Protection of Amines by the Pyridine-2-sulfonyl Group and Its Cleavage under Mild Conditions (SmI_2 or Electrolysis)

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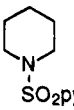
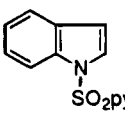
Arenesulfonamides, in spite of the drastic conditions required for their reductive cleavage,[1,2] are often used as amine protecting groups because of the powerful electron-withdrawing effect of the arylsulfonyl group, their high stability, and their ease of formation.

Recently, a new method for the deprotection of *N*-(arylsulfonyl)amines was described.[3] The authors used SmI_2 in a refluxing mixture of THF and DMPU in order to obtain the parent primary or secondary amine. SmI_2 is a powerful one-electron reducing agent;[4] its reductive potential is increased by the presence, as cosolvent, of either a one-electron donor source, such as DMPU,[4e] or a proton source. These severe conditions are not compatible with many functional groups, such as a cinnamoyl group.[4b,f] We report here the preparation of pyridine-2-sulfonamides from primary or secondary amines and pyridine-2-sulfonyl chloride and their deprotection under mild conditions either by using SmI_2 without an additive or by electrolysis.

The pyridine-2-sulfone group[5] can be cleaved by SmI_2 without using HMPA (which is required in the case of phenylsulfonyl) because of its low LUMO energy level.[5] We thought that a similar type of cleavage could be considered for pyridine-2-sulfonamides. Moreover, Lewis acid catalysis by Sm(III) ions could also be involved in the mechanism, and the rate of reaction could be increased in the presence of the pyridine nitrogen atoms.

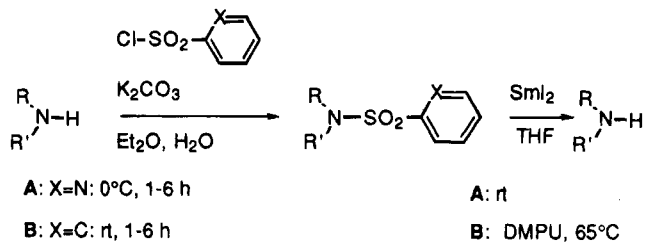
The various pyridine-2-sulfonamides[6] **A** were derived from primary and secondary alkylamines (Table 1, entries 1–5) or from aromatic amines (entries 7 and 8). They were generally obtained in good yields by treatment of the corresponding amines with pyridine-2-sulfonyl chloride[7] in the presence of aqueous potassium carbonate[8] (Scheme 1).

Table 1. Cleavage of 2-Pyridylsulfonamides to Amines with SmI_2[a]

entry	yield of formation[b], %	2-pyridyl sulfonamide	isolated yield (%) of amine
1	**1** (93)	2-pyrSO_2NBn_2	85
2			86[c]
3	**2** (98)	2-pyr$SO_2N(CH_2CH{=}CH_2)_2$	90
4	**3** (97)	(L)-2-pyrSO_2NHCBnHCO_2tBu	76[d]
5	**4** (98)		93
6	**5** (94)	(D)-2-pyrSO_2NHCHPhMe	83[e]
7	**6** (70)	2-pyrSO_2NHPh	94
8	**7** (64)[f]		81

[a] Typical procedure: 0.5 mmol of **1** + 30 mL of 0.1 M SmI_2/THF (preparation: ref 4f), well degassed, was stirred for 4 h at rt under argon. The product was obtained by simple acid–base extraction and purified by chromatography on silica gel (85%). [b] See refs 7 and 8. [c] In the presence of 2 mL of DMPU for 0.5 mmol of **1**, the deprotection was finished after 30 min at rt and the dibenzylamine was obtained in 86% yield after purification. [d] Phenylalanine *tert*-butyl ester was isolated with 46% ee (ee was determined by comparison of the specific optical rotations with that of the commercially available compound). [e] No racemization was observed. [f] **7** was prepared by reaction of the anion of indole (1.3 equiv of NaH, DMF; 45 min, 0 °C) with 2-pyrSO_2Cl (1.1 equiv) for 2 h at 0 °C.

Scheme 1



Deprotection proceeded readily using SmI_2 in THF at room temperature, the reaction being complete within 4 h. These results were quite noteworthy because deprotection of the benzenesulfonamide **B**, an analogue of **A**, required approximately the same time[3] in the presence of DMPU at 65 °C. The polarographically-measured half-wave potentials of **1**, its benzene analogue **8**, and its tosyl analogue **9** are presented in Table 2. The differences in these potentials result from the lower LUMO energies of the pyridine-2-sulfonamides. As in the case of arenesulfonamides, we noticed that the rates of cleavage of pyridine-2-sulfonamides, which had been derived from primary or secondary amines, were equivalent. This result suggests that steric effects are not crucial in these reactions. The cleavage of compound **4** occurred with a good yield and at a similar rate. This suggests that the S–N cleavage in all of these sulfonamides probably occurs by the same pathway.

Chiral α-methyl benzylamine can be protected and deprotected under our conditions, without noticeable racemization (see entry 6, Table 1). However, as previously described,[3] the deprotection of an amino acid

(1) (a) Kovacs, J.; Ghatak, U. R. *J. Org. Chem.* **1966**, *31*, 119. (b) Closson, W. D.; Ji, S.; Schulenberg, S. *J. Am. Chem. Soc.* **1970**, *92*, 650.

(2) (a) Cottrell, P. T.; Mann, C. K. *J. Am. Chem. Soc.* **1971**, *93*, 3579. (b) Quaal, K. S.; Ji, S.; Khim, Y. M.; Closson, W. D.; Zubieta, J. A. *J. Org. Chem.* **1978**, *43*, 1311. (c) Roemmele, R. C.; Rapoport, H. *J. Org. Chem.* **1988**, *53*, 2367. (d) Lebouc, A.; Martigny, P.; Carlier, R.; Simonet, J. *Tetrahedron* **1985**, *41*, 1251.

(3) Vedejs, E.; Lin, S. *J. Org. Chem.* **1994**, *59*, 1602.

(4) Reviews of SmI_2 chemistry: (a) Molander, G. A. *Chem. Rev.* **1992**, *92*, 29. (b) Inanaga, J. *Rev. Heteroatom. Chem.* **1990**, *3*, 75. (c) Kagan, H. B.; Sasaki, M.; Collin, J. *Pure Appl. Chem.* **1988**, *60*, 1725. (d) Curran, D. P.; Fevig, T. L.; Jasperse, C. P.; Totleben, M. J. *Synlett* **1992**, 943. (e) Hasegawa, E.; Curran, D. P. *J. Org. Chem.* **1993**, *58*, 5008. (f) For the preparation of SmI_2 see: Girard, P.; Namy, J. L.; Kagan, H. B. *J. Am. Chem. Soc.* **1980**, *102*, 2693.

(5) Mazéas, D.; Skrydstrup, T.; Doumeix, O.; Beau, J. M. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1383 and references cited therein.

(6) All of the compounds depicted in this paper exhibited satisfactory spectral and analytical data.

(7) Pyridine-2-sulfonyl chloride was prepared by bubbling chlorine gas through a solution of concd HCl containing 2-mercaptopyridine at 0 °C during 1.5 h. See: Hanessian, S.; Kagotani, M.; Komaglou, K. *Heterocycles* **1989**, *28*, 1115.

(8) The pyridine-2-sulfonamides were prepared by stirring the corresponding amines in a 1:1 mixture of ether/4 M K_2CO_3 in H_2O in the presence of 2-pyrSO_2Cl (1.2 equiv) for 1–6 h at 0 °C. For the preparation of arenesulfonamide by a similar procedure, see: Fiedler, W. J.; Hesse, M. *Helv. Chim. Acta* **1993**, *76*, 1511.

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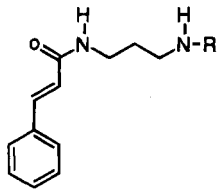
Table 2. Half-Wave Potentials $E_{1/2}$ in V (vs SCE; in EtOH, Supporting Electrolyte n-$Bu_4N^+Br^-$)

entry	sulfonamide	structure	$E^1_{1/2}$ (V)	$E^2_{1/2}$ (V)	$E^3_{1/2}$ (V)
1	2-pyrSO_2NBn_2	**1**	-1.73	/	-2.25
2	$PhSO_2NBn_2$	**8**	/	/	-2.12
3	$MeC_6H_4SO_2NBn_2$	**9**	/	/	-2.23
					
4	R=Ts	**10a**	/	-1.82	-2.45
5	R=$PhSO_2$	**10b**	/	-1.82	-2.39
6	R=2-pyrSO_2	**10c**	-1.72	-1.84	-2.18

derivative led to a partial racemization of the acidic proton (see entry 4, Table 1).

In the course of our work on the biosynthesis and synthesis of polyamine alkaloids[9] containing one or more cinnamoyl groups, we investigated the deprotection of the model compound **10c** and its arenesulfonamide analogues **10a** and **10b** (Scheme 2). It is known that α,β-unsaturated amides are efficiently reduced to amides upon treatment with SmI_2 in the presence of a proton source[4f] or an additive solvent,[4b] such as HMPA. Accordingly, deprotection of **10a** and **10b** was accompanied by the reduction of the C−C double bond of the cinnamoyl moiety. The cleavage of pyridine-2-sulfonamide **10c** by SmI_2, at room temperature and without an additive, allowed us to obtain the amine **11** contaminated by only 8% of the dihydro derivative **13**.

A polarographic study of compounds **10a−c** was performed in order to examine the feasibilty of the selective removal of the *N*-(pyridine-2-sulfonyl) group in **10c**, without interfering with the activated C−C double bond of the cinnamoyl moiety.[10] It is known that a selective electrolysis is possible if the polarographic half-wave potentials between two electrode reactions[11,12] differ by at least 150−200 mV. From these results (Table 2), it can clearly be seen that $E^1_{1/2}$ is due to the reductive cleavage of the N−S bond at the pyridine-2-sulfonamide group, whereas $E^2_{1/2}$ corresponds with the reduction of the activated double bond in the cinnamoyl moiety. $E^3_{1/2}$ in **1** and **10c** is probably due to the reduction of the pyridine nucleus, whereas in **10a** and **10b** $E^3_{1/2}$ corresponds with the cleavage of the N−S bond of the arenesulfonamide.[13]

The potential difference between the first and second cathodic wave in **10c** is 120 mV. A preparative electrolysis of **10c** at a cathode potential of −1.72 V vs SCE (saturated calomel electrode) yielded the deprotected product **11** and its dihydro derivative **13** in a ratio of 41/59. In a second preparative electrolysis, the cathode potential was set to the value at which approximately 25% of the cathodic current of the first wave (−1.65 V vs SCE) had been observed. The potential difference between this value and the second wave was now 190 mV, and under these electrolysis conditions, we obtained the deprotected compound **11** with a yield of 90% and contaminated by only 4% of **13**.

The use of the *N*-(pyridine-2-sulfonyl) group is a new and versatile method for the protection of primary and secondary amines, arylamines, and amino acid derivatives. The resulting sulfonamides are obtained in good yield, are often crystalline, and are easy to handle. They can be deprotected under very mild conditions either by using SmI_2 in THF solution at room temperature or by electrolysis. Moreover, these reductive deprotection reactions could be carried out in the presence of ester or cinnamoyl residues.

Experimental Section

General Methods. All NMR chemical shifts are reported as δ values (ppm) relative to internal tetramethylsilane. Mass spectra (MS) were obtained using chemical ionization (CI), with NH_3 as the reactant gas, and electron impact (EI) at 70 eV. Optical rotations were measured in a 1 dm cell, and concentrations are given in g/100 mL. The polarographic measurements were carried out using differential pulse polarography, pulse amplitude −50 mV. Solvent supporting electrolyte (SSE): 0.1 M n-$Bu_4N^+Br^-$ in 94% ethanol. T = 23 °C. Working electrode: dropping mercury electrode (DME), drop time: 1 s, reference electrode: aqueous saturated calomel electrode (SCE); depolarizer: c = 1. 10^{-3} M; $E_{1/2}$ potentials vs SCE.

THF was distilled over sodium and benzophenone. The L-(+)-phenylalanine *tert*-butyl ester and the D-(+)-α-methylbenzylamine were obtained from Fluka. Pyridine-2-sulfonyl chloride was prepared according to the literature.[7] Products were crystallized from ethyl acetate/hexane.

General Procedure for the Preparation of Pyridine-2-sulfonamides. A solution of 4 mmol of amine and 4.8 mmol (0.853 g) of pyridine-2-sulfonyl chloride in a 1:1 mixture of ether (8 mL) and 4 M solution of K_2CO_3 (8 mL) was stirred vigorously for 1−6 h at 0 °C. The aqueous phase was extracted with dichloromethane (2 × 20 mL), dried (Na_2SO_4), and evaporated to dryness. Flash chromatography of the residue (silica gel, eluent: ethyl acetate/hexane) provided pyridine-2-sulfonamide as a white solid.

***N,N*-Dibenzylpyridine-2-sulfonamide (1).** Compound **1** was obtained at 0 °C (3 h) from dibenzylamine in 93% yield after purification by chromatography (eluent ethyl acetate/hexane (2:3)): mp 76.6−78.7 °C; IR ($CHCl_3$) 1170, 1335 cm^{-1}. ^1H NMR ($CDCl_3$) δ 4.51 (s, 4H), 7.07−7.27 (m, 10H), 7.45−7.49 (m, 1H), 7.80−7.87 (m, 1H), 7.91−7.99 (m, 1H), 8.65 (d, 1H, J = 4.8 Hz); ^{13}C NMR ($CDCl_3$) δ 51.22, 122.11, 126.20, 127.50, 128.24, 128.54, 149.82, 158.80; MS m/z 339 $(M + H)^+$; Anal. Calcd for $C_{19}H_{18}N_2O_2S$: C, 67.43; H, 5.36; N, 8.28; S, 9.47. Found: C, 67.67; H, 5.28; N, 8.21; S, 9.40.

***N,N*-Diallylpyridine-2-sulfonamide (2).** Compound **2** was obtained at 0 °C (1 h 30) from allylamine in 98% yield as a colorless oil after purification by chromatography (eluent: ethyl acetate/hexane (3:7)): IR ($CHCl_3$) 1170, 1345 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.96 (d, 4H, J = 6.2 Hz), 5.11−5.18 (m, 4H), 5.60−5.74 (m, 2H), 7.46−7.50 (m, 1H), 7.86−7.89 (m, 1H), 7.91−7.98 (m, 1H), 8.69 (d, 1H, J = 4.4 Hz); ^{13}C NMR ($CDCl_3$) δ 50.08, 118.79, 122.33, 129.15, 132.87, 137.88, 150.02, 158.55; MS m/z 239 $(M + H)^+$. Anal. Calcd for $C_{11}H_{14}N_2O_2S$ + 1/20 C_6H_{14}: C, 55.94; H, 6.11; N, 11.55; S, 13.21. Found: C, 55.74; H, 6.37; N, 11.88; S, 13.13.

***tert*-Butyl 2-Benzyl-2-[(pyridine-2-sulfonyl)amino]acetate (3).** Compound **3** was obtained at 0 °C (6 h) from L-(+)-phenylalanine *tert*-butyl ester in 97% yield after purification by chromatography (eluent: ethyl acetate/hexane (7:13)): mp 73.5−76.3 °C; IR ($CHCl_3$) 1150, 1345, 1725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.12 (s, 9H), 2.94 (d, 2H, J = 5.9 Hz), 4.33−4.36 (m, 1H), 5.42 (br s, 1H), 7.03−7.11 (m, 5H), 7.29−7.31 (m, 1H), 7.70−7.73 (m, 1H), 7.76−7.79 (m, 1H), 8.47 (d, 1H, J = 4.8 Hz); ^{13}C NMR ($CDCl_3$) δ 27.66, 39.87, 57.70, 82.38, 121.59, 126.49, 126.92, 128.23, 129.59, 135.37, 137.90, 149.76, 157.84, 169.71; MS m/z

(9) Schäfer, A.; Benz, H.; Fiedler, W.; Guggisberg, A.; Bienz, S.; Hesse, M. In *The Alkaloids*; Cordell, G., Brossi, A., Eds.; Academic Press: Orlando, 1994; Vol. 45, p 1.

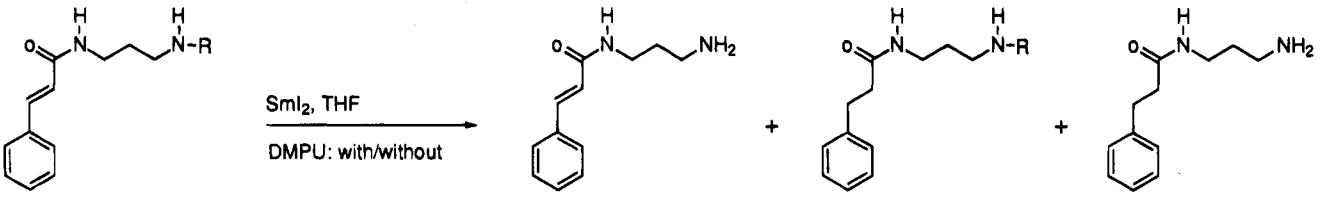
(10) Compounds **10a−c** were derived from **11**.[8] Amine **11** was prepared in two steps, starting from cinnamoyl chloride and commercial *N*-Boc-1,3-diaminopropane, in the presence of triethylamine and toluene (20 °C, 5 h, 75%). The resulting Boc derivative was deprotected by treatment with TFA in dichloromethane (20 °C, 4 h, 98%).

(11) Horner, L.; Singer, R. J. *Liebigs Ann. Chem.* **1969**, *723*, 1.

(12) Lund, H. In *Organic Electrochemistry*; Lund, H., Baizer, M. M., Eds.; Marcel Dekker: New York, 1991; p 257.

(13) Mairanovsky, V. G. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 281.

Scheme 2



10 (a, b or c) 11 12 (a or b) 13

entry	starting sulfonamides	R	conditions: additive	conditions: temp (°C)/ time (h)	products: total yield[a] (%)	products: ratio of 11:12:13
1	**10a**	Ts	DMPU	reflux/10	75	0:68:32
2	**10b**	$PhSO_2$	DMPU	reflux/4	79	0:61:39
3	**10c**	2-pyrSO_2	/	rt/4	60	92:0:8

[a] Yields are not optimized

363 $(M + H)^+$. Anal. Calcd for $C_{18}H_{22}N_2O_4S$: C, 59.65; H, 6.12; N, 7.73; S, 8.85. Found: C, 59.57; H, 6.02; N, 8.06; S, 8.83.

Piperidin-1-yl Pyridin-2-yl Sulfone (4). Compound **4** was obtained at 0 °C (3.5 h) from piperidine in 98% yield after purification by chromatography (eluent: ethyl acetate/hexane (2:3)): mp 55.2 °C; IR ($CHCl_3$) 1175, 1335 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.35–1.62 (m, 6H), 3.12–3.25 (m, 4H), 7.36–7.49 (m, 1H), 7.84–7.89 (m, 2H), 8.67 (d, 1H, J = 4.6 Hz); ^{13}C NMR ($CDCl_3$) δ 23.53, 25.29, 47.28, 122.82, 126.33, 137.72, 149.83, 156.51; MS m/z 227 $(M + H)^+$. Anal. Calcd for $C_{10}H_{14}N_2O_2S$: C, 53.08; H, 6.23; N, 12.38; S, 14.17. Found: C, 52.95; H, 6.06; N, 12.36; S, 14.42.

***N*-(α-Methylbenzyl)pyridine-2-sulfonamide (5).** Compound **5** was obtained at 0 °C (1.5 h) from D-(+)-α-methyl benzylamine in 94% yield after purification by chromatography (eluent: ethyl acetate/hexane (2:3)): mp 114.9 °C; IR ($CHCl_3$) 1175, 1335 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.47 (d, 3H, J = 6.9 Hz), 4.63 (q, 1H, J = 6.9 Hz), 6.57 (d, 1H, J = 7.4 Hz), 7.03–7.17 (m, 5H), 7.28–7.35 (m, 1H), 7.62–7.77 (m, 2H), 8.45 (d, 1H, J = 4.7 Hz); ^{13}C NMR ($CDCl_3$) δ 23.10, 54.19, 122.15, 126.26, 126.47, 127.26, 128.29, 137.75, 141.95, 149.61, 157.84; MS m/z 263 $(M + H)^+$. Anal. Calcd for $C_{13}H_{14}N_2O_2S$: C, 59.52; H, 5.38; N, 10.68; S, 12.22. Found: C, 59.18; H, 5.52; N, 10.58; S, 12.47.

***N*-Phenylpyridine-2-sulfonamide (6).** Compound **6** was obtained at 0 °C (2 h) from aniline in 70% yield after purification by chromatography (eluent: ethyl acetate/hexane (7:13)): mp 170.3 °C; IR ($CHCl_3$) 1175, 1350 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.06–7.11 (m , 1H), 7.18–7.21 (m, 4H), 7.43–7.47 (m, 1H), 7.78–7.81 (m, 1H), 7.83–7.90 (m, 1H), 7.96 (s, 1H), 8.73 (d, 1H, J = 4.7 Hz); ^{13}C NMR ($CDCl_3$) δ 122.55, 123.00, 125.55, 126.84, 129.09, 136.00, 137.90, 149.97, 156.12; MS m/z 234 $(M)^+$. Anal. Calcd for $C_{11}H_{10}N_2O_2S$: C, 56.40; H, 4.30; N, 11.96; S, 13.68. Found: C, 56.18; H, 4.51; N, 11.88; S, 13.61.

1-(Pyridine-2-sulfonyl)-1*H*-indole (7). Indole (0.250 g, 2.13 mmol) was added to a suspension of 60% NaH (0.111 g, 2.77 mmol) in DMF (9 mL) over 30 min at 0 °C. The reaction mixture was stirred for 15 min, and a solution of pyridine-2-sulfonyl chloride (0.417 g, 2.35 mmol) in DMF (1 mL) was then added dropwise at 0 °C. The solution was stirred for 2 h at 0 °C. The corresponding sulfonamide was obtained as a light-brown solid in 64% yield (0.352 g) after flash column chromatography (silica gel, eluent: ethyl acetate/hexane (3:7)): mp 51.3–52.2 °C; IR ($CHCl_3$) 1180, 1370 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.62–6.72 (d, 1H, J = 3.7 Hz), 7.19–7.32 (m, 2H), 7.35–7.42 (m, 2H), 7.62–7.70 (m, 1H), 7.80–8.15 (m, 3H), 8.51 (d, 1H, J = 4.6 Hz); ^{13}C NMR ($CDCl_3$) δ 108.76, 113.57, 121.26, 122.18, 123.36, 124.41, 127.23, 127.47, 130.70, 134.87, 138.02, 150.36, 155.30; MS m/z 259 $(M + H)^+$. Anal. Calcd for $C_{13}H_{10}N_2O_2S$: C, 60.45; H, 3.90; N, 10.84; S, 12.41. Found: C, 60.76; H, 4.00; N, 10.97; S, 12.73.

General Procedure for the Deprotection of Pyridine-2-sulfonamides. A well-degassed solution of pyridine-2-sulfonamide (0.5 mmol) in THF (1 mL) was added dropwise to a 0.1 M solution of SmI_2 in THF (30 mL, 3 mmol) under argon, at rt. After being stirred for 4 h, the solution was poured into a mixture of 2 g of KOH and 15 g of ice. The slurry mixture was then extracted with ether (3 × 40 mL), washed with brine (10 mL), dried with Na_2SO_4, and evaporated to dryness. Purification of the residue by flash column chromatography on silica gel yielded the deprotected amine. The amine was identified by comparison with a commercial sample (IR, ^1H NMR, ^{13}C NMR).

Dibenzylamine was obtained from **1** in 85% yield after purification by chromatography (eluent: ethyl acetate/hexane (2:3)).

Allylamine was obtained from **2** and isolated as its hydrochloride salt by addition of 4 N HCl.

Phenylalanine *tert*-butyl ester was obtained from **3** in 76% yield after purification by chromatography (eluent: ethyl acetate/hexane (2:3) to (3:2)) and then isolated as its hydrochloride salt: $[\alpha]^{20}_D$ +20.9 (c = 1, ethanol) ($[\alpha]^{20}_D$ +45.5 (c = 2, ethanol from Fluka).

Piperidine was obtained from **4** and isolated as its hydrochloride salt in 93% yield.

D-(+)-α-methylbenzylamine was obtained from **5** (600 mg; 2.29 mmol) in 83% yield after purification by chromatography (eluent: chloroform/methanol/ammonia water 25% (90:10:0.5)): $[\alpha]^{20}_D$ +31 (c = 1, ethanol) ($[\alpha]^{20}_D$ +31 (c = 10, ethanol) from Fluka).

Aniline was obtained from **6** and isolated as its hydrochloride salt in 94% yield.

Indole was obtained from **7** in 81% yield after purification by chromatography (eluent: ethyl acetate/hexane (1:9) to (3:7)).

(*E*)-*N*-(3-Aminopropyl)-3-phenylprop-2-enamide (11). A solution of cinnamoyl chloride (1.77g, 10.6 mmol) in toluene (20 mL) was added, over 1 h at rt, to a solution of *N*-Boc-1,3-diaminopropane (10.6 mmol, 1.85 g) and Et_3N (1.61g, 15.9 mmol) in toluene (50 mL). The resulting mixture was stirred for 4 h and then filtered. The filtrate was washed with several portions of dichloromethane. The organic phases were combined and washed four times with water (5 mL), dried (Na_2SO_4), and evaporated to dryness to give 2.31 g of *tert*-butyl *N*-[3-[(*E*)-3-phenylprop-2-enamido]propyl]carbamate (75% yield): mp 107–108 °C; IR ($CHCl_3$) 1625, 1660, 1690, 3340, 3370 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.46 (s, 9H), 1.68 (p, 2H, J = 6.0 Hz), 2.09 (d, 1H, J = 0.5 Hz), 3.21 (q, 2H, J = 6.0 Hz), 3.43 (q, 2H, J = 5.9 Hz), 5.03 (br s, 1H), 6.46 (d, 1H, J = 15.6Hz), 7.27–7.50 (m, 5H), 7.62 (d, 1H, J = 15.6 Hz); ^{13}C NMR ($CDCl_3$) δ 28.36, 30.21, 35.98, 37.00, 79.32, 120.94, 127.71, 128.71, 129.50, 134.82, 140.64, 156.75, 166.29; MS m/z 304 $(M)^+$. Anal. Calcd for $C_{17}H_{24}N_2O_3$: C, 67.08; H, 7.95; N, 9.20. Found: C, 66.88; H, 7.74; N, 9.03.

A solution of *tert*-butyl *N*-[3-[(*E*)-3-phenylprop-2-enamido]-propyl]carbamate (2.31 g, 7.88 mmol) and TFA (5.2 mL, 7.09 mmol) in dichloromethane (35 mL) was stirred for 4 h under nitrogen. After evaporation of the dichloromethane, 70 mL of methanol and 70 mL of 1 N HCl were added, followed by evaporation of the methanol (repeated three times). Compound **11** was isolated as its hydrochloride salt in 98% yield: mp 170.3–173.6 °C (MeOH); IR (KBr) 1620, 1650, 3420 cm^{-1}; ^1H NMR (CD_3OD) δ 1.84 (p, 2H, J = 6.1 Hz), 2.90 (t, 2H, J = 6.1 Hz),

3.33 (t, 2H, J = 6.1 Hz), 6.56 (d, 1H, J = 15.6 Hz), 7.21–7.50 (m, 6H), 11.6 (s, 1H); ^{13}C NMR (CD_3OD) δ 27.60, 35.80, 37.06, 120.11, 127.64, 128.73, 129.72, 134.86, 141.00, 168.14; MS m/z 205 (M + H)$^+$. Anal. Calcd for $C_{12}H_{16}N_2O$·1HCl: C, 59.87; H, 7.12; N, 11.64. Found: C, 59.91; H, 6.93; N, 11.39.

(*E*)-3-Phenyl-*N*-[3-[(toluene-4-sulfonyl)amino]propyl]-prop-2-enamide (10a). A solution of **11** (0.344 g, 1.42 mmol) and 1.46 mmol (0.281 g) of toluene-4-sulfonyl chloride in a 1:1 mixture of ether (2 mL) and 4 M solution of K_2CO_3 (2 mL) was stirred vigorously for 2 h at rt. The aqueous phase was extracted with dichloromethane (2 × 20 mL), dried (Na_2SO_4), and evaporated to dryness. Flash chromatography of the residue (silica gel, eluent: ethyl acetate/hexane (7:3)) provided 0.422 g (83%) of compound **10a** as a white solid: mp 130.8–131.3 °C (EtOH/Et_2O); IR ($CHCl_3$) 1160, 1320, 1610, 1655, 3285 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.68 (p, 2H, J = 6.0 Hz), 2.36 (s, 3H), 2.94 (q, 2H, J = 6.0 Hz), 3.49 (q, 2H, J = 6.0 Hz), 5.58 (t, 1H, J = 6.0 Hz), 6.33 (t, 1H, J = 6.0 Hz), 6.35 (d, 1H, J = 15.6 Hz), 7.35–7.49 (m, 8H), 7.50 (d, 1H, J = 15.6 Hz), 7.75 (d, 1H, J = 8.2 Hz); ^{13}C NMR ($CDCl_3$) δ 21.34, 29.51, 36.01, 39.87, 120.23, 126.92, 127.73, 128.71, 129.58, 129.65, 134.58, 136.94, 141.16, 143.16, 166.72; MS m/z 359 (M + H)$^+$. Anal. Calcd for $C_{19}H_{22}N_2O_3S$: C, 63.66; H, 6.19; N, 7.81; S, 8.94. Found: C, 63.88; H, 6.14; N, 7.78; S, 8.85.

(*E*)-*N*-[3-[(Phenylsulfonyl)amino]propyl]-3-phenylprop-2-enamide (10b). A solution of **11** (0.480g, 1.99 mmol) and 2.19 mmol (0.362 g) of phenylsulfonyl chloride in a 1:1 mixture of ether (4 mL) and 4 M K_2CO_3 (4 mL) was stirred vigorously for 2 h at rt. After separation of the two phases, the aqueous phase was extracted with dichloromethane (2 × 20 mL), dried (Na_2SO_4), and evaporated to dryness. Flash chromatography of the residue (silica gel, eluent: ethyl acetate/hexane (7:3)) provided 0.540 g (79%) of compound **10b** as a white solid: mp 115.7–116.7 °C; IR ($CHCl_3$) 1160, 1330, 1625, 1665, 3380 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.70 (p, 2H, J = 6.0 Hz), 2.94 (q, 2H, J = 6.0 Hz), 3.41 (q, 2H, J = 6.0 Hz), 6.31 (t, 1H, J = 6.0 Hz), 6.41 (d, 1H, J = 15.8 Hz), 6.63 (t, 1H, J = 6.0 Hz), 7.28–7.48 (m, 9H), 7.54 (d, 1H, J = 15.8 Hz), 7.85 (d, 1H, J = 7.7 Hz); ^{13}C NMR ($CDCl_3$) δ 29.46, 36.04, 39.93, 120.35, 126.84, 127.73, 128.73, 128.98, 129.66, 132.41, 134.56, 139.90, 141.07, 166.91; MS m/z 345 (M + H)$^+$. Anal. Calcd for $C_{18}H_{20}N_2O_3S$: C, 62.77; H, 5.85; N, 8.13; S, 9.31. Found: C, 62.92; H, 5.82; N, 7.94; S, 9.45.

(*E*)-3-Phenyl-*N*-[3-[(pyridine-2-sulfonyl)amino]propyl]-prop-2-enamide (10c). Following the general procedure, a solution of **11** (0.440 g, 1.83 mmol) and 2.74 mmol (0.487 g) of pyridine-2-sulfonyl chloride in a 1:1 mixture of ether (6 mL) and 4 M solution of K_2CO_3 (6 mL) was stirred vigorously for 4 h at 0 °C. After separation of the two phases, the aqueous phase was extracted with dichloromethane (2 × 20 mL), dried (Na_2SO_4), and evaporated to dryness. Flash chromatography of the residue (silica gel, eluent: ethyl acetate/hexane (4:1)) provided 0.600 g (92%) of compound **10c** as a white solid: mp 88.6–89.9 °C (ethyl acetate/ether); IR ($CHCl_3$) 1175, 1335, 1620, 1660, 3370 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.75 (p, 2H, J = 6.1 Hz), 3.31 (q, 2H, J = 6.1 Hz), 3.48 (q, 2H, J = 6.1 Hz), 6.06 (br s, 1H), 6.37 (t, 1H, J = 6.1 Hz), 6.44 (d, 1H, J = 15.6 Hz), 7.33–7.50 (m, 6H), 7.62 (d, 1H, J = 15.6 Hz), 7.86–8.10 (m, 2H), 8.68 (d, 1H, J = 4.2 Hz); ^{13}C NMR ($CDCl_3$) δ 29.87, 36.19, 40.76, 120.50, 122.12, 126.68, 127.84, 128.83, 129.73, 138.16, 141.19, 149.99, 166.64; MS m/z 346 (M + H)$^+$. Anal. Calcd for $C_{17}H_{19}N_3O_3S$: C, 59.11; H, 5.54; N, 12.17. Found: C, 58.97; H, 5.57; N, 12.36.

General Procedure for the Deprotection of Compounds 10a,b. A well-degassed solution of the 2-arenesulfonamide **10a,b** (0.6 mmol) in THF (4 mL) was added dropwise to a heterogenous mixture of DMPU (2.39 mL, 19.8 mmol) and SmI_2 in THF (0.1 M, 36 mL, 3.6 mmol) under argon, at rt. After refluxing, the reaction mixture was cooled to rt and was poured into a mixture of 2.5 g of KOH and 15 g of ice. The slurry mixture was then extracted with ether (3 × 50 mL), washed with brine (10 mL), dried (Na_2SO_4), and evaporated to dryness. Products **13** and **12a,b** were isolated after flash column chromatography on silica gel.

3-Phenyl-*N*-[3-[(toluene-4-sulfonyl)amino]propyl]propanamide (12a) and *N*-(3-Aminopropyl)-3-phenylpropanamide (13). Following the general procedure, the deprotection of **10a** (reflux, 10 h) provided 110 mg (51%) of **12a** and 30 mg (24%) of **13** after purification by chromatography (eluent: ethyl acetate/hexane (4:1)) and chloroform/methanol/ammonia water 25% (85:14:1)).

12a: mp 91.0–93.8 °C; IR ($CHCl_3$) 1160, 1330, 1660, 3380 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.46 (p, 2H, J = 6.1 Hz), 2.30 (s, 3H), 2.34 (t, 3H, J = 7.9 Hz), 2.68 (q, 2H, J = 6.1 Hz), 2.78 (t, 2H, J = 7.9 Hz), 3.15 (q, 2H, J = 6.1 Hz), 5.86 (t, 1H, J = 6.1 Hz), 6.08 (t, 1H, J = 6.1 Hz), 7.01–7.21 (m, 7H), 7.63 (d, 2H, J = 8.2 Hz); ^{13}C NMR ($CDCl_3$) δ 14.03, 29.45, 31.71, 35.74, 38.08, 39.64, 126.08, 126.88, 128.19, 128.35, 129.58, 137.03, 140.57, 143.19, 173.11; MS m/z 361 (M + H)$^+$. Anal. Calcd for $C_{19}H_{24}N_2O_3S$ + 2/5 C_6H_{14}: C, 65.08; H, 7.55; N, 7.09; S, 8.12. Found: C, 65.17; H, 7.39; N, 6.92; S, 8.26.

13 Hydrochloride: mp 141.8–142.8 °C (ethanol/ether); IR (KBr) 1660, 3300 cm^{-1}; ^{1}H NMR (CD_3OD) δ 1.80 (p, 2H, J = 6.6 Hz), 2.54 (t, 2H, J = 7.3 Hz), 2.78 (t, 2H, J = 7.3 Hz), 2.93 (t, 2H, J = 7.3 Hz), 3.25 (t, 2H, J = 6.6 Hz), 4.94 (br s, 3H), 7.16–7.31 (m, 5H); ^{13}C NMR (CD_3OD) δ 27.08, 31.28, 35.29, 36.60, 37.19, 125.81, 127.99, 128.03, 140.53, 174.43; MS m/z 207 (M + H)$^+$. Anal. Calcd for $C_{12}H_{18}N_2O$·1HCl + 1/5 EtOH: C, 59.11; H, 8.08; N, 11.12. Found: C, 58.99; H, 8.12; N, 10.82.

***N*-[3-[(Phenylsulfonyl)amino]propyl]-3-phenylpropanamide (12b) and 13.** Following the general procedure, the deprotection of **10b** (reflux, 4 h) provided 106 mg (48%) of **12b** and 38 mg (31%) of **13** (see above for characterization data) after purification by chromatography (eluent: ethyl acetate/hexane (7:3)) and chloroform/methanol/ammonia water 25% (85:14:1)).

12b: mp 87.2–88.2 °C; IR ($CHCl_3$) 1160, 1330, 1660, 3400 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.47 (p, 2H, J = 6.0 Hz), 2.36 (t, 2H, J = 7.8 Hz), 2.71 (q, 2H, J = 6.0 Hz), 2.81 (t, 2H, J = 7.8 Hz), 3.16 (q, 2H, J = 6.0 Hz), 5.87 (t, 1H, J = 6.0 Hz), 6.01 (t, 1H, J = 6.0 Hz), 7.04–7.50 (m, 9H), 7.78 (d, 1H, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$) δ 29.50, 31.58, 35.62, 38.15, 39.57, 126.10, 126.82, 127.70, 128.30, 128.92, 132.33, 140.22, 140.57, 173.02; MS m/z 347 (M + H)$^+$. Anal. Calcd for $C_{18}H_{22}N_2O_3S$ + 7/100 C_6H_{14}: C, 62.77; H, 6.57; N, 7.94. Found: C, 62.40; H, 6.68; N, 7.55.

***(E)*-*N*-(3-Aminopropyl)-3-phenylprop-2-enamide (11).** Following the general procedure for the deprotection of pyridine-2-sulfonamide a well-degassed solution of **10c** (200 mg, 0.58 mmol) in THF (2 mL) was added dropwise to a 0.1 M solution of SmI_2 in THF (35 mL, 3.5 mmol) under argon, at rt. After being stirred for 4 h, the solution was poured into a mixture of 2.5 g of KOH and 15 g of ice. The slurry mixture was then extracted with ether (3 × 50 mL), washed with brine (10 mL), dried (Na_2SO_4), and evaporated to dryness. Purification of the residue by flash column chromatography on silica gel (eluent: chloroform/methanol/ammonia water 25% (85:14:0.1) yielded 71 mg (60%) of compound **11** contaminated by 8% of **13** (see above for characterization data). The product ratio was estimated by ^{1}H NMR (integration of the signal CH_2=C*H*C_6H_5 for **11** and $CH_2C_6H_5$ for **13**).

General Procedure for Electrochemical Deprotection. Controlled-potential electrolysis was carried out in a cylindrical, three electrode, divided cell using an electronic potentiostat. Stirred mercury pool (area: 44 cm^2) adjusted to the required potential of the reaction; counter electrode: graphite rod. Reference electrode: SCE; SSE: 0.1 M n-$Bu_4N^+Br^-$ in 94% ethanol as catholyte and anolyte. T = 5 °C; argon atmosphere. After depletion of the electrolysis current to 10 mA background level (recorded i/t curve), the reaction was complete. (Consumption: approximately 125% of the calculated number of Coulombs). The catholyte was evaporated to dryness, and the residue was dissolved in a minimum amount of water saturated with solid K_2CO_3 and extracted three times with dichloromethane. The organic layer was then dried (Na_2SO_4) and evaporated to yield a residue which was flash chromatographed on silica gel (chloroform/methanol/ammonia water 25% (90:10:0.5) to (85:14:1)). The ratio of **11** to **13** was estimated by ^{1}H NMR (integration of the signal CH_2=C*H*C_6H_5 for **11** and $CH_2C_6H_5$ for **13**).

The first experiment, conducted at −1.72 V on 100 mg of compound **10c**, yielded 52 mg (88%) of a mixture (41:59) of **11** and **13**.

The second experiment, conducted at −1.65 V on the same scale, yielded 53 mg (90%) of a (24:1) mixture of **11** and **13**.

See above for characterization of compounds **11** hydrochloride and **13** hydrochloride.

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