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TETRAHEDRON

A Facile Rearrangement of N-Alkyl, N-(0 or p-NitrophenylSulfonamide)-α-Amino Esters

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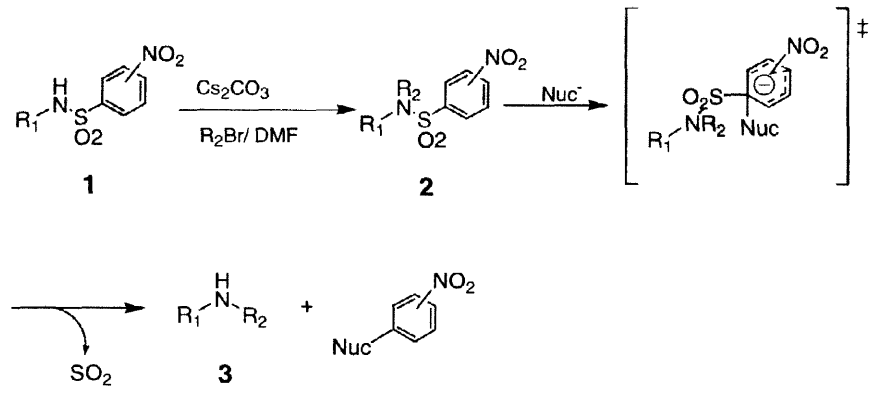
***Abstract**: The N-alkylation of primary nitrophenylsulfonamides followed by removal of the nitrophenylsulfonamide moiety under nucleophilic conditions to provide secondary amines has become an established literature procedure. Application of this methodology with less reactive alkylating agents can give rise to side products resulting from a nitrogen to carbon transfer of the nitrophenyl ring. This side product predominates when tetrabutylammonium hydroxide is used in place of metal carbonate bases in the N-alkylation step.* © 1999 Elsevier Science Ltd. All rights reserved.

***Keywords:** amines, ammonium salts, migration, nitro compounds, rearrangement.*

Recently several reports have appeared on the use of o-and p-nitro-phenylsulfonamides towards selective N-alkylation of primary amines[1a,b] and esters of α-amino-acids.[1c,d] The synthetic sequence supplants the use of the analogous tosylate and methanesulfonate protecting groups which require more forceful methods for their removal.[2] The scheme begins with the generation of a secondary nitrophenyl-sulfonamides from the appropriately substituted amine followed by alkylation under various basic conditions. Subsequent removal of the nitro-phenyl moiety through an S_NAr aromatic displacement of the nitro-phenyl ring via a Meisenheimer complex affords the desired secondary amine **3** and a 2- or 4-substituted nitrobenzene (**Scheme 1**). Various approaches have incorporated remote polar functional groups into the nucleophile moiety in order to facilitate purification by simple aqueous, or solid phase extraction. [1b]



Scheme 1. General Nitrophenylsulfonamide N-Alkylation Procedure

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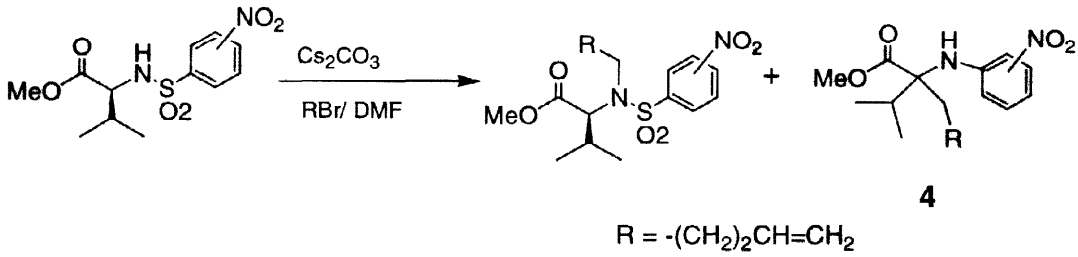
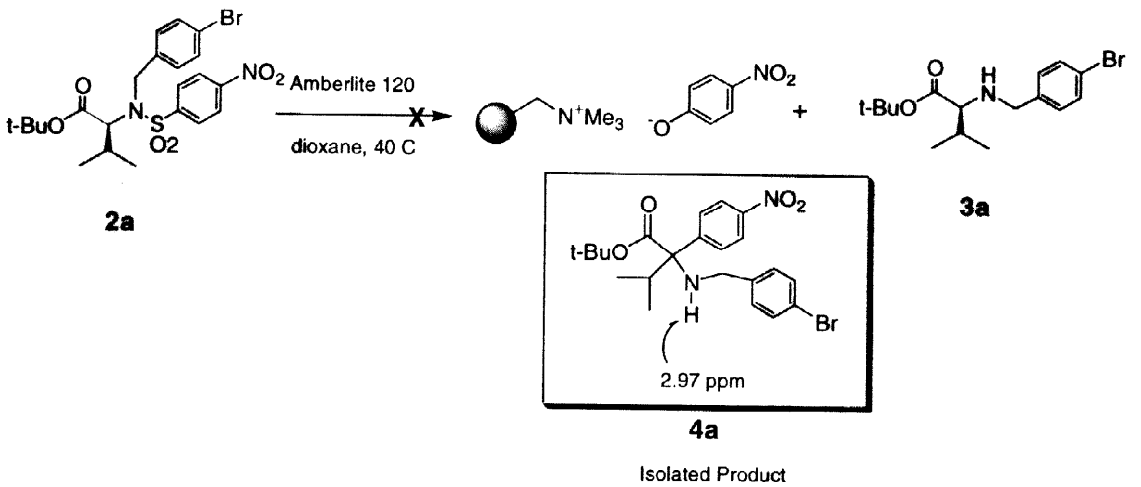
This procedure has found utility with esters of α-amino-acids in the solution phase as well as the generation of N-alkyl peptides on solid support. [3a-c] Although the reactions are reported to proceed in high yield for methyl iodide, benzyl halides and allyl bromide, unactivated alkylating agents are reported to give only moderate to good yields of desired products. A recent report has described the generation of a byproduct produced under forcing conditions with both o- and p-nitrophenylsulfonamide protecting groups and an unactivated alkyl bromide.[1c] Complete analytical characterization was not reported, however the impurity was postulated to be product **4** produced from a Stevens type rearrangement followed by an intramolecular attack of the amine anion into the nitrophenylsulfonamide ring. That is, the nitrogen to α-carbon migration of the previously introduced alkyl group followed by a S_NAr attack of the amine into the aromatic ring to give product **4** (**Scheme 2**). This byproduct was reported in 7% yield in one example.



Scheme 2. Proposed impurity formed under prolonged heating

We now propose an alternative structure for **4** and describe a method for the efficient generation of α-substituted-α-2- or 4-nitrophenyl-α-amino esters.

In the course of investigating the application of the N-alkylation scheme to a series of N-p-nitrobenzenesulfonamide substituted tert-butyl esters of naturally occurring α-amino acids an alternate method for the removal of the nitro-phenylsulfonamides group was investigated. The initial approach used the reaction of strongly basic amberlite resin in the attempted S_NAr attack of hydroxide into the 4 position of the p-nitrophenyl ring to provide desired product **3a** along with p-nitrophenol. It was envisioned the phenol would be sufficiently acidic to form a salt with the quaternary amine moiety of the Amberlite® resin. Filtration should then allow for the removal of the phenoxide byproduct as in the manner of an ion exchange resin. It was discovered upon heating **2a** in the presence of excess Amberlite® IRA-400(OH) for 16 hr a single product was formed which was tentatively assigned the structure **4a** by ^1H NMR analysis (**Scheme 3**). Mass spectral analysis was consistent with an absence of SO_2 (m-64). ^1H NMR revealed the α-methine proton (4.83 ppm) had vanished and a new signal (triplet) appeared at 2.97 ppm integrating for a single proton.



Scheme 3. ^{1}H NMR assignment of **4a**

A subsequent D_20 wash indicated the proton was exchangeable with solvent. In addition the methylene protons corresponding to the benzylic position of the N-4-bromobenzyl moiety also displayed a simplification in nuclear coupling upon exchange of the nitrogen proton with deuterated solvent implying direct coupling with the exchangeable N-H. Based on the chemical shift of the N-H proton with its coupling to the benzylic protons of the N-benzyl group we were confident of our assignment. Several unsuccessful attempts were made to crystallize the product for X-ray confirmation. The lipophilic nature of **4a** would only allow for the formation of low melting solids unsuitable for such an analysis. However, the HCl salt of the related N-methyl analog **4b** gave suitable crystals for X-ray crystallographic analysis (**Figure 1**). The racemic nature of **4b** was confirmed by the presence of c glide planes in the crystal lattice.

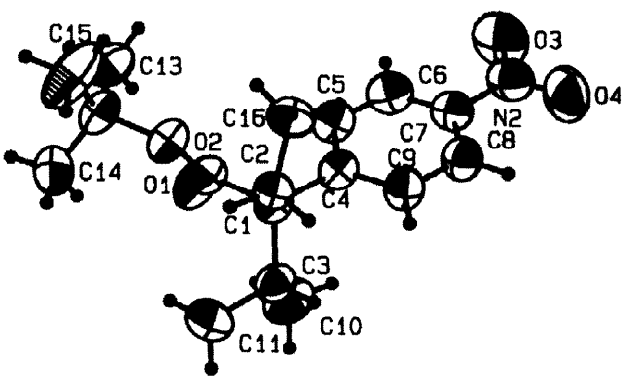
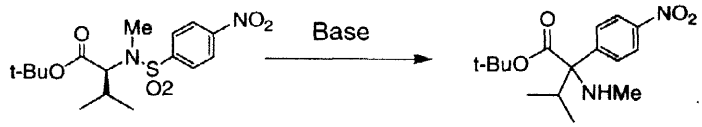


Figure 1. Ortep representation of **4b**

Further investigation revealed that product **4** could be obtained by simply stirring **2** with a stoichiometric amount of 50% aqueous tetrabutylammonium hydroxide in dioxane at room temp for 0.25 hr. Other bases gave no or trace of amounts of **4b** (**Table 1**). Heating **2b** at 80 °C with two equivalents Cs_2CO_3 for 24 hr provided **4b** in 4.7% yield after chromatography and crystallization. The balance of material remaining was accounted for in unrearranged **2b**. In comparison tetrabutylammonium hydroxide provided 69% of identical product **4b** entries **2** and **6**.

Table 1. Effect of base on rearrangement

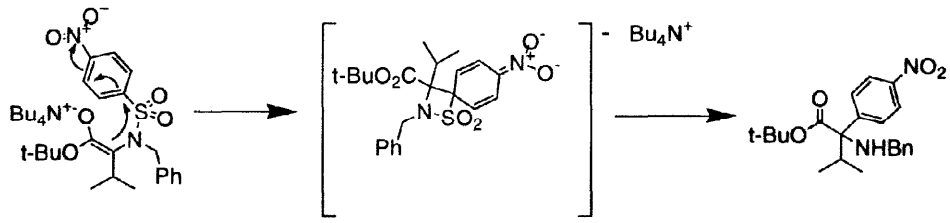


2b **4b**

Entry	Base[a]	Yield
1	K t-butoxide	28
2	Cs_2CO_3[b]	4.7
3	NaH[b]	trace
4	2 M NaOH[b]	none
5	Amberlite IRA-400(OH)[b]	60
6	50% aqu. $Bu_4N^+OH^-$	69

a) All reactions were conducted at rt unless otherwise noted. b) Heated at 80-85 °C for 24 hr.

The rearrangement is believed to result from the intramolecular nucleophilic attack of the enolate **5** into the nitrophenyl ring to generate the Meisenheimer intermediate **6** (**Scheme 4**). Subsequent electron rearrangement followed loss of SO_2 gas gives products **4a-g** in good yield. An analogous rearrangement has been reported for a 9-(N-4-nitrobenzenesulfonyl-N-methylamino) fluorene system[4] and 2-cyano-(N-4-ntirobenzenesulfonyl)-acetamide.[5]



5 **6** **4c**

Scheme 4. Proposed mechanism for sulfonamide rearrangement

Evidence for this intramolecular mechanism includes an HPLC experiment wherein equal molar amounts of the N-2-nitrophenyl analog **2d** and N-4-nitrophenyl analog **2f** were reacted in the same vessel to give only the products corresponding to intramolecular products **4d** and **4f**. No traces of crossover products were observed by HPLC comparison to authentic samples **4c** and **4e** (**Figure 2**).

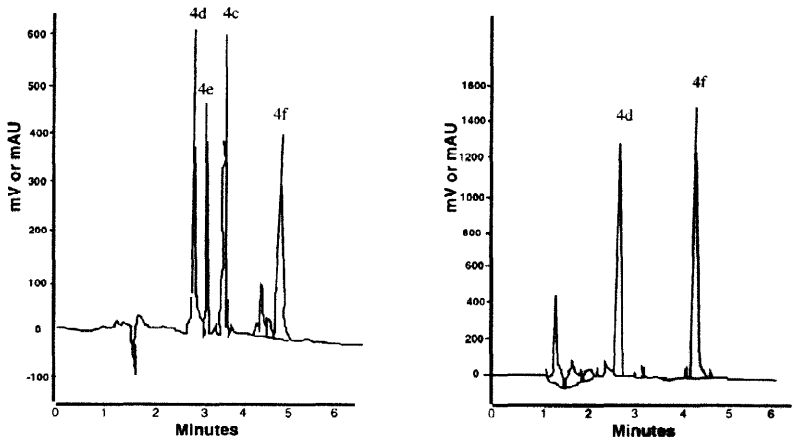
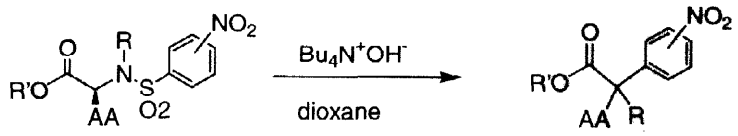


Figure 2. a) HPLC of physical mixture of **4c-f**. b) HPLC of the rearrangement products obtained from the single pot treatment of **2d** and **2f** with Bu_4NOH.

The generality of the rearrangement can be seen in **Table 2**. The rearrangement tolerates various functionality about the α-carbon of the naturally occurring amino acid esters. The N-p-nitrobenzenesulfonyl derivatives give cleaner products than the corresponding N-ortho-nitro analogs entries **3**, **4** and **5**, **6**. This is presumably due to unfavorable steric interactions in the 4-membered transition state. Multiple uncharacterized products account for the mass balance of entries **4** and **11**. β-elimination of butoxide was the major observed product with threonine (O-tBu) entry **5**. All N-p-nitrobenzenesulfonyl derivatives gave good yields of the rearranged products. The intramolecular transfer of the p-nitrophenyl group appeared to be unaffected by the nature of the R group and the α-substituent on the amino ester. The more sterically demanding phe, val, and thr amino-esters provided products in similar yield to the less demanding ala, entries **1**, **3**, **6** and **10**. It is interesting to note that the p-nitrophenyl migration occurs in comparable yield to the o-nitrophenyl when Cs_2CO_3 was used as base entries **2** and **11** and accompanying footnotes.
Not surprisingly, the nature of the ester appears important in that saponification competes with enolate formation/ aryl migration when Bu_4NOH is used as base entries **4** and **7.**

Table 2. Yields of Rearranged Products **4** Upon Bu_4NOH Treatment of **2**



2 **4**

Entry	Number	NO_2	Ester (R')	Amino Acid (AA)	R	Yield[a]
1	4a	para	tert-Bu-	phe	4-BrBn-	76
2	4b	para	tert-Bu-	val	Me-	69[b]
3	4c	para	tert-Bu-	val	Bn-	78
4	4d	ortho	tert-Bu-	val	Bn-	21
5	4e	ortho	tert-Bu-	thr(Ot-Bu)	Bn-	12
6	4f	para	tert-Bu-	thr(Ot-Bu)	Bn-	60
7	4g	ortho	Me-	val	Bn-	5.4[c]
8	4h	para	tert-Bu-	ser(t-Bu)	Me-	78
9	4i	para	tert-Bu-	val	$C_6H_{11}CH_2CH_2$-	81
10	4j	para	tert-Bu-	ala	Me-	74
11	4k	ortho	tert-Bu-	val	$-(CH_2)_3C{=}CH_2$	17[d]

a) Yields based on isolated products. b) 4.7% yield when Cs_2CO_3 was used in place of Bu_4NOH to promote rearrangement. c) Major product was unrearranged acid. d)) 4.9% yield when Cs_2CO_3 was used in place of Bu_4NOH.

In conclusion the use of nitrophenylsulfonamide activation towards the monoalkylation of secondary amines derived from amino esters has found general utility in the current literature. However when the scheme is applied to unactivated alkylating agents under more rigorous reaction conditions a byproduct derived from the intramolecular transfer of the nitrophenyl group to the α-carbon of the amino ester was observed. Although this rearrangement product is produced in less than 10% yield when the precursor sulfonamide is heated with Cs_2CO_3, the product predominates when Bu_4NOH is employed as the base. The transformation proceeds in higher yield with N-p-nitrobenzenesulfonamide than with the corresponding N-o-nitrobenzenesulfonamides although complete consumption of starting material occurs in both. This intramolecular transformation may explain some of the abbreviated peptidic impurities reported with the use of this methodology on the solid supported synthesis of peptides. [3a-c]

EXPERIMENTAL

General

All reagents and solvents were obtained commercially and used without further purification or drying. Melting points were determined on a Thomas Hoover Unimelt melting point apparatus and are uncorrected. Analytical HPLC were performed on a Alltima C18 column (4.6 mm ID, 15cm length , the mobile phase (acetonitrile/ water, 1.0mL/ min) with a linear gradient of 40%-90% acetonitrile over 14 min. Detection was at

210 nm. Mass spectra were obtained on a Fison Instruments VG Platform II mass spectrometer using atmospheric pressure chemical ionization in both positive and negative switching modes. Proton NMR were recorded on a Varian Unity 400. The chemical shifts are reported in parts per million and the *J* values in hertz. Infrared spectra were recorded on a Matson FT-IR.

Synthesis of Sulfonamides

A) General Method for alkylation of sulfonamide α-amino-esters

***(N-4-Bromobenzyl-N-(4-nitrophenylsulfonyl)-L-phenylalanine tert-butyl ester)* 2a**

To a solution of the sulfonamide **2a** (1.5 mmol) in DMF (10mL) was added Cs_2CO_3 (2.3 mmol) followed by 4-bromobenzylbromide (1.5 mmol) in one portion. The resulting mixture was stirred 16 h at room temp. The mixture was diluted with 1:1 EtOAc/Et_2O (30 mL) washed with sat. brine (4x20 mL), and dried $MgSO_4$. The mixture was filtered through a pad of flash silica gel (15 g) with EtOAc eluent and concentrated on a rotary evaporator to provide (0.52 g, 60%) of a light yellow oil which solidified on standing, mp 109.5 °C. IR: υ_{max} 2978w, 1739s (CO), 1529s (NO_2), 1368m, 1350s (SO_2/NO_2), 1164s, 1134s. ^{1}H NMR ($CDCl_3$): δ 1.25 (9 H, s, t-Bu), 2.86 (1 H, dd, *J* 7.7, 14.5) and 3.61 (1 H, dd, *J* 7.2, 14.9, PhC$\underline{H}_2$), 4.38 (1 H, d, *J* 15.9) and 4.67 (1 H, d, *J* 15.9, 4-Br-PhC$\underline{H}_2$), 4.83 (1 H, t, *J* 7.7, α-CH), 7.06-7.11 (4 H, m, ArH), 7.21-7.33 (5 H, m, ArH), 7.77-7.79 (2 H, m, ArH), 8.18-8.22 (2 H, m, ArH). MS: m/z (APCI, AP$^-$) 575 [M$^-$]$^-$. $C_{26}H_{27}BrN_2O_6S$. Calcd: C, 54.27; H, 4.73; N, 4.87; Br,13.88. Found: C, 54.35; H, 4.68; N, 4.83; Br, 5.55.

***(N-Methyl-N-(4-nitrophenylsulfonyl)-L-valine tert-butyl ester)* 2b**

Pale yellow oil (71%). ^{1}H NMR ($CDCl_3$): δ 0.98 (3 H d, *J* 3.5) and 1.00 (3 H, d, *J* 3.5, CH(C$\underline{H}_3$)$_2$), 1.26 (9 H, s, t-Bu), 2.05-2.14 (1 H, m, C$\underline{H}$(CH$_3$)$_2$), 2.92 (3 H, s, N-CH$_3$), 4.06 (1 H, d, *J* 10.6, α-CH), 8.00-8.03 (2 H, m, ArH), 8.32-8.35 (2 H, m, ArH). ^{13}C NMR δ ($CDCl_3$): 13.8, 14.0, 22.6, 22.8, 25.0, 60.8 (α-$\underline{C}$H), 77.0, 118.9, 123.5, 140.2 (Ar-CS), 144.8, 163.6. MS: m/z (APCI, AP$^-$) 372 [M$^-$]$^-$. $C_{16}H_{24}N_2O_6S$. Calcd: C, 51.60; H, 6.50; N, 7.43; S, 8.61. Found: C, 51.73; H, 6.64; N, 7.52; S, 8.50.

***(N-Benzyl-N-(4-nitrophenylsulfonyl)-L-valine tert-butyl ester)* 2c**

Pale yellow oil (87 %). IR: υ_{max} 2972s, 1722s (CO), 1537s (NO_2), 1368m, 1352s (SO_2/NO_2), 1167s, 1138s. ^{1}H NMR ($CDCl_3$): δ 0.92 (3 H, d, *J* 5.3) and 0.94 (3 H, d, *J* 5.3, CH(C$\underline{H}_3$)$_2$) 1.38 (9 H, s, t-Bu), 2.04-2.14 (1 H, m, C$\underline{H}$(CH$_3$)$_2$), 4.21 (1 H, d, *J* 10.8, α-CH), 4.47 (1 H, d, *J* 14.8) and 4.74 (1 H, d, *J* 14.8, PhC$\underline{H}_2$), 7.13-7.38 (5 H, m, ArH), 7.69-7.72 (2 H, m, ArH), 8.11-8.14 (2 H, m, ArH). MS: m/z (APCI, AP$^-$) 448 [M$^-$]$^-$. $C_{22}H_{28}N_2O_6S$. Calcd: C, 58.91; H, 6.29; N, 6.25. Found: C, 58.95; H, 6.31; N, 5.86.

***(N-Benzyl-N-(2-nitrophenylsulfonyl)-L-valine tert-butyl ester)* 2d**

Pale yellow solid (89%). mp 76.5-77.0 °C. IR: υ_{max} 2975w, 1722s (CO), 1547s (NO_2), 1376m, 1348m (SO_2/NO_2), 1159s. ^{1}H NMR ($CDCl_3$): δ 0.86 (3 H, d, *J* 6.7) and 0.92 (3 H, d, *J* 6.7, CH(C$\underline{H}_3$)$_2$), 1.35 (9 H, s, t-Bu), 2.01-2.16 (1 H, m, C$\underline{H}$(CH$_3$)$_2$), 4.17 (1 H, d, *J* 10.0, α-CH), 4.56 (1 H, d, *J* 15.4) and 4.98 (1 H, d, *J* 15.4, PhC$\underline{H}_2$), 7.16-7.19 (3 H, m, ArH), 7.39-7.47 (3 H, m, ArH), 7.57-7.58 (2 H, m, ArH), 7.73 (1 H, m, ArH). MS: m/z (APCI, AP$^-$) 448 [M$^-$]$^-$. $C_{22}H_{28}N_2O_6S$. Calcd: C, 58.91; H, 6.29; N,6.25. Found: C, 58.92; H, 6.25; N, 6.04.

***(N-Benzyl-N-(2-nitrophenylsulfonyl)-L-(O-tert-butyl)threonine tert-butyl ester)* 2e**

Pale yellow oil (71%). IR: υ_{max} 2977s, 1736s (CO), 1545s (NO_2), 1369s, 1356s (SO_2/NO_2), 1190m, 1144s. ^{1}H NMR ($CDCl_3$): δ 1.13 (9 H, s, t-butyl), 1.35 (3 H, d, *J* 6.5, CH_3), 1.45 (9 H, s, t-butyl), 4.11-4.51 (1 H, m, C$\underline{H}$(CH$_3$)Ot-Bu), 4.63 (1 H, d, *J* 15.4) and 5.06 (1 H, d, *J* 15.4, PhC$\underline{H}_2$), 4.70 (1 H, d, *J* 3.4, α-CH), 7.11-7.12 (3 H, m, ArH), 7.27-7.54 (6 H, m, ArH). MS: m/z (APCI, AP$^-$) 506 [M$^-$]$^-$. $C_{25}H_{34}N_2O_7S$. Calcd: C, 59.27; H, 6.76; N, 5.53; S, 6.33. Found: C, 59.64; H, 7.03; N, 5.87; S, 5.97.

***(N-Benzyl-N-(4-nitrophenylsulfonyl)-L-(O-tert-butyl)threonine tert-butyl ester)* 2f**
Clear glass (79%). IR: υ_{max} 2977s, 1738s (CO), 1531s (NO_2), 1368m, 1350s (SO_2/NO_2), 1165s, 1144s. ^{1}H NMR ($CDCl_3$): δ 1.09 (9 H, s, t-butyl), 1.24 (3 H, d, *J* 6.2, CH_3), 1.40 (9 H, s, t-butyl), 4.42-4.45 (1 H, m, C<u>H</u>(CH_3)Ot-Bu), 4.55 (1 H, d, *J* 3.4, α-CH), 4.72 (1 H, d, *J* 15.7) and 4.82 (1 H, d, *J* 15.7, PhC<u>H</u>$_2$), 7.19-7.21 (3 H, m, ArH), 7.46-7.47 (2 H, m, ArH),), 7.65-7.67 (2 H, m, ArH), 8.13-8.15 (2 H, m, ArH). MS: m/z (APCI, AP$^-$) 506 [M$^-$]$^-$. $C_{25}H_{34}N_2O_7S$. Calcd: C, 59.27; H, 6.76; N, 5.53; S, 6.33. Found: C, 59.52; H, 7.01; N, 5.38; S, 6.18.

***(N-Benzyl-N-(2-nitrophenylsulfonyl)-L-valine methyl ester)* 2g**
Pale yellow oil (70%). IR: υ_{max} 2975w, 1738s (CO), 1542s (NO_2), 1368m, 1340s (SO_2/NO_2), 1142m, 1158m. ^{1}H NMR ($CDCl_3$): δ 0.85 (3 H, d, *J* 6.8) and 0.88 (3 H, d, *J* 6.6, CH(C<u>H</u>$_3$)$_2$), 2.05-2.15 (1 H, m, C<u>H</u>(CH_3)$_2$), 3.52 (3 H, s, OCH_3), 4.27 (1 H, d, *J* 10.3, α-CH), 4.51 (d, *J* 15.1) and 4.88 (2 H, d, *J* 15.4, PhC<u>H</u>$_2$), 7.09-7.19 (3 H, m, ArH), 7.31-7.40 (3 H, m, ArH), 7.51-7.55 (2 H, m, ArH), 7.59 (1 H, d, *J* 7.8, ArH). MS: m/z (APCI, AP$^-$) 406 [M$^-$]$^-$. $C_{19}H_{22}N_2O_6S$. Calcd: C, 56.15; H, 5.46; N, 6.89; S, 7.89. Found: C, 56.41; H, 5.45; N, 6.85; S, 7.70.

***(N-Methyl-N-(4-nitrophenylsulfonyl)-L-serine (t-Bu) tert-butyl ester)* 2h**
Pale yellow oil (93%). IR: υ_{max} 3109w, 2976s, 1742s (CO), 1531s (NO_2), 1366s, 1348s (SO_2/NO_2), 1141s. ^{1}H NMR ($CDCl_3$): δ 1.13 (9 H, s, t-Bu), 1.39 (9 H, s, t-Bu), 2.98 (3 H, s, NCH_3), 3.69- 3.78 (2 H, m, C<u>H</u>$_2$Ot-Bu), 4.73 (1 H, m, α-CH), 8.03-8.05 (2 H, m, ArH), 8.31- 8.33 (2 H, m, ArH). MS: m/z (APCI, AP$^-$) 416 [M$^-$]$^-$. $C_{18}H_{28}N_2O_7S$. Calcd: C, 51.91; H, 6.78; N, 6.73; S, 7.70. Found: C, 51.77; H, 6.84; N, 6.59; S, 8.00.

***(N-2-ethylcyclohexyl-N-(4-nitrophenylsulfonyl)-L-valine tert-butyl ester)* 2i**
Pale yellow oil (78%). IR: υ_{max} 3104w, 2928s, 1734s (CO), 1528s (NO_2), 1368m, 1348s (SO_2/NO_2), 1163m, 1140m. ^{1}H NMR ($CDCl_3$): δ 0.84-0.98 (2 H, m), 0.97 (3 H, d, *J* 6.5) and 1.05 (3 H, d, *J* 6.5, CH(C<u>H</u>$_3$)$_2$), 1.14-1.21 (3 H, m), 1.29 (9 H, s, t-Bu), 1.30-1.50 (1 H, *m*), 1.61-1.67 (7 H, m), 2.05-2.18 (1 H, m), 3.16-3.25 (1 H, m), 3.41-3.55 (1 H, m), 4.03 (1 H, d, *J* 10.1, α-CH), 8.05 (2 H, m, ArH), 8.32 (2 H, m, ArH). MS: m/z (APCI, AP$^-$) 468 [M$^-$]$^-$. $C_{23}H_{36}N_2O_6S$. Calcd: C, 58.95; H, 7.74; N, 5.98. Found: C, 58.74; H, 7.75; N, 5.68.

***(N-Methyl-N-(4-nitrophenylsulfonyl)-L-alanine tert-butyl ester)* 2j**
Pale yellow solid (89%). mp 78-79 °C. IR: υ_{max} 3109w, 2982m, 1731s (CO), 1524s (NO_2), 1370m, 1341s (SO_2/NO_2), 1192m, 1155s. ^{1}H NMR ($CDCl_3$): δ 1.32 (9 H, s, t-Bu), 1.41 (3 H, d, *J* 7.3, CHC<u>H</u>$_3$), 2.89 (3 H, s, NCH_3), 4.68 (1 H, q, *J* 7.3, α-CH), 7.26-8.05 (2 H, m, ArH), 8.32-8.36 (2 H, m, ArH). MS: m/z (APCI, AP$^-$) 344 [M$^-$]$^-$. $C_{14}H_{20}N_2O_6S$. Calcd: C, 48.83; H, 5.85; N, 8.17; S, 9.31. Found: C, 48.79; H, 5.81; N, 8.13; S, 9.05.

***(N-4-pentenyl-N-(2-nitrophenylsulfonyl)-L-valine tert-butyl ester)* 2k**
Pale yellow oil (91%). IR: υ_{max} 3105w, 2970s, 1724s (CO), 1645w (C=C), 1535s (NO_2), 1371s, 1348s (SO_2/NO_2), 1142s. ^{1}H NMR ($CDCl_3$): δ 0.98 (3 H, d, *J* 6.5) and 1.03 (3 H, d, *J* 6.6, CH(C<u>H</u>$_3$)$_2$), 1.29 (9 H, s, t-Bu), 1.66-1.91 (2 H, m), 2.00-2.19 (3 H, m), 3.42-3.51 (2 H, m), 4.03 (1 H, d, *J* 10.1, α-CH), 4.96-5.05 (2 H, m, =C<u>H</u>$_2$), 5.74-5.81 (1 H, m, C<u>H</u>=CH$_2$), 7.55-7.57 (1 H, m, ArH), 7.63-7.69 (2 H, m, ArH), 8.01-8.04 (1 H, m, ArH). MS: m/z (APCI, AP$^-$) 426 [M$^-$]$^-$. $C_{20}H_{30}N_2O_6S$. Calcd: C, 56.32; H, 7.09; N, 6.57; S, 7.52. Found: C, 56.57; H, 6.95; N, 6.53; S, 7.60.

Rearrangements

***(N-4-Bromobenzyl-2-(4-nitrophenyl)-phenylalanine tert-butyl ester · hydrochloride)* 4a**
A solution of sulfonamide **2a** in dioxane (1.5 mL) was treated with tetrabutyl ammonium hydroxide (40% wt. solution in water, 1.5mmol). The resulting mixture was stirred 0.25 hr at room temperature before filtering

through a plug of silica gel (flash, 230-400 mesh, 5.0 g) with EtOAc eluent and concentrating. The dark residue was dissolved in $CHCl_3$ and purified by flash chromatography EtOAc/ hexane to provide (0.11 g, 76%) of a clear oil. Treatment with saturated ethereal HCl and crystallization from EtOAc/ hexane provided the hydrochloride salt which was characterized mp 137 °C. IR: υ_{max} 2976s, 1738s (CO), 1524s (NO_2), 1350s (NO_2), 1150s. ^{1}H NMR (DMSO-d_6): δ 1.37 (9 H, s, t-Bu), 2.97 (1 H, b t, *J* 7.7, NH), 3.24-3.38 (2 H, m, PhC<u>H</u>$_2$), 3.47 (1 H, dd, *J* 7.7, 13.5) and 3.61 (1 H, dd, *J* 7.2, 13.5, 4-Br-PhC<u>H</u>$_2$), 6.90-6.92 (2 H, m, ArH), 7.11 (3 H, m, ArH), 7.29 (2 H, m, *J* 8.4, ArH), 7.48-7.54 (4 H, m, ArH), 8.12 (2 H, d *J* 8.9, ArH); D_2O wash- 2.97 absent, 3.47 (1 H, d, *J* 13.5) and 3.61 (1 H, d, *J* 13.5, 4-Br-PhC<u>H</u>$_2$). MS: m/z (APCI, AP$^+$) 512 [M + H]$^+$. $C_{26}H_{27}BrN_2O_4 \cdot HCl$. Calcd: C, 57.00; H, 5.15; N, 5.11. Found: C, 56.88; H, 5.46; N, 4.78.

(N-Methyl-2-(4-nitrophenyl)-valine tert-butyl ester · hydrochloride) **4b**
White solid (69%). mp 177-179 °C. IR: υ_{max} 2973m, 1732s (CO), 1524s (NO_2), 1350s (NO_2), 1155s. ^{1}H NMR ($CDCl_3$): δ 0.69 (3 H, d, *J* 6.7) and 0.84 (3 H, d, *J* 6.7, CH(C<u>H</u>$_3$)$_2$), 1.51 (9 H, s, t-Bu), 1.54 (1 H, br s, NH), 2.34 (3 H, s, NCH_3), 2.33 (1 H, m, C<u>H</u>(CH$_3$)$_2$), 7.68-7.73 (2 H, m, ArH), 8.11-8.19 (2 H, m, ArH). ^{13}C NMR δ ($CDCl_3$): 12.6, 13.3, 23.0, 25.8, 32.1, 70.7 (α-<u>C</u>H), 81.9, 118.9, 124.8, 134.6 (NO_2Ar-<u>C</u>N), 143.1, 159.7. MS: m/z (APCI, AP$^-$) 308 [M$^-$]$^-$. $C_{16}H_{24}N_2O_4 \cdot HCl$. Calcd: C, 55.73; H, 7.31; N, 8.12; Cl, 10.31. Found: C, 55.59; H, 7.26; N, 8.02; Cl, 10.28.

(N-Benzyl-2-(4-nitrophenyl-valine tert-butyl ester · hydrochloride) **4c**
Pale yellow solid (78%). mp 149.5-150 °C. IR: υ_{max} 3442m, 2976m, 1734s (CO), 1526s (NO_2), 1350s (NO_2), 1156 s. ^{1}H NMR ($CDCl_3$): δ 0.82 (3 H, d, *J* 6.3) and 1.23 (3 H, d, *J* 5.9, CH(C<u>H</u>$_3$)$_2$), 1.61 (9 H, s, t-Bu), 1.67 (1 H, m, NH), 3.50 (2 H, br s, PhC<u>H</u>$_2$), 3.65 (1 H, m, C<u>H</u>(CH$_3$)$_2$), 7.22-7.25 (3 H, m, ArH), 7.42 (2 H, m, ArH), 8.12 (2 H, m, ArH), 8.30 (2 H, m, ArH). MS: m/z (APCI, AP$^-$) 384 [M$^-$]$^-$. $C_{22}H_{28}N_2O_4 \cdot HCl$. Calcd: C, 62.77; H, 6.94; N, 6.65. Found: C, 62.89; H, 7.05; N, 6.55.

(N-Benzyl-2-(2-nitrophenyl-valine tert-butyl ester · hydrochloride) **4d**
Pale yellow solid (21%). mp 131-132 °C. IR: υ_{max} 3433m, 2980m, 1738s (CO), 1534s (NO_2), 1362m (NO_2), 1150s. ^{1}H NMR ($CDCl_3$): δ 0.96 (3 H, d, *J* 6.9) and 1.10 (3 H, d, *J* 6.7, CH(C<u>H</u>$_3$)$_2$), 1.47 (9 H, s, t-Bu), 2.21 (1 H, br s, NH), 2.82-2.88 (1 H, m, C<u>H</u>(CH$_3$)$_2$), 3.44 (2 H, br s, PhC<u>H</u>$_2$), 7.18-7.32 (5 H, m, ArH), 7.37-7.39 (1 H, m, ArH), 7.42-7.57 (1 H, m, ArH), 7.75-7.80 (1 H, m, ArH), 7.86-7.89 (1 H, m, ArH). MS: m/z (APCI, AP$^-$) 384 [M$^-$]$^-$. $C_{22}H_{28}N_2O_4 \cdot HCl$. Calcd: C, 62.77; H, 6.94; N, 6.65. Found: C, 62.42; H, 7.05; N, 6.50.

(N-Benzyl-2-(2-nitrophenyl)- (O-tert-butyl)threonine tert-butyl ester · hydrochloride) **4e**
Pale yellow oil (12%). ^{1}H NMR ($CDCl_3$): δ 1.14 (9 H, s, t-Bu), 1.23 (9 H, s, t-Bu), 1.27 (3 H, d, *J* 6.0, CHC<u>H</u>$_3$), 3.77-3.90 (2 H, m, PhC<u>H</u>$_2$), 4.09-4.15 (1 H, m, C<u>H</u>CH$_3$), 7.26-7.28 (2 H, m, ArH), 7.67-7.89 (5 H, m ArH), 7.89-7.92 (1 H, m, ArH), 8.02-8.05 (1 H, ArH). MS: m/z (APCI, AP$^-$) 442 [M$^-$]$^-$. $C_{25}H_{34}N_2O_5 \cdot HCl$. Calcd: C, 62.69; H, 7.36; N, 5.85; Cl, 7.40. Found: C, 62.54; H, 7.32; N, 5.78; Cl, 7.29.

(N-Benzyl-2-(4-nitrophenyl)-(O-tert-butyl)threonine tert-butyl ester · hydrochloride) **4f**
Low melting solid (60%). IR: υ_{max} 2977m, 1723s (CO), 1528s (NO_2), 1360m (NO_2), 1156s. ^{1}H NMR ($CDCl_3$): δ1.13 (3 H, br s, CH_3), 1.18 (9 H, s, t-Bu), 1.61 (9 H, br s, t-Bu), 3.65-3.71 (1 H, m, C<u>H</u>CH$_3$), 3.42 (1 H) and 3.82 (1 H, m, PhC<u>H</u>$_2$), 7.26-7.39 (3 H, m, ArH), 7.45-7.47 (2 H, m, ArH), 7.85-7.87 (2 H, m, ArH), 8.23-8.35 (2 H, m, ArH). MS: m/z (APCI, AP$^-$) 442 [M$^-$]$^-$. $C_{25}H_{34}N_2O_5 \cdot HCl$. Calcd: C, 62.69; H, 7.36; N, 5.85; Cl, 7.40. Found: C, 62.32; H, 7.42; N, 5.66; Cl, 7.34.

(N-Benzyl-N-(2-nitrophenyl)-valine methyl ester · hydrochloride) **4g**
Pale yellow oil (5.4%). IR: υ_{max} 2969w, 1749s (CO), 1528s (NO_2), 1360m (NO_2), 1023m. ^{1}H NMR ($CDCl_3$): δ 1.00 (3 H, d, *J* 6.8) and 1.10 (3 H, d, *J* 6.6, CH(C<u>H</u>$_3$)$_2$), 1.61 (1 H, br s, NH), 2.84-2.88 (1 H, m, C<u>H</u>(CH$_3$)$_2$), 3.44 (2 H, s, PhC<u>H</u>$_2$), 3.71 (3 H, s, OCH_3), 7.21-7.32 (5 H, m, ArH), 7.42-7.46 (1 H, m, ArH), 7.57-7.61 (1 H,

m, ArH), 7.76-7.78 (1 H, m, ArH), 7.88-7.90 (1 H, m, ArH). MS: m/z (APCI, AP$^-$) 342 [M$^-$]$^-$. $C_{19}H_{22}N_2O_4 \cdot HCl$. Calcd: C, 60.24; H, 6.12; N, 7.39; Cl, 9.36. Found: C, 59.96; H, 6.04; N, 7.20; Cl, 9.35.

(N-Methyl-2-(4-nitrophenyl)-(O-tert-butyl)serine tert-butyl ester) **4h**
Pale yellow oil (78%). IR: υ_{max} 2974m, 1726s (CO), 1518s (NO_2), 1347s (NO_2), 1158s. ^{1}H NMR ($CDCl_3$): δ1.16 (9 H, s, t-Bu), 1.45 (9 H, s, t-Bu), 2.23 (3 H, s, $NHC\underline{H}_3$), 3.78 (1 H, d, *J* 8.1) and 3.88 (1 H, d, *J* 7.9, $C\underline{H}_2O$-tBu), 7.71-7.72 (2 H, m, ArH), 8.17- 8.20 (2 H, m, ArH). MS: m/z (APCI, AP$^-$) 352 [M$^-$]$^-$. $C_{18}H_{28}N_2O_5$. Calcd: C, 61.34; H, 8.01; N, 7.95. Found: C, 61.49; H, 6.84; N, 7.76.

(N-2-Ethylcyclohexyl-2-(4-nitrophenyl)-valine tert-butyl ester) **4i**
Pale yellow oil (81%). IR: υ_{max} 2967m, 2921s, 1725s (CO), 1520s (NO_2), 1349s (NO_2), 1160s; ^{1}H NMR ($CDCl_3$): δ 0.69 (3 H, d, *J* 6.9) and 0.83 (3 H, d, *J* 6.7, $CH(C\underline{H}_3)_2$), 0.86-0.93 (3 H, m), 1.11- 1.49 (5 H, m), 1.51 (9 H, s, t-Bu), 1.66-1.75 (6 H, *m*), 2.26-2.44 (3 H, m), 7.27-7.74 (2 H, m, ArH), 8.12-8.14 (2 H, m, ArH). MS: m/z (APCI, AP$^-$) 404 [M$^-$]$^-$. $C_{23}H_{36}N_2O_4$. Calcd: C, 68.29; H, 8.97; N, 6.92. Found: C, 67.93; H, 8.79; N, 6.87.

(N-Methyl-2-(4-nitrophenyl)-alanine tert-butyl ester) **4j**
Pale yellow oil (65%). IR: υ_{max} 3115w, 2969m, 1728s (CO), 1524s (NO_2), 1349s (NO_2), 1143s. ^{1}H NMR ($CDCl_3$): δ 1.43 (9 H, s, t-Bu), 1.59 (3 H, s, CH_3), 2.33 (3 H, s, NCH_3), 7.63-7.66 (2 H, m, ArH), 8.17-8.21 (2 H, m, ArH). MS: m/z (APCI, AP$^-$) 280 [M$^-$]$^-$. $C_{14}H_{20}N_2O_4$. Calcd: C, 59.99; H, 7.19; N, 9.76. Found: C, 59.68; H, 7.01; N, 9.99.

(N-4-pentenyl-2-(2-nitrophenyl)-valine tert-butyl ester) **4k**
Pale yellow oil (17%). IR: υ_{max} 3369w, 2976s, 1726s (CO), 1640w (C=C), 1534s (NO_2), 1366s (NO_2), 1152s. ^{1}H NMR ($CDCl_3$): δ 0.93 (3 H, d, *J* 6.7) and 1.08 (3 H, d, *J* 6.7, $CH(C\underline{H}_3)_2$), 1.26-1.43 (2 H, m), 1.44 (9 H, s, t-Bu), 1.46-1.65 (2 H, *m*), 1.93 (1 H, br s, NH), 2.00- 2.18 (2 H, m), 2.73-2.79 (1 H, m, $C\underline{H}(CH_3)_2$), 4.87-4.99 (2 H, m, $=C\underline{H}_2$), 5.68-5.81 (1 H, m, $C\underline{H}=CH_2$), 7.35-7.41 (1 H, m, ArH), 7.49-7.55 (1 H, m, ArH), 7.70-7.78 (2 H, m, ArH). MS: m/z (APCI, AP$^-$) 362 [M$^-$]$^-$. $C_{20}H_{30}N_2O_4$. Calcd: C, 66.27; H, 8.34; N, 7.73. Found: C, 66.62; H, 8.43; N, 7.72.

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