Pergamon

Tetrahedron 55 (1999) 237–254

TETRAHEDRON

Synthetic and Photochemical Studies of *N*-Arenesulfonyl Amino Acids

George Papageorgiou and John E.T. Corrie*

National Institute for Medical Research, The Ridgeway, Mill Hill, London NW7 1AA, U.K.

Received 26 August 1998; revised 12 October 1998; accepted 29 October 1998

Abstract: Near-UV irradiation of *N*-arenesulfonyl amino acids in aqueous solution in the presence of a water-soluble 1,5-dialkoxynaphthalene as light absorber and single electron source results in cleavage of the sulfonamide with very sub-stoichiometric release of the intact amino acid because of concurrent decarboxylation during photocleavage. In compounds with a single carboxylate group *ortho* to the sulfonamide this decarboxylation is significantly suppressed, presumably because the additional carboxylate is a preferred target for the oxidative decarboxylation. However, release of free amino acid is at best 30% of the converted starting material and the yield is not further improved if the sulfonamide is flanked by two carboxylate groups. The data suggest that fragmentation of the initially generated sulfonamide radical anion occurs by two pathways, only one of which can be intercepted by an *ortho*-carboxylate. Synthetic routes to the 2,6-disubstituted arenesulfonamides are based on *ortho*-directed metalation reactions followed by quenching with SO_2 and efficient conversion of the resulting arenesulfinates to arenesulfonyl chlorides. © 1998 Elsevier Science Ltd. All rights reserved.

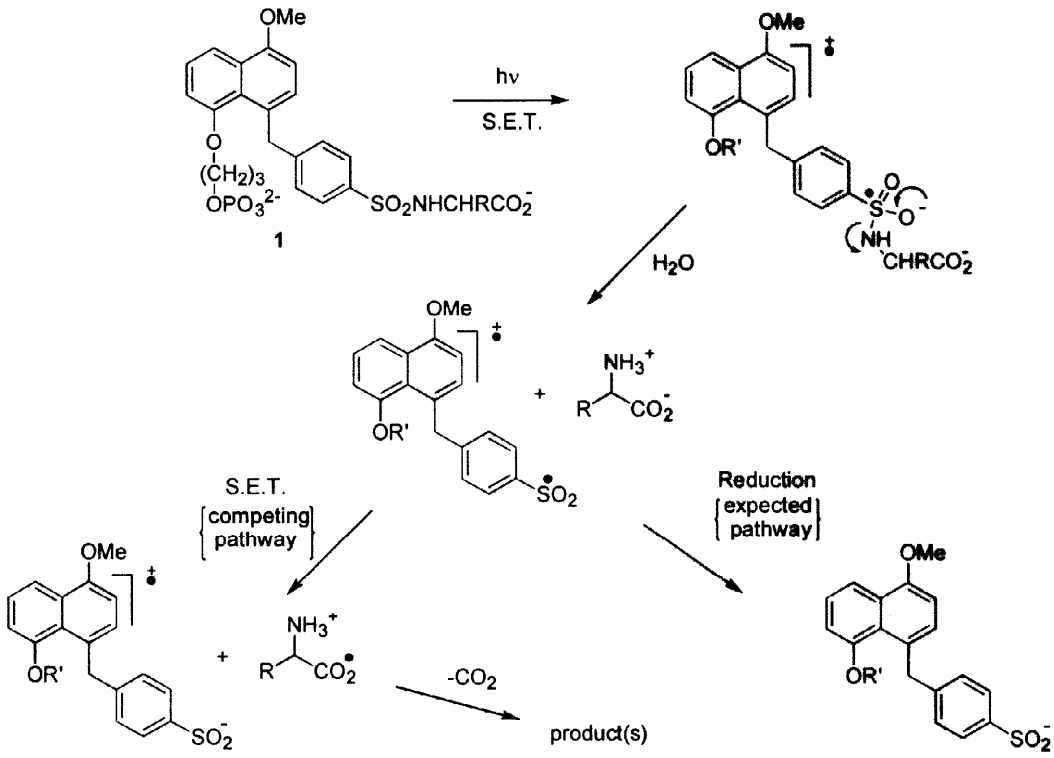
Keywords: Amino acids and derivatives; Decarboxylation; Photochemistry; Sulfonamides

INTRODUCTION

As part of our continuing development and application of photolabile precursors of biological effector molecules,[1] colloquially known as caged compounds,[2] we required reagents that would release neuroactive amino acids, particularly L-glutamate, upon irradiation. Other groups[3-5] have shared this goal with us[6,7] but compounds meeting the requirements of fast (sub-millisecond), efficient and localised release of an amino acid, while themselves being stable to hydrolysis and having no agonist or antagonist properties, have remained elusive. Based on earlier studies by Hamada *et al.*,[8] we have described photolabile sulfonamides that appeared promising in terms of rapid and efficient photoconversion but that released grossly sub-stoichiometric amounts of intact α-amino acids because of concurrent decarboxylation during photolysis.[7] Suggested mechanisms of the expected reaction and the competing decarboxylation are shown in Scheme 1. For the glycine derivative **1** (R = H) the yield of free glycine upon photolysis with near-UV light was only 6% of the converted starting compound. Decarboxylation could not be prevented by addition of a large excess of exogenous carboxylate salts (acetate or phenylacetate) but we suggested[7] that installation of an intramolecular "sacrificial" carboxylate near the sulfonamide group might efficiently intercept the reactive sulfonyl radical shown in Scheme 1, thereby enhancing the yield of intact amino acid. Synthesis and photochemistry of five compounds bearing one or two such carboxylate groups are now reported. Photochemical results from these

0040-4020/99/$ - see front matter © 1998 Elsevier Science Ltd. All rights reserved.
PII: S0040-4020(98)01029-1

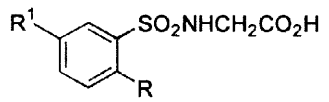
compounds indicate that this interception strategy is effective but that the photocleavage mechanism is more complex than originally proposed.[8]



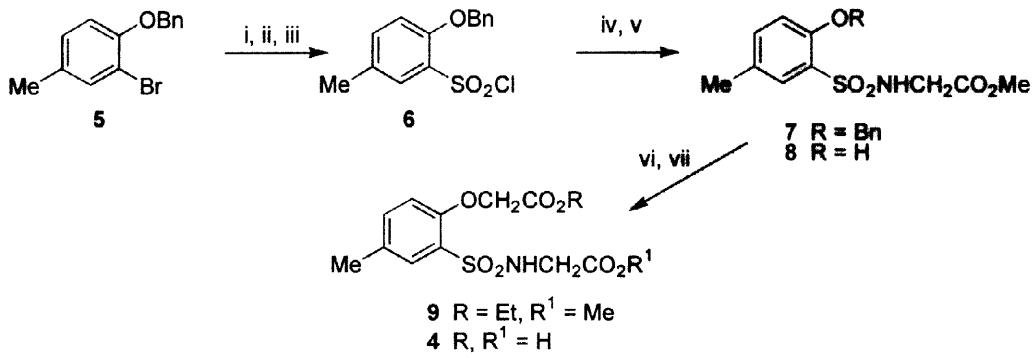
Scheme 1

RESULTS AND DISCUSSION

To evaluate our strategy we proposed to study several attachment modes of a potential sacrificial carboxylate group and to minimise the synthetic effort we changed from the intramolecular photochemistry shown in Scheme 1 to an intermolecular version, i.e. with the light acceptor/electron donor as a separate molecule to the arenesulfonamide. This intermolecular photochemistry has been previously established by Hamada *et al.*[8a] As indicated in Scheme 1, we felt that only the sulfonyl moiety would be involved in the decarboxylation and therefore envisaged that the intermolecular reaction, although less efficient, would validly probe the effects of carboxylate substitution. In practice it transpired that the intermolecular variant allowed some additional insight on the photolysis mechanism (see below). For simplicity, glycine was used as the model amino acid throughout most of this work and we initially made compounds **2**, **3** and **4** that were derivatives of benzoic, phenylacetic and phenoxyacetic acids respectively. Compounds **2** and **3** were obtained by minor variations of published procedures (see Experimental). Compound **4** was prepared as shown in Scheme 2.

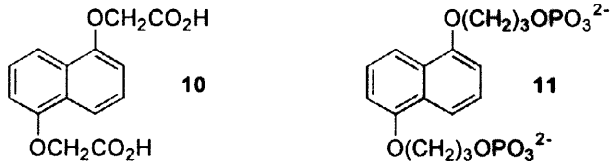


2 R = CO_2H, R^1 = H
3 R = CH_2CO_2H, R^1 = H
4 R = OCH_2CO_2H, R^1 = Me



Scheme 2: *Reagents*; i) *n*-BuLi-TMEDA; ii) SO_2; iii), NCS; iv) Methyl glycinate.HCl-NMM; v) H_2-Pd/C; vi) $BrCH_2CO_2Et$-DIPEA; vii) NaOH

The photochemistry of sulfonamides **2-4** had to be studied in aqueous solution, since the intended application was to living biological systems, and a water-soluble 1,5-dialkoxynaphthalene was needed as the light-absorbing co-reagent. The known bis-carboxylic acid **10** and the bis-phosphate **11** were prepared and examined for photostability in pH 7 aqueous solution under near-UV irradiation. Under a standard set of conditions used throughout this work and in the presence of atmospheric oxygen, 73% of the bis-carboxylate **10** was destroyed during a 10 min irradiation, while only 21% of the bis-phosphate **11** was destroyed. The greater instability of **10** probably arises from photo-decarboxylation, as has been described for other aryloxyacetic acids.[9] All subsequent experiments therefore used bis-phosphate **11** as the co-reagent.



Equimolar pH 7 aqueous solutions of **11** with each of the three sulfonamides **2-4** in turn were irradiated and consumption of the sulfonamides was monitored by HPLC. As a control, a parallel experiment was performed with *N*-tosylglycine. In all cases glycine formation was monitored by quantitative amino acid analysis. All photolyses were conducted in the absence of a reducing agent such as ascorbate,[7,8a] since the aim was to determine the efficacy of the intramolecular carboxylate group. Results are shown in Table 1, which gives corresponding data for irradiation in the absence of the naphthalene **11**. Several features are apparent.

First, the efficiency of glycine release (i.e. fractional formation of glycine per molecule of photolysed sulfonamide) from *N*-tosylglycine was very low, in agreement with the intramolecular results.[7] Second, photolysis of each of **2-4** in the presence of the naphthalene **11** gave a substantially higher efficiency of glycine release (up to ~7-fold) than was obtained from *N*-tosylglycine, suggesting that the intramolecular carboxylate group was partially effective at intercepting decarboxylation of the photoreleased amino acid.

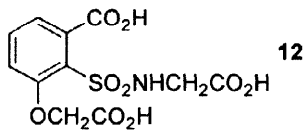
Third, the different compounds showed substantial differences in their photosensitivity, e.g. **2** was only one-third photolysed in 15 min while **4** was almost two-thirds photolysed in 3 min. Lastly each compound except *N*-tosylglycine was photolysed to a similar extent whether or not **11** was present, though in every case the yield of photoreleased glycine was greater when **11** was present. Features of these results are discussed below in parallel with the data of Table 2.

Table 1. Theoretical and actual product yields for photolysis of *N*-tosylglycine and compounds **2-4**

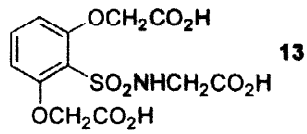
Compound	Photolysis Time (min)	11 Present	% Photolysis[a]	Glycine Yield (%)[b]	Actual Yield[c] / Theoretical Yield
N-Tosylglycine	10	Yes	39.8	1.6	0.04
N-Tosylglycine	10	No	0	0	-
2	15	Yes	33.7	10.3	0.31
2	15	No	31.2	4.1	0.13
3	3	Yes	27.0	5.2	0.19
3	3	No	24.5	0.6	0.02
4	3	Yes	63.7	12.9	0.20
4	3	No	78.5	7.8	0.10

[a] Consumption of starting material measured by HPLC
[b] Identified and quantified by amino acid analysis
[c] Ratio of measured % yield of glycine to % photolysis of starting material

Given the partial success of the sacrificial carboxylate strategy, we considered whether two carboxylate groups flanking the sulfonamide would achieve further improvement and set out to synthesise the two disubstituted sulfonamides **12** and **13**. In the event, synthesis of these highly functionalised 1,2,3-trisubstituted benzenes required some innovation, so the results described below may have wider application. The successful syntheses of **12** and **13** were based on two pivotal reactions: the use of directed *ortho*-metalation[10] to achieve the required 1,2,3-substitution pattern and then the convenient preparation of sulfonyl chlorides by two-phase oxidation of sulfinates with NCS.[7]



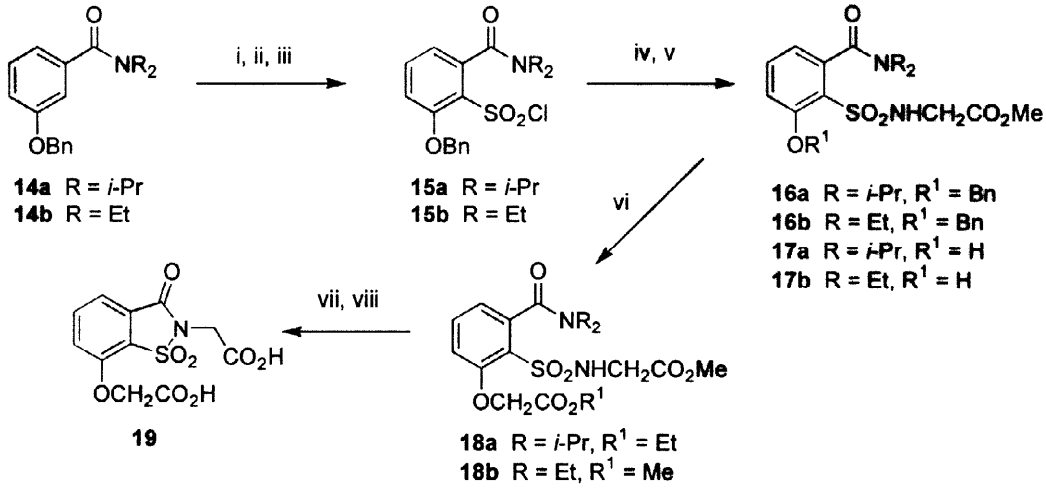
12



13

Synthesis of **12** (Scheme 3) began with *tert*-butyl lithium–TMEDA metalation of the *N,N*-diisopropyl-benzamide **14a**, followed by quenching with sulfur dioxide. Oxidation of the crude sulfinate gave the crystalline sulfonyl chloride **15a**, from which the sulfonamide **16a** was readily obtained. Hydrogenolysis of the benzyl ether and alkylation of the derived phenol **17a** smoothly gave the fully-protected derivative **18a** but we could not hydrolyse the diisopropyl amide under any conditions that did not cause gross degradation. The problem of this difficult hydrolysis has been recognised as a drawback of the directed *ortho*-metalation

strategy as applied to *N,N*-dialkylbenzamides.[10] However, *O*-alkylation of amides with a trialkyloxonium fluoroborate followed by acidic or alkaline hydrolysis has been used in other contexts to effect amide cleavage.[11] In model studies, we found the *N,N*-diisopropylbenzamide **14a** was unreactive towards Et_3OBF_4, but with the same reagent the diethylamide **14b** was ~50% converted to the corresponding ethyl ester (after acidic hydrolysis). Therefore the sequence of Scheme 3 was repeated in the *N,N*-diethyl (**b**) series, and treatment of **18b** with Et_3OBF_4 followed by aqueous H_2SO_4 gave the benzisothiazolone **19** in 91% yield.

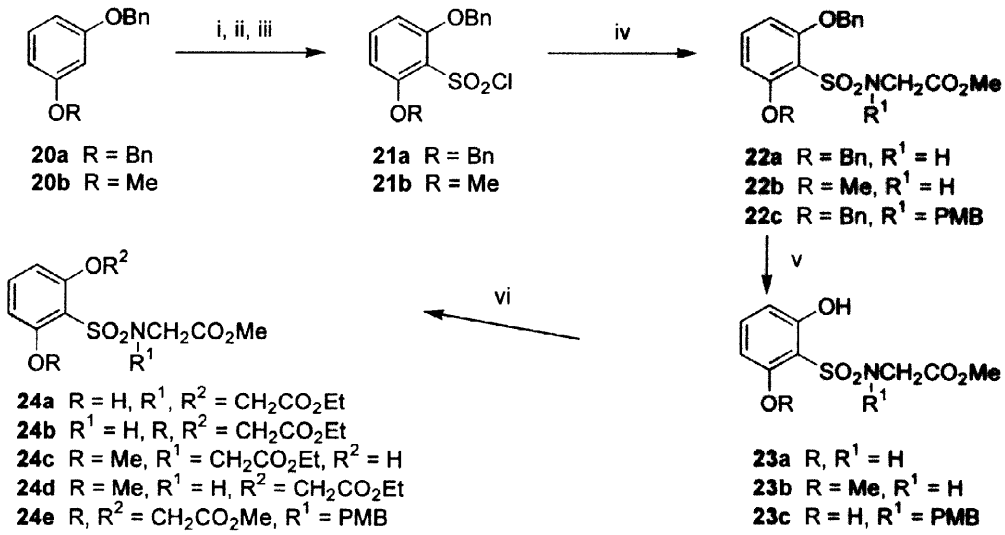


Scheme 3: *Reagents*; i) *t*-BuLi-TMEDA; ii) SO_2; iii) NCS; iv) Methyl glycinate.HCl-NMM; v) H_2-Pd/C; vi) $BrCH_2CO_2R$-DIPEA; vii) Et_3OBF_4; viii) aq. H_2SO_4

Cleavage of dialkylbenzamides assisted by the introduced *ortho*-substituent is a common feature of directed *ortho*-metalation strategies[10] and the additional activation provided here by *O*-alkylation of the amide may be useful in other applications of the method. In the present case the simultaneous hydrolysis of the two ester groups elsewhere in the molecule was a convenient collateral benefit. Alkaline hydrolysis of **19** gave the salt of the required compound **12**, which was stable at neutral pH but slowly recyclised to **19** under even mildly acidic conditions (pH <4). Thus the pure free acid form of **12** could not be isolated and its sodium salt was generated as required without separation from inorganic salts (see Experimental).

For synthesis of diacid **13** (Scheme 4), directed *ortho*-metallation of **20a** followed by SO_2 quench and NCS oxidation cleanly gave the sulfonyl chloride **21a**, which was converted to the *N*-sulfonylglycine ester **22a**. Hydrogenolysis over Pd–C readily gave the resorcinol **23a** but alkylation using $BrCH_2CO_2Et$–DIPEA gave the *O,N*- and *O,O*-disubstituted compounds **24a** and **24b**, respectively, in an isolated ratio of 1.8:1. It appeared that the first alkylation was at one of the phenolic groups but that the second occurred preferentially at the sulfonamide nitrogen. To confirm this, one phenolic group was blocked by repeating the reaction sequence with the benzyl methyl ether **20b**, which ultimately gave the monomethoxysulfonamide **23b**. Treatment of this compound with $BrCH_2CO_2Et$–DIPEA gave the *N*- and *O*-alkylated products **24c** and **24d**,

respectively, in an isolated ratio of 3.6:1, thereby confirming the preferential *N*-alkylation. Relative preferences for *O*- versus *N*-alkylation in these compounds are evidently finely balanced since under identical conditions the phenolic sulfonamides **17a** and **17b** underwent only clean *O*-alkylation, as described above.



20a R = Bn
20b R = Me

21a R = Bn
21b R = Me

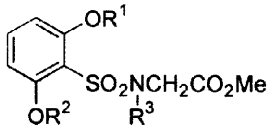
22a R = Bn, R^1 = H
22b R = Me, R^1 = H
22c R = Bn, R^1 = PMB

23a R, R^1 = H
23b R = Me, R^1 = H
23c R = H, R^1 = PMB

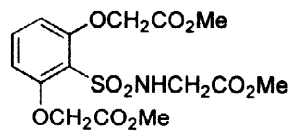
24a R = H, R^1, R^2 = CH_2CO_2Et
24b R^1 = H, R, R^2 = CH_2CO_2Et
24c R = Me, R^1 = CH_2CO_2Et, R^2 = H
24d R = Me, R^1 = H, R^2 = CH_2CO_2Et
24e R, R^2 = CH_2CO_2Me, R^1 = PMB

Scheme 4: *Reagents*; i) *n*-BuLi-TMEDA; ii) SO_2; iii) NCS; iv) $MeO_2CCH_2NHR^1$-NMM; v) H_2-Pd/C; vi) $BrCH_2CO_2R$-DIPEA

In an attempt to prevent *N*-alkylation, **22a** was *N*-acetylated (Ac_2O–NaOAc) to give **25**, from which the protecting benzyl groups were readily cleaved by hydrogenolysis. The ^1H NMR spectrum of the crude product confirmed structure **26**. However, during attempted crystallisation the acetyl group underwent migration to one of the adjacent phenolic oxygens to give a 1:4 mixture of the *N*- and *O*-acetyl compounds **26** and **27** respectively. The presence of the *O*-acetate was revealed by the appearance of new signals in the ^1H NMR spectrum, e.g. a triplet for the NH at δ 5.84 and a corresponding doublet for the adjacent methylene group at δ 3.84. The methoxy group of the ester also showed an upfield shift from 3.76 to 3.62 ppm. The ratio of the two components was not changed by further heating (1 h reflux in MeCN), confirming that equilibration was complete during the attempted crystallisation. *N*- to *O*-Migration of an acyl group is unusual under neutral or mildly basic conditions but Ellman and co-workers have recently shown that deacylation of *N*-acylsulfonamides can be activated by an *N*-cyanomethyl substituent.[12] The *N*-methoxycarbonylmethyl substituent in **26** has a similar activating effect and the presence of the phenolic groups as suitably sited internal nucleophiles establishes a favorable situation for acyl migration.



25 R^1, R^2 = Bn, R^3 = Ac
26 R^1, R^2 = H, R^3 = Ac
27 R^1, R^3 = H, R^2 = Ac



28

The undesired *N*-alkylation of **23a** was eventually blocked by protecting the nitrogen as its *p*-methoxybenzyl derivative. Thus condensation of the sulfonyl chloride **21a** with methyl *N*-(*p*-methoxybenzyl)glycinate and hydrogenolysis of the *O*-benzyl groups gave the resorcinol derivative **23c** (Scheme 4). No hydrogenolysis of the *N*-PMB substituent was observed under the conditions used. *O*-Alkylation of the two phenolic groups with $BrCH_2CO_2Me$–DIPEA cleanly gave the triester **24e**, from which the *N*-PMB group was readily removed by CAN[13] to give **28**. The required triacid **13** was then obtained by alkaline hydrolysis.

With the target compounds **12** and **13** in hand, their photolysis was examined under the same conditions as for the monosubstituted compounds **2**-**4**, and results are shown in Table 2. Disappointingly, the additional carboxylate group in either of the disubstituted compounds had no additional effect on the fractional release of free glycine from the starting compounds and the maximum conversion efficiency obtained with any of these compounds is 30% for **2** (Table 1).

Table 2. Theoretical and actual product yields for photolysis of compounds **12** and **13**

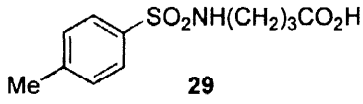
Compound	Photolysis Time (min)	**11** Present	% Photolysis[a]	Glycine Yield (%)[b]	Actual Yield[c] / Theoretical Yield
12	3	Yes	69.8	13.3	0.19
12	3	No	82.3	4.8	0.06
13	3	Yes	52.0	10.4	0.20
13	3	No	63.8	2.8	0.04

[a] Consumption of starting material measured by HPLC
[b] Identified and quantified by amino acid analysis
[c] Ratio of measured % yield of glycine to % photolysis of starting material

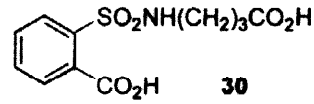
The failure of a second carboxylate group to have an incremental effect, taken together with the 5–7-fold effect of a single carboxylate, suggests that pathways other than as shown in Scheme 1 must be considered for photocleavage of these sulfonamides. At least two such routes may be considered to account for the 70-80% of material that undergoes photolysis (i.e. disappearance of starting material as measured by HPLC) but does not release glycine. The first is that cleavage of the sulfonamide radical anion depicted in Scheme 1 may occur not only as shown to produce a sulfonyl radical and an amine (the mechanism proposed by Hamada *et al.*[8]) but also in the opposite sense to give a sulfinate anion and an aminyl radical. Cleavage of sulfonamide radical anions in this sense has been proposed by Simonet and co-workers[14] and confirmed by them in further work.[15] Formation of the aminyl radical (or its conjugate protonated amino radical cation) of α-amino acids is known to result in decarboxylation[16] and this process is unlikely to be intercepted by a carboxylate group on the departing arenesulfinyl residue. Thus sulfonamide photocleavage mediated by single electron transfer probably takes a dual course, one branch of which is inherently likely to result in destruction of a departing α-amino acid. A second consideration is that all the compounds studied, with the exception of *N*-tosylglycine, were

consumed to a similar extent upon irradiation whether or not the naphthalene **11** was present. Direct excitation is possible because of spectral overlap of the chromophores of the various compounds with the transmission band of the filter used in the irradiations. Notably those compounds with one or two oxygen substituents on the aromatic ring, i.e. **4**, **12** and **13**, that have more intense chromophores overlapping to a greater extent with the irradiating light, undergo more extensive direct photolysis. In all cases the yield of glycine from direct photolysis was substantially lower than from photolysis in the presence of the naphthalene **11**, both in absolute terms and as a fraction of the converted starting material. Arenesulfonamides are known to undergo homolytic photocleavage upon direct irradiation[17] and this would be expected to lead to efficient decarboxylation for the same reason as discussed above.

To determine whether the problems encountered above were specific to α-amino acids, photolysis of compounds **29** and **30** derived from γ-aminobutyric acid was examined in the presence of naphthalene **11**. The ratios of actual to theoretical photolysis yields of GABA were 0.17 and 0.34 for **29** and **30** respectively. The higher release of intact amino acid from *N*-tosylGABA **29** than from *N*-tosylglycine is consistent with our previous observation[7] that β-alanine was released more efficiently than glycine, i.e. a carboxylate group further from the α-position of the amino acid apparently suffers less decarboxylation during photocleavage. Even so, the presence of a carboxyl group *ortho* to the sulfonamide as in **30** results in a 2-fold increase in the efficiency of GABA release but nevertheless, 66% of **30** undergoes photolysis without releasing intact GABA.



29



30

The results described above clearly demonstrate that pathways other than the intended sulfonamide cleavage are available for photodecomposition of these sulfonamides. The present data and those of other workers[14,15] strongly suggest that cleavage of sulfonamide radical anions can occur by heterolysis, as shown in Scheme 1, or by homolysis to generate a sulfinate and an aminyl radical. In addition, for the particular case of compounds studied here, photodecarboxylation[18] of the phenylacetic or phenoxyacetic acid side chains, whether by direct or sensitised irradiation, may consume the compounds without necessarily leading to glycine release. Although we have not sought fully to define the photolysis products of the various sulfonamides described, the results show that these reagents cannot provide an effective means for photorelease of α-amino acids. Even in the most favorable case (compound **2**) the fraction of converted starting material that yields free glycine is only 30% and the remaining proportion seems likely to decompose by way of reactive species that could be significantly damaging to biological samples. The results suggest that photocleavage of arenesulfonamides may merit further study, particularly in view of continued interest in their use as photocleavable protecting groups.[19] Furthermore, the efficient syntheses of sulfonyl chlorides bearing relatively complex substituents as described here may have wider application.

EXPERIMENTAL

General Procedures. Microanalyses were carried out by MEDAC Ltd., Brunel University, Uxbridge, U.K. Amino acid analyses were performed at the Department of Biochemistry, University of Cambridge using a Pharmacia AlphaPlus analyser with ninhydrin detection. ^{1}H NMR spectra were determined in $CDCl_3$ with tetramethylsilane as internal standard unless otherwise stated on JEOL FX90Q or Bruker AM400 WB spectrometers. *J* values are given in Hz. Positive ion FAB mass spectra at high resolution were obtained on a VG ZAB-SE instrument and negative ion spectra at low resolution were obtained by nanoelectrospray on a Thermoquest LCQ ion trap instrument. Merck 9385 silica gel was used for flash chromatography. Organic extracts were dried over Na_2SO_4 and solvents were evaporated under reduced pressure. Sodium or ammonium phosphate buffer solutions were prepared from $NaH_2PO_4{\cdot}2H_2O$ or $NH_4H_2PO_4$ at the specified molarities in water and adjusted to the required pH value with 2 M aq. NaOH. Anion exchange chromatography was performed on a column of DEAE-cellulose (2.5 × 40 cm). Triethylammonium bicarbonate (TEAB) buffer for elution was prepared by bubbling CO_2 into an ice-cold 1 M solution of triethylamine in water until the pH stabilised at ~7.4. Pooled column fractions were evaporated at ~1 mmHg and freed from buffer salts by repeated evaporation with MeOH. For NMR spectroscopy, triethylammonium salts were converted into sodium salts by treatment with Dowex 50 (Na form). HPLC data were obtained on Waters equipment using either a reversed phase column [Merck Lichrosphere RP8 column (Cat. No. 50832)] or an anion exchange column [Whatman Partisphere SAX column, (Cat. No. 4621-0505)]. UV detection was with a Waters 484 tunable wavelength detector at wavelengths given in Table 3. Details of mobile phases are also given in Table 3 and flow rates were 1.5 ml min^{-1} in all cases. The following compounds were prepared by established methods or minor variations thereof: **2**,[20] **3**,[21] **10**,[22] **29**,[23] and **30**.[24]

2-Benzyloxy-5-methylbenzenesulfonyl chloride **6**. A solution of 2-benzyloxy-5-methylbromobenzene **5**[25] (2.77 g, 10 mmol) in dry Et_2O (50 ml) was cooled under nitrogen to -78 °C and treated with TMEDA (1.8 ml, 12 mmol) and 1.6 M *n*-BuLi in hexane (7.5 ml, 12 mmol). The solution was stirred at -78 °C for 1 h and transferred with a PTFE cannula to a vigorously stirred solution of sulfur dioxide (5 ml) in dry Et_2O (50 ml) at -78 °C. A white solid precipitated instantly and the mixture was kept at -78 °C for 15 min, then allowed to warm to rt over 1 h. The solvent was evaporated and the residue was resuspended in dry Et_2O and re-evaporated, then suspended in aq. sodium phosphate (500 mM, pH 6.0; 100 ml) and readjusted to pH 6.0. EtOAc (100 ml) was added and the flask was cooled in an ice bath. *N*-Chlorosuccinimide (4.00 g, 30 mmol) was added and the two-phase mixture was stirred vigorously for 1 h. The organic phase was separated and the aqueous phase was washed with EtOAc. The combined organic phases were washed with water, dried, and evaporated. Flash chromatography [EtOAc–hexanes (1:9)] gave **6** as white crystals (2.19 g, 74%), mp 101 °C (Et_2O–hexanes): IR (Nujol) 1365, 1260 cm^{-1}; ^{1}H NMR (90 MHz) δ 7.76 (d, *J* 2.2, 1H), 7.24-7.56 (m, 6H), 7.01 (d, *J* 8.8, 1H), 5.30 (s, 2H), 2.34 (s, 3H). Calcd for $C_{14}H_{13}ClO_3S$: C, 56.66; H, 4.42. Found: C, 56.59; H, 4.41.

Methyl N-*(2-benzyloxy-5-methylbenzenesulfonyl)glycinate* **7**. Methyl glycinate hydrochloride (2.63 g, 21 mmol) and *N*-methylmorpholine (NMM) (4.25 g, 42 mmol) were added to a solution of **6** (2.08 g, 7 mmol) in MeCN (50 ml) under nitrogen and the mixture was refluxed for 3 h. After cooling to rt the solvent was evaporated and the residue was dissolved in CH_2Cl_2 (120 ml) and washed successively with 2 M aq. HCl, saturated aq. $NaHCO_3$ and water, dried and evaporated. Flash chromatography [EtOAc–hexanes (3:7)] gave **7** as white crystals (1.68 g, 68%), mp 102-103 °C (EtOAc–hexanes): IR (Nujol) 3295, 1745, 1320, 1150 cm^{-1}; ^{1}H NMR (90 MHz) δ 7.68 (d, *J* 2.2, 1H), 7.16-7.56 (m, 6H), 6.94 (d, *J* 8.2, 1H), 5.46 (t, *J* 5.3, 1H), 5.21 (s, 2H), 3.74 (d, *J* 5.3, 2H), 3.57 (s, 3H), 2.31 (s, 3H). Calcd for $C_{17}H_{19}NO_5S$: C, 58.44; H, 5.48; N, 4.01. Found: C, 58.67; H, 5.50; N, 4.00.

Methyl N-*(2-hydroxy-5-methylbenzenesulfonyl)glycinate* **8**. A solution of **7** (1.13 g, 3.2 mmol) in EtOH (100 ml) was stirred with 10% Pd–C (0.2 g) under hydrogen (1 atm) until gas consumption ceased (~10 min). The solution was filtered through Celite and the filtrate was concentrated and re-evaporated from $CHCl_3$ to give **8** as a white solid (1.03 g, 94%), mp 127-129 °C (EtOAc–hexanes): IR (Nujol) 3345, 3285, 1740, 1295, 1135 cm^{-1}; ^1H NMR (90 MHz) δ 9.69 (s, 1H), 7.49 (d, *J* 1.8, 1H), 7.20 (dd, *J* 8.3 and 1.8, 1H), 6.89 (d, *J* 8.3, 1H), 6.60 (br t, *J* 4.8, 1H), 3.74 (d, *J* 4.8, 2H), 3.63 (s, 3H), 2.28 (s, 3H). Calcd for $C_{10}H_{13}NO_5S$: C, 46.33; H, 5.05; N, 5.40. Found: C, 46.36; H, 5.33; N, 5.44.

Methyl N-*[2-(ethoxycarbonylmethoxy)-5-methylbenzenesulfonyl]glycinate* **9**. A solution of **8** (389 mg, 1.5 mmol), DIPEA (388 mg, 3 mmol) and ethyl bromoacetate (501 mg, 3 mmol) in dry MeCN (30 ml) was refluxed for 17 h, cooled to rt and the solvent was evaporated. The residue was dissolved in Et_2O (100 ml) and washed with 2 M aq. HCl and brine, dried and evaporated. Flash chromatography [EtOAc–hexanes (1:1)] gave **9** as white crystals (400 mg, 77%), mp 64-65 °C (Et_2O–hexanes): IR (Nujol) 3240, 1735, 1610, 1330, 1155 cm^{-1}; ^1H NMR (90 MHz) δ 7.64 (d, *J* 1.8, 1H), 7.30 (dd, *J* 8.3 and 1.8, 1H), 6.79 (d, *J* 8.3, 1H), 6.64-6.88 (m, 2H), 4.76 (s, 2H), 4.30 (q, *J* 7.5, 2H), 3.84 (d, *J* 5.7, 2H), 3.53 (s, 3H), 2.33 (s, 3H), 1.72 (t, *J* 7.5, 3H). Calcd for $C_{14}H_{19}NO_7S$: C, 48.69; H, 5.54, N, 4.05. Found: C, 48.72; H, 5.52; N, 4.04.

N-*[2-(Carboxymethoxy)-5-methylbenzenesulfonyl]glycine* **4**. A solution of **9** (363 mg, 1.05 mmol) in 0.2 M methanolic NaOH (10 ml) was refluxed for 2 h, acidified with conc. HCl, saturated with NaCl and extracted with EtOAc. The combined organic phases were washed with brine, dried and evaporated to give **4** as white crystals (273 mg, 86%), mp 154-156 °C (acetone–hexanes): UV (EtOH) λ_{max}/nm 287 (ε/$M^{-1}cm^{-1}$ 2900); UV (25 mM ammonium phosphate, pH 7) λ_{max}/nm 290 (ε/$M^{-1}cm^{-1}$ 3280); IR (Nujol) 3180 br, 1740, 1720, 1325, 1140 cm^{-1}; ^1H NMR (400 MHz) δ 7.65 (d, *J* 1.9, 1H), 7.30 (dd, *J* 8 and 1.9, 1H), 7.02 (t, *J* 5.7, 1H), 6.85 (d, *J* 8, 1H), 4.74 (s, 2H), 3.73 (d, *J* 5.7, 2H), 2.33 (s, 3H), 2.17 (s, 6H, acetone solvent): HRMS (FAB) *m/z* 304.0941 $(M + H)^+$ ($C_{11}H_{13}NO_7S$ + H requires 304.1500). Calcd for $C_{11}H_{13}NO_7S{\cdot}Me_2CO$: C, 46.53; H, 5.30; N, 3.88. Found: C, 46.44; H, 4.97; N, 4.31.

1,5-Bis[3-(dihydroxyphosphoryloxy)propoxy]naphthalene **11**. A solution of 2-methyl-2-butene (2 M in THF; 50.6 ml, 101.25 mmol) was cooled to 0 °C under nitrogen and treated with $BH_3{\cdot}Me_2S$ (10 M in THF; 4.5 ml, 45 mmol). The mixture was stirred at rt for 2 h, cooled in ice and a solution of 1,5-bis(allyloxy)naphthalene[26] (4.81 g, 20 mmol) in dry THF (50 ml) was added dropwise. After 5 min the ice bath was removed and the mixture was stirred at rt for 2.5 h. The solution was cooled in ice and sequentially treated with EtOH (25 ml), water (10 ml), 2 M aq. NaOH (15 ml) and 30% aq. H_2O_2 (10 ml), then refluxed for 1 h. After cooling to rt the solution was poured into water (100 ml) and extracted with CH_2Cl_2. The combined organic phases were washed with water, dried and evaporated to yield *1,5-bis(3-hydroxypropoxy)naphthalene* as white crystals (2.94 g, 53%), mp 150-151 °C (EtOH); IR (Nujol) 3360, 3295 cm^{-1}; ^1H NMR (90 MHz, DMSO-d_6) δ 7.76 (d, *J* 8, 2H), 7.32 (t, *J* 8, 2H), 6.87 (d, *J* 8, 2H), 4.41 (t, *J* 5, 2H, exchanged with D_2O), 4.23 (t, *J* 6, 4H), 3.81 (t after D_2O exchange, *J* 6, 4H), 2.09 (quintet, *J* 6, 4H). Calcd for $C_{16}H_{20}O_4$: C, 69.54; H, 7.30. Found: C, 69.69; H, 7.48.

1*H*-Tetrazole (314 mg, 4.5 mmol) was added under nitrogen to a stirred solution of 1,5-bis(3-hydroxypropoxy)naphthalene (276 mg, 1 mmol) and bis-(2-cyanoethyl) *N,N*-diisopropylphosphoramidite[27] (678 mg, 2.5 mmol) in dry THF (40 ml). After 4 h at rt the mixture was cooled in an ice bath and treated dropwise over 5 min with a solution of *m*-chloroperbenzoic acid (55% peracid; 1.04 g, 3.3 mmol) in CH_2Cl_2 (10 ml). The solution was stirred at 4 °C for 1 h then diluted with CH_2Cl_2 (40 ml) and washed with 10% aq. $Na_2S_2O_5$. The organic phase was separated and the aqueous phase was re-extracted with $CHCl_3$. The combined organic phases were washed successively with 1 M aq. HCl, saturated aq. $NaHCO_3$ and brine, dried and

evaporated under reduced pressure. Flash chromatography [MeOH–EtOAc (3:7)] gave *1,5-bis{3-[bis(2-cyanoethoxy)phosphoryloxy]propoxy}naphthalene* as a white solid (302 mg, 47%), mp 74-75 °C (aq. EtOH); IR (Nujol) 2250, 1270 cm^{-1}; ^1H NMR (90 MHz) δ 7.82 (d, *J* 8, 2H), 7.37 (t, *J* 8, 2H), 6.86 (d, *J* 8 H, 2H), 3.96-4.64 (m, 16H), 2.61 (t, *J* 6, 8H), 2.32 (quintet, *J* 6, 4H). Calcd for $C_{28}H_{34}N_4O_{10}P_2$: C, 51.86; H, 5.28; N, 8.63. Found: C, 51.79; H, 5.34; N, 8.39.

A sample of the bis-phosphotriester (117 mg, 180 μmol) was dissolved in MeOH (27 ml) and 2 M aq. NaOH (3 ml) and kept at 50 °C for 1 h. The solution was concentrated under reduced pressure (~10 ml), diluted with water, adjusted to pH 7 with 1 M aq. HCl and washed with Et_2O. The aqueous solution was diluted with water to a conductivity of 800 μS cm^{-1} and purified by anion exchange chromatography using a linear gradient formed from 10 and 1000 mM TEAB (each 1000 ml). Fractions containing the product, which eluted at ~195 mM TEAB, were processed as described above to afford **11** as its tetrakis(triethylammonium) salt (62 μmol, 34%); negative ion MS *m/z* 435 $(M + 3H)^-$ ($C_{16}H_{18}O_{10}P_2$+ 3H requires 435). The sodium salt had ^1H NMR (400 MHz, D_2O, acetone ref.) δ 7.91 (d, *J* 8, 2H), 7.50 (t, *J* 8, 2H), 7.12 (d, *J* 8, 2H), 4.35 (t, *J* 6, 4H), 4.07 (dt, *J* 6, $J_{H,P}$ 6, 4H), 2.23 (quintet, *J* 6, 4H).

3-Benzyloxy-N,N-*diisopropylbenzamide* **14a**. A solution of 3-benzyloxybenzoic acid[28] (11.41 g, 50 mmol) and $SOCl_2$ (7.3 ml, 100 mmol) in dry benzene (150 ml) was refluxed for 1 h. The solvent was evaporated, the residual oil was dissolved in dry benzene (150 ml) and treated with di-isopropylamine (35 ml, 250 mmol) and the mixture was refluxed for 0.75 h. The solvent was evaporated and the residue was dissolved in Et_2O and washed with 2 M aq. HCl, saturated aq. $NaHCO_3$ and brine, dried and evaporated to give **14a** as white needles (13.6 g, 87%), mp 86-87 °C (hexanes): IR (Nujol) 1620 cm^{-1}; ^1H NMR (90 MHz) δ 7.16-7.52 (m, 6H), 6.80-7.04 (m, 3H), 5.06 (s, 2H), 3.32-3.92 (m, 2H), 0.8-1.60 (m, 12H). Calcd for $C_{20}H_{25}NO_2$: C, 77.14; H, 8.09, N, 4.50. Found: C, 77.08; H, 8.19; N, 4.51.

3-Benzyloxy-N,N-*diethylbenzamide* **14b**. Prepared as for **14a** as a pale viscous oil (22.58 g, 100%) which was used without further purification; IR (film) 1630 cm^{-1}; ^1H NMR (90 MHz) δ 7.06-7.44 (m, 6H), 6.76-7.04 (m, 3H), 5.04 (s, 2H), 2.80-3.72 (m, 4H), 0.72-1.32 (m, 6H).

*2-Benzyloxy-6-(*N,N-*diisopropylcarbamyl)benzenesulfonyl chloride* **15a**. Prepared as for **15b**, white crystals (68%), mp 161 °C (EtOAc–hexanes): IR (Nujol) 1640, 1350 cm^{-1}; ^1H NMR (400 MHz) δ 7.60 (dd, *J* 7.6 and 0.7, 2H), 7.53 (dd, *J* 8.5 and 7.5, 1H), 7.39-7.43 (m, 3H), 7.11 (dd, *J* 8.5 and 0.9, 1H), 6.84 (dd, *J* 7.5 and 0.9, 1H), 5.35 (s, 2H), 3.58 (septet, *J* 6.7, 1H), 3.52 (septet, *J* 6.7, 1H), 1.56 (d, *J* 6.8, 3H), 1.53 (d, *J* 6.8, 3H), 1.24 (d, *J* 6.8, 3H), 1.07(d, *J* 6.8, 3H). Calcd for $C_{20}H_{24}ClNO_4S$: C, 58.60; H, 5.90; N, 3.42. Found: C, 58.57; H, 5.91; N, 3.44.

*2-Benzyloxy-6-(*N,N-*diethylcarbamyl)benzenesulfonyl chloride* **15b**. A solution of **14b** (3.07 g, 10.8 mmol) in dry Et_2O (100 ml) was cooled under nitrogen to -78 °C and treated with TMEDA (1.96 ml, 13 mmol) and 1.7 M *tert*-BuLi in hexane (7.6 ml, 13 mmol). After 1 h at -78 °C the solution was transferred with a PTFE cannula to a vigorously stirred solution of SO_2 (5 ml) in dry Et_2O (50 ml) at -78 °C. A white solid precipitated instantly and the mixture was kept at -78 °C for 15 min, then allowed to warm to rt over 1 h. The solvent was evaporated and the residue was resuspended in dry Et_2O and re-evaporated. The residual solid was oxidised with NCS (4.32 g, 32.4 mmol) as described for preparation of compound **6**. Flash chromatography [EtOAc–hexanes (1:1)] gave **15b** as white crystals (1.77 g, 47%), mp 111-113 °C (EtOAc–hexanes): IR (Nujol) 1645, 1370, 1175 cm^{-1}; ^1H NMR (400 MHz) δ 7.61 (dd, *J* 8.5 and 7.5, 1H), 7.52 (dd, *J* 7.2 and 1.3, 2H), 7.41 (t, *J* 7.2, 2H), 7.34 (tt, *J* 7.2 and 1.3, 1H), 7.14 (dd, *J* 8.5 and 0.9, 1H), 6.90 (dd, *J* 7.5 and 0.9, 1H), 5.36 (s, 2H), 3.77 (dq, *J* 14 and 7, 1H), 3.34 (dq, *J* 14 and 7, 1H), 3.10-3.24 (m, 2H), 1.25 (t, *J* 7, 3H), 1.08 (t,

J 7, 3H). Calcd for $C_{18}H_{20}ClNO_4S$: C, 56.62; H, 5.28; N, 3.67. Found: C, 56.81; H, 5.22; N, 3.64.

Methyl N-*[2-benzyloxy-6-(*N,N-*diisopropylcarbamyl)benzenesulfonyl]glycinate* **16a**. Prepared as for **16b**, white crystals (83%), mp 138-139°C (EtOAc–hexanes): IR (Nujol) 3170, 1740, 1615, 1340, 1150 cm^{-1}; ^1H NMR (400 MHz) δ 7.56 (dd, *J* 8.1 and 0.8, 2H), 7.45 (t, *J* 7.8, 1H), 7.34-7.43 (m, 3H), 7.05 (dd, *J* 8.1 and 0.8, 1H), 6.81 (dd, *J* 7.5 and 0.8, 1H), 5.65 (t, *J* 5.2, 1H), 5.28 and 5.24 (ABq, *J* 17.2, 2H), 4.02 (dd, *J* 18.2 and 5.6, 1H), 3.84 (dd, *J* 18.2 and 4.9, 1H), 3.67 (septet, *J* 6.8, 1H), 3.49 (septet, *J* 6.8, 1H), 3.58 (s, 3H), 1.56 (d, *J* 6.8, 3H), 1.52 (d, *J* 6.8, 3H), 1.24 (d, *J* 6.8, 3H), 1.06 (d, *J* 6.8, 3H). Calcd for $C_{23}H_{30}N_2O_6S$: C, 59.72; H, 6.54; N, 6.05. Found: C, 59.69; H, 6.60; N, 5.97.

Methyl N-*[2-benzyloxy-6-(*N,N-*diethylcarbamyl)benzenesulfonyl]glycinate* **16b**. A solution of the sulfonyl chloride **15b** (5.73 g, 15 mmol) in MeCN (150 ml) was treated with methyl glycinate hydrochloride (5.64 g, 45 mmol) and NMM (9.9 ml 9.11 g, 90 mmol) as described above for preparation of **7**. Flash chromatography [EtOAc–hexanes (4:1)] gave **16b** as white crystals (4.55 g, 70%), mp 94-95 °C (EtOAc–hexanes): IR (Nujol) 3140br, 1740, 1375, 1155 cm^{-1}; ^1H NMR (400 MHz) δ 7.55 (dd, *J* 8.1 and 1.4, 2H), 7.50 (dd, *J* 8.1 and 7.5, 1H), 7.42 (t, *J* 7.2, 2H), 7.36 (tt, *J* 7.2 and 1.3, 1H), 7.08 (dd, *J* 8.1 and 0.9, 1H), 6.86 (dd, *J* 7.5 and 0.9, 1H), 5.66 (t, *J* 5.5, 1H), 5.25 and 5.30 (ABq, *J* 17.3, 2H), 3.99 (dd, *J* 18.3 and 5.5, 1H), 3.85 (dd, *J* 18.3 and 5.5, 1H), 3.70 (dq, *J* 14 and 7, 1H), 3.58 (s, 3H), 3.37 (dq, *J* 14 and 7, 1H), 3.20 (q, *J* 7, 2H), 1.26 (t, *J* 7, 3H), 1.08 (t, *J* 7, 3H). Calcd for $C_{21}H_{26}N_2O_6S$: C, 58.05; H, 6.03; N, 6.44. Found: C, 57.82; H, 6.00; N, 6.41.

Methyl N-*[2-hydroxy-6-(*N,N-*diisopropylcarbamyl)benzenesulfonyl]glycinate* **17a**. Prepared as for **17b**, (71%), mp 72-73 °C (EtOAc–hexanes): IR (Nujol) 3280, 1765, 1750, 1355, 1155 cm^{-1}; ^1H NMR (400 MHz) δ 9.45 (s, 1H), 7.42 (t, *J* 7.9, 1H), 7.01 (dd, *J* 8.6 and 1.0, 1H), 6.75 (dd, *J* 1.0 and 7.5, 1H), 6.60 (t, *J* 5.7, 1H), 3.90 (dd, *J* 17.4 and 6.7, 1H), 3.74 (dd, *J* 17.4 and 5.0, 1H), 3.71 (septet, *J* 6.6, 1H), 3.65 (s, 3H), 3.51 (septet, *J* 6.6, 1H), 1.57 (d, *J* 6.6, 3H), 1.50 (d, *J* 6.6, 3H), 1.20 (d, *J* 6.6, 3H), 1.14 (d, *J* 6.6, 3H). HRMS (FAB) ***m/z*** 373.1426 $(M + H)^+$ ($C_{16}H_{24}N_2O_6S$ + H requires 373.1433).

Methyl N-*[2-hydroxy-6-(*N,N-*diethylcarbamyl)benzenesulfonyl]glycinate* **17b**. Compound **16b** (4.15 g, 9.5 mmol) was debenzylated as described above for preparation of **8** to give **17b** as a crystalline solid (2.69 g, 82%), mp 77-78 °C (EtOAc–hexanes): IR (Nujol) 3245, 1765, 1155 cm^{-1}; ^1H NMR (400 MHz) δ 9.44 (s, 1H, exchanged with D_2O), 7.44 (dd, *J* 8.5 and 7.3, 1H), 7.04 (dd, *J* 8.5 and 1, 1H), 6.81 (dd, *J* 7.3 and 1, 1H), 6.56 (t, *J* 5.6, 1H), 3.92 (dq, *J* 17.2 and 6.7, 1H), 3.75 (dq, *J* 17.2 and 4.9, 1H), 3.65 (dq, *J* 14 and 7, 1H), 3.66 (s, 3H), 3.43 (dq, *J* 14 and 7, 1H), 3.15-3.27 (m, 2H), 1.25 (t, *J* 7, 3H), 1.13 (t, *J* 7, 3H). Calcd for $C_{14}H_{20}N_2O_6S$: C, 48.83; H, 5.85; N, 8.13. Found: C, 48.87; H, 5.90; N, 7.90.

Methyl N-*[2-(ethoxycarbonylmethoxy)-6-(*N,N-*diisopropylcarbamyl)benzenesulfonyl]glycinate* **18a**. A solution of **17a** (1.12 g, 3 mmol) in dry MeCN (90 ml) was treated with DIPEA (1.05 ml, 6 mmol) and ethyl bromoacetate (0.67 ml, 6 mmol) and the mixture was refluxed for 16 h. The solvent was evaporated and the residue was dissolved in Et_2O (100 ml) and washed with 2 M aq. HCl and brine, dried and evaporated. Flash chromatography [EtOAc–hexanes (7:3)] gave **18a** as white crystals (919 mg, 67%), mp 95-97 °C (EtOAc–hexanes): IR (Nujol) 3210, 1755, 1735, 1630, 1340, 1160 cm^{-1}; ^1H NMR (400 MHz) δ 7.48 (t, *J* 8.0, 1H), 7.04 (t, *J* 5.4, 1H), 6.88 (d, *J* 8.0, 1H), 6.85 (d, *J* 8.0, 1H), 4.83 and 4.77 (ABq, *J* 14.9, 2H), 4.32 (q, *J* 7.3, 2H), 4.05 (dd, *J* 18.4 and 6.7, 1H), 3.91 (dd, *J* 18.4 and 4.4, 1H), 3.61 (septet, *J* 6.7, 1H), 3.52 (s, 3H), 3.48 (septet, *J* 6.7, 1H), 1.56 (d, *J* 6.7, 3H), 1.52 (d, *J* 6.7, 3H), 1.33 (t, *J* 7.3, 3H), 1.23 (d, *J* 6.7, 3H), 1.04 (d, *J* 6.7, 3H). Calcd for $C_{20}H_{30}N_2O_8S$: C, 52.39; H, 6.59, N, 6.11. Found: C, 52.43; H, 6.66; N, 6.09.

Methyl N-*[2-(methoxycarbonylmethoxy)-6-(*N,N-*diethylcarbamyl)benzenesulfonyl]glycinate* **18b**. A solution of **17b** (2.41 g, 7 mmol), DIPEA (1.8 ml, 14 mmol) and methyl bromoacetate (1.33 ml, 14 mmol) in dry MeCN (210 ml) was treated as described for preparation of **18a**. Flash chromatography (EtOAc) gave **18b** as white crystals (2.31 g, 79%), mp 41-43 °C (CH_2Cl_2–hexanes): IR (Nujol) 3150br, 1765, 1740, 1615, 1155 cm^{-1}; ^1H NMR (400 MHz) δ 7.50 (t, *J* 8, 1H), 7.05 (dd, *J* 6.8 and 4.4, 1H), 6.92 (dd, *J* 8.2 and 1, 1H), 6.90 (dd, *J* 7.4 and 1, 1H), 5.30 (s, 1H, 0.5 CH_2Cl_2 solvent), 4.86 and 4.79 (ABq, *J* 14.9, 2H), 4.04 (dd, *J* 18.5 and 6.8, 1H), 3.89 (dd, *J* 18.5 and 4.4, 1H), 3.84 (s, 3H), 3.73 (dq, *J* 14 and 7, 1H), 3.52 (s, 3H), 3.34 (dq, *J* 14 and 7, 1H), 3.16 (q, *J* 7, 2H), 1.24 (t, *J* 7, 3H), 1.04 (t, *J* 7, 3H). Calcd for $C_{17}H_{24}N_2O_8S{\cdot}\frac{1}{2}CH_2Cl_2$: C, 45.80; H, 5.49, N, 6.10. Found: C, 45.95; H, 5.36; N, 6.10.

*2-Carboxymethyl-7-carboxymethoxy-1,2-benzisothiazol-3(*2H*)-one-1,1-dioxide* **19**. A solution of **18b** (833 mg, 1.8 mmol) in dry CH_2Cl_2 (15 ml) was treated with triethyloxonium tetrafluoroborate (1 M solution in CH_2Cl_2, 10 ml, 10 mmol) and the mixture stirred at rt for 22 h. The solvent was evaporated and the residue was dissolved in 0.5 M aq. H_2SO_4 and refluxed for 1 h, then diluted with water, saturated with NaCl and extracted with EtOAc. The combined organic phases were washed with brine, dried and evaporated to give a solid which was washed with chloroform to give **19** as white crystals (519 mg, 91%), mp 250-252 °C (acetone–hexanes): UV (EtOH) λ_{max}/nm 304 (ε/$M^{-1}cm^{-1}$ 3740), UV [EtOH–water (1:4)] λ_{max}/nm 308 (ε/$M^{-1}cm^{-1}$ 4000); IR (Nujol) 1750, 1730 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.93 (t, *J* 8, 1H), 7.67 (d, *J* 7.5, 1H), 7.61 (d, *J* 8.6, 1H), 5.09 (s, 2H), 4.44 (s, 2H). HRMS (FAB) *m/z* 337.9930 $(M + H)^+$ ($C_{11}H_9NO_8S$+ H requires 337.9947). Calcd for $C_{11}H_9NO_8S$: C, 41.91; H, 2.88; N, 4.44. Found: C, 41.71; H, 2.96; N, 4.30. The sodium salt had ^1H NMR (400 MHz, D_2O, acetone ref.) δ 7.89 (dd, *J* 8.5 and 7.5, 1H), 7.67 (d, *J* 7.5, 1H), 7.38 (d, *J* 8.5, 1H), 4.76 (s, 2H), 4.29 (s, 2H).

N-*[(2-Carboxy-6-carboxymethoxy)benzenesulfonyl]glycinate* **12**. A solution of **19** (0.5 g, 1.58 mmol) in 2.5 M aq. NaOH (20 ml) was refluxed for 3 h. The progress of the reaction was followed by anion exchange HPLC (see Table 3 for retention times). The solution was diluted with water, adjusted to pH 7.6 with 1 M aq. HCl and washed with Et_2O. The aqueous solution was diluted with water to a conductivity of 2500 μS cm^{-1} and purified by anion exchange chromatography using a linear gradient formed from 10 and 400 mM TEAB (each 1000 ml). Fractions containing the product, which eluted at ~ 160 mM TEAB, were processed as described above to afford **12** as its tris(triethylammonium) salt (1.26 mmol, 80%). UV (50 mM Na phosphate, pH 7.0) λ_{max}/nm 287 (ε/$M^{-1}cm^{-1}$ 4000); negative ion MS *m/z* 332 $(M + 2H)^-$ ($C_{11}H_8NO_9S$+ 2H requires 332). ^1H NMR (sodium salt) (400 MHz, D_2O, acetone ref.) δ 7.59 (dd, *J* 8.3 and 7.6, 1H), 7.00 (dd, *J* 0.8 and 8.3, 1H), 6.96 (dd, *J* 0.9 and 7.6, 1H), 4.66 (s, 2H), 3.46 (s, 2H).

On storage the triethylammonium salt slowly recyclised to **19**, and a pure sample for photolysis was prepared by hydrolysis of **19** (18 mg, 57 μmol) in 0.25 M aq. NaOH (2 ml) under reflux for 2 h, when HPLC analysis (see Table 3) showed that hydrolysis was complete. The solution was diluted to 25 ml with 25 mM ammonium phosphate, pH 7 and the pH was readjusted to 7 to give a solution of **12** (2.28 mM) which was used to prepare solutions for photolysis as described below.

2,6-Bis(benzyloxy)benzenesulfonyl chloride **21a**. A solution of resorcinol dibenzyl ether[29] **20a** (7.26 g, 25 mmol) in dry Et_2O (200 ml) was cooled to 0 °C and treated with TMEDA (4.52 ml, 30 mmol) and 1.6 M *n*-BuLi in hexane (18.75 ml, 30 mmol). After 1 h at 0 °C the solution was transferred with a PTFE cannula to a solution at -78 °C of SO_2 (10 ml) in dry Et_2O (50 ml). The mixture was kept at -78 °C for 15 min and allowed to warm to rt over 1 h. The solvent was evaporated and the residue was resuspended in dry Et_2O and re-evaporated. The crude sulfinate salt was oxidised with NCS as described for preparation of **6** and the product was flash chromatographed [EtOAc–hexanes (3:7)] to give **21a** as white crystals (6.01 g, 62%), mp 95-96 °C

(Et_2O–hexanes): IR (Nujol) 1370, 1250 cm^{-1}; ^1H NMR (90 MHz) δ 7.20-7.60 (m, 11H), 6.66 (d, J 8.3, 2H), 5.24 (s, 4H). Calcd for $C_{20}H_{17}ClO_4S$: C, 61.77; H, 4.41. Found: C, 61.91; H, 4.41.

2-Benzyloxy-6-methoxybenzenesulfonyl chloride **21b**. Prepared as for **21a** from 3-benzyloxyanisole **20b**,[30] white crystals (75%), mp 101-102 °C (Et_2O–hexanes): IR (Nujol) 1365, 1170 cm^{-1}; ^1H NMR δ (90 MHz) 7.24-7.60 (m, 6H), 6.66 (d, J 9, 1H), 6.63 (d, J 9 Hz, 1H), 5.25 (s, 2H), 3.96 (s, 3H). Calcd for $C_{14}H_{13}ClO_4S$: C, 53.76; H, 4.19. Found: C, 53.83; H, 4.19.

Methyl N-*(2,6-dibenzyloxybenzenesulfonyl)glycinate* **22a**. A mixture of **21a** (4.67 g, 12 mmol), methyl glycinate hydrochloride (3.01 g, 24 mmol) and NMM (4.85 g, 48 mmol) in MeCN (120 ml) was treated as described for preparation of **7**. Flash chromatography [EtOAc–hexanes (2:3)] gave **22a** as white crystals (4.13 g, 78%), mp 70-71 °C (EtOAc–hexanes): IR (Nujol) 3275, 1745, 1360, 1245, 1170 cm^{-1}; ^1H NMR (90 MHz) 7.20-7.60 (m, 11H), 6.67 (d, J 8.8, 2H), 5.84 (t, J 5.6, 1H), 5.19 (s, 4H), 3.83 (d, J 5.6, 2H), 3.54 (s, 3H). Calcd for $C_{23}H_{23}NO_6S$: C, 62.57; H, 5.52; N, 3.17. Found: C, 62.79; H, 4.95; N, 3.17.

Methyl N-*(2-benzyloxy-6-methoxybenzenesulfonyl)glycinate* **22b**. Prepared as described for **22a**, colourless viscous oil (75%); IR 3340, 1740, 1345, 1160 cm^{-1}; ^1H NMR δ (90 MHz) 7.20-7.56 (m, 6H), 6.64 (d, J 8, 1H), 6.60 (d, J 8, 1H), 5.88 (t, J 6, 1H), 5.18 (s, 2H), 3.92 (s, 3H), 3.80 (d, J 6, 2H), 3.58 (s, 3H).

Methyl N-*(4-methoxybenzyl)glycinate*. A mixture of *p*-anisaldehyde (6.81 g, 50 mmol), methyl glycinate hydrochloride (6.28 g, 50 mmol) and Et_3N (6.97 ml, 50 mmol) in benzene (50 ml) was refluxed for 7 h using a Dean-Stark trap. The solution was washed with water and the organic phase was dried and evaporated to give a pale yellow oil which crystallised on standing under vacuum. Recrystallisation (Et_2O–hexanes) gave *methyl* N-*(4-methoxybenzylidene)glycinate* as white crystals (8.44 g, 81%), mp 69-70 °C: IR (Nujol) 1745, 1650 cm^{-1}; ^1H NMR (90 MHz) δ 8.20 (s, 1H), 7.70 (d, J 9, 2H), 6.90 (d, J 9, 2H), 4.37 (s, 2H), 3.83 (s, 3H), 3.76 (s, 3H). Calcd for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; N, 6.76. Found: C, 63.90; H, 6.28; N, 6.68.

A solution of the imine (8.37 g, 40 mmol) in MeOH (50 ml) was cooled in an ice bath and treated portionwise with $NaBH_4$ (3.78 g, 100 mmol). The mixture was stirred for 1 h at rt, concentrated *in vacuo* and the residue was mixed with water and extracted with Et_2O. The organic phase was dried, evaporated and fractionally distilled to give the title ester as a colourless oil (5.53 g, 62%), bp 114-120 °C/0.5 mmHg: IR (film) 3330, 1740 cm^{-1}; ^1H NMR (400 MHz) δ 7.23-7.26 (m, 2H), 6.84-6.87 (m, 2H), 3.79 (s, 3H), 3.73 (s, 2H), 3.72 (s, 3H), 3.40 (s, 2H), 2.01 (br s, 1H).

Methyl N-*(2,6-dibenzyloxybenzenesulfonyl)*-N-*(4-methoxybenzyl)glycinate* **22c**. A mixture of the sulfonyl chloride **21a** (6.04 g, 15.5 mmol), methyl *N*-(4-methoxybenzyl)glycinate (4.45 g, 21.3 mmol) and NMM (2.75 ml, 25 mmol) in MeCN (120 ml) was treated as described above for preparation of **7**. Flash chromatography [EtOAc–hexanes (3:7)] gave **22c** as white crystals (7.53 g, 81%), mp 75-77 °C (EtOAc–hexanes): IR (Nujol) 1755, 1345, 1160 cm^{-1}; ^1H NMR (90 MHz) δ 7.16-7.64 (m, 11H), 7.03 (d, J 9, 2H), 6.56-6.88 (m, 4H), 5.14 (s, 4H), 4.38 (s, 2H), 3.76 (s, 5H), 3.42 (s, 3H). Calcd for $C_{31}H_{31}NO_7S$: C, 66.29; H, 5.56; N, 2.49. Found: C, 66.27; H, 5.53; N, 2.54.

Methyl N-*(2,6-dihydroxybenzenesulfonyl)glycinate* **23a**. Compound **22a** (2.43 g, 5.5 mmol) was debenzylated as described above for **8** to give **23a** as a white solid (1.4 g, 79%), mp 148-150 °C (EtOAc–hexanes): IR (Nujol) 3330, 3290, 1725, 1610, 1130 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$–DMSO-d_6) δ 7.24 (t, J 8, 1H), 6.45 (d, J 8, 2H), 3.79 (s, 2H), 3.65 (s, 3H). Calcd for $C_9H_{11}NO_6S$: C, 41.38; H, 4.24; N, 5.36. Found: C, 41.42; H, 4.34; N, 5.33.

Methyl N-*(2-hydroxy-6-methoxybenzenesulfonyl)glycinate* **23b**. Prepared as described for **23a**, colourless viscous oil (73%); IR 3390, 1745, 1225, 1130 cm^{-1}; ^1H NMR δ (90 MHz) 9.56 (s, 1H), 7.36 (t, *J* 8, 1H), 6.60 (d, *J* 8, 1H), 6.48 (d, *J* 6.6, 1H), 5.82 (t, *J* 5, 1H), 5.18 (s, 2H), 3.92 (s, 3H), 3.78 (d, *J* 5, 2H), 3.64 (s, 3H).

Alkylation of **23a**. A solution of **23a** (261 mg, 1 mmol), DIPEA (0.7 ml, 4 mmol) and ethyl bromoacetate (0.44 ml, 4 mmol) in dry MeCN (20 ml) was refluxed for 18 h. Two products were isolated after the workup procedure described for **9** and flash chromatography [EtOAc–hexanes (1:1)]. The major product was *methyl* N-*(2-ethoxycarbonylmethoxy-6-hydroxybenzenesulfonyl)-N-(ethoxycarbonylmethyl)glycinate* **24a** (229 mg, 53%), mp 144-146 °C (Et_2O–hexanes): IR (Nujol) 3270, 1765, 1745, 1325, 1130 cm^{-1}; ^1H NMR (400 MHz) δ 9.86 (s, 1H), 7.31 (t, *J* 8.2, 1H), 6.63 (d, *J* 8.9, 1H) 6.33 (d, *J* 7.8, 1H), 4.63 (s, 2H), 4.36 (s, 2H), 4.30 (s, 2H), 4.28 (q, *J* 7.2, 2H), 4.08 (q, *J* 7.2, 2H), 3.65 (s, 3H), 1.32 (t, *J* 7.2, 3H), 1.19 (t, *J* 7.2, 3H). Calcd for $C_{17}H_{23}NO_{10}S$: C, 47.11; H, 5.35, N, 3.23. Found: C, 46.86; H, 5.30; N, 3.33.

The minor product was *methyl* N-*[2,6-bis(ethoxycarbonylmethoxy)benzenesulfonyl]glycinate* **24b**, colourless oil (124 mg, 29%): ^1H NMR (90 MHz) δ 7.20-7.44 (m, 2H), 6.60 (d, *J* 8, 2H), 4.74 (s, 4H), 4.26 (q, *J* 7.5, 2H), 3.94 (d, *J* 6, 2H), 3.53 (s, 3H), 1.28 (t, *J* 7.5, 3H).

Alkylation of **23b**. A mixture of the phenol **23b** (826 mg, 3 mmol), DIPEA (775 mg, 6 mmol) and ethyl bromoacetate (1.00 g, 6 mmol) was treated as described for compound **18a**. Flash chromatography [EtOAc–hexanes (1:1)] gave two major products. The less polar product was *methyl* N-*(2-hydroxy-6-methoxybenzenesulfonyl)*-N-*(ethoxycarbonylmethyl)glycinate* **24c** as white crystals (632 mg, 58%), mp 87-88 °C (EtOAc–hexanes): IR (Nujol) 3250, 1750, 1335, 1125 cm^{-1}; ^1H NMR δ (90 MHz) 9.76 (s, 1H), 7.32 (t, *J* 8, 1H), 6.56 (d, *J* 8, 1H), 6.40 (d, *J* 8, 1H), 4.31 (s, 2H), 4.29 (s, 2H), 4.08 (q, *J* 7.5, 2H), 3.87 (s, 3H), 3.66 (s, 3H), 1.21 (t, *J* 7.5, 3H). Calcd for $C_{14}H_{19}NO_8S \cdot \frac{1}{2}EtOAc$: C, 47.40; H, 5.72; N, 3.45. Found: C, 47.37; H, 5.41; N, 3.63. The more polar product was *methyl* N-*(2-ethoxycarbonylmethoxy)-6-methoxybenzenesulfonyl-glycinate* **24d** (169 mg, 16%), mp 71-72 °C (EtOAc–hexanes): IR (Nujol) 3250, 1755, 1735, 1355, 1115 cm^{-1}; ^1H NMR (90 MHz) δ 7.40 (t, *J* 8, 1H), 7.06 (t, *J* 6, 1H), 6.70 (d, *J* 8, 1H), 6.52 (d, *J* 8, 1H), 4.75 (s, 2H), 4.28 (q, *J* 7.5, 2H), 3.92 (d, *J* 6.3, 2H), 3.87 (s, 3H), 3.56 (s, 3H), 1.31 (t, *J* 7.5, 3H). Calcd for $C_{14}H_{19}NO_8S$: C, 46.53; H, 5.30, N, 3.87. Found: C, 46.47; H, 5.23; N, 3.87.

Methyl N-*(2,6-dihydroxybenzenesulfonyl)*-N-*(4-methoxybenzyl)glycinate* **23c**. Compound **22c** (6.89 g, 12.3 mmol) was debenzylated as described for **8** to give **23c** as white needles (3.59 g, 77%), mp 131-132 °C (EtOAc–hexanes): IR (Nujol) 3320, 3220, 1125 cm^{-1};^1H NMR (90 MHz) δ 8.64 (br s, 2H), 7.32 (t, *J* 8, 1H), 6.96-7.20 (m, 2H), 6.68-6.92 (m, 2H), 6.56 (d, *J* 8, 2H), 4.39 (s, 2H), 3.94 (s, 2H), 3.78 (s, 3H), 3.62 (s, 3H). Calcd for $C_{17}H_{19}NO_7S$: C, 53.54; H, 5.02; N, 3.67. Found: C, 53.43; H, 5.01; N, 3.64.

Methyl N-*[2,6-bis(methoxycarbonylmethoxy)benzenesulfonyl]*-N-*(4-methoxybenzyl)glycinate* **24e**. A solution of **23c** (1.91 g, 5 mmol), DIPEA (8.7 ml, 50 mmol) and methyl bromoacetate (4.73 ml, 50 mmol) in dry MeCN (150 ml) was refluxed for 67 h. The solvent was evaporated and the residue was dissolved in MeOH (150 ml) and stirred at rt for 1.5 h with Et_3N (10 ml). The solution was concentrated and the residue was mixed with 2 M aq. HCl and extracted with Et_2O. The combined organic phases were washed with brine, dried, evaporated and flash chromatographed [EtOAc–hexanes (3:2)] to give **24e** as a light brown oil (2.48 g, 94%) which was used in the next step without further purification. IR (film) 1750, 1345, 1120 cm^{-1}; ^1H NMR (90 MHz) δ 7.36 (t, *J* 7, 1H), 7.16 (d, *J* 8, 2H), 6.78 (d, *J* 8, 2H), 6.60 (d, *J* 7, 2H), 4.69 (s, 4H), 4.59 (s, 2H), 4.12 (s, 2H), 3.77 (s, 3H), 3.76 (s, 6H), 3.53 (s, 3H); HRMS (FAB) *m/z* 526.1403 $(M + H)^+$ ($C_{23}H_{27}NO_{11}S$ + H requires 526.1383).

Methyl N-*(2,6-dibenzyloxybenzenesulfonyl)*-N-*acetylglycinate* **25**. A solution of **22a** (0.93 g, 2.1 mmol) in Ac_2O (40 ml) and fused sodium acetate (0.8 g) was refluxed for 3 h, then diluted with water and washed with EtOAc. The combined organic phases were washed with 1 M aq. KOH and water, dried and evaporated. Flash chromatography [EtOAc–hexanes (2:3] gave **25** as white crystals (0.93 g, 82%), mp 109-110 °C (EtOAc–hexanes): IR (Nujol) 1750, 1690, 1370, 1095 cm^{-1}; ^1H NMR (90 MHz) δ 7.24-7.56 (m, 11H), 6.68 (d, *J* 8, 2H), 5.16 (s, 4H), 4.17 (s, 2H), 3.63 (s, 3H), 2.29 (s, 3H). Calcd for $C_{25}H_{25}NO_7S$: C, 62.10; H, 5.21; N, 2.90. Found: C, 62.10; H, 5.17; N, 2.87.

Methyl N-*(2,6-dihydroxybenzenesulfonyl)*-N-*acetylglycinate* **26**. A solution of **25** (0.82 g, 1.7 mmol) in EtOH (50 ml) was stirred with 10% Pd–C (0.35 g) under hydrogen as described for compound **17a**. Flash chromatography [EtOAc–hexanes (3:2)] gave **26** as a white solid (0.39 g, 76%): ^1H NMR (90 MHz, $CDCl_3$–DMSO-d_6) δ 7.28 (t, *J* 8, 1H), 6.48 (d, *J* 8, 2H), 4.60 (s, 2H), 3.76 (s, 3H), 2.34 (s, 3H). Attempted recrystallisation (EtOAc–hexanes) resulted in equilibration with the 2-*O*-acetyl isomer (see Discussion).

Methyl N-*[2,6-bis(methoxycarbonylmethoxy)benzenesulfonyl]glycinate* **28**. A solution of **24e** (2.36 g, 4.5 mmol) in MeCN (90 ml) was treated at 0 °C with a solution of ceric ammonium nitrate (7.40 g, 13.5 mmol) in water (60 ml) and the mixture was stirred at 0 °C for 3 h. The solution was diluted with EtOAc and washed with water. The organic phase was washed successively with saturated aq. $NaHCO_3$, saturated aq. Na_2SO_3 and brine, dried and evaporated. Flash chromatography [EtOAc–hexanes (3:2)] gave **28** as white crystals (1.63 g, 89%), mp 101-102 °C (EtOAc–hexanes): UV (EtOH) λ_{max}/nm 287 (ε/$M^{-1}cm^{-1}$ 4400); UV [EtOH–25 mM ammonium phosphate, pH 7 (5:95)] λ_{max}/nm 289 (ε/$M^{-1}cm^{-1}$ 4600); IR (Nujol) 3220, 1755, 1740, 1335, 1115 cm^{-1}; ^1H NMR (90 MHz) δ 7.16-7.36 (m, 2H), 6.65 (d, *J* 8, 2H), 4.76 (s, 4H), 3.96 (d, *J* 6, 2H), 3.81 (s, 6H), 3.57 (s, 3H). Calcd for $C_{15}H_{19}NO_{10}S$: C, 44.44; H, 4.72; N, 3.45. Found: C, 44.24; H, 4.72; N, 3.38.

N-*[2,6-Bis(carboxymethoxy)benzenesulfonyl]glycine* **13**. A mixture of **28** (811 mg, 2 mmol) in MeOH (36 ml) and 5 M aq. NaOH (4 ml) was refluxed for 2 h. The solution was cooled to rt and the residue was diluted with water, acidified with conc. HCl, saturated with NaCl and extracted with EtOAc. The combined organic layers were dried and evaporated to give a white solid. Recrystallisation gave **13** as white crystals (508 mg, 70%), mp 204-205 °C (acetone–hexanes): UV (25 mM ammonium phosphate, pH 7.0) λ_{max}/nm 291.5 (ε/$M^{-1}cm^{-1}$ 5100); IR (Nujol) 3285, 3250, 1760, 1740, 1720, 1315, 1120 cm^{-1};^1H NMR (400 MHz, DMSO-d_6) δ 7.55 (t, *J* 5.7, 1H), 7.41 (t, *J* 8.2, 1H), 6.67 (d, *J* 8.2, 2H), 6.52 (br s, 3H), 4.73 (s, 4H), 3.75 (d, *J* 5.7, 2H). Calcd for $C_{12}H_{13}NO_{10}S$: C, 39.67; H, 3.61; N, 3.85. Found: C, 39.84; H, 3.62; N, 3.67.

Photolysis conditions. Solutions of compounds for photolysis (i.e. **2-4**, **12**, **13** and *N*-tosylglycine) were prepared at 0.5 mM concentration ± naphthalene bisphosphate **11** (0.5 mM) in 25 mM ammonium phosphate, pH 7.0. Aliquots (0.2 ml) were irradiated in a 1 mm path length cell, using light from a 100 W xenon arc lamp which passed through a Hoya U340 filter before illuminating the cell. The extent of conversion of starting compounds was determined by HPLC analysis (Table 3). Quantification was based on peak heights compared to those of unphotolysed controls. Yields of free amino acids were determined on an automated amino acid analyser.

Table 3. Conditions for HPLC analysis

Compound	Column	Detection wavelength (nm)	Mobile Phase	t_R (min)	t_R of **11** (min)
2	RP8	230	500 mM NH_4 phosphate, pH 5.8	4.6	-[a]
3	RP8	230	100 mM NH_4 phosphate, pH 5.8	6.6	-[a]
4	RP8	230	25 mM NH_4 phosphate, pH 5.8 + 5% MeCN	5.8	44
N-Tosylglycine	RP8	230	25 mM Na phosphate, pH 4.0 + 20% MeCN	7.2	3.6
10	RP8	313	25 mM Na phosphate, pH 5.5 + 10% MeCN	3.2	-[b]
11	RP8	313	25 mM NH_4 phosphate, pH 5.8 + 10% MeCN	10.2	
12	SAX	284	125 mM NH_4 phosphate, pH 4.0	5.7	15.2
13	RP8	284	100 mM NH_4 phosphate, pH 4.0 + 10% MeOH	5.8	-[a]
19	SAX	284	125 mM NH_4 phosphate, pH 4.0	1.6	-[b]

[a] **Compound 11** retained >50 min on column.
[b] **Compound 11** not co-injected.

ACKNOWLEDGEMENTS

We are grateful to the MRC Biomedical NMR Centre for access to facilities and to Dr. V.R.N. Munasinghe for recording NMR spectra. We thank Dr. K.J. Welham (School of Pharmacy, University of London) and Dr. S.A. Howell (NIMR) for mass spectral data and Mr. P. Sharratt (Biochemistry Department, University of Cambridge) for assistance with amino acid analysis. This work was supported by the Medical Research Council under the Neurosciences Approach to Human Health Initiative.

REFERENCES

1. Corrie, J.E.T.; Trentham, D.R. In *Biological Applications of Photochemical Switches*; Morrison, H., Ed.; Wiley: New York, 1993; pp 243-305.
2. Kaplan, J.H.; Forbush, B.; Hoffman, J.F. *Biochemistry*, **1978**, *17*, 1929-1935.
3. (a) Ramesh, D.; Wieboldt, R.; Niu, L.; Carpenter, B.K.; Hess, G.P. *Proc. Natl. Acad. Sci. USA* **1993**, *90*, 11074-11078; (b) Gee, K.R.; Wieboldt, R.; Hess, G.P. *J. Am. Chem. Soc.* **1994**, *116*, 8366-8367; (c) Wieboldt, R.; Ramesh, D.; Carpenter, B.K.; Hess, G.P. *Biochemistry*, **1994**, *33*, 1526-1533; (d) Wieboldt, R.; Gee, K.R.; Niu, L.; Ramesh, D.; Carpenter, B.K.; Hess, G.P. *Proc. Natl. Acad. Sci. USA* **1994**, *91*, 8752-8756; (e) Gee, K.R.; Niu, L.; Schaper, K.; Hess, G.P. *J. Org. Chem.* **1995**, *60*, 4260-4263.
4. Givens, R.S.; Jung, A.; Park, C.H.; Weber, J.; Bartlett, W. *J. Am. Chem. Soc.* **1997**, *119*, 8369-8370.
5. Rossi, F.M.; Margulis, M.; Tang, C.M.; Kao, J.P.Y. *J. Biol. Chem.* **1997**, *272*, 32933-32939.
6. (a) Corrie, J.E.T.; DeSantis, A.; Katayama, Y.; Khodakhah, K.; Messenger, J.B.; Ogden, D.C.; Trentham, D.R. *J. Physiol.* **1993**, *465*, 1-8; (b) Papageorgiou, G.; Corrie, J.E.T. *Tetrahedron* **1997**, *53*, 3917-3932.
7. Corrie, J.E.T.; Papageorgiou, G. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1583-1592.
8. (a) Hamada, T.; Nishida, A.; Yonemitsu, O. *J. Am. Chem. Soc.* **1986**, *108*, 140-145; (b) Hamada, T.; Nishida, A.; Yonemitsu, O. *Tetrahedron Lett.* **1989**, *30*, 4241-4244.
9. Davidson, R.S.; Steiner, P.S. *J. Chem. Soc. (C)* **1971**, 1682-1689.
10. Snieckus, V. *Chem. Rev.* **1990**, *90*, 879-933.

11. (a) Birch, A.J.; Corrie, J.E.T.; MacDonald, P.L.; Subba Rao, G. *J. Chem. Soc., Perkin Trans. 1* **1972**, 1186-1193; (b) Kalivretenos, A.; Stille, J.K.; Hegedus, L.S. *J. Org. Chem.* **1991**, *56*, 2883-2894.
12. Backes, B.J.; Virgilio, A.A.; Ellman, J.A. *J. Am. Chem. Soc.* **1996**, *118*, 3055-3066.
13. Yoshimura, J.; Yamaura, M.; Suzuki, T.; Hashimoto, H. *Chem. Lett.* **1983**, 1001-1002.
14. Lebouc, A.; Martigny, P.; Carlier, R.; Simonet, J. *Tetrahedron* **1985**, *41*, 1251-1258.
15. Kossai, R.; Emir, B.; Simonet, J.; Mousset, G. *J. Electroanal. Chem.* **1989**, *270*, 253-260.
16. (a) Hiller, K.O.; Masloch, B.; Göbl, M.; Asmus, K.D. *J. Am. Chem. Soc.* **1981**, *103*, 2734-2743; (b) Mönig, J.; Chapman, R.; Asmus, K.D. *J. Phys. Chem.* **1985**, *89*, 3139-3144.
17. (a) Pincock, J.A.; Jurgens, A. *Tetrahedron Lett.* **1979**, 1029-1030; (b) Badr, M.Z.A.; Aly, M.M.; Fahmy, A.M. *J. Org. Chem.* **1981**, *46*, 4784-4787.
18. Givens, R.S.; Levi, N. In *The Chemistry of Functional Groups, Suppl. B. The Chemistry of Acid Derivatives*; Patai, S., Ed.; Wiley: Chichester, 1979; pp 641-753.
19. (a) Bruncko, M.; Crich, D. *J. Org. Chem.*, **1994**, *59*, 4239-4249; (b) McDonald, F.E.; Danishefsky, S.J. *J. Org. Chem.*, **1992**, *57*, 7001-7002; (c) Garigipati, R.S.; Adams, J.L. *PCT Int. Patent Appl.* WO 9630337 (*Chem. Abstr.* **1996**, *125*, 32828).
20. Pettit, G.R.; Kadunce, R.E. *J. Org. Chem.* **1962**, *27*, 4566-4570; Abe, K.; Tsukamoto, Y.; Ishimura, A. *J. Pharm. Soc. Jpn.* **1953**, *73*, 1319-1322 (*Chem. Abstr.* **1955**, *49*, 177).
21. Adger, B.M.; Young, R.G. *Tetrahedron Lett.* **1984**, *25*, 5219-5222; Rousseau, V.; Lindwall, H.G. *J. Am. Chem. Soc.* **1950**, *72*, 3047-3051; Sianesi, E.; Redaelli, R.; Bertani, M.; Da Re, P. *Chem. Ber.* **1970**, *103*, 1992-2002; Sienesi, E.; Setnikar, I.; Massarani, E.; Da Re, P. *Ger. Patent* 2,022,694 (*Chem. Abstr.* **1971**, *74*, 141829).
22. Lafon, L. *Ger. Patent* 2,038,836 (*Chem. Abstr.* **1971**, *75*, 35528); Whittaker, K. *Br. Patent* 926,999 (*Chem. Abstr.* **1963**, *59*, 11716).
23. Todd, D.; Teich, S. *J. Am. Chem. Soc.* **1953**, *75*, 1895-1900.
24. Blanco, M.; Perillo, I.A.; Schapira, C.B. *J. Heterocycl. Chem.* **1995**, *32*, 145-154.
25. Kametani, T.; Fukumoto, K. *J. Chem. Soc.* **1964**, 6141-6146.
26. Takahashi, I.; Nomura, A.; Kitajima, H. *Synth. Commun.* **1990**, *20*, 1569-1575.
27. Uhlmann, E.; Engels, J. *Tetrahedron Lett.* **1986**, *27*, 1023-1026; Bannwarth, W.; Trzeciak, A. *Helv. Chim. Acta* **1987**, *70*, 175-186.
28. Cleaver, L.; Nimgirawath, S.; Ritchie, E.; Taylor, W.C. *Aust. J. Chem.* **1976**, *29*, 2003-2021.
29. Rowe, E.J.; Kaufman, K.L.; Piantadosi, C. *J. Org. Chem.* **1958**, *23*, 1622-1624.
30. Testaferi, L.; Tiecco, M.; Tingoli, M.; Montanucci, D. *Tetrahedron* **1982**, *24*, 3687-3692.