Synthesis and cathodic cleavage of a set of substituted benzenesulfonamides including the corresponding *tert*-butyl sulfonylcarbamates: pK_a of sulfonamides

Barthélémy Nyasse,[a] Leif Grehn,[a] Ulf Ragnarsson,[a,*] Hernani L. S. Maia,[b] Luis S. Monteiro,[b] Ivo Leito,[c] Ilmar Koppel[c] and Juta Koppel[c]

[a] *Department of Biochemistry, University of Uppsala, Biomedical Center, PO Box 576, S-751 23 Uppsala, Sweden*
[b] *Departamento de Quimica, Universidade do Minho, Largo de Paço, 4719 Braga Codex, Portugal*
[c] *Institute of Chemical Physics, Tartu University, EE-2400 Tartu, Estonia*

From a series of substituted benzenesulfonic acids, most of which have previously been employed for the protection of amino functions and including a few such known to facilitate cleavage by acid, benzylamides **1a–k** have been derived and studied. Initially their electrochemical cleavage potentials were determined by cyclic voltammetry in order to further explore selective deprotection within this substance group. In parallel, the corresponding *tert*-butyl sulfonylcarbamates **2a–k** have also been prepared and studied. Among the sulfonamides investigated S–N bond cleavage was found to take place over a wide range of potentials from −1.67 to −2.64 V (excluding the nitro derivative), the most acid-labile groups requiring more negative potentials, whereas this cleavage was facilitated by 0.19–0.30 V for the sulfonylcarbamates. Small scale electrolyses of **2** at controlled potential with determination of the cleavage products formed were subsequently performed. For the *N*-benzylbenzenesulfonamides **1**, the pK_as in DMSO and in some cases also in water have been determined and found to be in the range 14.0–16.4 and 10.07–11.53, respectively.

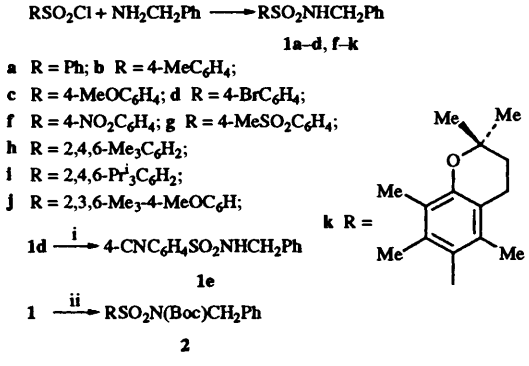
For a long time aromatic sulfonic acids have been used in the derivatization of amines and the protection of amino functions. Simple sulfonamides are among the most stable derivatives available for such compounds,[1a] thus requiring rather drastic conditions for subsequent regeneration of the amines. Hence, for cleavage of the prototype *N*-tosyl group, reagents like sodium in liquid ammonia,[2] refluxing concentrated strong acid such as HBr in the presence of phenol[3] and sodium naphthalenide[4] have been applied. The need for such harsh conditions restricted the use of tosyl and other related protecting groups to only very stable molecules and excluded the simultaneous application of many other labile protecting groups currently used. However, the scope for this application widened with the advent of efficient electrochemical methods for tosyl cleavage.[5] In parallel, efforts have been made to modify the tosyl group to make it more labile to acid. As a result of these efforts, a new generation of arenesulfonyl protecting groups have emerged primarily for the purpose of semi-permanent protection of the guanidine function in arginine.[6] Among these are the 4-methoxybenzenesulfonyl (Mbs),[7] the 4-methoxy-2,3,6-trimethylbenzenesulfonyl (Mtr)[8] and, more recently, the 2,2,5,7,8-pentamethylchromane-6-sulfonyl (Pmc) residues.[9]

Nowadays a very large number of useful and convenient protecting groups for various functional groups, including those present in peptides, are available,[1b] many of which are stable when subjected to the conditions under which sulfonamides undergo electrochemical cleavage. Therefore, in recent years we have investigated different aspects of cathodic S–N bond cleavage with particular reference to selective deprotection. Thus, these experiments have shown that selective detosylation of a primary sulfonamide can be accomplished on a preparative scale in the presence of a secondary one.[10] Further cleavage experiments on imidodicarbonates and acylcarbamates, including tosylcarbamates,[11] indicated that it might be worthwhile to investigate a series of substituted benzenesulfonylcarbamates in order to find out whether selective cleavage could be accomplished by substitution within the benzene ring. Such selectivity was previously achieved by the introduction of a second acyl group on the nitrogen atom as first reported by Singer and Sharpless.[12]

Results

Synthesis of the compounds studied

The *N*-benzylbenzenesulfonamides **1a–1d** and **1f–1k** were conveniently prepared from the appropriate arenesulfonyl chloride and benzylamine according to Scheme 1, as described



Scheme 1 *Reagents:* i, CuCN; ii, Boc_2O, DMAP

in detail in the Experimental section. We found that this procedure, using triethylamine as base and dichloromethane as solvent, gave a more facile work-up in comparison with performing the reaction in pyridine.[10] Compound **1e** was obtained by refluxing **1d** with an excess of CuCN in dry DMF.[13] This route to **1e** was chosen because of the high yield in this exchange reaction and also because the otherwise required 4-cyanobenzenesulfonyl chloride[14] was not readily available, thus requiring additional synthetic efforts.

The sulfonamides **1a–k** were smoothly converted into the corresponding *tert*-butyl sulfonylcarbamates $RSO_2N(Boc)$-

Table 1 Chemical properties of RSO_2NHBzl (compounds **1a**, **1c–k**)

Compound (formula)	R	Yield (%) (crude)	Mp (°C) (recr. solv.)	δ_H(270 MHz; rel. TMS)	Elemental analyses found (calc.)
1a ($C_{13}H_{13}NO_2S$)	Ph	100	86.5–87[a] (Et_2O–LP)	4.13 (2 H, d, NCH_2), 4.91 (1 H, t, NH), 7.16–7.30 (5 H, complex signal, Bzl aryl-H), 7.47–7.62 and 7.85–7.89 (together 5 H, complex signal, SO_2Ph-H)	—
1c ($C_{14}H_{15}NO_3S$)	4-$MeOC_6H_4$	95	107.5–108 (CH_2Cl_2–Et_2O)	3.87 (3 H, s, MeO), 4.10 (2 H, d, NCH_2), 4.86 (1 H, t, NH), 6.96 and 7.80 (4 H, ABq, SO_2 aryl-H), 7.17–7.31 (5 H, complex signal, Bzl aryl-H)	C, 60.7; H, 5.6; N, 5.1 (C, 60.6; H, 5.5; N, 5.1)
1d ($C_{13}H_{12}BrNO_2S$)	4-BrC_6H_4	99	121–122[b] (EtOAc–heptane)	4.13 (2 H, d, NCH_2), 5.00 (1 H, t, NH), 7.14–7.30 (5 H, complex signal, Bzl aryl-H), 7.61 and 7.69 (4 H, ABq, SO_2 aryl-H)	—
1e ($C_{14}H_{12}N_2O_2S$)	4-CNC_6H_4	99	141–142 (EtOAc–heptane)	4.19 (2 H, d, NCH_2), 5.19 (1 H, t, NH), 7.13–7.28 (5 H, complex signal, Bzl aryl-H), 7.74 and 7.90 (4 H, ABq, SO_2 aryl-H)	C, 61.7; H, 4.6; N, 10.2 (C, 61.7; H, 4.4; N, 10.3)
1f ($C_{13}H_{12}N_2O_4S$)	4-$NO_2C_6H_4$	100	126.5–127[c] (EtOAc–heptane)	4.22 (2 H, d, NCH_2), 5.18 (1 H, t, NH), 7.14–7.26 (5 H, complex signal, Bzl aryl-H), 7.97 and 8.29 (4 H, ABq, SO_2 aryl-H)	—
1g ($C_{14}H_{15}NO_4S_2$)	4-$MeSO_2C_6H_4$	81	171–172 (EtOAc)	3.10 (3 H, s, $MeSO_2$), 4.21 (2 H, d, NCH_2), 4.91 (1 H, t, NH), 7.16–7.29 (5 H, complex signal, Bzl aryl-H), 8.02 and 8.05 (4 H, ABq, SO_2 aryl-H)	C, 51.6; H, 4.7; N, 4.3 (C, 51.7; H, 4.6; N, 4.3)
1h ($C_{16}H_{19}NO_2S$)	2,4,6-$Me_3C_6H_2$	96	100–101 (Et_2O)	2.31 (3 H, s, 4-Me), 2.63 (6 H, s, 2,6-Me_2), 4.06 (2 H, d, NCH_2), 4.74 (1 H, t, NH), 6.96 (2 H, s, SO_2 aryl-H), 7.15–7.30 (5 H, complex signal, Bzl aryl-H)	C, 66.7; H, 6.3; N, 4.7 (C, 66.4; H, 6.6; N, 4.8)
1i ($C_{22}H_{31}NO_2S$)	2,4,6-$Pr^i_3C_6H_2$	98	94–94.5 (Et_2O–heptane)	1.25 [12 H, d, 2,6-(CH*Me*$_2$)$_2$], 1.27 (6 H, d, 4-CH*Me*$_2$), 2.92 (1 H, m, 4-C*H*Me_2), 4.15 (2 H, d, NCH_2), 4.17 [2 H, m, 2,6-(C*H*Me_2)$_2$], 4.57 (1 H, t, NH), 7.18 (2 H, s, SO_2 aryl-H), 7.17–7.32 (5 H, complex signal, Bzl aryl-H)	C, 71.0; H, 8.2; N, 3.6 (C, 70.7; H, 8.4; N, 3.7)
1j ($C_{17}H_{21}NO_3S$)	2,3,6-Me_3-4-$MeOC_6H$	98	128–129 (CH_2Cl_2–Et_2O)	2.13, 2.55 and 2.69 (3 × 3 H, 3 s, aryl-Me_3), 3.86 (3 H, s, MeO), 4.06 (2 H, d, NCH_2), 4.68 (1 H, t, NH), 6.59 (1 H, s, SO_2 aryl-H), 7.13–7.30 (5 H, complex signal, Bzl aryl-H)	C, 63.7; H, 6.7; N, 4.2 (C, 63.9; H, 6.6; N, 4.4)
1k ($C_{21}H_{27}NO_3S$)	2,2,5,7,8-Me_5-chroman-6-yl	96	132–132.5 (CH_2Cl_2–Et_2O)	1.33 (6 H, s, aliph. Me_2), 1.84 (2 H, t, CCH_2), 2.12, 2.53 and 2.55 (3 × 3 H, 3 s, aryl-Me_3), 2.64 (2 H, t, aryl-CH_2), 4.08 (2 H, d, NCH_2), 4.64 (1 H, t, NH), 7.14–7.28 (5 H, complex signal, Bzl aryl-H)	C, 67.6; H, 7.1; N, 3.8 (C, 67.5; H, 7.3; N, 3.7)

[a] Lit.,[16] mp 88 °C; LP = light petroleum (bp 40–65 °C). [b] Lit.,[17] mp 117 °C. [c] Lit.,[18] mp 126.0–128.8 °C (*sic*).

CH_2Ph **2a–k** by exhaustive *tert*-butoxycarbonylation using a slight excess of Boc_2O in dry acetonitrile, in the presence of a catalytic amount of 4-dimethylaminopyridine (DMAP).[15] After conventional work-up the desired products were all obtained as solids. The relevant data for compounds **1** and **2** are collected in Tables 1 and 2.

Cyclic voltammetry experiments

The sulfonamides **1a–k** as well as their corresponding *tert*-butyl sulfonylcarbamates **2a–k** were investigated by cyclic voltammetry. The experiments were performed at a vitreous carbon electrode at a substrate concentration of approximately 0.005 mol dm^{-3} in DMF, using Bu_4NBF_4 (0.1 mol dm^{-3}) as supporting electrolyte in the absence of a proton donor. A few typical cyclic voltammograms are shown in Fig. 1. Since the Boc group is not electroactive, the peaks observed in the voltammograms of **2** were obviously related to the substituted benzenesulfonyl group. The assignment of the first reduction peak to the cleavage of the substituted sulfonyl protecting group was achieved by electrolysing the *tert*-butyl sulfonylcarbamate at a potential slightly more negative than that corresponding to this peak followed by HPLC analysis of the products. Table 3 presents the potential, E_p, corresponding to the first cathodic peak for each of the substituted benzylamides **1a–k**, the potential, E'_p, for the corresponding *tert*-butyl sulfonylcarbamates **2a–k** and the shifts, ΔE and $\Delta E'$, caused by the substituent in both types of compounds, together with that, $\Delta E''$, caused by the Boc group.

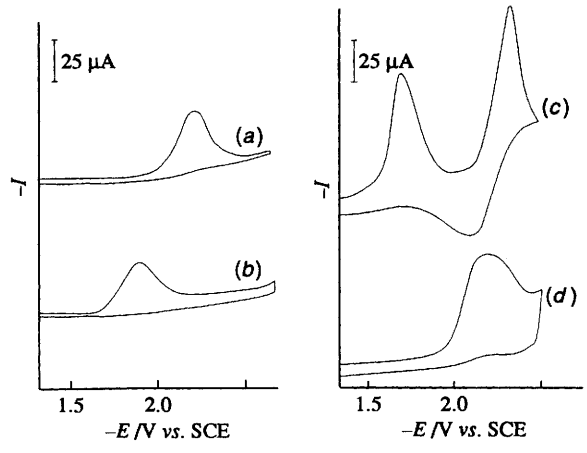


Fig. 1 Cyclic voltammograms at a vitreous carbon electrode of 0.005 mol dm^{-3} solutions of (*a*) **1a** (*b*) **2a** (*c*) **1e** (*d*) **1d** in DMF with 0.1 mol dm^{-3} Bu_4NBF_4 as supporting electrolyte at a sweep rate of 100 mV s^{-1} (SCE = saturated calomel electrode)

Electrolyses

As mentioned above, to confirm the previous assignment of the first voltammetry peak to cleavage of the substituted benzenesulfonyl group, small-scale electrolyses at controlled potential were carried out. In addition, the yields of deprotected product were determined to assess the feasibility of preparative

Table 2 Chemical properties of $RSO_2N(Boc)Bzl$ (compounds **2a**, **2c–k**)

Compound (formula)	R	Yield (%) (crude)	Mp (°C)[a] (recr. solv.)	δ_H(270 MHz; rel. TMS)	Elemental analyses found (calc.)
2a ($C_{18}H_{21}NO_4S$)	Ph	96	94.5–95.5 (Et_2O–LP)	1.30 (9 H, s, Boc-Me_3), 5.05 (2 H, s, NCH_2), 7.27–7.46 (5 H, complex signal, Bzl aryl-H), 7.53–7.59 and 7.66–7.71 (together 5 H, complex signal, SO_2Ph-H)	C, 62.2; H, 6.2; N, 3.9 (C, 62.2; H, 6.1; N, 4.0)
2c ($C_{19}H_{23}NO_5S$)	4-$MeOC_6H_4$	93[a]	100–101 (Et_2O–heptane)	1.34 (9 H, s, Boc-Me_3), 3.85 (3 H, s, MeO), 5.03 (2 H, s, NCH_2), 6.87 and 7.61 (4 H, ABq, SO_2 aryl-H), 7.29–7.41 (5 H, complex signal, Bzl aryl-H)	C, 60.5; H, 6.4; N, 3.6 (C, 60.5; H, 6.1; N, 3.7)
2d ($C_{18}H_{20}BrNO_4S$)	4-BrC_6H_4	91	121.5–122 (Et_2O–LP)	1.35 (9 H, s, Boc-Me_3), 5.03 (2 H, s, NCH_2), 7.30–7.39 (5 H, complex signal, Bzl aryl-H), 7.49 and 7.54 (4 H, ABq, SO_2 aryl-H)	C, 50.3; H, 4.7; N, 3.0 (C, 50.7; H, 4.7; N, 3.3)
2e ($C_{19}H_{20}N_2O_4S$)	4-CNC_6H_4	97	107–107.5 (Et_2O–LP)	1.35 (9 H, s, Boc-Me_3), 5.05 (2 H, s, NCH_2), 7.33–7.38 (5 H, complex signal, Bzl aryl-H), 7.69 and 7.71 (4 H, ABq, SO_2 aryl-H)	C, 61.0; H, 5.5; N, 7.4 (C, 61.3; H, 5.4; N, 7.5)
2f ($C_{18}H_{20}N_2O_6S$)	4-$NO_2C_6H_4$	96	131–132 (CH_2Cl_2–Et_2O)	1.36 (9 H, s, Boc-Me_3), 5.07 (2 H, s, NCH_2), 7.37 (5 H, perturbed signal, Bzl aryl-H), 7.78 and 8.23 (4 H, ABq, SO_2 aryl-H)	C, 55.1; H, 5.2; N, 7.1 (C, 55.1; H, 5.1; N, 7.1)
2g ($C_{19}H_{23}NO_6S_2$)	4-$MeSO_2C_6H_4$	94	116–116.5 (Et_2O)	1.35 (9 H, s, Boc-Me_3), 3.06 (3 H, s, $MeSO_2$), 5.06 (2 H, s, NCH_2), 7.34–7.40 (5 H, complex signal, Bzl aryl-H), 7.79 and 7.97 (4 H, ABq, SO_2 aryl-H)	C, 53.3; H, 5.3; N, 3.1 (C, 53.6; H, 5.4; N, 3.3)
2h ($C_{21}H_{27}NO_4S$)	2,4,6-$(Me_3)C_6H_2$	89[a]	115–115.5 (Et_2O–heptane)	1.26 (9 H, s, Boc-Me_3), 2.32 (3 H, s, 4-Me), 2.61 (6 H, s, 2,6-Me_2), 5.02 (2 H, s, NCH_2), 6.97 (2 H, s, SO_2 aryl-H), 7.26–7.38 and 7.47–7.50 (5 H, complex signal, Bzl aryl-H)	C, 65.0; H, 6.8; N, 3.4 (C, 64.8; H, 7.0; N, 3.6)
2i ($C_{27}H_{39}NO_4S$)	2,4,6-$(Pr^i_3)C_6H_2$	100	106–106.5 (crude)	1.13 (9 H, s, Boc-Me_3), 1.25 [18 H, d $(CHMe_2)_3$], 2.92 (1 H, m, 4-C*H*Me_2), 3.97 [2 H, m, 2,6-(C*H*$Me_2)_2$], 5.00 (2 H, s, NCH_2), 7.16 (2 H, s, SO_2 aryl-H), 7.24–7.38 and 7.49–7.53 (5 H, complex signal, Bzl aryl-H)	C, 68.7; H, 8.2; N, 3.0 (C, 68.5; H, 8.3; N, 3.0)
2j ($C_{22}H_{29}NO_5S$)	2,3,6-(Me_3)-4-$MeOC_6H$	92[a]	137–138 (CH_2Cl_2–hexane)	1.14 (9 H, s, Boc-Me_3), 2.16, 2.48 and 2.69 (3 × 3 H, 3 s, aryl-Me_3), 3.87 (3 H, s, CH_3O), 5.03 (2 H, s, NCH_2), 6.61 (1 H, s, SO_2 aryl-H), 7.26–7.37 and 7.47–7.50 (together 5 H, complex signal, Bzl aryl-H)	C, 62.8; H, 6.6; N, 3.3 (C, 63.0; H, 7.0; N, 3.3)
2k ($C_{26}H_{35}NO_5S$)	2,2,5,7,8(Me$_5$)-chroman-6-yl	63[a,b]	148.5–149 (CH_2Cl_2–hexane)	1.10 (9 H, s, Boc-Me_3), 1.33 (6 H, s, 2,2-Me_2), 1.84 (2 H, t, CCH_2), 2.13 and 2.49 (3 H + 6 H, 2 s, 5,7,8-Me_3), 2.66 (2 H, t, aryl-CH_2), 5.03 (2 H, s, NCH_2), 7.23–7.37 and 7.48–7.51 (together 5 H, complex signal, Bzl aryl-H)	C, 66.2; H, 7.4; N, 3.0 (C, 65.9; H, 7.4; N, 3.0)

[a] Recrystallized; LP = light petroleum (bp 40–65 °C). [b] Sluggish reaction requiring 2 equiv. of Boc_2O and prolonged reaction time for completion.

Table 3 Peak potentials and peak potential shifts obtained by cyclic voltammetry of compounds RSO_2NHBzl and $RSO_2N(Boc)Bzl$[a]

		RSO_2NHBzl **1**		$RSO_2N(Boc)Bzl$ **2**		
Compound	R	$-E_P$/V (*vs.* SCE)	ΔE[b]/V	$-E'_P$/V (*vs.* SCE)	$\Delta E'$[b]/V	$\Delta E''$[c]/V
a	Ph	2.30	—	2.05	—	0.25
b	4-MeC_6H_4	2.41	−0.11	2.14	−0.09	0.27
c	4-$MeOC_6H_4$	2.50	−0.20	2.28	−0.23	0.22
d	4-BrC_6H_4	~2.2	~0.1	~1.95	~0.1	~0.25
e	4-CNC_6H_4	1.67	0.63	1.44	0.61	0.23
f	4-$NO_2C_6H_4$	(0.75)		(0.70)[d]		
g	4-$MeSO_2C_6H_4$	1.81	0.49	1.51	0.54	0.30
h	2,4,6-$Me_3C_6H_2$	2.40	−0.10	2.19	−0.14	0.21
i	2,4,6-$Pr^i_3C_6H_2$	2.47	−0.17	2.26	−0.21	0.21
j	2,3,6-Me_3-4-$MeOC_6H$	2.59	−0.29	2.40	−0.35	0.19
k	2,2,5,7,8-Me_5-chroman-6-yl	2.64	−0.34	2.43	−0.38	0.21

[a] Cathode: vitreous carbon. Solvent: DMF. Supporting electrolyte: Bu_4NBF_4 0.1 mol dm^{-3}. [b] $\Delta E = E_P - E_H$, $\Delta E' = E'_P - E'_H$ where E_H and E'_H are the peak potentials of the unsubstituted compounds **1a** and **2a**, respectively, and E_P and E'_P are those of the substituted derivatives **b–k**. [c] $\Delta E'' = E'_P - E_P$. [d] No cleavage.

cathodic cleavage under the experimental conditions previously developed.[10,11,19] All the *tert*-butyl sulfonylcarbamates were electrolysed in acetonitrile (~0.005 mol dm^{-3} of substrate) containing Et_4NCl (0.1 mol dm^{-3}) as supporting electrolyte and Et_3NHCl (0.015 mol dm^{-3}) as proton donor. The reactions were carried out at a potential 50 mV more negative than that related to the first reduction peak of the corresponding voltammogram, as obtained from Table 3. All reactions were monitored by HPLC and interrupted when essentially all the starting material had been consumed. The yields of Boc-NHBzl as measured by

Table 4 Yields of Boc-NHBzl from small scale electrolyses at controlled potential of compounds $RSO_2N(Boc)Bzl$ **2**[a]

Compound 2	R	Yield by HPLC (%)
a	Ph	95
b	4-MeC_6H_4	96
c	4-$MeOC_6H_4$	92
d	4-BrC_6H_4	79
e	4-CNC_6H_4	40
f	4-$NO_2C_6H_4$	0
g	4-$MeSO_2C_6H_4$	67
h	2,4,6-$Me_3C_6H_2$	79
i	2,4,6-$Pr^i_3C_6H_2$	86
j	2,3,6-Me_3-4-$MeOC_6H$	81
k	2,2,5,7,8-Me_5-chroman-6-yl	67

[a] Cathode: vitreous carbon. Solvent: acetonitrile. Supporting electrolyte: Et_4NCl 0.1 mol dm^{-3}. Substrate concentration: 0.005 mol dm^{-3}. Proton donor: Et_3NHCl 0.015 mol dm^{-3}.

Table 5 Acidities of some NH-acids RSO_2NHCH_2Ph in dimethyl sulfoxide and aqueous solution at 25 °C

		pK_a	
Compound	R	DMSO	H_2O[a]
1a	Ph	15.7	11.25[16]
1b	4-MeC_6H_4	16.1	11.55[16]
1c	4-$MeOC_6H_4$	16.4	11.53
—	4-FC_6H_4	—	11.05[16]
—	4-ClC_6H_4	—	10.75[16]
1d	4-BrC_6H_4	15.3	10.71
1e	4-CNC_6H_4	14.3	10.35
—	3-$NO_2C_6H_4$	—	9.84[16]
1f	4-$NO_2C_6H_4$	14.0	10.07
1g	4-$MeSO_2C_6H_4$	14.4	10.25
1h	2,4,6-$Me_3C_6H_2$	16.4	
1i	2,4,6-$Pr^i_3C_6H_2$	15.9	
1j	2,3,6-Me_3-4-$MeOC_6H$	16.2	
1k	2,2,5,7,8-Me_5-chroman-6-yl	16.4	

[a] The pK_a values in ref. 16 were determined at 20 °C.

HPLC analysis of the electrolyses products are presented in Table 4. In none of these electrolyses was concomitant base-induced cleavage of the Boc-group observed.

Determination of pK_a values for compounds 1

For a large number of arenesulfonamides, including **1a** and **1b**, pK_a values in water have previously been determined and correlated with respect to substituents present in the benzenesulfonyl moiety.[16] We have now extended this work to include additional compounds in an aqueous medium and furthermore determined the pK_a values of compounds **1a–k** in DMSO. Such determinations were recently performed for a series of compounds consisting of imidodicarbonates and a few sulfonylcarbamates and for which the pK_a data turned out to be most illuminating.[20] The results of these measurements, together with some relevant literature data,[16] are compiled in Table 5.

Discussion

Cyclic voltammetry data

The voltammograms of compounds **2a–c** and **h–k** showed only one irreversible cathodic peak. The 4-bromo derivative (compound **2d**) presented two such peaks, which overlapped to form a broad wave with a current maximum at approximately −2.2 V *versus* SCE. As previously reported by other authors,[21] for the 4-cyano derivatives (compound **2e**) two cathodic waves were also noticed, *i.e.* (i) an irreversible peak at −1.67 V *versus* SCE and (ii) a peak at a more negative potential with a corresponding anodic peak in the reverse sweep. The 4-nitro derivative **2f** displayed three cathodic peaks and none could be detected in the reverse sweep. Finally, the 4-methylsulfonyl derivative **2g** presented two cathodic peaks and no anodic signals in the reverse sweep.

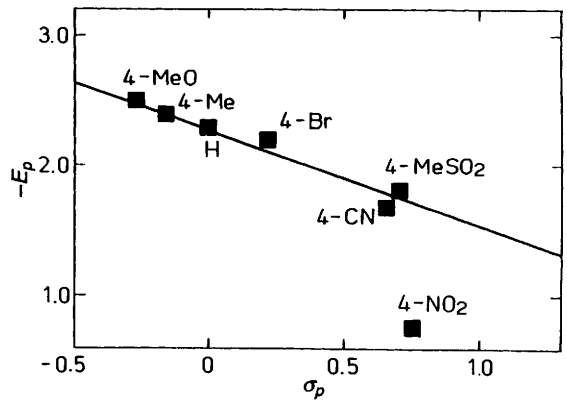


Fig. 2 Plot of peak potentials E_p *vs.* σ_p for *para*-substituted *N*-benzylbenzenesulfonamides **1**

A preliminary assignment of the first cathodic peak to cleavage of the protecting group allows the following conclusions to be drawn from the results in Table 3 with regard to the effect of the substituents on the peak potentials. Benzenesulfonyl has a cleavage potential slightly less negative than the corresponding 4-methyl substituted group (tosyl). This is in agreement with the mild electron-donating properties of alkyl groups. However, the effect of further substitution with alkyl groups is negligible. Substitution with a methoxy group shifts the reduction potential to more negative values due to its electron-releasing resonance effect; the effect of simultaneous alkyl and methoxy substitution is roughly additive in compounds **2j** and **k**. In agreement with previous observations, the methylsulfonyl[22] and the cyano[21,22] groups shift the reduction potential towards values less negative than those associated with reduction of the unsubstituted benzenesulfonyl group, whereas bromine substitution causes a small shift to less negative values of the reduction potential. Finally, the 4-nitrobenzenesulfonyl derivative **2f** displayed cathodic peaks at significantly less negative potentials, in agreement with those found previously for other nitro substituted protecting groups.[19,23,24] For this compound, however, at this potential no cleavage was observed.[25]

The electrochemical cleavage of the substituted benzenesulfonyl groups in compounds **1** could be rationalized by setting up a simple Hammett-type equation [eqn. (1)] in coordinates

$$-E_P = (2.30 \pm 0.08) - (0.78 \pm 0.08)\sigma_p \qquad (1)$$
$$n = 5 \quad s = 0.08 \quad r = 0.977$$

E_P *vs.* σ_p[26] (Fig. 2). *ortho*-Substituted derivatives were excluded from this correlation.

Compound **1f** deviates remarkably from this relationship (*ca.* 1 V) and this deviation cannot be eliminated by using π-electron acceptor (−R) substituent constants σ_p^- instead of σ_p.[26]

Electrolysis

Cathodic reduction of compounds **2a–c** gave high yields of Boc-NHBzl, whereas lower yields were obtained with the polysubstituted benzenesulfonyl derivatives. This might be due to steric hindrance to coplanarity as referred to by Zuman,[27] since in compounds **2h–k** an alkyl group is *ortho* to the sulfonyl function. In fact, this author postulated that such an electron

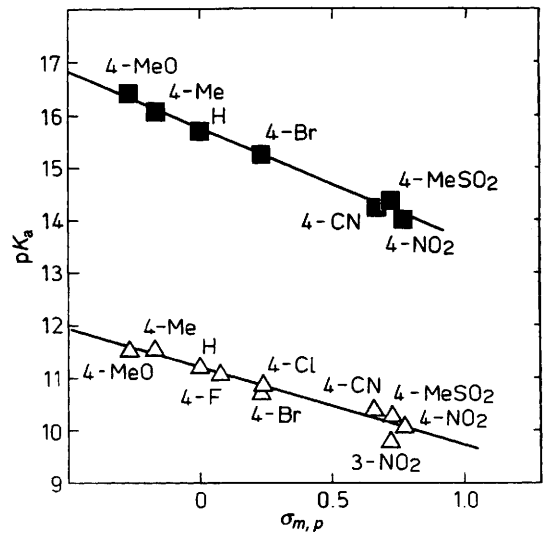


Fig. 3 Plot of pK_as *vs.* $\sigma_{m,p}$ for *para*-substituted *N*-benzylbenzenesulfonamides **1**; ■: in DMSO; △: in H_2O

interaction leading to conjugation effects is only fully possible when the interacting bonds are coplanar. Bulky substituents in the vicinity of these bonds may prevent them from achieving coplanarity and so limit their interaction. The author found that such an effect resulted in a more negative half-wave potential for *ortho* substituted derivatives as compared with the *meta* and *para* analogues.

During electrolysis of the bromo derivative, formation of the unsubstituted *tert*-butyl sulfonylcarbamate could be detected by HPLC analysis. The amount of this compound increased at the beginning of the electrolysis but then decreased steadily to almost zero. As the unsubstituted compound thus formed has a reduction potential similar to that of the bromo derivative, it underwent further electrolysis to Boc-NHBzl. This behaviour further suggests that the two overlapping peaks detected in the cyclic voltammograms of *N*-benzyl-4-bromobenzenesulfonamide and the respective *tert*-butyl sulfonylcarbamate corresponded to cleavage both of the protecting group and to that of the C–Br bond.

For the cyano derivative **2e** the yield of Boc-NHBzl was fairly low. At the end of the electrolysis the catholyte gave several HPLC peaks in addition to that corresponding to Boc-NHBzl. This might be due to electrolytic cleavage of the C–CN bond, which was noticed in certain aromatic nitriles with electron-deficient rings.[28–30] Other side reactions of cyano substituted groups such as the reduction of the cyano function[28] or formation of the dianion derived from 4-cyanobenzenesulfinic acid, which could react with the starting material,[21] have also been proposed to occur.

When electrolysis was carried out with the nitro derivative under comparable experimental conditions, no Boc-NHBzl could be detected. The same was the case in experiments using DMF instead of acetonitrile and when MeOH was substituted for Et_3NHCl as proton donor or when no proton donor was used and this is in agreement with previous work.[23,31]

The yield obtained in the electrolysis of the methylsulfonyl derivative was only moderate. However, since an HPLC peak corresponding to **2a** was not observed, this could not be related to cleavage of the methylsulfonyl group, which is known to occur in aqueous solution.[22]

pK_a Data for compounds 1

Compounds **1a–k** are moderately weak acids in both DMSO and aqueous media.[16] A closer comparison of their pK_a values with those of other compounds[20,32,33] recently investigated shows that the weaker ones approach Boc_2NH [pK_a (DMSO) = 16.9,[20] pK_a (H_2O) = 11.0[33]] in acidity, whereas at the other end of the scale the slightly more acidic ones are in the region between Z_2NH [pK_a (DMSO) = 14.2,[20] pK_a (H_2O) = 10.3[33]] and ZNHCOPh [pK_a (DMSO) = 13.7,[32] pK_a (H_2O) = 9.4[33]]. The literature data[16] further indicates that for fixed benzenesulfonyl groups in aqueous solution the *N*-benzyl compounds are slightly more acidic (by *ca.* 0.2–0.3 pK_a units) than the corresponding *N*-methyl derivatives.

The maximum variation in acidity in DMSO within the series of compounds studied is 2.4 pK_a units whereas in aqueous solution the range is even lower. As a rule, for these compounds, going from water to DMSO decreases the acidity by 4–5 pK_a units which is characteristic of NH-acids of similar structure.[33]

Inspection of Tables 3 and 5 shows that a rough qualitative correlation exists between the electrochemical cleavage potentials E_P and the pK_a values within this series of compounds. As a rule acid-labile compounds like **1c**, **1j** and **1k** are the least acidic and require the most negative potential for electrochemical cleavage. Therefore, the acidic deprotection and electrochemical cleavage might turn out to be complementary methods for this type of derivative.

As reflected by the Hammett plot, for the *para* and *meta* substituted derivatives, the acidity of compounds **1a–g** (or **j**) increases with increasing σ-constants of the substituent attached to the aromatic ring:

$$\text{DMSO} \quad pK_a = (15.8 \pm 0.1) - (2.1 \pm 0.1)\sigma_p \qquad n = 7 \quad s = 0.12 \quad r = 0.995$$

$$H_2O \quad pK_a = (11.2 \pm 0.1) - (1.48 \pm 0.12)\sigma_{m,p} \qquad n = 10 \quad s = 0.12 \quad r = 0.973$$

As shown by the corresponding ρ-values, the sensitivity towards substituent effects is *ca.* 1.5 times higher in DMSO than in water. Like E_P, pK_a also exhibits a low sensitivity to change on successive introduction of several alkyl groups into the benzenesulfonyl moiety.

In contrast to the cleavage potentials, the Hammett plots for the pK_a-values do not reveal any exceptional substituent effect of the 4-NO_2-group in **1f** (Fig. 3). The anomalous cathodic behaviour of **2f** is presumably due to reduction of the nitro function.

Conclusions

In benzylamides, the unsubstituted benzenesulfonyl group has a cleavage potential 0.1 V less negative than that exhibited by tosyl and the yields obtained in the cathodic cleavage of both are comparable. Hence, the former should be used instead of the latter in combination with other groups when a shift of this size may improve selective cleavage of the S–N bond. The 4-methoxybenzenesulfonyl group has a cleavage potential 0.1 V more negative than tosyl and good yields are also obtained in its reductive cleavage. It could offer a similar advantage over tosyl if it is to remain intact in an electrochemical experiment.

On the other hand, protecting groups of this type containing substituents with strong electron-withdrawing effects, which significantly shift the cathodic cleavage to less negative potentials, seem to be subject to side reactions that lower the yield of deprotected product. These difficulties could not be overcome by changes in experimental conditions. No cleavage could be achieved for compound **2f**.

Experimental

General procedures

All solvents used in the synthetic procedures were dried over molecular sieves (4 Å). Analytical grade Et_4NCl was used

without further purification. Et_3NHCl and Bu_4NBF_4 were prepared by procedures described elsewhere.[11] Acetonitrile was purified by distillation from CaH_2 under nitrogen. DMF was stored over $MgSO_4$ and then distilled from CaH_2 at reduced pressure. All HPLC experiments were run on a Shimadzu instrument, type 6A, connected to a Merck prepacked column, LiChrospher 100 RP-18, 5 μm, 250 × 4 mm with a mixture of acetonitrile and water as eluent. The peaks were measured with a Shimadzu integrator, type C-R6A Chromatopack.

Preparation of *N*-benzyl-4-bromobenzenesulfonamide 1d. Typical procedure

Freshly distilled benzylamine (4.33 g, 40.4 mmol) in dichloromethane (DCM, 100 cm^3) was chilled in ice with the exclusion of moisture and then triethylamine (4.40 g, 44 mmol) was added to it. The resulting solution was treated dropwise under stirring with 4-bromobenzenesulfonyl chloride (10.24 g, 40.0 mmol) also dissolved in DCM (40 cm^3) over 1 h at 0 °C and then left overnight at ambient temperature. After concentration to *ca.* 100 cm^3 the solution was partitioned between EtOAc (600 cm^3) and 1 mol dm^{-3} $KHSO_4$ (300 cm^3) and the organic extract was washed successively with 1 mol dm^{-3} $KHSO_4$, 1 mol dm^{-3} $NaHCO_3$ and sat. NaCl (3 × 150 cm^3 each). The extract was dried (Na_2SO_4) and then evaporated to give the title compound **1d** as a white solid (12.93 g, 99%), TLC gave one spot (toluene–MeCN, 2:1; Cl_2–dicarboxidine[34]); the product was recrystallized from EtOAc–heptane (1:4) (25 cm^3 g^{-1}; carbon) to give white fluffy crystals, mp 121–122 °C (lit.,[17] 117 °C). For additional data, see Table 1.

Preparation of *N*-benzyl-4-cyanobenzenesulfonamide 1e

Recrystallized **1d** (4.89 g, 15.0 mmol) was dissolved in *N*,*N*-dimethylformamide (DMF) (23 cm^3) and finely ground, carefully dried CuCN (2.00 g, 22.5 mmol) was added to it. The slurry was stirred at 150 °C under nitrogen for 18 h, giving a clear, yellowish solution which was treated with $FeCl_3$ (8 g, 49 mmol) in 2 mol dm^{-3} HCl (15 cm^3) at 70 °C giving a dark sludge. After being stirred at this temperature for 30 min, the resulting mixture was partitioned between EtOAc (600 cm^3) and 1 mol dm^{-3} HCl (300 cm^3). The green, aq. phase was discarded and the pale yellow organic extract was washed in turn with 1 mol dm^{-3} HCl and sat. NaCl (3 × 150 cm^3 each) and dried (Na_2SO_4). Evaporation provided a dirty yellow solid residue which was taken up in DCM (75 cm^3). The turbid solution was treated with carbon, filtered and taken to dryness to give the title compound **1e** (4.03 g, 99%), TLC as above gave one spot; an analytical specimen was obtained by recrystallisation from EtOAc–heptane (1:3) (40 cm^3 g^{-1}) as white, shiny flakes, mp 141–142 °C (see also Table 1).

4-Dimethylaminopyridine (DMAP) catalysed *tert*-butoxycarbonylation of sulfonamides. Preparation of *N*-benzyl-*N*-*tert*-butoxycarbonyl-4-cyanobenzenesulfonamide 2e. Typical procedure

A solution of **1e** (1.36 g, 5.00 mmol) and Boc_2O (1.20 g, 5.50 mmol) in MeCN (15 cm^3) was treated with DMAP (61 mg, 0.50 mmol) and left overnight under nitrogen. Most of the solvent was evaporated off and the oily residue was partitioned between diethyl ether (100 cm^3) and 0.2 mol dm^{-3} citric acid (50 cm^3). The pale yellow ethereal extract was washed successively with 0.2 mol dm^{-3} citric acid, 1 mol dm^{-3} $NaHCO_3$ and sat. aq. NaCl (3 × 25 cm^3) and dried ($MgSO_4$). After carbon treatment evaporation gave a colourless solid (1.80 g, 97%), TLC as above gave one spot, white, fluffy needles were obtained after recrystallization from diethyl ether–light petroleum (1:3) (45 cm^3 g^{-1}), mp 107–107.5 °C (see also Table 1).

Electrochemical apparatus and experimental procedures

The electrochemical apparatus and experimental procedures used for cyclic voltammetry were identical with those described elsewhere.[11] In all cases solutions of the substrate (approximately 0.005 mol dm^{-3}) in DMF containing Bu_4NBF_4 (0.1 mol dm^{-3}) as the supporting electrolyte were used. The sweep rate was 100 mV s^{-1}.

The electrochemical apparatus and experimental procedures used for small-scale controlled-potential electrolysis were also identical with those described elsewhere.[11] In all cases acetonitrile was used as solvent with Et_4NCl (0.1 mol dm^{-3}) as supporting electrolyte and Et_3NHCl (0.015 mol dm^{-3}) as a proton donor. The substrate concentration used was approximately 0.005 mol dm^{-3}.

Determination of pK_a values

The pK_a measurements of NH acids in dimethyl sulfoxide (DMSO) were performed as described earlier.[20,32,33] The experimental uncertainties range within ±0.2–0.3 pK_a units. The pK_a measurements for compounds **1c–g** in aqueous solution were performed using a spectrophotometric technique.[35] The experimental uncertainty of these pK_a values is ±0.02–0.05 pK_a units.

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