π-Deficient 2-(Arylsulfonyl)ethyl Esters as Protecting Groups for Carboxylic Acids

Diego A. Alonso, Carmen Nájera,* Montserrat Varea
Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Alicante, Apdo. 99, 03080 Alicante, Spain
Fax +34(96)5903549; E-mail: cnajera@ua.es
Received 5 November 2002

Abstract: Several π-deficient 2-(arylsulfonyl)ethyl groups have been studied as carboxylic acid protecting groups. The 2-[3,5-bis(trifluoromethyl)phenylsulfonyl]ethyl group is the most easily removed protecting group for acids under mild basic conditions using aqueous NaHCO₃.

Key words: alcohols, carboxylic acids, eliminations, protecting groups, sulfones

There is a permanent need for the protection of functional groups under mild and specific reaction conditions in the synthesis of complex molecules. In the case of carboxylic acids, mainly esters are used as blocking functions.² The base-labile protecting groups 2-(p-toluenesulfonyl)ethyl (TSE),² 2-(phenylsulfonyl)ethyl (PSE)³ and 2-(methanesulfonyl)ethyl⁴ esters (Figure 1) have been widely used and can be cleaved by a base-induced β-elimination mechanism. These protecting groups have been employed in several total syntheses of different natural macrolides such as (+)-pyrenophorin,²ᵃᵇ colletodiol,²ᵈ⁻ᶠ (--)-collétallol³ᵃ and pyrenophorol.³ᵇ They have been used as well in the synthesis of bacterial cell wall precursor UDP-N-acetylmuramylpentapeptide and in the synthesis of carbohydrates⁴ employed in the discovery of new antibotics, the natural products (+)-surugatoxin⁴ and the peptide calcitonin.³ᵇ These β-hydroxyalkyl sulfone-derived esters can be prepared by carbodiimide-mediated esterification and cleaved using organic bases such as DBU. Alternatively, NaOH or Na₂CO₃ (but not NaHCO₃) in aqueous dioxane at room temperature²⁻⁴ or tetrabutylammonium fluoride in THF at 0 °C,²¹ can be used for the β-elimination process. In order to favour the cleavage of the protecting group, the simplest strategy is to improve the lability of the arylsulfonyl group by means of electron-withdrawing substituents. This strategy has been studied with (arylsulfonyl)ethoxycarbonyl groups such as the p-nitro-, p-bromo- and p-methylsulfonyl-derivatives (Nsc, Bsc and Mpc), for the carbamate protection of amino acids¹¹,¹² (Figure 1). We have recently shown that π-deficient α-(arylsulfonyl)acetates such as the 3,5-bis(trifluoromethyl)phenylsulfonyl derivatives (Figure 1), are very soft nucleophiles and efficient precursors for the one-pot synthesis of (E)-aconitines.⁵ In this communication we have studied diverse π-deficient 2-(arylsulfonyl)ethanols as protecting groups for carboxylic acids in order to find the mildest reaction conditions for the deprotection of the carboxy function.

The π-deficient 2-(arylsulfonyl)ethanols 3 were prepared in very good yields by reaction of thiophenols 1 with 2-bromoethanol using Et₃N as base in acetonitrile at room temperature to afford the corresponding sulfides 2, which were purified and further oxidized with H₂O₂ (30%) in the presence of a buffer solution of NaHCO₃ and catalytic amounts of MnSO₄ ⋅ H₂O (1 mol%) in acetonitrile at room temperature⁶ (Scheme 1, Table 1). Sulfones 3 were obtained pure and did not need any further purification. The oxidation step could be carried out with Oxone⁶, but the yields were generally lower and purification by flash
To optimize the conditions for the protection reaction and find the most efficient protecting group, hydrocinnamic and trans-cinnamic acids were chosen as the model substrates. The coupling reactions were performed in the presence of EDC [1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride], and DMAP in ethanol-free CH$_2$Cl$_2$ [Scheme 2, R = PhCH$_2$CH$_2$, trans-PhCH=CH]. When DCC was used as coupling agent, the resulting esters had to be purified by flash chromatography, purification that was avoided with the water soluble reagent EDC. Furthermore, when the solvent contained EtOH, we could observe the formation of ethyl esters as secondary products in the protection reaction, which decreased to some extent the yield of the reaction. The best results in the protection step, were obtained with 2-[3,5-bis(trifluoromethyl)phenylsulphonyl]ethanol (3a), 2-(4-nitrophenylsulphonyl)ethanol (3c) and 2-(3,4-dichlorophenylsulphonyl)ethanol (3d) (Table 2, Entries 1, 2 and 5–8), where the corresponding crude esters were obtained pure, as determined by $^1$H NMR, and in high yields. The low yield observed with the 3-(trifluoromethyl)phenylsulphonyl derivative, was due to partial decomposition of the alcohol under the reaction conditions (Table 2, Entries 3 and 4). Under the above mentioned reaction conditions, 2-(phenylsulphonyl)ethanol (3e), a frequently used carboxylic acid protecting group, afforded the corresponding esters 4ea and 4eb in a low yield (Table 2, Entries 9 and 10).

Table 1 Synthesis of $\pi$-Deficient 2-(Arylsulfonyl)ethanols 3

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar</th>
<th>2 No.</th>
<th>Yield (%)</th>
<th>R$_f$</th>
<th>3 No.</th>
<th>Yield (%)</th>
<th>Mp (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3,5-(CF$_3$)$_2$C$_6$H$_3$</td>
<td>2a</td>
<td>97</td>
<td>0.49</td>
<td>3a</td>
<td>93 (79)</td>
<td>116–117</td>
</tr>
<tr>
<td>2</td>
<td>3-CF$_3$C$_6$H$_4$</td>
<td>2b</td>
<td>80</td>
<td>0.40</td>
<td>3b</td>
<td>80 (70)</td>
<td>0.66</td>
</tr>
<tr>
<td>3</td>
<td>4-NO$_2$C$_6$H$_4$</td>
<td>2c</td>
<td>86</td>
<td>0.22</td>
<td>3c</td>
<td>81 (81)</td>
<td>118–119</td>
</tr>
<tr>
<td>4</td>
<td>3,4-Cl$_2$C$_6$H$_3$</td>
<td>2d</td>
<td>82</td>
<td>0.46</td>
<td>3d</td>
<td>72 (68)</td>
<td>81–82</td>
</tr>
<tr>
<td>5</td>
<td>Ph</td>
<td>2e</td>
<td>–</td>
<td>0.37</td>
<td>3e</td>
<td>68 (62)</td>
<td>0.59</td>
</tr>
</tbody>
</table>

a Isolated yield after flash chromatography.
b Hexane–EtOAc, 2:1.
c Isolated crude yield. All crude alcohols gave satisfactory spectroscopic data (1H and 13C NMR, IR and MS). In brackets, isolated yield of sulfones employing Oxone® as oxidant.
d Hexane–CH$_2$Cl$_2$.
e EtOAc.
f Lit. $^{7}$ 126–127 °C (CHCl$_3$).
g Commercially available.

Table 2 Protection of Cinnamic and Hydrocinnamic Acids with 2-(Arylsulfonyl)ethanols 3

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar R Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhCH$_2$CH$_2$ 4aa</td>
</tr>
<tr>
<td>2</td>
<td>PhCH=CH 4ab</td>
</tr>
<tr>
<td>3</td>
<td>PhCH$_2$CH$_2$ 4ba</td>
</tr>
<tr>
<td>4</td>
<td>PhCH=CH 4bb</td>
</tr>
<tr>
<td>5</td>
<td>PhCH$_2$CH$_2$ 4ca</td>
</tr>
<tr>
<td>6</td>
<td>PhCH=CH 4cb</td>
</tr>
<tr>
<td>7</td>
<td>PhCH$_2$CH$_2$ 4da</td>
</tr>
<tr>
<td>8</td>
<td>PhCH=CH 4db</td>
</tr>
<tr>
<td>9</td>
<td>PhCH$_2$CH$_2$ 4ea</td>
</tr>
<tr>
<td>10</td>
<td>PhCH=CH 4eb</td>
</tr>
</tbody>
</table>

a Isolated crude yield. All crude compounds gave satisfactory spectroscopic data (1H and 13C NMR, IR and MS).
b Hexane–CH$_2$Cl$_2$.
c Hexane–EtOAc, 2:1.
The optimization of the reaction conditions for the deprotection of carboxylic esters 4 was carried out with compound 4ab as a model substrate. Ester 4ab, derived from 2-[3,5-bis(trifluoromethyl)phenylsulfonyl]ethanol and trans-cinnamic acid, was subjected to deprotection under different basic conditions (Scheme 3, Table 3). When using NaOAc as base, very low conversions for the deprotection reaction were observed both in aqueous methanol and aqueous acetone (Table 3, Entries 1–4). When the reaction was carried out in MeOH–H₂O (1:1) at 65 °C, an 80% yield of methyl ether 6 was obtained as a consequence of a Michael addition of the solvent over the previously formed vinyl sulfone 5a (Scheme 4). With stronger bases such as KOH, only decomposition products were observed when the reaction was carried out in acetone–H₂O (1:1) (Table 3, Entry 5). Changing the solvent to MeOH or t-BuOH led to high conversions of ether 6 and dimeric sulfone 7, respectively. Sulfone 7 was generated as a result of a Michael addition of alcohol 3a (probably generated by hydrolysis of ester 4ab) to the previously formed vinyl sulfone 5a (Scheme 4). TBAF, which has been previously reported for efficient deprotection of TSE-protected carboxylic acids, gave very poor results in the deprotection reaction at 0 °C of the 3,5-bis(trifluoromethyl)phenylsulfonyl derivative 4ab (30 and 21% of recovered sulfone and carboxylic acid, respectively) (Table 3, Entry 8). When TBAOH was used as base, a 64% yield of dimeric sulfone 7 was obtained instead of the vinylic sulfone (Scheme 4, Table 3, Entry 9). Finally, we found that the best conditions for the deprotection of ester 4ab employed 1.5 equivalents of NaHCO₃ in acetone–H₂O (1:1), yielding the vinylic sulfone and the recovered trans-cinnamic acid with very high yields after the acid–base extractive work-up (Table 3, Entries 10 and 11).

Once we optimized the conditions for the deprotection step, and in order to find out the π-deficient derivative with the best ability as leaving group, we carried out the deprotection of the diverse π-deficient esters 4 previously prepared under the above-mentioned conditions (Scheme 5, Table 4).

![Scheme 3](image-url)

**Table 3** Deprotection of Ester 4ab; Reaction Conditions Optimization

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base (equiv)</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>t (h)</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaOAc (2.2)</td>
<td>MeOH–H₂O (1:1)</td>
<td>25</td>
<td>48</td>
<td>38 (30)</td>
</tr>
<tr>
<td>2</td>
<td>NaOAc (2.2)</td>
<td>MeOH–H₂O (1:1)</td>
<td>65</td>
<td>24</td>
<td>– (40)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>NaOAc (2.2)</td>
<td>acetone–H₂O (1:1)</td>
<td>25</td>
<td>48</td>
<td>25 (20)</td>
</tr>
<tr>
<td>4</td>
<td>NaOAc (2.2)</td>
<td>acetone–H₂O (1:1)</td>
<td>60</td>
<td>24</td>
<td>28 (25)</td>
</tr>
<tr>
<td>5</td>
<td>KOH (1.5)</td>
<td>acetone–H₂O (1:1)</td>
<td>25</td>
<td>12</td>
<td>–&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>6</td>
<td>KOH (1.5)</td>
<td>MeOH–H₂O (1:1)</td>
<td>25</td>
<td>12</td>
<td>– (37)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>7</td>
<td>KOH (1.5)</td>
<td>t-BuOH–H₂O (1:1)</td>
<td>25</td>
<td>12</td>
<td>– (51)&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>8</td>
<td>TBAF (3)</td>
<td>THF</td>
<td>0</td>
<td>5</td>
<td>30 (21)&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td>9</td>
<td>TBAOH (3)</td>
<td>THF</td>
<td>0</td>
<td>1</td>
<td>– (41)&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td>10</td>
<td>NaHCO₃ (1.5)</td>
<td>MeOH–H₂O (1:1)</td>
<td>25</td>
<td>12</td>
<td>80 (91)</td>
</tr>
<tr>
<td>11</td>
<td>NaHCO₃ (1.5)</td>
<td>acetone–H₂O (1:1)</td>
<td>25</td>
<td>12</td>
<td>87 (96)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Isolated crude yield of vinyl sulfone 5a. In brackets, isolated crude yield of trans-cinnamic acid. All crude compounds gave satisfactory spectroscopic data (¹H and ¹³C NMR, IR and MS).

<sup>b</sup> Compound 6 (see Scheme 4) was also obtained in a 80% yield.

<sup>c</sup> Only decomposition of starting material was observed (¹H NMR).

<sup>d</sup> Compound 7 (see Scheme 4) was also obtained in an 88% yield.

<sup>e</sup> Compound 7 (see Scheme 4) was also obtained in a 22% yield.

<sup>f</sup> Compound 7 (see Scheme 4) was also obtained in a 64% yield.
Scheme 4

Table 4  Deprotection of Cinnamic and Hydrocinnamic Esters

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar</th>
<th>R</th>
<th>No.</th>
<th>5</th>
<th>Mp (°C) or Rf</th>
<th>Recovered Acid Yield (%)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhCH₂CH₂</td>
<td>4aa</td>
<td>84</td>
<td>112–114</td>
<td>93</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>PhCH=CH</td>
<td>4ab</td>
<td>87</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>PhCH₂CH₂</td>
<td>4ba</td>
<td>60</td>
<td>0.62</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>PhCH=CH</td>
<td>4bb</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>PhCH₂CH₂</td>
<td>4ca</td>
<td>74</td>
<td>115–117</td>
<td>74</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>PhCH=CH</td>
<td>4cb</td>
<td>69</td>
<td></td>
<td>57</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>PhCH₂CH₂</td>
<td>4da</td>
<td>82</td>
<td>59–60</td>
<td>68</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>PhCH=CH</td>
<td>4db</td>
<td>77</td>
<td></td>
<td>61</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>PhCH₂CH₂</td>
<td>4ea</td>
<td>60</td>
<td>69–70c</td>
<td>62</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>PhCH=CH</td>
<td>4eb</td>
<td>58</td>
<td></td>
<td>60</td>
<td></td>
</tr>
</tbody>
</table>

a Isolated crude yield. All crude compounds gave satisfactory spectroscopic data (1H and 13C NMR, IR and MS).
b Hexane–CH₂Cl₂.
c Hexane–EtOAc, 2:1.
d Only decomposition products were observed in the crude reaction mixture (1H NMR).
e Commercially available.
In all the cases, the deprotection process took place easily and under very mild conditions, except for the 3-trifluoromethylphenyl sulfanyl protecting groups such as Fmoc remaining intact in the case of the reaction of Fmoc-protected phenylalanine (Table 5, Entry 10).

Finally, reaction of different carboxylic acids with alcohol 3a under the above mentioned conditions, afforded pure esters after extractive work-up [Scheme 2, Ar = 3,5-bis(trifluoromethyl)phenyl, Table 5]. Yields were generally high for the protection and deprotection processes and the reactions took place easily with aliphatic and aromatic carboxylic acids, even in the case of hindered substrates (Table 5, Entries 6 and 7). Enantiomerically pure carboxylic acids were protected and deprotected with no loss in the optical yield (Table 5, Entries 8, 10, 11 and 12). Base-sensitive N-protecting groups such as Fmoc remained intact as in the case of the reaction of Fmoc-protected phenylalanine (Table 5, Entry 10).

In conclusion, we have introduced the 2-[3,5-bis(trifluoromethyl)phenylsulfonyl]-1-ethanol (3a) as a new stable and crystalline reagent, which can be used as an efficient protecting group for carboxylic acids. The high yields, simplicity and very mild conditions required for the protection–deprotection sequence favour this new reagent as a good alternative to established carboxylic acid base-labile protecting agents.

To a stirred solution of the corresponding thiold 1 (5 mmol) and Et,N (1.4 mL; 10 mmol) in MeCN (15 mL), was added 2-bromoethanol (908 µL; 5.5 mmol). The reaction was stirred for 1 d at r.t., treated with sat. aq NH₄Cl (10 mL) and extracted with EtOAc (2 × 20 mL). The combined organic layers were dried (Na₂SO₄), the solvents were removed and, after flash chromatography of the residue (silica gel; hexane–EtOAc), pure sulfides 2 were obtained. Yields and physical data are included in Table 1. Spectral and analytical data follow.

2-[3,5-Di(trifluoromethyl)phenylsulfonyl]-1-ethanol (2a)
IR (film): 3368, 1323, 1274, 1169, 1128 cm⁻¹.

1H NMR (300 MHz, CDCl₃–TMS): δ = 7.24 (d, 1 H, ArH), 7.42 (d, 1 H, J = 8.4, ArH), 7.26 (dd, 1 H, J = 8.4, 2.1, ArH), 3.76 (t, 2 H, J = 6.2, CH₂O), 3.37 (br s, 1 H, OH), 3.14 (t, 2 H, J = 6, 2, CH₂S).

13C NMR (75 MHz, CDCl₃–TMS): δ = 170.3 (ArC), 137.08 (q, 76.2, ArCH), 131.15 (q, 76.2, ArCH), 127.97, 127.92, 119.43 (ArCH), 122.91 (q, 76.2, ArCH), 122.7, 122.67 (ArCH), 122.26 (q, 76.2, ArCH), 60.24 (CH₂O), 36.08 (CH₂S).

MS: m/z = 228 [(M + H)⁺, 31], 227 (M⁺, 32), 193 (24), 192 (34), 192 (36), 191 (30), 179 (13), 178 (100), 177 (31), 172 (14), 171 (23), 170 (36), 159 (70), 158 (31), 157 (34), 145 (34), 133 (12), 127 (34), 125 (13), 122 (10), 114 (22), 109 (10), 108 (25), 95 (16), 75 (12), 69 (12), 63 (10).

HRMS: m/z calcd for C₁₈H₁₈O₂S₂: 291.0655 (M⁺); found: 291.0676.

2-[3-(Trifluoromethyl)phenylsulfanyl]-1-ethanol (2b)
IR (film): 3394, 1378, 1274, 1169, 1128 cm⁻¹.

1H NMR (300 MHz, CDCl₃–TMS): δ = 7.59 (s, 1 H, ArH), 7.51 (d, 1 H, J = 7.3, ArH), 7.44–7.33 (m, 2 H, ArH), 3.78 (t, 2 H, J = 6.2, CH₂O), 3.37 (br s, 1 H, OH), 3.14 (t, 2 H, J = 6, 2, CH₂S).

13C NMR (75 MHz, CDCl₃–TMS): δ = 137.4 (ArC), 131.2 (q, 76.2, ArCH), 127.89, 127.84, 117.15 (ArCH), 122.81 (q, 76.2, ArCH), 122.70, 122.67 (ArCH), 122.26 (q, 76.2, ArCH), 60.24 (CH₂O), 36.08 (CH₂S).

MS: m/z (%) = 220 [(M + H)⁺, 48], 222 (M⁺, 70), 195 (13), 193 (68), 192 (13), 191 (100), 180 (40), 179 (11), 178 (59), 156 (17), 155 (13), 145 (13), 144 (14), 143 (23), 142 (34), 121 (13), 111 (12), 109 (20), 108 (12), 107 (13), 75 (15), 74 (14), 63 (12).

HRMS: m/z calcd for C₁₈H₁₈O₂S₂: 221.9673 (M⁺); found: 221.9699.

Oxidation of Thioethers 2 with H₂O₂–MnSO₄–NaHCO₃: General Procedure

To a stirred solution of the corresponding thioether 1 (1 mmol) and MnSO₄·H₂O (2 mg, 1 mol%) in MeCN (23 mL) was added at r.t. a mixture, previously prepared at 0 °C, of H₂O₂ (30%; 515 µL, 5 mmol) and a buffer solution of NaHCO₃ (0.2 M; 17 mL). The reaction mixture was vigorously stirred for 15–30 min at r.t., treated with sat. aq NaCl (30 mL) and extracted with EtOAc (2 × 20 mL). The combined organic layers were dried (Na₂SO₄), and evaporation...
Table 5  Protection–Deprotection of Carboxylic Acids with 2-[3,5-Bis(trifluoromethyl)phenylsulfonyl]ethanol (3a)

<table>
<thead>
<tr>
<th>Entry</th>
<th>RCO₂H</th>
<th>4 No.</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Mp (°C)&lt;sup&gt;b&lt;/sup&gt; or R&lt;sub&gt;f&lt;/sub&gt;</th>
<th>Yield (%)&lt;sup&gt;d&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph–CO₂H</td>
<td>4aa</td>
<td>80</td>
<td>0.63</td>
<td>84 (93)</td>
</tr>
<tr>
<td>2</td>
<td>Ph–CO₂H</td>
<td>4ab</td>
<td>92</td>
<td>98–99</td>
<td>84 (91)</td>
</tr>
<tr>
<td>3</td>
<td>–CO₂H</td>
<td>4ac</td>
<td>86</td>
<td>0.64</td>
<td>91 (95)</td>
</tr>
<tr>
<td>4</td>
<td>Br–CO₂H</td>
<td>4ad</td>
<td>98</td>
<td>0.52</td>
<td>81 (94)</td>
</tr>
<tr>
<td>5</td>
<td>N–CO₂H</td>
<td>4ae</td>
<td>79</td>
<td>160–161</td>
<td>79 (91)</td>
</tr>
<tr>
<td>6</td>
<td>OMe–CO₂H</td>
<td>4af</td>
<td>40</td>
<td>0.38</td>
<td>91 (98)</td>
</tr>
<tr>
<td>7</td>
<td>N–NH₂</td>
<td>4ag</td>
<td>65</td>
<td>167–168</td>
<td>84 (83)</td>
</tr>
<tr>
<td>8</td>
<td>Me–HO₂C–NHboc</td>
<td>4ah</td>
<td>90&lt;sup&gt;e&lt;/sup&gt;</td>
<td>0.61</td>
<td>80 (73)&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td>9</td>
<td>–CO₂H</td>
<td>4ai</td>
<td>96</td>
<td>0.52</td>
<td>98 (99)&lt;sup&gt;g&lt;/sup&gt;</td>
</tr>
<tr>
<td>10</td>
<td>Me–HO₂C–NHFmoc</td>
<td>4aj</td>
<td>87&lt;sup&gt;e&lt;/sup&gt;</td>
<td>168–169</td>
<td>83 (85)&lt;sup&gt;h&lt;/sup&gt;</td>
</tr>
<tr>
<td>11</td>
<td>Me–HO₂C–NHCl</td>
<td>4ak</td>
<td>&gt;99</td>
<td>0.67</td>
<td>94 (97)&lt;sup&gt;i&lt;/sup&gt;</td>
</tr>
<tr>
<td>12</td>
<td>Me–CO₂H</td>
<td>4al</td>
<td>98</td>
<td>0.60</td>
<td>92 (87)&lt;sup&gt;j&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Isolated crude yield. All crude compounds gave satisfactory spectroscopic data (¹H and ¹³C NMR, IR and MS).
<sup>b</sup> Hexane–CH₂Cl₂.
<sup>c</sup> Hexane–EtOAc, 2:1.
<sup>d</sup> Isolated crude yield of vinyl sulfone 5. In brackets, isolated yield of recovered carboxylic acid. Both products gave satisfactory spectroscopic data (¹H and ¹³C NMR, IR and MS).
<sup>e</sup> Isolated yield after flash chromatography.
<sup>f</sup> [α]<sub>D</sub><sup>25</sup> = −25 (c 2.26, HOAc) {lit.<sup>i</sup> [α]<sub>D</sub><sup>25</sup> = −27 (c 2.26, HOAc)}.
<sup>g</sup> 6 Equiv of NaHCO₃ were used.
<sup>h</sup> [α]<sub>D</sub><sup>25</sup> = −31 (c 1, DMF) {lit.<sup>i</sup> [α]<sub>D</sub><sup>25</sup> = −37.6 (c 1, DMF)}.
<sup>i</sup> 3 Equiv of NaHCO₃ were used.
<sup>j</sup> [α]<sub>D</sub><sup>26</sup> = +64 (c 1, CHCl₃) {lit.<sup>i</sup> [α]<sub>D</sub><sup>25</sup> = +66 (c 1, CHCl₃)}.
<sup>k</sup> [α]<sub>D</sub><sup>29</sup> = +18 (c 1, CH₂Cl₂) {lit.<sup>i</sup> [α]<sub>D</sub><sup>29</sup> = +18.1 (c 1, CH₂Cl₂)}.
under reduced pressure of the organic solvents, afforded the corresponding pure sulfones 3 (>95% by 1H NMR).

**Oxidation of Thioethers 2 with Oxone®; General Procedure**

To a stirred solution of the corresponding thioether 2 (1 mmol) in MeOH–H₂O (1:1; 20 mL) was added portionwise at 0 °C Oxone® (15.37 g, 10 mmol). The reaction mixture was vigorously stirred for 1 h at r.t. After evaporation of the MeOH, CH₂Cl₂ (20 mL) was added, and the mixture was washed with a sat. aq NaCl (3 × 20 mL). The organic layer was dried (Na₂SO₄) and solvent removal and flash chromatography of the residue (silica gel; hexane–EtOAc) afforded pure sulfones 3. Yields and physical data are included in Table 1. Spectral and analytical data follow.

**3-[3,5-Bis(trifluoromethyl)phenylsulfonyl]-1-ethanol (3a)**

[IR (KBr): 3531, 1534, 1348, 1289, 1137, 1080, 1026 cm⁻¹.]

1H NMR (300 MHz, CDCl₃–TMS): δ = 8.41 (s, 2 H, ArH), 8.18 (s, 1 H, ArH), 4.13 (t, 2 H, J = 4.9, CH₂O), 3.47 (t, 2 H, J = 4.9, CH₃S), 2.47 (br s, 1 H, OH).

**2-[3-(Trifluoromethyl)phenylsulfonyl]-1-ethanol (3b)**

[IR (film): 1696, 1382, 1281, 1192, 1138 cm⁻¹.]

1H NMR (300 MHz, CDCl₃–TMS): δ = 8.22 (s, 1 H, ArH), 8.16 (d, 1 H, J = 7.9, ArH), 7.96 (d, 1 H, J = 7.9, ArH), 7.78 (t, 1 H, J = 7.9, ArH), 4.46 (t, 2 H, J = 5.8, CH₂O), 3.55 (t, 2 H, J = 5.8, CH₃S), 3.50 (br s, 1 H, OH).

**13C NMR (75 MHz, CDCl₃–TMS):** δ_c = 140.44 (ArC), 131.80 (q, J_{CF} = 32.5, CF₃), 130.67, 130.25, 125.12, 125.07 (ArCH), 122.96 (q, J_{CF} = 272.2, CCF₃), 58.24 (CH₂O), 56.08 (CH₃S).

MS: m/z (%) = 254 (M⁺, 8), 225 (58), 226 (42), 227 (12), 194 (55), 193 (49), 192 (110), 180 (12). Yields and physical data are included in Tables 2 and 5. Spectral and analytical data follow.

**2-[3,5-Bis(trifluoromethyl)phenylsulfonyl]ethyl 3-Phenylpropanoate (4aa)**

[IR (film): 1744, 1358, 1336, 1281, 1182, 1146, 1111 cm⁻¹.]

1H NMR (300 MHz, CDCl₃–TMS): δ = 8.39 (s, 2 H, ArH), 8.17 (s, 1 H, ArH), 7.30–7.14 (m, 3 H, ArH), 7.09 (d, 2 H, J = 6.9, ArH), 4.47 (t, 2 H, J = 5.9, CH₂O), 3.47 (t, 2 H, J = 5.9, CH₃S), 2.81 (t, 2 H, J = 6.9, CH₂CO), 2.39 (t, 2 H, J = 7.6, PhCH₃).

13C NMR (75 MHz, CDCl₃–TMS): δ_c = 171.85 (C=O), 142.50, 139.72 (ArC), 133.26 (q, J_{CF} = 34.0, 2 × CF₃), 128.65, 128.47, 128.10, 127.54, 126.40 (ArCH), 122.25 (q, J_{CF} = 274.4, 2 × CCF₃), 57.13 (CH₂O), 55.22 (CH₃S), 30.44 (CH₃Ph).

MS: m/z (%) = 454 (M⁺, 1), 453 (M⁺–1, 51), 277 (11), 213 (97), 133 (12), 131 (10), 107 (19), 105 (100), 104 (12), 103 (26), 91 (45), 79 (19), 79 (12), 72 (28).

HRMS: m/z calcd for C₁₀H₁₄SO₄F₆: 456.0674 (M⁺); found: 456.0653.

**2-[3,5-Bis(trifluoromethyl)phenylsulfonyl]ethyl (E)-3-Phenyl-2-propenoate (4ab)**

[IR (film): 1696, 1382, 1281, 1192, 1138 cm⁻¹.]

1H NMR (300 MHz, CDCl₃–TMS): δ = 8.41 (s, 2 H, ArH), 8.05 (s, 1 H, ArH), 7.51–7.35 (m, 6 H, ArH and CH₃S), 6.01 (d, 1 H, J = 16.1, CH₃S), 4.60 (t, 2 H, J = 5.6, CH₂O), 3.70 (t, 2 H, J = 5.6, CH₃S).

13C NMR (75 MHz, CDCl₃–TMS): δ_c = 165.75 (C=O), 142.70, 139.72 (ArC), 146.53, 115.58 (CH=CH₂), 133.29 (q, J_{CF} = 34.0, 2 × CF₃), 130.89, 128.96, 128.93, 128.65, 128.14 (ArCH₂), 122.25 (q, J_{CF} = 273.3, 2 × CCF₃), 57.59 (CH₂O), 55.38 (CH₃S).

MS: m/z (%) = 452 (M⁺, 5), 213 (95), 175 (10), 148 (11), 147 (12), 103 (45), 102 (100), 77 (97).

HRMS: m/z calcd for C₁₀H₁₄O₄F₆: 452.0517 (M⁺); found: 452.0529.
2-(3-Trifluoromethyl)phenylsulfonyl)ethyl 3-Phenylpropanoate (4ba)

IR (film): 1716, 1637, 1327, 1277, 1142, 1073 cm⁻¹.

1H NMR (300 MHz, CDCl₃–TMS): δ = 8.03 (d, 2 H, ArH), 8.15 (d, 2 H, J = 7.9, ArH), 7.86 (d, 1 H, J = 7.9, ArH), 7.71 (t, 1 H, J = 7.9, ArH). 7.49–7.39 (m, 5 H, ArH and CH=), 6.06 (d, 1 H, J = 16.1, CH=), 4.95 (t, 2 H, J = 5.8, CH₂O), 3.60 (t, 2 H, J = 5.8, CH₂S).

13C NMR (75 MHz, CDCl₃–TMS): δ = 165.90 (C=O), 140.99, 133.81 (ArC), 146.10, 116.15 (CH=CH), 132.29 (q, Jₑ₋₋₋C = 34.0, 2 x CF₃), 131.53, 130.75, 130.53, 130.17, 128.95, 128.14, 125.39 (ArCH), 122.15 (q, Jₑ₋₋₋C = 273.2, 2 x CCF₃), 57.68 (CH₂O), 55.31 (CH₂S).

HRMS: m/z calc for C₁₇H₁₅SO₂Cl: 384.0643 (M⁺); found: 384.0639.

2-(4-Nitrophenylsulfonyl)ethyl 3-Phenylpropanoate (4ca)

IR (KBr): 1733, 1532, 1349, 1291, 1229, 1145, 1081 cm⁻¹.

1H NMR (300 MHz, CDCl₃–TMS): δ = 8.37 (d, 2 H, J = 8.7, ArH), 8.07 (d, 2 H, J = 8.7, ArH). 7.33–7.06 (m, 5 H, ArH), 4.43 (t, 2 H, J = 5.9, CH₂O), 3.47 (t, 2 H, J = 5.9, CH₂S), 2.82 (t, 2 H, J = 7.7, CH₂O), 2.38 (t, 2 H, J = 7.7, PhCH₂).

13C NMR (75 MHz, CDCl₃–TMS): δ = 171.93 (C=O), 150.88, 144.92, 139.85 (ArC), 129.64, 128.53, 128.11, 126.44, 124.41 (ArCH), 57.18 (CH₂O), 55.00 (CH₂S), 35.27 (CH₂O), 30.44 (PhCH₂).

MS: m/z (%): 363 (M⁺, 3), 308 (68), 186 (27), 140 (75), 122 (100), 107 (19), 106 (19), 105 (70), 104 (15), 103 (90), 39 (31), 84 (17), 81 (11), 79 (62), 78 (11), 77 (37), 76 (65), 65 (16).

HRMS: m/z calc for C₁₇H₁₅NO₃S: 363.0776 (M⁺); found: 363.0768.

2-(4-Nitrophenylsulfonyl)ethyl (E)-3-Phenyl-2-propenoate (4eb)

IR (KBr): 1712, 1628, 1529, 1328, 1300, 1262, 1141, 1079 cm⁻¹.

1H NMR (300 MHz, CDCl₃–TMS): δ = 8.39 (d, 2 H, J = 8.5, ArH), 8.16 (d, 2 H, J = 8.5, ArH), 7.48–7.35 (m, 6 H, ArH, CH=), 6.03 (d, 1 H, J = 15.9, CH=), 4.59 (t, 2 H, J = 5.5, CH₂O), 3.63 (t, 2 H, J = 5.5, CH₂S).

13C NMR (75 MHz, CDCl₃–TMS): δ = 165.70 (C=O), 150.82, 145.24, 133.51 (ArC), 146.18, 115.93 (CH=CH₂), 130.94, 129.73, 129.03, 127.99, 124.43 (ArCH), 57.51 (CH₂O), 55.20 (CH₂S).

MS: m/z (%): 361 (M⁺, 99), 170 (15), 147 (98), 102 (100), 77 (27), 76 (14), 75 (11), 56 (41).

HRMS: m/z calc for C₁₇H₁₅NO₃S: 361.0620 (M⁺); found: 361.0637.

2-(3,4-Dichlorophenylsulfonyl)ethyl 3-Phenylpropanoate (4da)

IR (KBr): 1743, 1302, 1287, 1141, 1098, 833, 698 cm⁻¹.

1H NMR (300 MHz, CDCl₃–TMS): δ = 8.00 (s, 1 H, ArH), 7.70 (d, 1 H, J = 8.4, ArH), 7.62 (d, 1 H, J = 8.4, ArH), 7.31–7.12 (m, 5 H, ArH), 4.42 (t, 2 H, J = 6.0, CH₂O), 3.42 (t, 2 H, J = 6.0, CH₂S), 2.83 (t, 2 H, J = 7.5, CH₂CO), 2.43 (t, 2 H, J = 7.5, PhCH₂).

13C NMR (75 MHz, CDCl₃–TMS): δ = 171.94 (C=O), 139.88, 139.14, 139.08, 134.02 (ArC), 131.34, 130.17, 128.49, 128.14, 127.17, 126.35 (ArCH), 57.32 (CH₂O), 55.11 (CH₂S), 35.24 (CH₂O), 30.48 (PhCH₂).

MS: m/z (%): 388 [(M + 2)⁺, 2], 386 (M⁺, 4), 195 (19), 145 (99), 109 (11), 105 (100), 103 (20), 91 (39), 79 (14).

HRMS: m/z calc for C₁₇H₁₄NO₃Cl: 386.0146 (M⁺); found: 386.0146.

2-(4-Nitropyridinesulfonyl)ethyl (E)-3-Phenyl-2-propenoate (4db)

IR (film): 1705, 1638, 1323, 1298, 1181, 1144, 827, 721 cm⁻¹.

1H NMR (300 MHz, CDCl₃–TMS): δ = 8.04 (d, 1 H, J = 2, ArH), 7.76 (dd, 1 H, J = 8.5, 2.1, ArH), 7.61 (dd, 1 H, J = 8.5, 2.1, ArH), 7.49–7.37 (m, 6 H, ArH, CH=), 6.10 (d, 1 H, J = 16.1, CH=), 4.58 (t, 2 H, J = 5.6, CH₂O), 3.57 (t, 2 H, J = 5.6, CH₂S).

13C NMR (75 MHz, CDCl₃–TMS): δ = 165.82 (C=O), 139.45, 139.08, 134.11, 133.76 (ArC), 146.20, 116.11 (CH=CH), 131.37, 130.78, 130.30, 128.94, 128.21, 127.23 (ArCH), 57.68 (CH₂O), 55.34 (CH₂S).

MS: m/z (%): 386 [(M + 2)⁺, 2], 385 [(M + 1)⁺, 1], 384 (M⁺, 28), 209 (11), 195 (12), 175 (67), 147 (99), 145 (99), 104 (34), 103 (100).

HRMS: m/z calc for C₁₇H₁₄NO₃Cl: 349.0301 (M⁺); found: 349.0351.
**2-[3,5-Bis(trifluoromethyl)phenylsulfonyl]ethyl Butyrate (4ac)**

IR (film): 1744, 1359, 1337, 1281, 1181, 1146, 1107 cm⁻¹.

MS: m/z (%) = 433 [M + 1]⁺, 15, 442 (M⁺, 56), 279 (10), 277 (18), 213 (99), 194 (12), 165 (100), 163 (10), 122 (12), 120 (77), 92 (16).

HRMS: m/z calcd for C₁₆H₁₇SO₂F₆N₂⁺: 442.0424 (M⁺); found: 442.0430.

**2-[3,5-Bis(trifluoromethyl)phenylsulfonyl]ethyl 2-Bromopropionate (4ad)**

IR (film): 1749, 1359, 1321, 1181, 1146, 1108 cm⁻¹.

MS: m/z (%) = 323 [M – CF₃]⁻, 19, 305 (35), 277 (79), 273 (23), 261 (35), 214 (27), 213 (67), 194 (19), 163 (14), 115 (100), 91 (12), 75 (12), 71 (47), 70 (98), 69 (14).


**2-[3-(4-Cyanophenylcarboxyloxy)ethylsulfonyl]-3,5-di(trifluoromethyl)benzene (4ae)**

IR (KBr): 2229, 1734, 1333, 1279, 1141, 1113 cm⁻¹.

**2-[3-(4-Cyanophenylcarboxyloxy)ethylsulfonyl]-2,4-di(trifluoromethyl)benzene (4af)**

IR (film): 1724, 1609, 1334, 1280, 1178, 1145, 1090 cm⁻¹.

**2-[3-(4-Cyanophenylcarboxyloxy)ethylsulfonyl]ethyl 2,4-Dimethoxybenzoate (4aj)**

IR (film): 1742, 1388, 1297, 1186, 1147, 1106 cm⁻¹.

HRMS: m/z calcd for C₁₆H₁₇SO₂F₆N₂⁺: 321.0020 (M⁺); found: 321.0098.

**2-[3-(4-Cyanophenylcarboxyloxy)ethylsulfonyl]ethyl 4-(1,5-Dihydro-6-pyrenyl)butanoate (4ai)**

IR (film): 1742, 1388, 1297, 1186, 1147, 1106 cm⁻¹.
1H NMR (300 MHz, CDCl3–TMS): δ = 8.83 (s, 2 H, ArH), 8.18 (s, 1 H, ArH), 7.76 (d, 2 H, J = 7.4, ArH), 7.56–7.50 (m, 2 H, ArH), 7.43–7.19 (m, 8 H, ArH), 7.06 (d, 1 H, J = 5.8, ArH), 5.15 (d, 1 H, J = 7.7, NH), 4.58–4.27 (m, 5 H, CH2CH2O, CH2CH2O, CH2CH(O), 4.18 (t, 1 H, J = 6.7, CHN), 3.50–3.30 (m, 2 H, CH2S), 3.01–2.95 (m, 2 H, PhCH2).

13C NMR (75 MHz, CDCl3–TMS): δ = 171.01, 154.43 (C=O), 143.71, 143.64, 142.05, 141.29, 134.29, 127.88 (ArC), 133.43 (q, JCF = 35.1, 2 × CF3), 129.10, 128.10, 128.62, 127.93, 127.72, 127.33, 127.04, 125.03, 124.97, 119.98 (ArCH), 122.26 (q, JCF = 273.3, 2 × CF3), 67.00 (CH2CH2O), 57.57 (CH2CH(O), 54.90 (CH2S), 54.75 (CHN), 47.06 (CHC), 37.91 (PhCH2).

MS: m/z (%) = 691 (M+), 425 [M – NHFmoc]+, 452 (8), 261 (46), 213 (20), 179 (55), 178 (43), 166 (33), 165 (53), 104 (25), 91 (65), 57 (100), 55 (37).

HRMS: m/z calc for C34H27SO6F6N: 691.1463 (M+); found: 691.1431.

Anal. Calc for C34H27SO6F6N: C, 59.03; H, 3.94; S, 4.63; N, 2.03. Found: C, 58.97; H, 3.90; S, 4.49; N, 2.06.

2-[3,5-Bis(trifluoromethyl)phenylsulfonyl]ethyl 2-(6-Methoxy-2-naphthyl)propanoate (4ak)

IR (film): 1736, 1627, 1335, 1278, 1142, 1100, 1026 cm–1.

1H NMR (300 MHz, CDCl3–TMS): δ = 8.37 (s, 2 H, ArH), 8.14 (s, 1 H, ArH), 7.66 (d, 2 H, J = 2.7, ArH), 7.63 (s, 1 H, ArH), 7.25–7.05 (m, 3 H, ArH), 4.8–5.43 (m, 2 H, CH2O), 3.89 (s, 3 H, CH3O), 3.57–3.36 (m, 3 H, CH2S, CH2CH), 1.44 (d, 3 H, J = 7.1, CH2CH).

13C NMR (75 MHz, CDCl3–TMS): δ = 173.82 (C=O), 157.82, 142.43, 134.49, 133.77, 128.80 (ArC), 133.31 (q, JCF = 34.1, 2 × CF3), 129.18, 128.68, 128.62, 127.30, 125.85, 125.67, 119.21, 105.58 (ArCH2), 122.26 (q, JCF = 273.3, 2 × CF3), 57.44 (CH2O), 55.29 (CH2S), 55.24 (CHS), 54.00 (CH2CH), 18.32 (CH2CH).

MS: m/z (%): 536 [M + 2]+, 28, 535 [M + 1]+, 76, 534 (M–H2O)+, 487 (23), 261 (15), 213 (46), 212 (22), 186 (76), 195 (75), 184 (34), 171 (11), 170 (46), 169 (12), 155 (12), 154 (22), 142 (26), 141 (45), 115 (16), 92 (12).

HRMS: m/z calc for C34H27SO6F6N: 691.1463 (M+); found: 691.1431.

4-Nitrophenyl Vinyl Sulfone (5e)

IR (KBr): 1607, 1531, 1305, 1151 cm–1.

1H NMR (300 MHz, CDCl3–TMS): δ = 8.41 (d, 2 H, J = 8.6, ArH), 8.11 (d, 1 H, J = 7.9, ArH), 7.91 (d, 1 H, J = 7.9, ArH), 7.74 (t, 1 H, J = 7.9, ArH), 7.23 (dd, 1 H, J = 16.5, 9.5, CH2=CH), 6.65 (d, 1 H, J = 16.5, 1 × CH2=CH), 6.16 (d, 1 H, J = 9.5, 1 × CH2=CH).

13C NMR (75 MHz, CDCl3–TMS): δ = 140.89 (ArC), 137.66 (CH=CH), 131.98 (q, JCF = 34.0, 2 × CF3), 131.14, 130.25, 130.19, 124.91 (ArCH), 129.29 (CH2=CH), 123.00 (q, JCF = 273.3, 2 × CF3).

MS: m/z (%): 209 [M – CH2=CH]+, 13, 193 (11), 145 (100), 111 (17).

HRMS: m/z calc for C16H12O5S2: 363.0119; found: 363.0119.
1H NMR (300 MHz, CDCl₃–TMS): δ = 7.89 (s, 1 H, ArH), 7.68–7.53 (m, 2 H, ArH), 6.60 (dd, 1 H, J = 16.5, 9.8, CH₂=CH), 6.43 (d, 1 H, J = 16.5, 1 × CH₂=CH), 6.07 (d, 1 H, J = 9.8, 1 × CH₂=CH).

13C NMR (75 MHz, CDCl₃–TMS): δ = 139.27, 138.53, 133.81 (ArC); 137.51 (CH₂=CH), 131.34 (CH₂=CH), 129.65, 129.20, 126.84 (ArCH).

MS: m/z (%) = 239 [(M + 3)⁺, 4], 238 [(M + 2)⁺, 4], 237 [(M + 1)⁺, 3], 236 (M⁺, 6), 211 (32), 209 (60), 208 (31), 207 (60), 206 (91), 205 (93), 204 (76), 195 (28), 193 (45), 181 (17), 180 (10), 179 (95), 178 (15), 177 (100), 172 (12), 171 (24), 170 (32), 169 (66), 161 (13), 159 (12), 149 (12), 148 (17), 147 (69), 146 (22), 145 (84), 144 (34), 143 (14), 142 (94), 135 (15), 134 (29), 133 (20), 111 (25), 110 (16), 109 (55), 107 (14), 97 (12), 75 (28), 74 (21), 69 (15), 63 (11), 59 (13), 57 (18).

1-(2-Methoxyethylsulfonyl)-3,5-bis(trifluoromethyl)benzene (6)

IR (film): 1365, 1285, 1170, 1139 cm⁻¹.

Mp 66–67 °C.

1H NMR (300 MHz, CDCl₃–TMS): δ = 8.39 (s, 2 H, ArH), 8.13 (s, 1 H, ArH), 3.81 (t, 2 H, J = 5.2, CH₃O), 3.46 (t, 2 H, J = 5.2, CH₃), 3.18 (s, 3 H, CH₃O).

13C NMR (75 MHz, CDCl₃–TMS): δ = 143.32 (ArC), 132.67 (q, 1C = 235.3, 2 × CF₃), 65.89 (CH₂O), 58.53 (CH₃O), 56.84 (CH₂S).

Acknowledgement

This work has been supported by the Dirección General de Investigación of the Ministerio de Ciencia y Tecnología (MCYT), project: (BQU2001-0724-CO2-01). D. A. thanks the Spanish Ministerio de Ciencia y Tecnología (MCYT) for a contract under the program Ramón y Cajal.

References

(b) Kocienski, P. J. Protective Groups; Thieme: Stuttgart, 1994.
(j) Theodoridis, G. Tetrahedron 2000, 56, 2339.
(k) Albericio, F. Biopolymers (Peptide Science) 2000, 55, 123.


8. Commercially available compounds.


