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A Facile Method for the *N*-Alkylation of α-Amino Esters

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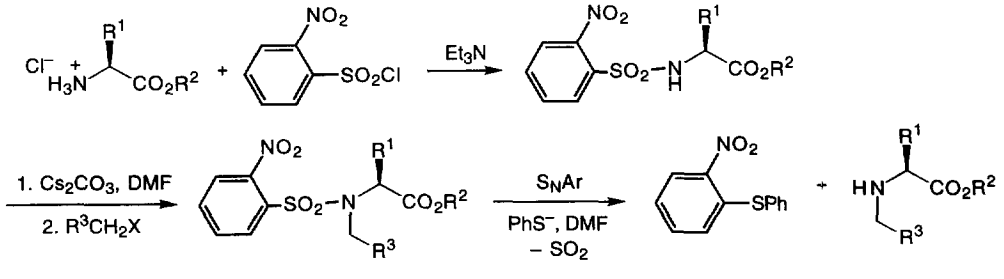
Abstract: Monoalkylation of the α-amino group of α-amino acid derivatives can be facilitated using 2- and 4-nitrophenylsulfonamide intermediates. The nitrophenylsulfonamides of α-amino esters can be alkylated using an equimolar amount of carbonate base and a variety of alkyl bromides. Ready removal of the nitrophenylsulfonyl group is facilitated by S_NAr reaction between the *N*-alkylated sulfonamide and phenylthiolate to give the *N*-alkylated α-amino esters in good yield without racemisation of the chiral α-centres. © 1997 Elsevier Science Ltd.

The synthesis of novel amino acids is of central importance in the search for new biologically active compounds, especially by the pharmaceutical industry. New methodology continues to be developed to facilitate all the required steps in the synthesis of target amino acids and their analogues. In our studies of new protocols for synthesising cyclic amino acids using radical cyclisation we needed to carry out a wide range of *N*-alkylations of the α-amino group of precursor amino acids.[1] To our surprise, we realised that there were no facile and general methods for carrying out *N*-alkylation. A literature search revealed relatively few examples of *N*-alkylation, the majority of which were *N*-methylations and *N*-benzylations.

A number of methods for *N*-alkylation of α-amino acids have been reported but none are general, and without problems. One of the more useful methods is the alkylation of the anions of sulfonamides of α-amino acids, typically tosylates, with both the formation of the sulfonamide and its subsequent alkylation proceeding in high yields. However, removal of the tosylate protecting group is difficult though can be achieved in reasonable yield by the use of sodium amalgam.[2] This method is troublesome and not practical on a large scale due to the large amount of toxic mercury released during the course of the reaction. The recently reported[3] use of 2- and 4-nitrophenylsulfonamides, and the facile removal of the sulfonyl groups by S_NAr substitution using phenylthiolate, for the monoalkylation of amines, offered a way round the problems of removing sulfonamide groups. During our studies to exploit this protocol for mono *N*-alkylation of α-amino acids, an example was published[4] which prompted us to publish our results to date. We believe that the general protocol shown in Scheme 1 provides a general and facile method for *N*-alkylation of α-amino acids and we have shown some of the variables involved.

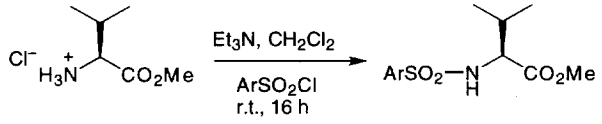


Scheme 1. General protocol for *N*-alkylation of α-amino acids

Racemic *N*-substituted amino acids may be synthesised by methods involving the formation of the α-centre, *e.g.* Strecker synthesis, but the advantage of using the readily available and enantiomerically pure amino acids is lost. The *N*-monoalkylation of primary amines is well known to be problematic with over alkylation typical.[5] One method used to overcome this problem has been to use a large excess of the amine with respect to the alkylating agent. This method works well though is limiting if the amine is expensive or is only available in small quantities. However, this route is generally precluded for α-amino acids because of the low nucleophilicity of α-amino esters, although used for *N*-methylation using methyl iodide, a very reactive electrophile. A measure of the low nucleophilicity caused by the electron-withdrawing α-ester is indicated by the pK_b of α-amino-esters which is *ca.* 10^3 times lower than equivalent amines. A number of other methods have been reported, the most successful of which is *in situ* reduction of Schiff bases of α-amino acids by $NaBH_3CN$.[6] This reductive amination protocol has also been reported for aliphatic aldehydes and ketones and has been applied to α-amino acids[7] and α-amino esters.[8] Use of this methodology with aliphatic aldehydes is troublesome and with variable results.[1,9]

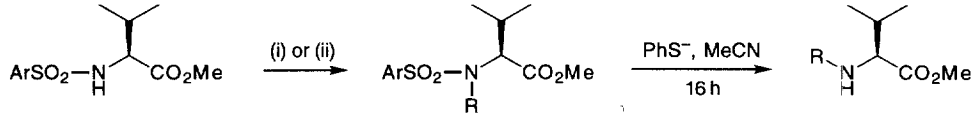
The potential for the protocol using nitrophenylsulfonamides[3] for the monoalkylation of amines to overcome problems with the removal of arenesulfonamide groups in amine synthesis has been commented upon, although not used, in a number of reports in the literature.[10] The use of heteroarene-2-sulfonyl groups, *e.g.* benzothiazole-2-sulfonyl, has been reported when removal of the *o*-nitrophenylsulfonyl using phenylthiolate has proved difficult.[11] The *o*-nitrophenylsulfonyl group has also been successfully used for protection and removed by this protocol in solid phase peptide synthesis.[12]

We chose the enantiomerically pure *L*- and *D*-valine methyl esters for investigation because of relative steric hindrance *alpha* to the nitrogen which could hinder *N*-alkylation. The literature[3] conditions were used as a basis for testing the methodology. Reactions between 2- and 4-nitro- and 4-cyano-phenylsulfonyl chlorides and the methyl esters of *L*- and *D*-valine gave the corresponding sulfonamides **1-4** in high yields (Scheme 2). Under the same conditions the *L*-valine did not form a 2-nitrophenylsulfonamide. A summary of the alkylation studies with 2- and 4-nitrophenylsulfonamides **1** and **2** are shown in Scheme 3.



1, *L*-Val, Ar = 2-nitrophenyl, 86%
2, *D*-Val, Ar = 2-nitrophenyl, 61%
3, *L*-Val, Ar = 4-nitrophenyl, 80%
4, *L*-Val, Ar = 4-cyanophenyl, 92%

Scheme 2. Synthesis of *N*-arylsulfonyl derivatives of valine



(i) Mild conditions for alkylation: cesium carbonate (ca. 1.5 equiv.), DMF, room temperature, 90 min.
1, Ar = 2-nitrophenyl, *L*-Val **5**, Ar = 2-nitrophenyl, R = allyl, 80% **6**, R = allyl, 60%
2, Ar = 2-nitrophenyl, *D*-Val **7**, Ar = 2-nitrophenyl, R = allyl **8**, R = allyl, 'one pot', 63%
1, Ar = 2-nitrophenyl, *L*-Val **9**, Ar = 2-nitrophenyl, R = Bn **10**, R = Bn, 'one pot', 76%

(ii) Vigorous conditions for alkylation: cesium carbonate (1.0 equiv.), DMF, 60° C, 6 h.
1, Ar = 2-nitrophenyl, *L*-Val **11**, Ar = 2-nitrophenyl, R = Bu, 77%
1, Ar = 2-nitrophenyl, *L*-Val **12**, Ar = 2-nitrophenyl, R = 4-pentenyl, 72% **13**, R = 4-pentenyl, 54%
3, Ar = 4-nitrophenyl, *L*-Val **14**, Ar = 4-nitrophenyl, R = 4-pentenyl, 87% **15**, R = 4-pentenyl, 54%

Scheme 3. *N*-Alkylation of valine

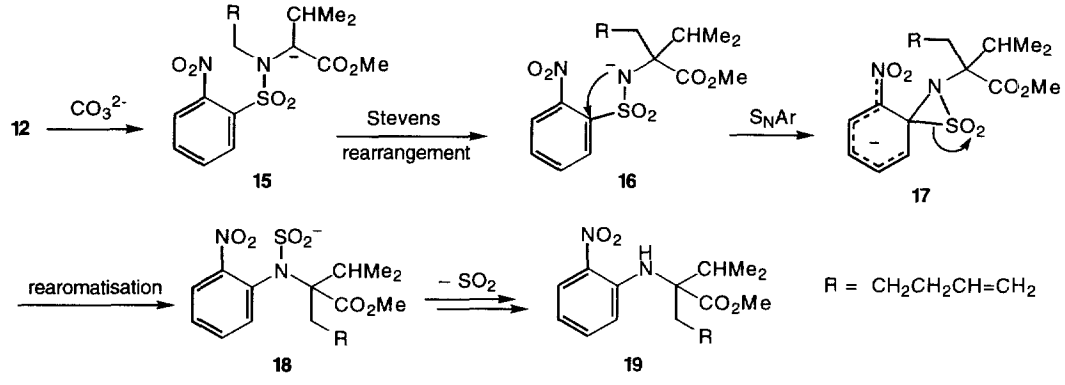
Alkylation of 2-nitrophenylsulfonamides **1** with allyl bromide proceeded rapidly under the reported mild conditions for amines[3] to yield **5**. We substituted cesium carbonate for potassium carbonate due to its better solubility in organic solvents. Acetonitrile can be used as a solvent in place of DMF but lower yields were obtained, *e.g.* alkylation of 2-nitrophenylsulfonamides **1** with allyl bromide gave **5** in 66% yield as opposed to 80% in DMF. Treatment of **5** with phenylthiolate under the reported conditions[3] (phenylthiolate in acetonitrile, 16 h) gave a good un-optimised yield of *N*-allylvaline **6**. 'One pot' alkylation and removal of the sulfonamide group was carried out for the reaction between the sulfonamide **1** and benzyl bromide and between sulfonamide **2** and allyl bromide respectively to yield the methyl esters of *N*-benzyl-*L*-valine **10** and *N*-allyl-*D*-valine **8**. Intermediate *N*-alkylated sulfonamides, **9** and **7** respectively, were isolated but not purified and reacted directly with phenylthiolate in acetonitrile without adversely affecting the overall yield. In some cases the alkylation and removal of the sulfonyl group were carried out in acetonitrile without any work up but the yields were lower. The methyl esters of *L*- and *D*-valine gave the sulfonamides **1** and **2** without racemisation. Allylation of these sulfonamides to yield the intermediate *N*-allyl sulfonamides **5** and **7**, followed by removal of the 2-nitrophenylsulfonyl groups, gave similar yields of the enantiomers **6** and **8** with opposite optical rotations within experimental error indicating little or no racemisation. The optical rotation for the methyl ester of *N*-benzyl-*L*-valine **10** also agreed with the literature value[8] indicating no racemisation.

The limitations of the application of the reported amine protocol[3] to amino acids were soon apparent when alkylation of the anion of sulfonamide **1** and the less electrophilic butyl bromide were attempted. No alkylated sulfonamide **11** was detected after several days and a reaction time of 3-4 weeks was required for the reaction to go to completion. The yellow colour associated with the sulfonamide anion did not disappear as had happened upon the addition of allyl and benzyl bromide. The first reactions used reactive electrophiles, *i.e.* allylic and benzylic bromides, and the reported[4] example of the use of this protocol for α-amino esters also involved an allylic bromide. Unlike the amine alkylations,[3] the anion of the nitrophenylsulfonamide is made less nucleophilic by the extra electron-withdrawing effect of the α-ester and reacts very slowly with less electrophilic alkyl bromides.

The parameters for facilitating alkylation using more vigorous conditions for alkylation using less reactive electrophiles was investigated. Optimal yields (87% to give **14**) were obtained by use of higher temperature (60 °C), longer reactions times (6 h) and exactly one equivalent of cesium carbonate (Scheme 3). Higher temperatures and excess cesium carbonate led to decomposition and rearrangement. Once the initial problems were overcome, the required target *N*-(4-pentenyl)valine methylester **13** was synthesised in un-optimsed 54% yields using both the 2- and 4-nitrophenylsulfonamides **1** and **3**. Removal of the sulfonyl groups from the intermediate *N*-alkylated sulfonamides **12** and **14** using phenylthiolate in S_NAr reactions proceeded without difficulty. The results indicate that there is little difference between the efficacy of 2- and 4-nitrophenylsulfonamides in this protocol and that the nature of the *N*-substituent does not affect the S_NAr reaction for removal of the 2- or 4-nitrophenylsulfonyl groups.

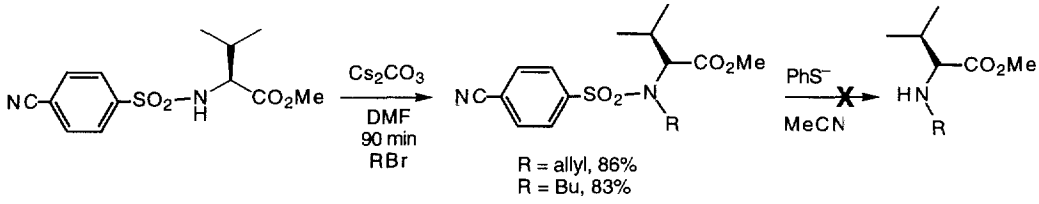
In our initial studies to use more vigorous conditions in the synthesis of the target *N*-(4-pentenyl)valine **13**, alkylation of sulfonamide **1** with 5-bromo-1-pentene was carried out at 60-80 °C with an excess of cesium carbonate. As before the yellow colour of the reaction mixture did not disappear upon addition of the alkyl halide and only darkened over time. GCMS analysis of the reaction mixture and subsequent separation indicated that starting material, the expected alkylated product **12** (23%) and a rearranged product, nitroaniline **19** (7%) (see Scheme 4). The sulfonamide **1** was stable under the reaction conditions (heated at 80 °C in DMF in the presence of cesium carbonate for 6 h; recovered in 88% yield with unchanged optical rotation). The alkylated sulfonamide **12** was stable to heating in DMF at 80 °C for 12 h, but decomposed and underwent rearrangement after the addition of cesium carbonate and heating for a further 6.5 h. GCMS analysis indicated that the main component was the nitroaniline **19**. Alkylation of the corresponding 4-nitrophenylsulfonamide **3** with 5-bromopentene under the standard conditions gave the alkylated product **14** in 87% yield although the corresponding 4-nitroaniline by-product was also evident from GCMS analysis of the reaction mixture if an excess of base was used. This suggests that the effect of the nitro group is inductive, *i.e.* to facilitate S_NAr rearrangement. From the above evidence we propose a putative mechanism for this unusual rearrangement to yield the nitroaniline **19** (Scheme 4). In the presence of excess base, the

intermediate alkylated sulfonamide **12** is deprotonated at the α-carbon to generate the anion **15** which undergoes a 1,2-alkyl shift[13] to the sulfonamide anion **16**. This shift could possibly be explained by a Stevens type rearrangement.[14] The mechanism of the Stevens arrangement is not fully understood. The 1,2 shift is followed by a S_NAr rearrangement *via* **17** to **18** which undergoes loss of SO_2 as a driving force. When no excess base was used no traces of the by-product could be detected.



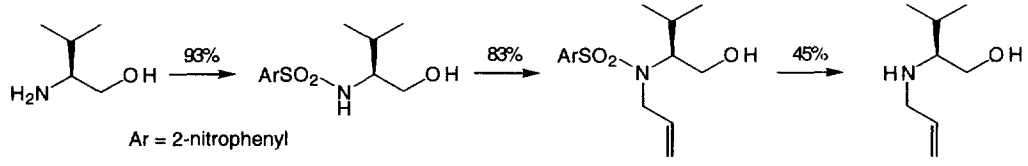
Scheme 4. Rearrangement of *N*-alkenylsulfonamide **12**

We also investigated the use of 4-cyanophenylsulfonamides to overcome the problem of alkylation with less reactive alkyl halides (Scheme 5). We hoped to overcome the problem of the slow alkylation of the nitrophenylsulfonamide anions by the use of cyanophenylsulfonamides which would be more nucleophilic. The alkylations of 4-cyanophenylsulfonamide **4** with allyl and butyl bromide were rapid and high yielding. The use of 4-cyanophenylsulfonamide in place of 2- or 4-nitrophenylsulfonamides overcame the alkylation problem. However, the 4-cyanophenylsulfonyl group could not be removed with phenylthiolate and under forcing conditions decomposition took place.



Scheme 5. Attempted alkylation using 4-cyanophenylsulfonamides

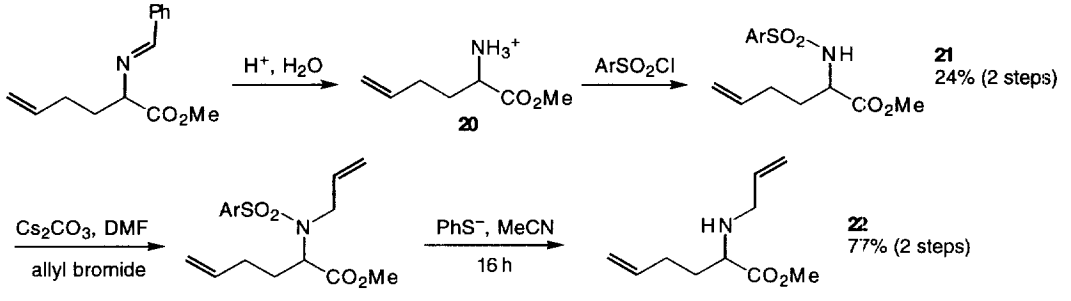
We successfully carried out the mono *N*-alkylation of a enantiomerically pure β-amino alcohol, *L*-valinol as shown in Scheme 6. Formation of the sulfonamide and alkylation gave good yields but the removal of the 2-nitrophenyl group gave only an un-optimised 45% yield.



Scheme 6. *N*-Allylation of *L*-valinol

In contrast, the *N*-alkylation of *L*-serine methyl ester was not successful. The 2-nitrophenylsulfonamide was formed in 82% yield and alkylated under the standard conditions with allyl bromide in good yield. The intermediate *N*-allylsulfonamide was not purified and treated with phenylthiolate. No isolable products were obtained indicating that side chain functional groups need to be protected.

Finally, we successfully applied the new protocol to the synthesis of one of our target precursors **22** for radical cyclisation studies.[1] The racemic butenyl glycine **20** was synthesised by alkylation of the benzal imine of glycine methyl ester and directly sulfonylated. The sulfonamide **21** was alkylated and, without purification, converted to the allyl derivative **22** in 77% yield (Scheme 7).



Scheme 7. Synthesis of methyl (±)-2-allylamino-5-hexenoate **23**

In conclusion we have shown that α-amino esters can be *N*-monoalkylated using one equivalent of alkylating agent and one equivalent of base in either DMF or acetonitrile, though yields are slightly better in DMF. The nitrophenylsulfonyl groups were easily removed from the intermediate *N*-alkylated sulfonamides without problem which clearly indicates the value of this new protocol for the mono *N*-alkylation of α-amino acids. The protocol also provides a useful method for the protection and deprotection of α-amino acids for other synthetic purposes.

Acknowledgements

We thank the EPSRC for postdoctoral funding (D.R.C.) and for a 400 MHz NMR spectrometer and the EPSRC Mass Spectrometry Unit at University of Wales, Swansea for mass spectra.

EXPERIMENTAL

General

Commercial dry solvents were used in all reactions. Light petroleum refers to the bp 40-60 °C fraction. Compounds were purified by flash column chromatography using silica gel 60. Melting points were determined on a Leica Galen III hot stage melting point apparatus and are uncorrected. Optical rotations were measured using a Optical Activity PolAAr 2001 polarimeter at 589 nm in a 2.5 cm cell; concentrations are expressed in g $100\ cm^{-3}$. $[\alpha]_D$ Values are given in 10^{-1} deg $cm^2\ g^{-1}$. Elemental analyses were determined on a Perkin Elmer 2400 CHN Elemental Analyser in conjunction with a Perkin Elmer AD-4 Autobalance. Infrared spectra were recorded on a Perkin-Elmer Paragon 1000 FT-IR spectrophotometer on NaCl plates. ^1H (250 MHz) and ^{13}C (62.5 MHz) NMR spectra were recorded on a Bruker AC-250 spectrometer as solutions of $CDCl_3$ with tetramethylsilane (TMS) as the internal standard for ^1H NMR spectra and deuteriochloroform the standard for ^{13}C NMR spectra unless otherwise specified. Chemical shifts are given in parts per million (ppm) and *J* values in hertz (Hz). Mass spectra were recorded on a Kratos MS80 spectrometer or carried out by the EPSRC Mass Spectrometry Service at University of Wales, Swansea. GCMS was carried out on Fisons 8000 series GCMS using a 15 m x 0.25 mm DB-5 column and an electron impact low resolution mass spectrometer.

Synthesis of sulfonamides

General synthesis of sulfonamides.

N-*(2-Nitrophenylsulfonyl)*-L-*valine methyl ester* **1**.

The syntheses were based on the method described in the literature.[3] 2-Nitrophenylsulfonyl chloride (13.9 g, 63 mmol) was added to an ice-cooled solution of *L*-valine methyl ester hydrochloride (10.6 g, 63 mmol) and triethylamine (20 cm^3, 143 mmol) in dichloromethane (500 cm^3). The mixture was warmed to room temperature and stirred overnight. The resulting solution was washed with water, dried and evaporated to dryness. Purification using chromatography with silica as absorbent and with ethyl acetate-light petroleum (1 : 3) as eluant gave N-*(2-nitrophenylsulfonyl)*-L-*valine methyl ester* **1** (17.2 g, 86%) as a pale yellow thick oil, $[\alpha]_D^{28.5}$ -214.5 ± 0.3 (*c* 3.8 in $CHCl_3$); (Found: C, 45.65; H, 4.9; N, 8.6. $C_{12}H_{16}N_2O_6S$ requires C, 45.6; H, 5.1; N, 8.9%); ν_{max}(neat)/cm^{-1} 3320m (NH), 3100w (ArH), 2968s (CH), 2878m (OCH_3), 1744s (C=O), 1594m (ArC=C), 1547s, 1538s (NO_2), 1443s, 1428s, 1392m, 1360s (SO_2/NO_2), 1301s, 1266,s 1209s, 1175s (SO_2), 1141s (C-O), 1127s, 1062m, 1048m, 1017w, 996m, 917w, 879w, 854m, 785m, 760m, 742s (ArH), 733m, 701w and 655s; δ_H 0.94 (3 H, d, *J* 6.8, Me), 1.01 (3 H, d, *J* 6.8, Me), 2.16 (1 H, m, β-CH), 3.44 (3 H. s, OMe), 4.01 (1 H, dd, *J* 5.2, 9.7, α-CH), 6.06 (1 H, d, *J* 9.7, NH), 7.71-7.79 (2 H, m) and 7.89-7.96 (1 H, m) and 8.02-8.08 (1 H, m, ArH); δ_C 17.4 (Me), 18.9 (Me), 31.4 (β-CH), 52.1 (OMe), 62.0 (α-CH), 125.5, 130.3, 132.8, 133.6 (Ar-*C*), 133.9 (Ar-*C*S), 147.5 (Ar-*C*N) and 171.0 (C=O); *m/z* (EI) 273 (0.8%), 257 (62), 186 (100), 170 (6), 92 (10), 88 (21), 77 (15), 71 (31), 70 (38), 55 (11) and 51 (11); (CI) (Found: $M^+ + NH_4$, 334.1073. $C_{12}H_{16}N_2O_6S + NH_4$ requires 334.1073).

N-*(2-Nitrophenylsulfonyl)*-D-*valine methyl ester* **2**

Thick pale yellow oil (61%) $[\alpha]_D^{30}$ +215.4 ± 0.4 (*c* 4.95 in $CHCl_3$); ν_{max} (neat)/cm^{-1} 3319m (NH), 3100w (ArH), 2968m (CH), 2878w (O*Me*), 1741s (C=O), 1594w (ArC=C), 1543s (NO_2), 1443s, 1427s, 1392m, 1360s, 1301s, 1266s, 1210s, 1174s (SO_2), 1141s (C-O), 1127s, 1062m, 1017w, 996w, 879w, 854m, 785m, 760m, 742s (ArH), 733m, 701w and 655s; δ_H 0.94 (3 H, d, *J* 6.8, Me), 1.01 (3 H, d, *J* 6.8, Me), 2.16 (1 H, d x sept, *J* 5, 6.8, β-CH), 3.44 (3 H, s, OMe), 4.01 (1 H, dd, *J* 5.3, 9.8, α-CH), 6.05 (1 H, d, *J* 9.7, NH), 7.70-7.77 (2 H, m) and 7.89-7.96 (1 H, m) and 8.02-8.09 (1 H, m, ArH); δ_C 17.5 (Me), 18.9 (Me), 31.5 (β-CH), 52.1 (OMe), 62.1 (α-CH), 125.6 , 130.4 (d), 132.8, 133.6, 134.0 (Ar-*C*S), 147.6 (Ar-*C*N) and 171.0 (C=O); *m/z* (EI) 273 (1%), 257 (76), 186 (100), 170 (7), 92 (30), 88 (26), 77 (25), 71 (38), 70 (44). 59 (18), 55 (19), 51 (25), 50 (20) and 43 (38); (CI) (Found: $M^+ + NH_4$, 334.1073. $C_{12}H_{16}N_2O_6S + NH_4$ requires 334.1073).

N-*(4-Nitrophenylsulfonyl)*-L-*valine methyl ester* **3**.

Yellow crystalline solid (80%), mp 101-102 °C; $[\alpha]_D^{26}$ +36.4 ± 0.6 (*c* 3.1 in $CHCl_3$); (Found: C, 45.4; H, 4.9; N, 8.9. $C_{12}H_{16}N_2O_6S$ requires C, 45.6; H, 5.1; N, 8.9%); ν_{max} (nujol)/cm^{-1} 3297w (NH), 3265w, 3109w (=*CH*), 1734s and 1714m (C=O), 1606w, 1528s (NO_2), 1348s (SO_2/NO_2), 1314m, 1291m, 1273m, 1244m, 1209m, 1174s (SO_2), 1138m, 1090m, 1000m, 921w, 856m, 834w, 770w, 741s, 684m and 619s; δ_H 0.88 (3 H, d, *J* 6.9, Me), 0.97 (3 H, d, *J* 6.8, Me), 2.11 (1 H, d x sept, *J* 5.0, 6.8, β-CH), 3.52 (3 H, s, OMe), 3.85 (1 H, dd, *J* 5.0, 10.0, α-CH), 5.54 (1 H, d, *J* 10.0, NH), 8.05 (2 H, ddd, *J* 1.9, 2.3, 8.8) and 8.35 (2 H, ddd, *J* 1.9, 2.3, 8.8, ArH); δ_C 17.2 (Me), 18.9 (Me), 31.5 (β-CH), 52.4 (OMe), 61.2 (α-CH), 124.1, 128.5 (Ar*C*), 145.9 (Ar-*C*S), 150.0 (Ar-*C*N) and 171.3 (C=O); *m/z* (EI) 273 (7%), 257 (100), 241 (3), 188 (6), 186 (32), 170 (3), 140 (3), 122 (48), 106 (7), 92 (11), 88 (33), 76 (21), 70 (43), 55 (10) and 43 (16); (CI) (Found: $M^+ + NH_4$, 334.1073. $C_{12}H_{16}N_2O_6S + NH_4$ requires 334.1073).

N-*(4-Cyanophenylsulfonyl)*-L-*valine methyl ester* **4**

Crystalline solid (92%), Mp 65-66°C; $[\alpha]_D^{26}$ +34.0 ± 0.5 (*c* 4.1 in $CHCl_3$); (Found: C, 52.7; H, 5.25; N, 9.6. $C_{13}H_{16}N_2O_4S$ requires C, 52.7; H, 5.4; N, 9.45%); ν_{max} (nujol)/cm^{-1} 3290m and 3260m (NH), 3096w (=*CH*), 2231m (C≡N), 1731s and 1708s (C=O), 1392m, 1362s (SO_2),1348s, 1326m, 1277m, 1246m, 1209m, 1183s, 1172s, 1138m, 1091m, 1074m, 998m, 980w, 921w, 877w, 853w, 833w, 784w, 777w, 720w, 648m and 638m;

δ_H 0.87 (3 H, d, *J* 6.9, Me), 0.96 (3 H, d, *J* 6.8, Me), 2.09 (1 H, m, β-CH), 3.51 (3 H, s, OMe), 3.81 (1 H, dd, *J* 5.0, 10.0, α-CH), 5.58 (1 H, d, *J* 10.0, NH), 7.81 (2 H, d, *J* 8.5, ArH) and 7.98 (2 H, d, *J* 8.5, ArH); δ_C 17.2 (Me), 18.8 (Me), 31.4 (β-CH), 52.3 (OMe), 61.1 (α-CH), 116.3, 117.2, 127.8, 132.7, 144.0 (Ar-*C*S) and 171.3 (C=O); *m/z* (EI) 253 (7%), 237 (100), 166 (38), 150 (4), 102 (74), 88 (28), 70 (36), 43 (23) and 41 (13); (CI) (Found: $M^+ + NH_4$, 314.1175. $C_{13}H_{16}N_2O_4S + NH_4$ requires 314.11745).

N-Alkylation of sulfonamides

a) General method for alkylation using mild conditions

N-*Allyl*-N-*(2-nitrophenylsulfonyl)*-L-*valine methyl ester* **5**.

Cesium carbonate (2.0 g, 6.1 mmol) was added to a solution of the sulfonamide **1** (1.3 g, 4.1 mmol) in DMF (40 cm^3). The reaction mixture was stirred at room temperature for 30 minutes before allyl bromide (0.7 cm^3, 8.1 mmol) was added. The reaction mixture was stirred for 90 minutes and then reduced under vacuum. Purification using chromatography and eluting with ethyl acetate-light petroleum (2 : 3) gave N-*allyl*-N-*(2-nitrophenylsulfonyl)*-L-*valine methyl ester* **5** (1.2 g, 80%) as a pale yellow liquid; $[\alpha]_D^{29}$ -62.4 ± 0.2 (*c* 3.6 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 3095w (ArH), 2969m (CH), 2878m (O*CH*3), 1741s (C=O), 1642w (C=C), 1590m (ArC=C), 1548s (NO_2), 1471m, 1438s, 1373s (NO_2), 1355s (SO_2), 1294s, 1205s, 1166s (SO_2), 1146s, 1126s, 1101m, 1062m, 1026s, 1002s, 931m, 885m, 852s, 777s, 760m, 740m and 653m; δ_H 0.96 (3 H, d, *J* 6.6, Me), 1.00 (3 H, d, *J* 6.7, Me), 2.24 (1 H, d x sept, *J* 10.2, 6.6, β-CH), 3.54 (3 H, s, OMe), 4.13 (2 H, d, *J* 6.5, NCH_2), 4.20 (1 H, d, *J* 10.2, α-CH), 5.09 (dd, *J* 1.0, 10.0) and 5.22 (2 H, dd, *J* 1.0, 17.0, $=CH_2$), 5.89 (1 H, ddt, *J* 10.3, 17.0, 6.5, CH=), 7.57-7.74 (3 H, m) and 8.00-8.05 (1 H, m, ArH); δ_C 19.5 (Me), 28.5 (d, β-CH), 48.6 (t, CH_2), 51.7 (OMe), 65.8 (α-CH), 118.1 ($=CH_2$), 123.9, 131.2, 131.4 (ArC), 133.4 (s, Ar-*C*S), 133.7 (Ar-*C*), 134.8 (CH=), 148.2 (ArC-N); *m/z* (EI) 313 (M^+ -C_3H_7, 6%), 297 (M^+ -CO_2Me 34), 267 (2), 186 (100), 170 (77), 156 (4), 128 (5), 111 (25), 110 (52), 68 (31), 59 (18), 55 (19), 43 (23), 41 (93); (CI) (Found: $M^+ + NH_4$, 374.1386. $C_{15}H_{20}N_2O_6S + NH_4$ requires 374.1386). The reaction has also been carried out in acetonitrile and after purification gave **5** (66%).

b) General method for alkylation using vigorous conditions

N-*(2-Nitrophenylsulfonyl)*-N-*(4-pentenyl)*-L-*valine methyl ester* **12**

Cesium carbonate (0.48 g, 1.5 mmol) was added to a stirred solution of the sulfonamide **1** (0.48 g, 1.5 mmol) in DMF (60 cm^3). The reaction mixture was heated to 60 °C then 5-bromopentene was added dropwise. The reaction mixture was heated for a further 6 h and then worked up by the same procedure as above to give N-*(2-nitrophenylsulfonyl)*-N-*(4-pentenyl)*-L-*valine methyl ester* **12** as a pale yellow oil (0.41 g, 72%); $[\alpha]_D^{26}$ -63.8 ± 0.3 (*c* 3.0 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 3079w (=*CH*), 2969m (CH), 1742s (C=O), 1642w (C=C), 1590w (Ar), 1548s (NO_2), 1470m, 1438m, 1373s and 1354s (NO_2/SO_2), 1292m, 1204m, 1166s (SO_2), 1147s, 1126m, 1106w, 1062w, 1006m, 995m. 916w, 893w, 852m, 776m, 751m, 652m; δ_H 0.96 3 H, d, *J* 6.5, Me), 1.01 (3 H, d, *J* 6.6, Me), 1.66-1.92 (2 H, m), 2.01 (2 H, q, *J* 6), 2.18 (1 H, d x sept, *J* 10.3, 6.6, β-CH), 3.40 (1 H, ddd, *J* 5.4, 7.5, 16.5, NC*H*H) and 3.50 (1 H, ddd, *J* 6.1, 7.5, 16.5, NCH*H*), 3.53 (3 H, s, OMe), 4.13 (1 H, d, *J* 10.3, α-CH), 4.98 (1 H, dq, *J* 10, 1.3, =C*H*H_{cis}) and 5.03 (1 H, dq, *J* 17, 1.5, =CH*H*$_{trans}$), 5.78 (1 H, ddt, *J* 10.3, 17.0, 6.5, CH=), 7.55-7.61 (1 H, m), 7.62-7.74 (2 H, m) and 7.95-8.03 (1 H, m, ArH); δ_C 19.4 (Me), 19.5 (Me), 28.7 (β-CH), 29.7 (*C*H_2C=), 31.1, 45.8 (NCH_2), 51.7 (OMe), 65.8 (α-CH), 115.2 ($=CH_2$), 123.7, 130.7, 131.2 (Ar-*C*), 132.9 (Ar-*C*S), 133.5, 137.2 (CH=), 148.2 (s, Ar-*C*N) and 170.6 (C=O); *m/z* (EI) 341 (1%), 325 (38), 301 (4), 281 (18), 271 (6), 198 (14), 186 (100), 170 (5), 139 (13), 138 (15), 124 (9), 96 (9), 84 (10), 69 (31), 55 (12) and 41 (52); (CI) (Found: $M^+ + NH_4$, 402.1699. $C_{17}H_{24}N_2O_6S + NH_4$ requires 402.1699).

Reaction of sulfonamide **1** (0.59 g, 1.9 mmol) with cesium carbonate (0.94 g, 2.9 mmol) and 5-bromo-1-pentene (0.39 g, 2.6 mmol) gave *N*-(2-nitrophenylsulfonyl)-*N*-(4-pentenyl)-*L*-valine methyl ester **12** (0.17 g, 23%) as well as methyl 2-isopropyl-2-(2-nitroanilino)-6-heptenoate **19** (40 mg, 7%) as a yellow oil; ν_{max}(neat)/cm^{-1} 3363w (NH), 3077w (=*CH*), 2936m (CH), 1738s (C=O), 1641w (C=C), 1608w, 1575w (Ar),

1537s (NO_2), 1471m, 1434m, 1360s (NO_2), 1240m, 1216m, 1149m, 1045w, 998m, 913m, 852w, 790w, 782w, 738m and 716w; δ_H 0.95 (3 H, d, *J* 6.7, Me), 1.03 (3 H, d, *J* 6.9, Me), 1.46-1.50 (2 H, m), 2.01 (2 H, brq, *J* 7), 2.14-2.30 (2 H, m), 2.77 (1 H, sept, *J* 6.8, β-CH), 3.67 (3 H, s, OMe), 4.89 (1 H, dd, *J* 1.8, 10, =C*H*H_{cis}), 4.95 (1 H, dd, *J* 1.8, 17.1, =CH*H*$_{trans}$), 5.73 (1 H, ddt, J 10.3, 17.0, 6, CH=), 7.39-7.43 (1 H, m), 7.5-7.6 (1 H, m) and 7.71-7.78 (2 H, m, ArH); δ_C 18.2 (Me), 18.9 (Me), 29.5 (CH_2), 31.3 (CH_2), 33.2 (β-CH), 42.3, 51.2 (OMe), 69.8, 114.5 (=CH_2), 125.3, 128.1, 130.2, 131.2 (Ar*C*), 134.4 (Ar-*C*NO_2), 138.4 (CH=), 150.6 (Ar-*C*NH) and 171.6 (C=O); *m/z* (EI) 321 (M^+ + H, 0.2%), 303 (0.6), 277 (100), 261 (45), 244 (6), 229 (6), 209 (13), 149 (23), 134 (12), 117 (14), 104 (18), 69 (70) and 41 (47).

N-*Butyl*-N-*(2-nitrophenylsulfonyl)*-L-*valine methyl ester* **11**

Pale yellow oil (77%); $[\alpha]_D^{25}$ -70.0 ± 0.6 (c 4.7 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 3098w (=*CH*), 2963s (CH), 2876m (OMe), 1742s (C=O), 1590w (ArC=C), 1547s (NO_2), 1470m, 1438m, 1374s and 1355s (NO_2/SO_2), 1291m, 1245m, 1204m, 1204m, 1166s (SO_2), 1146s, 1126m, 1101m, 1060m, 1020s, 946w, 922w, 891m, 852m, 777m, 757m, 742m, 730m and 652m; δ_H 0.91 (3 H, t, *J* 7.4, Me), 0.96 (3 H, d, *J* 6.6, Me), 1.02 (3 H, d, *J* 6.7, Me), 1.21-1.36 (2 H, m), 1.49-1.78 (2 H, m), 2.20 (1 H, d sept, *J* 10.3, 6.6, β-CH), 3.30-3.48 (2 H, m, NCH_2), 3.53 (3 H, s, OMe), 4.14 (1 H, d, *J* 10.3, α-CH), 7.54-7.60 (1 H, m) and 7.63-7.72 (2 H, m) and 7.98-8.02 (1 H, m, ArH); δ_C ($CDCl_3$) 13.6 (Me), 19.5 (Me), 19.6 (Me), 20.3 (CH_2), 28.8 (β-CH), 32.9 (CH_2), 46.2 (NCH_2), 51.7 (OMe), 66.0 (α-CH), 123.8, 130.8, 131.2, 133.3 (Ar-*C*S), 133.5 (Ar-*C*), 148.4 (Ar-*C*N) and 170.7 (C=O); *m/z* (EI) 329 (6%), 313 (39), 301 (3), 287 (7), 186 (100), 170 (3), 127 (18), 126 (12), 84 (11), 70 (15), 57 (15) and 55 (11); (CI) (Found: M^+ + NH_4, 390.1699. $C_{16}H_{24}N_2O_6S$ + NH_4 requires 390.1699).

N-*(4-Nitrophenylsulfonyl)*-N-*(4-pentenyl)*-L-*valine methyl ester* **14**

Pale yellow oil (87%); $[\alpha]_D^{25}$ -82.3 ± 0.3 (c 2.5 in $CHCl_3$); ν_{max} (neat)/cm^{-1} 3106w (ArH), 3078w (=*CH*), 2968s (CH), 2877m (O*Me*), 1742s (C=O), 1641w (C=C), 1606m, 1532s (NO_2), 1465m, 1436m, 1351s, 1313s, 1291m, 1262m, 1204s, 1166s (SO_2), 1146s, 1107m, 1090s, 1013m, 916m, 892w, 856s, 743s, 686m , 607s; δ_H 0.94 (3 H, d, *J* 6.5, Me), 1.07 (3 H, d, *J* 6.6, Me), 1.61-1.88 (2 H, m), 2.02 (2 H, brq, *J* 7) and 2.09-2.19 (1 H, m, β-CH), 3.17 (1 H, ddd, *J* 4.8, 11.4, 15.2), 3.4 (1 H, ddd, *J* 5.4, 11.1, 15.3, NCH*H*), 3.46 (3 H, s, OMe), 4.13 (1 H, d, *J* 10.6, α-CH), 5.00 (1 H, brd, *J* 10, =C*H*H_{cis}) and 5.02 (1 H, brd, *J* 17, =CH*H*$_{trans}$), 5.76 (1 H, ddt, *J* 10.3, 17.0, 6.5, CH=), 8.03 (2 H, dt, *J* 9.0, 2.2) and 8.35 (2 H, dt, *J* 8.9, 2.3, ArH); δ_C 19.3 (Me), 19.6 (Me), 28.6 (β-CH), 29.4, 31.0, 45.3 (NCH_2), 51.5 (OMe), 66.0 (α-CH), 115.5 (=CH_2), 123.9, 128.6, 137.0 (CH=), 145.6 (Ar-*C*S), 149.8 (Ar-*C*N) and 170.4 (C=O); *m/z* (EI) 341 (2%), 325 (100), 301 (9), 281 (51), 271 (24), 269 (13), 257 (11), 255 (13), 215 (11), 198 (20), 186 (21), 170 (4), 139 (19), 124 (20), 122 (37), 96 (19), 84 (19), 69 (91), 67 (28), 59 (22), 55 (24), 45 (53) and 41 (80); (Found: M^+ + H, 385.1433. $C_{17}H_{24}N_2O_6S$ + H requires 385.1433).

Removal of the nitrophenylsulfonyl group

General procedure for the cleavage of the nitrophenylsulfonyl group.

N-*Allyl*-L-*valine methyl ester* **6**

Deprotection is based on the method described in the literature.[3] Potassium carbonate (0.36 g, 2.6 mmol) was added to a solution of the *N*-allyl sulfonamide **5** (0.30 g, 0.8 mmol) and phenylthiol (0.1 cm^3, 0.9 mmol) in acetonitrile (40 cm^3). The reaction mixture was stirred at room temperature overnight. The resulting solution was reduced under vacuum and the residue taken up in diethyl ether. Hydrochloric acid solution (1 M) was added and the mixture stirred for 10 min. The organic layer was removed and washed with water, the combined aqueous layers were washed with diethyl ether followed by basification with solid potassium carbonate. The product was extracted from the basic aqueous layer with diethyl ether. The ether layer was washed with brine, dried and then evaporated to dryness to give the crude product which was distilled under vacuum (15 mmHg) using a Kugelrohr oven (150 °C) over glasswool to give N-*allyl* L-*valine methyl ester* **6** as a colourless liquid (90 mg, 60%) $[\alpha]_D^{23}$ -21.8 ± 0.2 (*c* 1.6 in $CHCl_3$); ν_{max} (neat)/cm^{-1} 3340w (NH),

3080w (=*CH*), 2962s (CH), 2875m, 2840m, 1733s (C=O), 1644w (C=C), 1467s, 1434s, 1420m, 1387m, 1366m, 1333m, 1307m, 1272m, 1240s, 1198s, 1180s, 1156s, 1114m, 1098m, 996s and 920s (C*H*=C*H*$_2$), 781m, 742w, 647w; δ_H 0.93 (3 H, d, *J* 6.8, Me), 0.94 (3 H, d, *J* 6.8, Me), 1.6 (1 H, brs, NH), 1.91 (1 H, octet, *J* 6.6, β-CH), 3.02 (1 H, d, *J* 6, α-CH), 3.06 (1 H, dd, *J* 6.1, 13.9, NC*H*H), 3.26 (1 H, dd, *J* 5.8, 13.9, NCH*H*), 3.72 (3 H, s, OMe), 5.07 (1 H, dd, *J* 1.2, 10.2, =C*H*H$_{cis}$), 5.17 (1 H, dd, *J* 1.6, 17.1, =CH*H*$_{trans}$), 5.84 (1 H, ddt, *J* 10.3, 17.0, 6.0, CH=); δ_C 18.4 (Me), 19.0 (Me), 31.5 (β-CH), 51.0 (CH$_2$), 51.1 (OMe), 66.2 (α-CH), 115.9 (=CH$_2$), 136.4 (CH=) and 175.5 (C=O); *m/z* (EI) 172 (M$^+$ +H, 3%), 171 (M$^+$, 2), 128 (88), 112 (100), 96 (6), 82 (8), 70 (18), 68 (62), 56 (36) and 41 (88); (Found: M$^+$ + H, 172.1338. $C_9H_{17}NO_2$ + H requires 172.1338).

N-*Allyl*-D-*valine methyl ester* **8**

Colourless liquid (63% from **2**, without purification of intermediate **7**) $[\alpha]_D^{23}$ +23.7 ± 0.2 (*c* 1.9 in $CHCl_3$); ν_{max} (neat)/cm^{-1} 3342w (NH), 3080w (=*CH*), 2962s (CH), 2875m, 2841m, 1735s (C=O), 1644w (C=C), 1469m 1434m, 1387w, 1367m, 1333w, 1307m, 1272m, 1239m, 1198s, 1180s, 1156s, 1098m, 1020m, 996s, 920m, 780m and 742w; δ_H 0.94 (3 H, d, *J* 6.8), 0.95 (3 H, d, *J* 6.8, Me), 1.6 (1 H, brs, NH), 1.91 (1 H, m, β-CH), 3.02 (1 H, d, *J* 5.9, α-CH), 3.07 (2 H, dd, *J* 6.0, 13.9, NC*H*H), 3.27 (1 H, dd, *J* 5.8, 13.9, NCH*H*), 3.72 (3 H, s, OMe), 5.07 (1 H, dd, *J* 1, 10, =C*H*H$_{cis}$), 5.17 (1 H, dd, *J* 1.5, 17, =CH*H*$_{trans}$), 5.84 (1 H, ddt, *J* 10.4, 17.0, 5.9, CH=); δ_C 18.6 (Me), 19.1 (Me), 31.5 (β-CH), 51.1 (CH$_2$), 51.2 (OMe), 66.3 (α-CH), 116.0 (=CH$_2$), 136.5 (CH=) and 175.6 (C=O); *m/z* (EI) 172 (M$^+$ + H, 2%), 171 (4), 128 (90), 112 (100), 96 (14), 82 (12), 70 (28), 68 (81), 56 (57), 55 (31), 43 (24), 41 (88); (Found: M$^+$ + H, 172.1338. $C_9H_{17}NO_2$ + H requires 172.1338).

N-*Benzyl*-L-*valine methyl ester* **10**

Colourless liquid (76% from **1**, no purification of intermediate **9**) $[\alpha]_D^{24}$ -51.5 ± 0.1 (*c* 2.1 in $CHCl_3$){lit.[8] $[\alpha]_D^{27}$ -50.2 (c 1.0 in MeOH)}; ν_{max}(neat)/cm^{-1} 3336w (NH), 3087w, 3064w, 3028m, 2961s (CH), 2874m, 2842w, 1735s (C=O), 1604w, 1496m, 1465m, 1454m, 1434m, 1386w, 1367m, 1334w, 1300w, 1266m, 1237m, 1197s (C-O), 1178s, 1149s, 1114m, 1075w, 1028w, 996m, 896w, 739m and 699s (ArH); δ_H 0.93 (3 H, d, *J* 6.7, Me), 0.95 (3 H, d, *J* 6.8, Me), 1.8 (1 H, br s, NH), 1.91 (1 H, m, β-CH), 3.01 (1 H, d, *J* 6.1, α-CH), 3.58 (1 H, d, *J* 13.1, PhC*H*H), 3.58 (3 H, s, OMe), 3.82 (1 H, d, *J* 13.1, PhCH*H*) and 7.20-7.35 (5 H, m, ArH); δ_C ($CDCl_3$) 18.6 (Me), 19.2 (Me), 31.6 (β-CH), 51.3 (OMe), 52.5 (PhCH$_2$), 66.5 (α-CH), 126.9, 128.2, 140.0 (Ar-*C*) and 175.7 (C=O); *m/z* (EI) 222 (M$^+$ +H, 2%), 221 (M$^+$, 1), 220 (1), 178 (65), 162 (84), 118 (11), 117 (12), 106 (54), 92 (44), 91 (100), 89 (12), 77 (9), 65 (51) and 41 (24); (Found: M$^+$ + H, 222.1494. $C_{13}H_{19}NO_2$ + H requires 222.1494).

N-*(4-Pentenyl)*-L-*valine methyl ester* **13**

Colourless liquid (54% from **12** and 54% from **14**) $[\alpha]_D^{26}$ -9.9 ± 0.6 (*c* 1.8 in $CHCl_3$); ν_{max} (neat)/cm^{-1} 3331w (NH), 3076w (=*CH*), 2959s and 2932s (CH), 2872m, 2843m, 1736s (C=O), 1640w (C=C), 1467m, 1449m, 1434m, 1384w, 1366w, 1333w, 1266m, 1235m, 1194s, 1178s, 1157s, 1117w, 1019w, 995m and 911m and 776w; δ_H 0.92 (3 H, d, *J* 6.8, Me), 0.94 (3 H, d, *J* 6.8, Me), 1.46 (s, NH) and 1.48-1.61 (2 H, m, NCC*H*$_2$CC=), 1.88 (1 H, octet, *J* 6.7, β-CH), 2.09 (2 H, brq, *J* 7), 2.41 (1 H, ddd, *J* 6.7, 7.6, 11.2, NC*H*H), 2.60 (1 H, ddd, *J* 7, 7, 11.2, NCH*H*), 2.96 (1 H, d, *J* 6.1, α-CH), 3.71 (3 H, s, OMe), 4.94 (1 H, dq, *J* 1, 10, =C*H*H$_{cis}$), 5.00 (1 H, dq, *J* 1.7, 17.1, =CH*H*$_{trans}$) and 5.80 (1 H, ddt, *J* 10.3, 17.0, 6.6, CH=); δ_C 18.7 (Me), 19.1 (Me), 29.3 (CH$_2$), 31.3 (CH$_2$), 31.6 (β-CH), 48.0 (NCH$_2$), 51.2 (OMe), 67.4 (α-CH), 114.5 (=CH$_2$), 138.4 (CH=) and 175.8 (C=O); *m/z* (EI) 200 (M$^+$ + H, 2%), 156 (52), 140 (100), 124 (12), 116 (13), 102 (38), 96 (26), 88 (11), 86 (15), 85 (23), 84 (30), 72 (24), 70 (28), 69 (51), 55 (29) and 41 (57); (Found: M$^+$ + H, 200.1651. $C_{11}H_{21}NO_2$ + H requires 200.1651).

Use of 4-cyanophenylsulfonyl groups for alkylation

N-*Allyl*-N-*(4-cyanophenylsulfonyl)*-L-*valine methyl ester*
Thick colourless oil (86%); $[\alpha]_D^{32}$ -108.5 ± 0.5 (*c* 3.9 in $CHCl_3$); (Found: C, 56.9; H, 5.8; N, 8.6. $C_{16}H_{20}N_2O_4S$ requires C, 57.1; H, 6.0; N, 8.3%); ν_{max} (neat)/cm^{-1} 3095w and 3044w (=*CH*), 2969m (CH), 2877w (O*Me*), 2234m (C≡N), 1741s (C=O), 1642w (C=C), 1488w, 1471m, 1436m, 1420w, 1394m, 1352s (SO_2), 1287m, 1204m, 1164s (SO_2), 1145s (C-O), 1088m, 1029m, 1015m, 931m, 905w, 885m, 842m, 809m, 786w, 748m and 633s; δ_H 0.93 (3 H, d, *J* 6.6, Me), 1.02 (3 H, d, *J* 6.6, Me), 2.18 (1 H, d x sept, *J* 10.6, 6.6, β-CH), 3.46 (3 H, s, OMe), 3.90 (1 H, dd, *J* 5.3, 16.3, NC*H*H), 4.05 (1 H, dd, *J* 7.6, 16.3, NCH*H*), 4.14 (1 H, d, *J* 10.6, α-CH), 5.10 (1 H, d, *J* 10.1, =C*H*H$_{cis}$), 5.20 (1 H, dd, *J* 1, 17, =CH*H*$_{trans}$) 5.75 (1 H, dddd, *J* 5.4, 7.7, 10.1, 17.4, CH=), 7.80 (2 H, d, *J* 8.4, ArH) and 7.95 (2 H, d, *J* 8.4, ArH); δ_C 19.2 (Me), 19.4 (Me), 28.0 (β-CH), 47.8 (NCH_2), 51.4 (OMe), 65.7 (α-CH), 116.0, 117.2, 118.3 (=CH_2), 128.1, 132.4, 134.0 (CH=), 144.2 (Ar-*C*S) and 170.3 (s, C=O); *m/z* (EI) 293 (11%), 277 (42), 170 (36), 166 (7), 126 (8), 110 (20), 102 (24), 68 (22) and 41 (100); (CI) (Found: $M^+ + NH_4$, 354.1488. $C_{16}H_{20}N_2O_4S + NH_4$ requires 354.1488).

N-*Butyl*-N-*(4-cyanophenylsulfonyl)*-L-*valine methyl ester*
Colourless solid (83%), mp 60-62 °C; $[\alpha]_D^{31}$ -90.0 ± 0.3 (*c* 3.5 in $CHCl_3$); (Found: C, 58.1; H, 6.8; N, 8.1. $C_{17}H_{24}N_2O_4S$ requires C, 57.9; H, 6.9; N, 7.95%); ν_{max} (neat)/cm^{-1} 3097w and 3045w (=*CH*), 2964s (CH), 2876m (O*Me*), 2234m, (C≡N), 1741s (C=O), 1488w, 1470m, 1436m, 1393m, 1371m, 1349s, (SO_2), 1288m, 1244w, 1204m, 1181s, 1164s (SO_2), 1145s (C-O), 1101m, 1088m, 1023m, 946w, 890m, 842m, 809m, 787m, 746m, 729m and 630s; δ_H 0.89 (3 H, t, *J* 7.4, Me), 0.93 (3 H, d, *J* 6.4, Me), 1.06 (3 H, d, *J* 6.6, Me), 1.24 (2 H, quintet, *J* 7.4), 1.44-1.74 (2 H, m), 2.14 (1 H, d x sept, *J* 10.6, 6.6, β-CH), 3.14 (1 H, ddd, *J* 5.2, 11.3, 15.2, NC*H*H), 3.37 (1 H, ddd, *J* 5.4, 11.1, 15.2, NCH*H*), 3.46 (3 H, s, OMe), 4.09 (1 H, d, *J* 10.6, α-CH), 7.78 (2 H, d, *J* 8.4, ArH) and 7.95 (2 H, d, *J* 8.4, ArH); δ_C 13.6 (Me), 19.4 (Me), 19.6 (Me), 20.3 (CH_2), 28.8 (β-CH), 32.6, 45.8 (NCH_2), 51.5 (OMe), 66.1 (α-CH), 116.1, 117.3, 128.1, 132.5, 144.4 (Ar-*C*S) and 170.5 (C=O); *m/z* (EI) 309 (7%), 293 (100), 281 (5), 267 (22), 253 (9), 237 (31), 186 (12), 166 (37), 150 (2), 126 (14), 102 (38), 84 (16), 70 (21), 57 (36), 45 (34) and 41 (21); (Found: M^+ + H, 353.1535. $C_{17}H_{24}N_2O_4S$ + H requires 353.1535).

N-Allyl-L-valinol

N-*(2-Nitrophenylsulfonyl)*-L-*valinol*
Pale yellow crystalline solid (93%), mp 102-103.5 °C; $[\alpha]_D^{26}$ +15.2 ± 0.3 (*c* 2.9 in $CHCl_3$); (Found: C, 45.6; H, 5.5; N, 9.7. $C_{11}H_{16}N_2O_5S$ requires C, 45.8; H, 5.6; N, 9.7%); ν_{max} (nujol)/cm^{-1} 3524w (NH), 3332s (OH), 3105w (=*CH*), 1595w, 1577w, 1537s (NO_2), 1394m, 1361s, 1336s, 1306m, 1286w, 1226w, 1167s (SO_2), 1147m, 1124m, 1082w, 1061m, 1034s (C-O), 967w, 930w, 909w, 856m, 789m, 743m, 730m, 698m and 654m; δ_H 0.86 (3 H, d, *J* 6.7), 0.88 (3 H, d, *J* 6.8, Me), 1.88 (1 H, octet, *J* 6.7, β-CH), 2.1 (1 H, brs, OH), 3.30 (1 H, m, α-CH), 3.60 (1 H, dd, *J* 4, 11.5, C*H*HO), 3.63 (1 H, dd, *J* 6, 11.5, CH*H*O), 5.54 (1 H, d, *J* 8.1, NH), 7.69-7.77 (2 H, m), 7.83-7.90 (1 H, m) and 8.11-8.17 (1 H, m); δ_C ($CDCl_3$) 18.2 (Me), 19.2 (Me), 29.4 (β-CH), 62.2 (α-CH), 63.1 (CH_2O), 125.2, 130.5, 132.9, 133.4, 134.7 (Ar-*C*S) and 147.6 (Ar-*C*N); *m/z* (EI) 257 (38%), 245 (9), 186 (100), 170 (6), 92 (8), 78 (7), 77 (9), 71 (23), 70 (24), 64 (5), 55 (9), 51 (13), 43 (8) and 41 (6); (CI) (Found: $M^+ + NH_4$, 306.1124. $C_{11}H_{16}N_2O_5S + NH_4$ requires 306.1124).

N-*Allyl*-N-*(2-nitrophenylsulfonyl)*-L-*valinol*
Pale yellow crystalline solid (83%), mp 67-68.5 °C; $[\alpha]_D^{24}$ +102.3 ± 0.2° (*c* 3.3 in $CHCl_3$); (Found: C, 51.35; H, 6.1; N, 8.5. $C_{14}H_{20}N_2O_5S$ requires C, 51.2; H, 6.1; N, 8.5%); ν_{max} (neat)/cm^{-1} 3559m (OH), 3093w (=*CH*), 2968m (CH), 2877m (O*Me*), 1640w, (C=C), 1590w (ArC=C), 1545s (NO_2), 1471m, 1439m, 1420m, 1373s, 1344s, 1296m, 1246w, 1163s (SO_2), 1125s, 1084m, 1061m, 1012m br, 926m, 881m, 852m, 771s, 740m, 727m and 654m; δ_H 0.78 (3 H, d, *J* 6.7, Me), 0.94 (3 H, d, *J* 6.6, Me), 1.87 (1 H, d x sept, *J* 9.6, 6.6, β-CH), 2.1 (1 H, brs, OH), 3.55-3.70 (2 H, m, CH_2O), 3.83-3.92 (1 H, m, NC*H*H), 4.15 (1 H, dd, *J* 6.5, 16.5, NCH*H*), 5.16 (1 H, dd, *J* 1.1, 10.1, =C*H*H$_{cis}$), 5.28 (1 H, dd, *J* 1.1, 17.2, =CH*H*$_{trans}$), 6.02 (1 H, ddt, *J* 10.2,

17.1, 6.4, CH=), 7.55-7.60 (1 H, m), 7.64-7.71 (2 H, m) and 8.04-8.11 (1 H, m, ArH); δ_C 20.0 (2xMe), 27.9 (β-CH), 47.1 (NCH_2), 61.7 (CH_2O), 66.0 (α-CH), 117.7 (=CH_2), 123.6, 131.2, 131.4, 133.4, 133.7 (Ar-*C*S), 135.7 (CH=) and 147.6 (Ar-*C*N); *m/z* (EI) 297 (24%), 285 (7), 215 (1), 186 (52), 170 (2), 111 (24), 110 (22), 98 (14), 77 (11), 68 (17), 55 (12), 51 (9), 43 (8) and 41 (100); (CI) (Found: $M^+ + NH_4$, 346.1436. $C_{14}H_{20}N_2O_5S + NH_4$ requires 346.1437).

N-*Allyl*-L-*valinol*

Colourless liquid (45%); $[\alpha]_D^{23}$ +31.2 ± 0.3 (*c* 1.5 in $CHCl_3$); ν_{max} (neat)/cm^{-1} 3330m (NH/OH), 3079m (=*CH*), 2959s and 2874s (CH), 1644w (C=C), 1466m, 1418m, 1387m, 1368m, 1228w, 1097m, 1046m (C-O), 995m and 918m (*CH*=*CH*$_2$), 821w and 737w; δ_H 0.90 (3 H, d, *J* 6.8, Me), 0.96 (3 H, d, *J* 6.8, Me), 1.82 (1 H, octet, *J* 6.7, β-CH), 2.3 (2 H, brs, NH/OH) and 2.42 (1 H, dt, *J* 4.3, 6.6, α-CH), 3.23 (1 H, dd, *J* 5.8, 14.0, NC*H*H), 3.30 (1 H, dd, *J* 6.2, 14.0, NCH*H*), 3.35 (1 H, dd, *J* 7.0, 10.6, C*H*HO), 3.60 (1 H, dd, *J* 4.2, 10.6, CH*H*O), 5.09 (1 H, dd, *J* 1.2, 10.2, =C*H*H_{cis}), 5.19 (1 H, dd, *J* 1.5, 17.2, =CHH_{trans}) and 5.90 (1 H, ddt, *J* 10.3, 17.1, 6.0, CH=); δ_C 18.3 (Me), 19.4 (Me), 28.8 (β-CH), 49.9 (NCH_2), 60.4 (CH_2O), 63.6 (α-CH), 115.7 (=CH_2) and 136.9 (CH=); *m/z* (EI) 144 (M^+ + H, 1%), 112 (100), 100 (79), 82 (19), 72 (17), 70 (19), 58 (19), 56 (28), 55 (26), 43 (18), 41 (79). (Found: M^+, 143.1319. $C_8H_{17}NO$ requires 143.1310).

Attempted alkylation of *L*-serine methyl ester

N-*(2-Nitrophenylsulfonyl)*-L-*serine methyl ester*

Pale yellow crystalline solid (82%), mp 110.5-112 °C; $[\alpha]_D^{24}$ -103.5 ± 0.4 (*c* 3.0 in MeOH); (Found: C, 39.7; H, 3.9; N, 9.2. $C_{10}H_{12}N_2O_7S$ requires C, 39.5; H, 4.0; N, 9.2%); ν_{max} (nujol)/cm^{-1} 3579s (OH), 3281s (NH), 3091w (=*CH*), 1743s (C=O), 1592w (ArC=C), 1442m, 1373s, 1355s, 1333m, 1301w, 1261s (C-O), 1230m, 1169s (SO_2), 1136s, 1055s, 974m, 912w, 871w, 855m, 791m, 772w, 746m, 731m, 708w, 668m and 656m; δ_H 2.2 (1 H, brs, OH), 3.60 (3 H, s, OMe), 3.97 (1 H, dd, *J* 3.8, 11.4), 4.03 (1 H, dd, *J* 3.7, 11.4, CH_2O), 4.27 (1 H, dt, *J* 8.2, 3.7, α-CH), 6.49 (1 H, d, *J* 8.1, NH), 7.72-7.79 (2 H, m, ArH), 7.93-7.96 (1 H, m, ArH) and 8.08-8.12 (1 H, m, ArH); δ_C 52.9 (d, α-CH), 58.5 (OMe), 63.8 (CH_2O), 125.7, 130.6, 133.0, 133.8, 134.1 (Ar-*C*S), 147.8 (Ar-*C*N) and 169.8 (C=O); *m/z* (EI) 256 (3), 245 (11), 186 (100), 170 (6), 151 (4), 133 (8), 104 (12), 92 (36), 88 (72), 78 (70), 77 (61), 76 (57), 65 (33), 64 (38), 63 (40), 51 (90), 50 (53); (CI) (Found: $M^+ + NH_4$, 322.0709. $C_{10}H_{12}N_2O_7S + NH_4$ requires 322.0709).

N-*Allyl*-N-*(2-nitrophenylsulfonyl)*-L-*serine methyl ester*

Thick yellow oil; $[\alpha]_D^{23}$ -12.2 ± 0.25 (*c* 2.4 in $CHCl_3$); ν_{max} (neat)/cm^{-1} 3550m (OH), 3095w (=*CH*), 2955m (CH), 2900w (O*Me*), 1744s (C=O), 1642w (C=C), 1590w (ArC=C), 1545s (NO_2), 1439m, 1373s, 1353s, 1297m, 1247m, 1205m, 1166s (SO_2), 1126s, 1061s, 1030m, 1004m, 915m, 882m, 852m, 779m, 763m, 737s, 653m; δ_H 2.4 (1 H, brs, OH), 3.64 (3 H, s, OMe), 3.96 (1 H, dd, *J* 7.1, 16.2, NC*H*H), 3.98 (1 H, dd, *J* 7.1, 12.2, C*H*HO), 4.09 (1 H, dd, *J* 5.0, 12.0, CH*H*O), 4.17 (1 H, dd, *J* 5.9, 16.4, NCH*H*), 4.77 (1 H, dd, *J* 5.2, 6.9, α-CH), 5.14 (1 H, d, *J* 10.2, =C*H*H_{cis}), 5.25 (1 H, d, *J* 17.2, =CHH_{trans}), 5.91 (1 H, ddt, *J* 10.3, 17.0, 6.3, CH=), 7.61-7.75 (3 H, m) and 8.07-8.14 (1 H, m, ArH); δ_C 49.5 (NCH_2), 52.4 (OMe), 61.0 (CH_2O), 61.4 (α-CH), 118.5 (=CH_2), 124.1, 131.1, 131.7, 133.0 (Ar-*C*S), 133.7, 134.3 (CH=), 147.8 and 169.7 (s, C=O); *m/z* (EI) 313 (2%), 285 (3), 186 (43), 158 (23), 128 (10), 98 (12), 78 (15), 70 (17), 68 (27), 59 (9), 51 (19) and 41 (100); (CI) (Found: $M^+ + NH_4$, 362.1022. $C_{13}H_{16}N_2O_7S + NH_4$ requires 362.1022.

Methyl 2-(allylamino)-5-hexenoate 22

Methyl 2-{[(2-nitrophenyl)sulfonyl]amino}-5-hexenoate **21**

Pale yellow solid (24%), mp 90.5-92.5 °C; (Found: C, 47.4; H, 4.6; N, 8.3. $C_{13}H_{16}N_2O_6S$ requires C, 47.6; H, 4.9; N, 8.5%); ν_{max}(nujol)/cm^{-1} 3297s (NH), 3100m (=*CH*), 1741s (C=O), 1640w (C=C), 1592w, 1574w, 1529s (NO_2), 1365s, 1312m, 1253m, 1236m, 1218m, 1203m, 1175s (SO_2), 1124m, 1099m, 1057m, 982m, 966m, 928m (=*CH*), 876w, 856m, 792m, 766m, 745s, 733s, 702m and 657s; δ_H 1.78-2.02 (2 H, m, CH_2CC=), 2.19 (2 H, brq, *J* 7, CH_2C=), 3.47 (3 H, s, OMe), 4.20 (1 H, ddd, *J* 5.3, 7.6, 9.1, α-CH), 5.02 (1 H, dd, *J* 1, 10,

=C*H*H$_{cis}$), 5.04 (1 H, dd, *J* 1, 17, =CH*H*$_{trans}$), 5.76 (1 H, ddt, *J* 10.3, 17.0, 6.5, CH=), 6.14 (1 H, d, *J* 9.1, NH), 7.72-7.79 (2 H, m, ArH), 7.88-7.93 (1 H, m, ArH) and 8.03-8.08 (1 H, m, ArH); δ_C 29.1 (CH_2), 32.2 (CH_2), 52.4 (OMe), 56.1 (α-CH), 116.3 (=CH_2), 125.6, 130.4 (d), 133.0, 133.8 (Ar-*C*S), 133.9, 136.3 (CH=), 147.6 (Ar-*C*N) and 171.5 (C=O); *m/z* (EI) 273 (1%), 269 (31), 205 (3), 186 (100), 170 (3), 142 (9), 128 (19), 92 (8), 88 (18), 82 (14), 67 (28) and 55 (11); (CI) (Found: $M^+ + NH_4$, 346.1073. $C_{13}H_{16}N_2O_6S + NH_4$ requires 346.1073).

Methyl 2-(allylamino)-5-hexenoate **22**

Colourless liquid (77%); ν_{max} (neat)/cm^{-1} 3335w (NH), 3078w (=*CH*), 2999w, 2950m (CH), 2843w (O*Me*), 1736s (C=O), 1642m (C=C), 1450m, 1435m, 1419w, 1290m, 1252m, 1198s, 1172s, 1158s, 1044w, 994s, 916s and 780m; δ_H 1.60 (1 H, brs, NH), 1.60-1.82 (2 H, m), 2.13 (2 H, brq, *J* 7, C*H*$_2$C=), 3.09 (1 H, dd, *J* 6.1, 13.8, NC*H*H), 3.24 (1 H, dd, *J* 4.3, 13.8, NCH*H*), 3.25 (1 H, d, *J* 6.6, α-CH), 3.71 (3 H, s, OMe), 5.01 (1 H, ddt, *J* 1.7, 10.0, 1, =C*H*H$_{cis}$), 5.06 (1 H, dq, *J* 17.1, 1.6, =CH*H*$_{trans}$), 5.10 (1 H, ddt, *J* 1.6, 10.2, 1.2, =C*H*H$_{cis}$), 5.20 (1 H, dq, *J* 17.1, 1.6, =CH*H*$_{trans}$), 5.82 (1 H, ddt, *J* 10.2, 17.0, 6.6, CH=) and 5.87 (1 H, ddt, J 10.2, 17.0, 6.0, CH=); δ_C 29.7 (CH_2), 32.5 (*C*H$_2$C=), 50.6 (NCH_2), 51.4 (OMe), 59.8 (α-CH), 115.0 and 116.1 (=CH_2), 136.2 and 137.4 (CH=) and 175.7 (C=O); *m/z* (EI) 168 (3%), 149 (2), 128 (6), 124 (45), 91 (10), 82 (21),68 (41), 56 (25), 55 (30), 43 (61) and 41 (100); (Found: $M^+ + H$, 184.1338. $C_{10}H_{17}NO_2 + H$ requires 184.13375).

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