Synthesis of pyrrolidin-2-ones by 5-*endo-trigonal* radical cyclisation of *N*-vinyl-2,2-bis(phenylsulfanyl)acetamides

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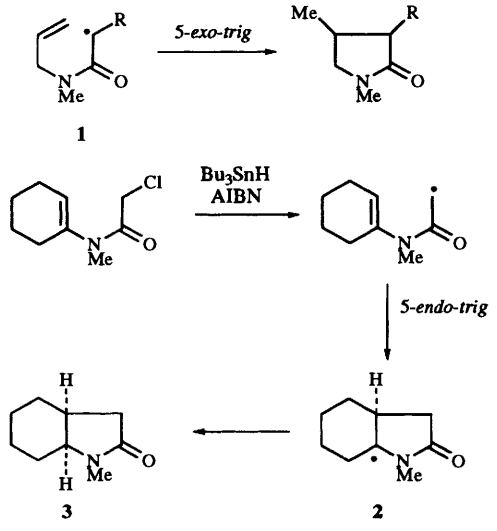
A series of *N*-methyl-*N*-(1-substituted or 1,2-disubstituted vinyl)-2,2-bis(phenylsulfanyl)acetamides, upon treatment with tributyltin hydride in the presence of a catalytic amount of AIBN in boiling toluene, underwent smooth cyclisation in a 5-*endo-trig* manner to give the corresponding pyrrolidin-2-ones. In contrast, the *N*-(1-unsubstituted 2-phenylvinyl) congener gave predominantly the reduction product. These results imply that, for the 5-*endo* cyclisation to proceed effectively, the developing α-acylamino radicals in the transition state of the 5-*endo* cyclisation must be stabilised by an aryl or an alkyl group. An application of this method to a synthesis of (±)-continine is also described.

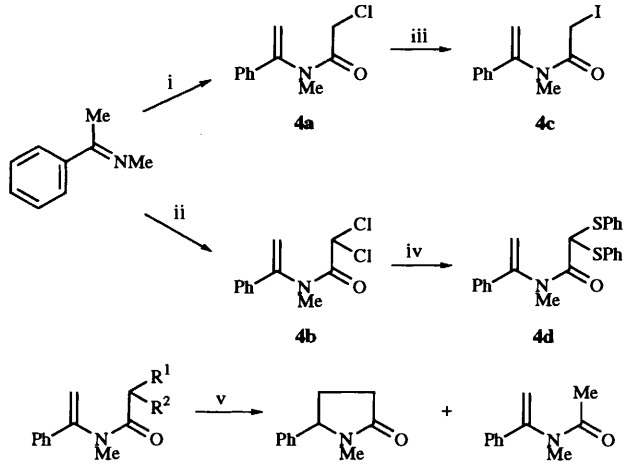
During the last decade, the use of radical cyclisations for the synthesis of nitrogen-containing heterocycles has increased dramatically.[1] We are interested in developing new synthetic methods for lactams by using cyclisation of carbamoylmethyl radicals and in applying them to the synthesis of biologically active compounds.[2] This radical approach was found to be very effective, particularly for the synthesis of five-membered lactams using a 5-*exo-trig* cyclisation of the *N*-allylic carbamoylmethyl radicals **1**. We were then led to examine the behaviour of the *N*-vinylic carbamoylmethyl radicals **2** and found that they undergo a so-called 'disfavoured' 5-*endo-trig* radical cyclisation [3] to give the fused five-membered lactams **3** (Scheme 1).[4] As an extension of these studies, we have now



Scheme 1

examined the radical cyclisation of *N*-(1- or 2-arylvinyl)-2-halo- or 2-(phenylsulfanyl)-substituted acetamides **4** in order to see the effect of the substituents on the vinylic double bond in 5-*endo-trig* cyclisation. In this paper, we describe the synthesis of 4- or 5-arylpyrrolidin-2-ones by tributyltin hydride-mediated radical cyclisation of the acetamides **4**.[5] An application of this method to a synthesis of (±)-cotinine,[6] a metabolite of nicotine, is also described.

We began our study with the *N*-(1-phenylvinyl)-2-halo- or 2-(phenylsulfanyl)-substituted acetamides **4**. The radical precursors **4a**, **b** were prepared by *N*-acylation of acetophenone *N*-methylimine with chloroacetyl chloride or dichloroacetyl chloride in 47 and 80% yields, respectively. The acetamides **4c**, **d** were synthesised by substitution of **4a** and **4b** with iodide ion and phenylthiolate ion, respectively, as shown in Scheme 2.



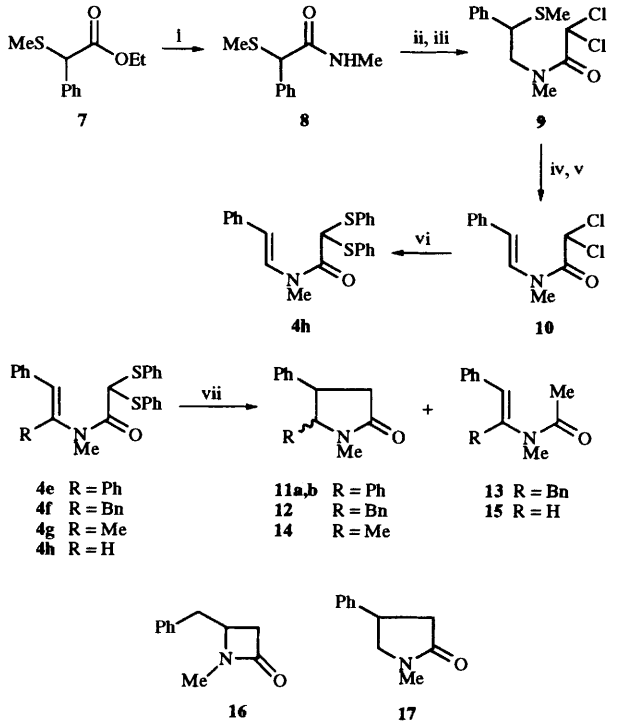
4a R^1 = Cl, R^2 = H
4b R^1 = R^2 = Cl
4c R^1 = I, R^2 = H
4d R^1 = R^2 = SPh

Scheme 2 *Reagents and conditions:* i, $ClCH_2COCl$, CH_2Cl_2; ii, $Cl_2CHCOCl$, CH_2Cl_2; iii, NaI, MeCN; iv, PhSNa, EtOH; v, Bu_3SnH, AIBN, toluene, reflux

In general, a mixture of tributyltin hydride (Bu_3SnH) (1.1 mol equiv.) and a catalytic amount of azoisobutyronitrile (AIBN) in toluene was added to a boiling solution of these substrates in toluene during 2 h, and the resulting mixture was refluxed for 5 h. In order to complete the reaction (since the reaction was very slow) and also to eliminate the second chlorine atom or phenylsulfanyl group from the initially formed cyclised product in the case of **4b**, **d** the same procedure was repeated two or three times. After evaporation of the solvent, the crude material was treated with 8% aqueous KF to remove the tin derivatives formed, and then chromatographed on silica gel to give the pyrrolidin-2-ones **5**. The cyclisation was found to be highly dependent upon the nature of the radical precursors. Thus, treatment of the monochloroacetamide **4a** with Bu_3SnH gave only a small amount of the cyclised product **5** (17%) along with the reduction product **6** (18%) and the recovery of a large amount of the starting material (50%). The dichloroacetamide **4b** failed to cyclise even after the prolonged refluxing time: a complex mixture was obtained from which the starting material

(39%) and the monochloroacetamide **4a** (6%) were isolated, but no cyclised product **5** was detected. In contrast, the more reactive iodide **4c** underwent cyclisation to give **5** in 47% yield together with the reduction product **6** (12%). The disulfanylacetal **4d** was found to be the radical precursor of choice and gave **5** as a sole product in 75% yield. The formation of different ratios of the cyclised and reduced products according to the leaving group may be explained as follows. The slow reaction of the tin radical on chlorine atoms is provoking a higher instantaneous concentration of tin hydride since it is not consumed as rapidly as it is added, which leads to an increased amount of reduced compound. With iodine, there is a faster consumption of tin hydride and as a result less reduced compound. With the sulfide, even if there is the formation of reduced compound, the presence of a second reactive function on this compound gives a second chance of cyclisation.

On the basis of these results, we next investigated the cyclisation of the *N*-(2-phenylvinyl)-2,2-bis(phenylsulfanyl)-acetamides **4e–h**. The radical precursors **4e–g** were prepared by acylation of the corresponding imines, prepared from the corresponding ketones and methylamine, with bis(phenylsulfanyl)acetyl chloride in the presence of triethylamine and 4-dimethylaminopyridine (DMAP) in 60, 69 and 22% yields, respectively. The bis(phenylsulfanyl)acetamide **4h** was not obtained by the same sequence starting from phenylacetaldehyde, but was prepared from ethyl 2-phenyl-2-(methylsulfanyl)-acetate **7** according to the following reaction sequence reported previously by us:[7] (1) treatment of **7** with methylamine in a sealed tube, (2) reduction of the amide **8** with borane–THF followed by *N*-acylation of the amine with dichloroacetic acid, (3) oxidation of the sulfide **9** with sodium metaperiodate, (4) heating of the resulting sulfoxide in xylene, and (5) treatment of the dichloroacetamide **10** with 2.2 equiv. of sodium phenylthiolate to give the desired **4h** (Scheme 3). The (*E*)-stereochemistry of **10** and **4h** was assigned on the basis of the observed large coupling constants between the two olefinic protons (*J* 14 and 14.5 Hz, respectively).

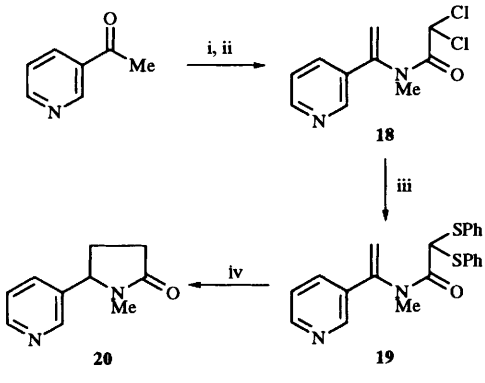


Scheme 3 *Reagents and conditions:* i, $MeNH_2$, toluene, 120 °C; ii, BH_3, THF; iii, Cl_2CHCO_2H, $Me_2N(CH_2)_3N{=}C{=}NEt{\cdot}HCl$, Et_3N, DMAP, CH_2Cl_2; iv, $NaIO_4$; v, $NaHCO_3$, xylene, reflux; vi, PhSNa, MeOH; vii, Bu_3SnH, AIBN, toluene, reflux

Radical cyclisation of **4e** with Bu_3SnH in the presence of AIBN gave a mixture of the *cis*- and *trans*-lactams **11a** and **11b** in 67 and 25% yields, respectively. The stereochemistry of **11a** and **11b** is based on an NOE experiment. Thus, when 5-H of the *cis* isomer **11a** was irradiated, the signal due to 4-H was enhanced (16%), and irradiation of 4-H in turn resulted in 10% enhancement of the signal due to 5-H. On the other hand, when the same experiments were performed on the *trans* isomer **11b**, only a small enhancement of the same signals (4 and 5%, respectively) was observed. Formation of the *cis*-isomer **11a** as the major product is consistent with the idea of a kinetically controlled tin hydride attack at the less hindered side of the acylamino radical intermediate. The acetamide **4f** afforded the isomeric lactams **12** (46%; the isomeric ratio of 72:28 was determined by GLC) as an inseparable mixture, along with the reduction product **13** (10%). The acetamide **4g** also underwent cyclisation to give an inseparable mixture of the isomeric lactams **14** (53%, 81 : 19). The stereochemistry of the lactams **12** and **14** is not known at present, but it is highly probable that the major isomers of **12** and **14** have the *cis* configuration for the same reason as that described for the formation of *cis*-**11a**. In contrast, the acetamide **4h** lacking a substituent at the 1-position of the vinyl group gave the reduction product **15** (68%) and a mixture (17%) of the lactams whose structures were assigned to be β-lactam **16**[8] and γ-lactam **17** on the basis of the IR (two carbonyl bands at 1755 and 1695 cm^{-1}, respectively) and ^1H NMR spectroscopic data (see Experimental).

These results revealed that, for the 5-*endo-trig* cyclisation of the acetamides **4** to proceed effectively, it is necessary that the developing α-acylamino radicals in the transition state of the cyclisation must be stabilised by an aryl or an alkyl group.

Finally, we applied this methodology to a synthesis of (±)-cotinine **20**. The key bis(phenylsulfanyl)acetamide **19** was prepared from 3-acetylpyridine in 77% yield according to the same procedure as that described for the preparation of **4d**. Treatment of **19** with Bu_3SnH and AIBN afforded (±)-cotinine **20** in 97% yield as a sole product (Scheme 4).



Scheme 4 *Reagents and conditions:* i, $MeNH_2$, toluene, 100 °C; ii, $Cl_2CHCOCl$, CH_2Cl_2; iii, PhSNa, EtOH; iv, Bu_3SnH, AIBN, toluene, reflux

Experimental

Mps were measured on a Yanaco MP-J3 micro melting point apparatus and are uncorrected. IR spectra were recorded on a JASCO-IR-A-100 spectrophotometer. ^1H NMR (60 and 300 MHz) and ^{13}C NMR (75.4 MHz) spectra were determined with a JEOL JNM-PMX 60 or a Varian XL-300 spectrometer for solutions in $CDCl_3$. δ-Values quoted are relative to tetramethylsilane, and *J*-values are given in Hz. Exact mass determinations were obtained on a Hitachi M-80 instrument at 20 eV. Column chromatography was performed on Silica gel 60 PF_{254} (Nacalai Tesque) under pressure.

2-Chloro-*N*-methyl-*N*-(1-phenylvinyl)acetamide 4a

A solution of acetophenone (2.0 g, 16.6 mmol) in toluene (10 cm^3) was added to methylamine (3 cm^3) at −78 °C and the mixture was heated in a sealed tube at 100 °C for 2 h. The reaction mixture was then concentrated and the residue was dissolved in dichloromethane (30 cm^3). Chloroacetyl chloride (2.26 g, 20.0 mmol) was added to the solution at 0 °C and the mixture was stirred at that temperature for 15 min when sat. aqueous $NaHCO_3$ (40 cm^3) was added to it and the whole was stirred for a further 30 min. The organic layer was separated and the aqueous layer was extracted with dichloromethane. The combined extracts were dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel [hexane–ethyl acetate (9:2)] to give the title compound (1.65 g, 47%) as colourless crystals, mp 49.5–50.5 °C (from hexane–ethyl acetate) (Found: C, 63.0; H, 5.8; N, 6.6. $C_{11}H_{12}ClNO$ requires C, 63.0; H, 5.8; N, 6.7%); $\nu_{max}(CCl_4)/cm^{-1}$ 1675; δ_H(60 MHz) 3.13 (3 H, s, NMe), 4.08 (2 H, s, $COCH_2$), 5.33 (1 H, s, one of the olefinic protons), 5.75 (1 H, s, one of the olefinic protons) and 7.42 (5 H, s, ArH).

2,2-Dichloro-*N*-methyl-*N*-(1-phenylvinyl)acetamide 4b

Following a procedure similar to that describd above for the preparation of **4a**, compound **4b** (1.62 g, 80%) was obtained by acylation of acetophenone *N*-methylimine prepared from acetophenone (1.0 g, 8.32 mmol) and methylamine (5 cm^3), with dichloroacetyl chloride (1.47 g, 9.99 mmol) as an oil (Found: C, 53.6; H, 4.5; N, 5.7. $C_{11}H_{11}Cl_2NO$ requires C, 54.1; H, 4.5; N, 5.7%); $\nu_{max}(CCl_4)/cm^{-1}$ 1695; δ_H(60 MHz) 3.14 (3 H, s, NMe), 5.38 (1 H, s, one of the olefinic protons), 5.80 (1 H, s, one of the olefinic protons), 6.37 (1 H, s, $CHCl_2$) and 7.41 (5 H, s, ArH).

2-Iodo-*N*-methyl-*N*-(1-phenylvinyl)acetamide 4c

Sodium iodide (228 mg, 1.52 mmol) was added to a solution of compound **4a** (300 mg, 1.43 mmol) in acetonitrile (15 cm^3) and the mixture was stirred at room temperature for 5 h when the precipitate was filtered off and the filtrate was concentrated. The residue was chromatographed on silica gel [hexane–ethyl acetate (5:1)] to give the title compound (345 mg, 80%) as an oil; $\nu_{max}(CCl_4)/cm^{-1}$ 1660; δ_H(60 MHz) 3.10 (3 H, s, NMe), 3.78 (2 H, s, $COCH_2$), 5.42 (1 H, s, one of the olefinic protons), 5.73 (1 H, s, one of the olefinic protons) and 7.40 (5 H, s, ArH). Due to its lability, this compound was used immediately for the cyclisation.

***N*-Methyl-*N*-(1-phenylvinyl)-2,2-bis(phenylsulfanyl)acetamide 4d**

Benzenethiol (993 mg, 9.01 mmol) was added to a solution of sodium ethoxide in ethanol [prepared from sodium (207 mg, 9.01 mmol) and ethanol (10 cm^3)] at 0 °C, and the mixture was stirred at room temperature for 30 min. A solution of compound **4b** (1.0 g, 4.1 mmol) in ethanol (5 cm^3) was added to the above solution and the mixture was stirred at room temperature for 16 h when the solvent was removed and the residue dissolved in dichloromethane. The solution was dried ($MgSO_4$) and concentrated and the residue was chromatographed on silica gel [hexane–ethyl acetate (7:1)] to give the title compound (1.49 g, 93%) as an oil (Found: C, 70.5; H, 5.4; N, 3.8. $C_{23}H_{21}NOS_2$ requires C, 70.55; H, 5.4; N, 3.6%); $\nu_{max}(CCl_4)/cm^{-1}$ 1665; δ_H(60 MHz) 3.06 (3 H, s, NMe), 4.90 (1 H, s, one of the olefinic protons), 5.10 [1 H, s, $CH(SPh)_2$], 5.39 (1 H, s, one of the olefinic protons) and 7.20 (15 H, br s, ArH).

Radical cyclisation of the chloroacetamide 4a

General procedure A. A solution of Bu_3SnH (725 mg, 2.66 mmol) and AIBN (40 mg, 0.24 mmol) in toluene (40 cm^3) was added to a boiling solution of compound **4a** (500 mg, 2.38 mmol) in toluene (30 cm^3) using a syringe pump over a period of 2 h and the mixture was heated under reflux for 6 h. Then, a solution of Bu_3SnH (775 mg, 2.66 mmol) and AIBN (40 mg, 0.24 mmol) in toluene (25 cm^3) was added to it during 1 h and the mixture was refluxed for a further 8 h. The solvent was removed, diethyl ether (30 cm^3) and 8% aqueous KF (30 cm^3) were added to the residue, and the mixture was stirred vigorously at room temperature for 30 min when the organic layer was separated, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel [hexane–ethyl acetate (2:1)]. The first fraction gave unchanged **4a** (248 mg, 50%). The second fraction gave *N*-methyl-*N*-(1-phenylvinyl)-acetamide **6**[9] (73 mg, 18%) as an oil; $\nu_{max}(CCl_4)/cm^{-1}$ 1660; δ_H(60 MHz) 2.02 (3 H, s, COMe), 3.09 (3 H, s, NMe), 5.20 (1 H, s, one of the olefinic protons), 5.66 (1 H, s, one of the olefinic protons) and 7.36 (5 H, s, ArH). The third fraction gave 1-methyl-5-phenylpyrrolidin-2-one **5**[10] (72 mg, 17%) as an oil; $\nu_{max}(CCl_4)/cm^{-1}$ 1695; δ_H(60 MHz) 1.48–2.94 (4 H, m), 2.67 (3 H, s, NMe), 4.51 (1 H, td, *J* 6.5 and 2.0) and 7.05–7.55 (5 H, m, ArH).

Radical cyclisation of the dichloroacetamide 4b

Following the general procedure A, compound **4b** (554 mg, 2.27 mmol) was treated two times with Bu_3SnH (771 mg, 2.65 mmol) and AIBN (40 mg, 0.24 mmol). Since TLC analysis showed that the starting material still remained, a solution of Bu_3SnH (771 mg, 2.65 mmol) and AIBN (40 mg, 0.24 mmol) in toluene (10 cm^3) was added to it, and the whole was refluxed for 15 h. After work-up as described in general procedure A, the crude material was chromatographed on silica gel [hexane–ethyl acetate (7:1)] to give unchanged **4b** (216 mg, 39%) and the monochloroacetamide **4a** (29 mg, 6%).

Radical cyclisation of the iodoacetamide 4c

Following the general procedure A, compound **4c** (342 mg, 1.13 mmol) was treated with Bu_3SnH (493 mg, 1.70 mmol) and AIBN (18 mg, 0.11 mmol) followed by Bu_3SnH (329 mg, 1.13 mmol) and AIBN (18 mg, 0.11 mmol), and the crude material was chromatographed on silica gel [hexane–ethyl acetate (2:1)]. The first fraction gave the amide **6** (24 mg, 12%) and the second fraction gave the lactam **5** (93 mg, 47%).

Radical cyclisation of the bis(phenylsulfanyl)acetamide 4d

General procedure B. A solution of Bu_3SnH (491 mg, 1.69 mmol) and AIBN (25 mg, 0.15 mmol) in toluene (50 cm^3) was added to a boiling solution of compound **4d** (600 mg, 1.53 mmol) in toluene (40 cm^3) over 2 h, and the whole was refluxed for 5 h. A solution of Bu_3SnH (491 mg, 1.69 mmol) and AIBN (25 mg, 0.15 mmol) in toluene (30 cm^3) was added to the reaction mixture over 1.5 h and the mixture was refluxed for a further 3 h. Again a solution of Bu_3SnH (491 mg, 1.69 mmol) and AIBN (25 mg, 0.15 mmol) in toluene (20 cm^3) was added to the reaction mixture over 1 h and the mixture was refluxed for 2 h when the solvent was evaporated off, diethyl ether (30 cm^3) and 8% aqueous KF (30 cm^3) were added to the residue, and the mixture was vigorously stirred at room temperature for 30 min. The organic layer was separated and the aqueous layer was extracted with diethyl ether. The combined organic phases were dried ($MgSO_4$) and concentrated and the residue was chromatographed on silica gel [hexane–ethyl acetate (2:1)] to give the lactam **5** (200 mg, 75%).

***N*-Methyl-*N*-(1,2-diphenylvinyl)-2,2-bis(phenylsulfanyl)-acetamide 4e**

A solution of benzyl phenyl ketone (2.0 g, 10.2 mmol) in toluene (10 cm^3) was added to methylamine (3 cm^3) at −78 °C and the mixture was heated in a sealed tube at 100 °C for 4 h. The

reaction mixture was then concentrated and the residue was dissolved in dichloromethane (30 cm^3) containing triethylamine (1.34 g, 13.3 mmol) and DMAP (0.13 g, 1.0 mmol). To the solution was added dropwise at 0 °C a solution of bis(phenylsulfanyl)acetyl chloride[11] (3.91 g, 13.3 mmol) in dichloromethane (10 cm^3) and the whole was stirred at room temperature for 30 min and then diluted with water. The organic layer was separated, washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel [hexane–ethyl acetate (10:1)] to give the title compound (2.9 g, 60%), mp 110.5–111 °C (from hexane–ethyl acetate) (Found: C, 74.7; H, 5.4; N, 3.0. $C_{29}H_{25}NOS_2$ requires C, 74.5; H, 5.4; N, 3.0%); $\nu_{max}(CCl_4)/cm^{-1}$ 1660; δ_H(60 MHz) 2.98 (3 H, s, NMe), 5.54 [1 H, s, C*H*(SPh)$_2$], 6.36 (1 H, s, PhC*H*=) and 6.6–7.9 (20 H, m, ArH).

N-Methyl-(1-benzyl-2-phenylvinyl)-2,2-bis(phenylsulfanyl)-acetamide 4f

Following a procedure similar to that described above for the preparation of **4e**, compound **4f** (3.17 g, 69%) was obtained by acylation of the *N*-methylimine, derived from dibenzyl ketone (2.0 g, 9.5 mmol) and methylamine, with bis(phenylsulfanyl)-acetyl chloride (3.6 g, 12.4 mmol) as an oil (Found: C, 74.6; H, 5.6; N, 3.0. $C_{30}H_{27}NOS_2$ requires C, 74.8; H, 5.65; N, 2.9%); $\nu_{max}(CCl_4)/cm^{-1}$ 1660; δ_H(60 MHz) 2.75 (3 H, s, NMe), 3.52 (2 H, br s, PhC*H*$_2$), 5.23 [1 H, s, C*H*(SPh)$_2$], 6.31 (1 H, s, PhC*H*=) and 6.75–7.7 (20 H, m, ArH).

N-Methyl-(1-methyl-2-phenylvinyl)-2,2-bis(phenylsulfanyl)-acetamide 4g

Following a procedure similar to that described for the preparation of **4e**, compound **4g** (0.33 g, 22%) was obtained by acylation of the *N*-methylimine, derived from benzyl methyl ketone (0.50 g, 3.7 mmol) and methylamine, with bis(phenylsulfanyl)acetyl chloride (1.4 g, 4.8 mmol) as an oil (Found: C, 71.2; H, 5.7; N, 3.4. $C_{24}H_{23}NOS_2$ requires C, 71.1; H, 5.7; N, 3.45%); $\nu_{max}(CCl_4)/cm^{-1}$ 1660; δ_H(60 MHz) 1.69 (3 H, s, CMe), 3.08 (3 H, s, NMe), 5.34 [1 H, s, C*H*(SPh)$_2$], 6.22 (1 H, br s, PhC*H*=) and 6.75–7.7 (15 H, m, ArH).

Radical cyclisation of the bis(phenylsulfanyl)acetamide 4e

Following the general procedure B, compound **4e** (600 mg, 1.28 mmol) was treated three times with Bu_3SnH (410 mg, 1.41 mmol) and AIBN (20 mg, 0.13 mmol) and the crude product was purified by chromatography on silica gel [hexane–ethyl acetate (3:1)]. The first fraction gave trans-1-*methyl*-4,5-*diphenylpyrrolidin*-2-*one* **11b** (80 mg, 25%), mp 127.5–128 °C (from hexane–ethyl acetate) (Found: C, 81.2; H, 6.9; N, 5.5. $C_{17}H_{17}NO$ requires C, 81.2; H, 6.8; N, 5.6%); $\nu_{max}(CCl_4)/cm^{-1}$ 1700; δ_H(300 MHz) 2.70 (1 H, ddd, *J* 17.0, 8.1 and 0.7, one of 3-H$_2$), 2.73 (3 H, s, NMe), 2.99 (1 H, ddd, *J* 17.0, 9.3 and 0.7, one of 3-H$_2$), 3.32 (1 H, ddd, *J* 9.3, 8.1 and 6.3, 4-H), 4.45 (1 H, d, *J* 6.3, 5-H), 7.09–7.15 (4 H, m, ArH) and 7.22–7.40 (6 H, m, ArH); δ_C 28.45 (NMe), 38.3 (3-C), 48.1 (4-C), 72.7 (5-C), 126.6, 127.1, 127.2, 128.3, 128.85, 129.0, 139.5, 141.5 and 174.3. The second fraction gave cis-1-*methyl*-4,5-*diphenylpyrrolidin*-2-*one* **11a** (216 mg, 67%), mp 171.5–173 °C (from hexane–ethyl acetate) (Found: C, 81.3; H, 6.8; N, 5.5%); $\nu_{max}(CCl_4)/cm^{-1}$ 1695; δ_H(300 MHz) 2.68 (1 H, ddd, *J* 16.7, 8.2 and 0.7, one of 3-H$_2$), 2.85 (3 H, s, NMe), 2.89 (1 H, dd, *J* 16.7 and 11.2, one of 3-H$_2$), 3.99 (1 H, dt, *J* 11.2 and 8.2, 4-H), 4.80 (1 H, d, *J* 8.2, 5-H), 6.70–6.82 (4 H, m, ArH) and 7.01–7.17 (6 H, m, ArH); δ_C 28.8 (NMe), 34.8 (3-C), 44.5 (C-4), 69.2 (C-5), 126.8, 127.0, 127.7, 127.9, 128.2, 135.9, 137.3 and 174.8.

Radical cyclisation of the bis(phenylsulfanyl)acetamide 4f

Following the general procedure B, compound **4f** (500 mg, 1.04 mmol) was treated three times with Bu_3SnH (333 mg, 1.14 mmol) and AIBN (17 mg, 0.10 mmol), and the crude product was purified by chromatography on silica gel [hexane–ethyl acetate (10:1)]. The first fraction gave an oily mixture of cis- and trans-5-*benzyl*-1-*methyl*-4-*phenylpyrrolidin*-2-*one* **12** (total 128 mg, total 46%; *cis*:*trans*, 72:28, determined by GLC) (Found: C, 81.5; H, 7.4; N, 5.1. $C_{18}H_{19}NO$ requires C, 81.5; H, 7.2; N, 5.3%); $\nu_{max}(CCl_4)/cm^{-1}$ 1695; for the major isomer: δ_H (300 MHz) 2.36 (1 H, ddd, *J* 17.1, 4.3 and 0.5, one of 3-H$_2$), 2.61 (1 H, ddd, *J* 17.1, 9.4 and 0.5, one of 3-H$_2$), 2.85 (1 H, dd, *J* 14.1 and 7.0, one of C*H*$_2$Ph), 2.91 (3 H, s, NMe), 3.01 (1 H, dd, *J* 14.1 and 4.9, one of C*H*$_2$Ph), 3.16 (1 H, dt, *J* 9.4 and 4.3, 4-H), 3.75 (1 H, ddd, *J* 7.0, 4.9 and 4.3, 5-H), 6.95–7.00 (2 H, m, ArH) and 7.11–7.33 (8 H, m, ArH); for the minor isomer: δ_H(300 MHz) 2.48 (1 H, dd, *J* 14.1 and 5.7, one of C*H*$_2$Ph), 2.54–2.65 (1 H, m, one of 3-H$_2$), 2.56 (1 H, dd, *J* 14.1 and 7.7, one of C*H*$_2$Ph), 2.63 (3 H, s, NMe), 2.71 (1 H, dd, *J* 15.5 and 9.5, one of 3-H$_2$), 3.71–3.80 (1 H, m, 4-H), 4.11 (1 H, td, *J* 7.7 and 5.7, 5-H), 6.84–6.90 (2 H, m, ArH) and 7.12–7.36 (8 H, m, ArH); for the major isomer: δ_C 28.5 (NMe), 38.0, 38.7, 41.5 (C-4), 69.1 (C-5), 126.5, 126.81, 126.84, 128.6, 128.8, 129.3, 136.55, 143.9 and 174.0; for the minor isomer: δ_C 29.5 (NMe), 34.9, 36.15, 42.6 (C-4), 65.4 (C-5), 126.4, 127.2, 128.1, 128.3, 128.5, 129.0, 137.8, 138.4 and 174.3. The second fraction gave N-(1-*benzyl*-2-*phenylvinyl*)-N-*methylacetamide* **13** (30 mg, 10%) as an oil (Found: M^+, 265.1472. $C_{18}H_{19}NO$ requires *M*, 265.1465); $\nu_{max}(CCl_4)/cm^{-1}$ 1660; δ_H(60 MHz) 1.57 (3 H, s, $COCH_3$), 3.01 (3 H, s, NMe), 3.60 (2 H, s, PhC*H*$_2$), 6.26 (1 H, br s, PhC*H*=) and 6.7–7.6 (10 H, m, ArH).

Radical cyclisation of the bis(phenylsulfanyl)acetamide 4g

Following the general procedure B, compound **4g** (400 mg, 0.98 mmol) was treated three times with Bu_3SnH (314 mg, 1.08 mmol) and AIBN (16 mg, 0.10 mmol), and the crude product was purified by chromatography on silica gel [hexane–ethyl acetate (10:1)] to give an oily mixture of cis- and trans-1,5-*dimethyl*-4-*phenylpyrrolidin*-2-*one* **14** (total 100 mg, total 53%; *cis*:*trans*, 81:19 determined by GLC) (Found: M^+, 189.1136. $C_{12}H_{15}NO$ requires *M*, 189.1153); $\nu_{max}(CCl_4)/cm^{-1}$ 1695; for the major isomer: δ_H(300 MHz) 0.80 (3 H, d, *J* 6.2, 5-Me), 2.66 (1 H, ddd, *J* 16.6, 8.5 and 0.7, one of 3-H$_2$), 2.77 (1 H, dd, *J* 16.6 and 9.0, one of 3-H$_2$), 2.86 (3 H, s, NMe), 3.70 (1 H, ddd, *J* 9.0, 8.5 and 7.5, 4-H), 3.87 (1 H, dq, *J* 7.5 and 6.6, 5-H), 7.14–7.19 (2 H, m, ArH) and 7.21–7.37 (3 H, m, ArH). The spectrum also exhibited a small doublet at δ 1.26 (*J* 6.2) due to a methyl group at the 5-position of the minor isomer.

N-Methyl-2-methylsulfanyl-2-phenylacetamide 8

A solution of ethyl 2-methylsulfanyl-2-phenylacetate **7**[12] (1.64 g, 7.80 mmol) and methylamine (*ca.* 10 cm^3) in toluene (5 cm^3) was heated in a sealed tube at 120 °C for 2 h when the reaction mixture was concentrated to give the title compound (1.49 g, 98%), mp 83–84 °C (from hexane–ethyl acetate) (Found: C, 61.7; H, 6.7; N, 7.1. $C_{10}H_{13}NOS$ requires C, 61.5; H, 6.7; N, 7.2%); δ_H(60 MHz) 2.08 (3 H, s, SMe), 2.82 (3 H, d, *J* 5.5, NMe), 4.47 (1 H, s, CH), 6.5–7.0 (1 H, br, NH) and 7.1–7.55 (5 H, m, ArH).

N-Methyl-*N*-(2-methylsulfanylphenethyl)-2,2-dichloro-acetamide 9

To borane–THF (1 mol dm^{-3}; 51.2 mmol) was added dropwise a solution of compound **8** (2.0 g, 10.2 mmol) in THF (40 cm^3) and the mixture was refluxed for 1 h when the excess of borane was decomposed with 6 mol dm^{-3} HCl and THF was evaporated off. The aqueous layer was made alkaline with 10% aqueous NaOH, and extracted with diethyl ether. The extract was dried (K_2CO_3) and concentrated and the residue was purified by chromatography on silica gel [hexane–ethyl acetate (1:1)] to give *N*-methyl-2-methylsulfanylphenethylamine (1.46

g, 78%). To a solution of the thus obtained amine (500 mg, 2.76 mmol), triethylamine (0.31 g, 3.04 mmol) and DMAP (34 mg, 0.28 mmol) in dichloromethane (50 cm^3) were added dichloroacetic acid (0.39 g, 3.04 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.79 g, 4.14 mmol) at 0 °C, and the whole was stirred at room temperature for 1.5 h. The mixture was washed successively with 1 mol dm^{-3} HCl, saturated aqueous $NaHCO_3$, and brine, then dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on silica gel [hexane–ethyl acetate (5:1)] to give the title compound (0.74 g, 91%) as an oil (Found: C, 49.0; H, 5.05; N, 4.5. $C_{12}H_{15}Cl_2NOS$ requires C, 49.3; H, 5.2; N, 4.8%); $\nu_{max}(CCl_4)/cm^{-1}$ 1685 and 1660; δ_H(60 MHz) 1.99 (3 H, s, SMe), 2.89 (3 H, s, NMe), 3.2–4.4 (3 H, m), 6.14 (1 H, s, $CHCl_2$) and 7.30 (5 H, s, ArH).

(*E*)-*N*-Methyl-*N*-(2-phenylvinyl)-2,2-dichloroacetamide 10

A solution of $NaIO_4$ (1.46 g, 6.84 mmol) in water (7 cm^3) was added to a solution of compound **9** (1.0 g, 3.42 mmol) in acetone (8 cm^3) and the mixture was stirred at room temperature for 1.5 h. The precipitated solid was filtered off, acetone was evaporated off, the aqueous solution was extracted with dichloromethane and the extract was dried ($MgSO_4$) and concentrated to give the crude sulfoxide. A mixture of this crude sulfoxide (0.97 g, 3.1 mmol) and $NaHCO_3$ (0.66 g) in xylene (10 cm^3) was refluxed for 2.5 h and the insoluble salt was filtered off. The filtrate was concentrated and the residue was purified by chromatography on silica gel [hexane–ethyl acetate (20:1)] to give the title compound (0.47 g, 61%), mp 73–73.5 °C (from hexane–ethyl acetate) (Found: C, 54.15; H, 4.55; N, 5.9. $C_{11}H_{11}Cl_2NO$ requires C, 54.1; H, 4.5; N, 5.7%); $\nu_{max}(CCl_4)/cm^{-1}$ 1700, 1675 and 1640; δ_H(60 MHz) 3.30 (3 H, s, NMe), 6.15 (1 H, d, *J* 14, PhC*H*=), 6.41 (1 H, s, $CHCl_2$), 7.30 (5 H, s, ArH) and 7.51 (1 H, d, *J* 14, NCH=).

(*E*)-*N*-Methyl-*N*-(2-phenylvinyl)-2,2-bis(phenylsulfanyl)-acetamide 4h

Following a procedure similar to that described for the preparation of **4d**, compound **4h** (0.75 g, 84%) was prepared from **10** (0.47 g, 1.93 mmol) and benzenethiol (0.47 g, 4.24 mmol) as an oil (Found: C, 70.5; H, 5.45; N, 3.9. $C_{23}H_{21}NOS_2$ requires C, 70.55; H, 5.4; N, 3.6%); $\nu_{max}(CCl_4)/cm^{-1}$ 1670 and 1635; δ_H(60 MHz) 3.19 (3 H, s, NMe), 5.30 [1 H, s, $(PhS)_2CH$], 5.99 (1 H, d, *J* 14.5, PhC*H*=) and 6.6–8.3 (16 H, m, NCH= and ArH).

Radical cyclisation of the bis(phenylsulfanyl)acetamide 4h

Following the general procedure B, compound **4h** (800 mg, 2.04 mmol) was treated three times with Bu_3SnH (654 mg, 2.25 mmol) and AIBN (34 mg, 0.20 mmol) and the crude product was purified by chromatograhy on silica gel [hexane–ethyl acetate (5:1)]. The first fraction gave N-*methyl*-N-(2-*phenylvinyl*)*acetamide* **15** (245 mg, 68%), mp 81–81.5 °C (from hexane) (Found: C, 75.6; H, 7.5; N, 8.1. $C_{11}H_{13}NO$ requires C, 75.4; H, 7.5; N, 8.0%); $\nu_{max}(CCl_4)/cm^{-1}$ 1680 and 1635; δ_H(60 MHz) 2.28 (3 H, s, $COCH_3$), 3.19 (3 H, s, NMe), 5.91 (1 H, d, *J* 14.0, PhC*H*=) and 7.0–7.5 (6 H, m, NCH= and ArH). The second fraction gave an oily mixture (*ca.* 1:1) of 4-*benzyl*-N-*methyl*-2-*azetidinone* **16** and *N*-methyl-4-phenylpyrrolidin-2-one **17**[13] (total 62 mg, total 17%), whose structures were assigned on the basis of their IR [$\nu_{max}(CCl_4)/cm^{-1}$ 1755 (for **16**) and 1695 (for **17**)] and ^1H NMR spectroscopic data; for **16**: δ_H(300 MHz) 2.65 (1 H, ddd, *J* 14.5, 2.3 and 0.9, one of 3-H_2), 2.74 (3 H, s, NMe), 2.80 (1 H, dd, *J* 13.9 and 7.8, one of PhCH_2), 2.98 (1 H, dd, *J* 14.5 and 4.9, one of 3-H_2), 3.06 (1 H, dd, *J* 13.9 and 5.9, one of PhCH_2), 3.72–3.78 (1 H, m, 4-H) and 7.15–7.8 (5 H, m); for **17**: δ_H(300 MHz) 2.56 (1 H, ddd, *J* 16.8 and 8.3, one of 3-H_2), 2.83 (1 H, dd, *J* 16.8 and 9.2, one of 3-H_2), 2.92 (3 H, s, NMe), 3.42 (1 H, dd, *J* 9.5 and 7.0, one of 5-H_2), 3.53–3.64 (1 H, m, 4-H), 3.76 (1 H, dd, *J* 9.5 and 8.3, one of 5-H_2) and 7.15–7.8 (5 H, m).

***N*-Methyl-2,2-dichloro-*N*-[1-(3-pyridyl)vinyl]acetamide 18**

Following a procedure similar to that described for the preparation of **4b**, compound **18** (2.07 g, quant.) was obtained from 3-acetylpyridine (1.0 g, 8.25 mmol), methylamine (5 cm^3) and dichloroacetyl chloride (1.46 g, 9.91 mmol), mp 121–123 °C (from hexane–ethyl acetate) (Found: C, 48.9; H, 4.1; N, 11.4. $C_{10}H_{10}Cl_2N_2O$ requires C, 49.0; H, 4.1; N, 11.4%); $\nu_{max}(CCl_4)/cm^{-1}$ 1680; δ_H(60 MHz) 3.16 (3 H, s, NMe), 5.51 (1 H, d, *J* 1.5, one of the olefinic protons), 5.89 (1 H, d, *J* 1.5, one of the olefinic protons), 6.40 (1 H, s, $CHCl_2$), 7.35 (1 H, dd, *J* 8 and 5, ArH), 7.72 (1 H, dt, *J* 8 and 2, ArH) and 8.6–8.8 (2 H, m, ArH).

***N*-Methyl-2,2-bis(phenylsulfanyl)-*N*-[1-(3-pyridyl)vinyl]-acetamide 19**

Following a procedure similar to that described for the preparation of **4d**, compound **19** (1.86 g, 77%) was obtained from the dichloroacetamide **18** (1.5 g, 6.1 mmol) and benzenethiol (1.48 g, 13.5 mmol) as a yellow oil (Found: C, 67.1; H, 5.0; N, 7.3. $C_{22}H_{20}N_2OS_2$ requires C, 67.3; H, 5.1; N, 7.1%); $\nu_{max}(CCl_4)/cm^{-1}$ 1670; δ_H(60 MHz) 3.04 (3 H, s, NMe), 5.01 (1 H, d, *J* 1.5, one of the olefinic protons), 5.09 [1 H, s, C*H*$(SPh)_2$], 5.48 (1 H, d, *J* 1.5, one of the olefinic protons), 6.95–7.5 (12 H, m, ArH) and 8.4–8.55 (2 H, m, ArH).

(±)-Cotinine 20

Following the general procedure B, the bis(phenylsulfanyl)acetamide **19** (700 mg, 1.78 mmol) was treated three times with Bu_3SnH (571 mg, 1.96 mmol) and AIBN (29 mg, 0.18 mmol). Workup gave (±)-1-methyl-5-(3-pyridyl)pyrrolidin-2-one (cotinine) **20** (304 mg, 97%) as an oil; $\nu_{max}(CHCl_3)/cm^{-1}$ 1680; δ_H(300 MHz) 1.73–2.96 (4 H, m), 2.71 (3 H, s, NMe), 4.63 (1 H, td, *J* 6.5 and 2.0, 5-H), 7.22–7.78 (2 H, m, ArH) and 8.48–8.70 (2 H, m, ArH); δ_C(75 Hz) 28.15, 29.9, 62.1, 124.0, 133.7, 136.6, 148.3, 149.6 and 175.35. The IR ($CHCl_3$) and ^1H NMR ($CDCl_3$) spectra were identical with those of an authentic sample.

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