron Lett.*, 1992, **33**, 6311; (*l*) J. E. Brumwell, N. S. Simpkins and N. K. Terrett, *Tetrahedron Lett.*, 1993, **34**, 1219; (*m*) T. A. K. Smith and G. H. Whitham, *J. Chem. Soc., Perkin Trans. 1*, 1989, 313.

4 O. Miyata, T. Shinada, T. Naito, I. Ninomiya, T. Date and K. Okamura, *Tetrahedron*, 1993, **49**, 8119; O. Miyata, T. Shinada, T. Naito, I. Ninomiya, T. Date, K. Okamura and S. Inagaki, *J. Org. Chem.*, 1991, **56**, 6556; O. Miyata, T. Shinada, N. Kawakami, K. Taji, I. Ninomiya, T. Naito, T. Date and K. Okamura, *Chem. Pharm. Bull.*, 1992, **40**, 2579; O. Miyata, T. Shinada, I. Ninomiya and T. Naito, *Tetrahedron Lett.*, 1991, **32**, 3519; T. Naito, T. Shinada, O. Miyata and I. Ninomiya, *Tetrahedron Lett.*, 1989, **30**, 2941.

5 (*a*) M. D. Bachi, F. Frolow and C. Hoornaert, *J. Org. Chem.*, 1983, **48**, 1841; (*b*) D. A. Burnett, J.-K. Choi, D. J. Hart and Y.-M. Tsai, *J. Am. Chem. Soc.*, 1984, **106**, 8201; (*c*) D. J. Hart and Y.-M. Tsai, *J. Am. Chem. Soc.*, 1984, **106**, 8209; (*d*) G. E. Keck and E. J. Enholm, *Tetrahedron Lett.*, 1985, **26**, 3311; (*e*) J. Knight and P. J. Parsons, *J. Chem. Soc., Perkin Trans. 1*, 1987, 1237; (*f*) S. J. Danishefsky and J. S. Panek, *J. Am. Chem. Soc.*, 1987, **109**, 917; (*g*) R. S. Jolly and T. Livinghouse, *J. Am. Chem. Soc.*, 1988, **110**, 7536; (*h*) J. M. Clough, G. Pattenden and P. G. Wight, *Tetrahedron Lett.*, 1989, **30**, 7469; (*i*) A. L. J. Beckwith and S. W. Westwood, *Tetrahedron*, 1989, **45**, 5269; (*j*) G. Stork and R. Mah, *Heterocycles*, 1989, **28**, 723; (*k*) P. M. Esch, H. Hiemstra and W. N. Speckamp, *Tetrahedron Lett.*, 1990, **31**, 759; (*l*) D. P. Curran and J. Tamine, *J. Org. Chem.*, 1991, **56**, 2746.

6 E. Schmitz, R. Urban, U. Heuck, G. Zimmermann and E. Grundemann, *J. Prakt. Chem.*, 1976, **318**, 185.

7 S. W. Berson, *Chem. Rev.*, 1978, **78**, 23.

8 T. Sato, Y. Wada, M. Nishimoto, H. Ishibashi and M. Ikeda, *J. Chem. Soc., Perkin Trans. 1*, 1989, 879.

9 E. Schmitz, R. Urban and G. Zimmermann, *Z. Chem.*, 1972, **12**, 100. [*Chem. Abstr.*, 1972, **77**, 48128q].

10 E. R. Laird and W. L. Jorgensen, *J. Org. Chem.*, 1990, **55**, 9.

11 (*a*) P. J. Wagner, J. H. Sedon and M. J. Lindstrom, *J. Am. Chem. Soc.*, 1978, **100**, 2579; (*b*) C. Walling and W. Helmreich, *J. Am. Chem. Soc.*, 1959, **81**, 1144.

12 Y. Schaafsma, A. F. Bickel and E. C. Kooyman, *Tetrahedron*, 1960, **10**, 76.

13 T. Sato, K. Tsujimoto, K. Matsubayashi, H. Ishibashi and M. Ikeda, *Chem. Pharm. Bull.*, 1992, **40**, 2308.

14 Y. Inoue, M. Taguchi and H. Hashimoto, *Bull. Chem. Soc. Jpn.*, 1983, **58**, 2721.

15 E. L. Eliel, N. L. Allinger, S. J. Angyal and G. A. Morrison, *Conformational Analysis*, John Wiley and Sons, Inc., New York, 1965, pp. 191–199.

16 (*a*) A. L. J. Beckwith and C. H. Schiesser, *Tetrahedron*, 1985, **41**, 3925; (*b*) R. J. Sundberg and R. J. Cherney, *J. Org. Chem.*, 1990, **55**, 6028.

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