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Electrochemical Cleavage of Sulfonamides: An Efficient and Tunable Strategy to Prevent β-Fragmentation and Epimerization

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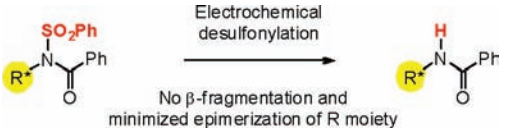
ABSTRACT



The electrochemical reduction of sensitive sulfonamides is described. The addition of a benzoyl group on the nitrogen atom facilitates the reductive cleavage of sulfonamides preventing β-fragmentation and epimerization. This strategy was successfully applied to the cyclopropylamine and to α-amino stannanes.

Sulfonamides play a pivotal role in amine chemistry, not only as a class of nitrogen protecting groups but also as activating groups or derivatization reagents.[1] In particular, *N*-arenesulfonyl groups are highly valued in synthetic chemistry for their ease of introduction, robustness, unreactivity toward a large range of nucleophiles, and the high crystallinity of the corresponding amino compounds. However, their major drawback lies in their removal which often requires harsh conditions thus lowering their synthetic appeal. Although several chemical deprotection methods of amines bearing an arenesulfonyl group have been reported,[2] the selective deprotection of functionalized molecules still remains a challenge. Besides chemical methods, electrochemical reduction has also emerged as a mild and tunable alternative for the cleavage of arenesulfonamides.[3] For instance, we have recently applied an electrochemical reduction for the

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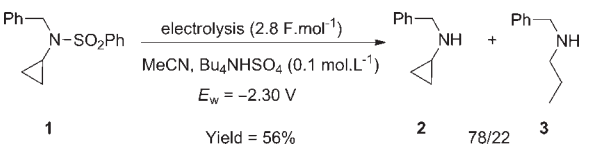
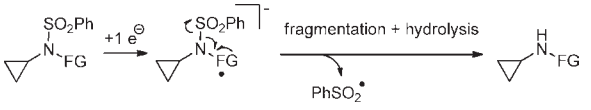
Scheme 1. Electrochemical Desulfonylation of **1**



smooth cleavage of a benzenesulfonamide derived from phenylglycinol and cyclopropylamine.[3f] During our studies on electrochemical desulfonylation of **1**, we observed the formation of not only the desired product **2** but also **3** due to ring opening of the cyclopropyl aminyl radical (Scheme 1).

We surmised that this side reaction could be suppressed by shifting the radical from the nitrogen to a neighboring group. With a suitable nitrogen substituent (FG), the electron could be transferred from the electrode onto this FG (Scheme 2). This would prevent the formation of the aminyl radical and would inhibit the opening of the cyclopropyl ring allowing the clean formation of a desulfonylated cyclopropylamine after hydrolysis. The nitrogen substituent (FG) needs to fulfill several criteria: (i) the LUMO must be localized on the FG. During electroreduction, an electron moves from the electrode to the LUMO of the substrate to produce a radical anion. This allows subsequent fragmentation to occur; for this reason the LUMO must be localized on the FG in order to receive the additional electron. (ii) The FG must be recovered after hydrolysis and workup procedure, and (iii) the FG should be easy to introduce and to cleave.

Scheme 2. Concept of the Electrochemical Desulfonylation Avoiding β-Fragmentation



To satisfy these conditions, we replaced the benzyl group by a benzoyl moiety ensuring that a previous report dealing with the chemical deprotection of *N*-acyl sulfonamides was taken into consideration.[2i,4] First, DFT calculations were performed to evaluate the influence of the benzoyl group on the electronic distribution. After optimization of the geometries of structures **1** and **4** at the B3LYP/6-31+G(d,p) level of theory, it was found that addition of one electron to these structures led to different localizations of the unpaired electron. In the case of $[\mathbf{1}]^{\bullet-}$, natural bond orbital (NBO) analysis pointed out that the additional electron was localized in a C=C antibonding π^* of the benzenesulfonyl moiety, whereas it was localized in the C=O antibonding π^* of the benzoyl group for $[\mathbf{4}]^{\bullet-}$ (Figure 1).

(4) Knowles, H. S.; Parsons, A. F.; Pettifer, R. M. *Synlett* **1997**, 271–272.

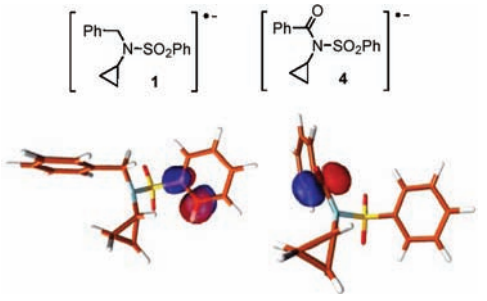


Figure 1. Localized SOMO for compounds **1** and **4** with one electron added.

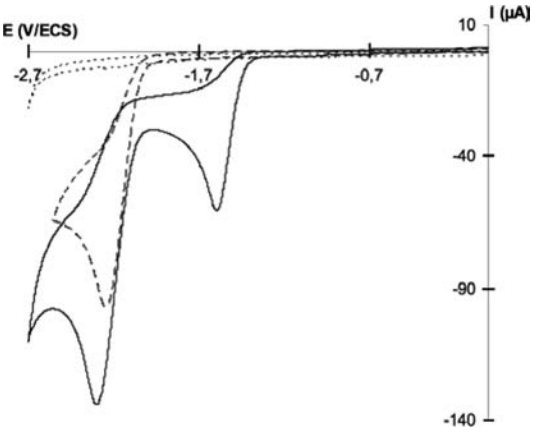
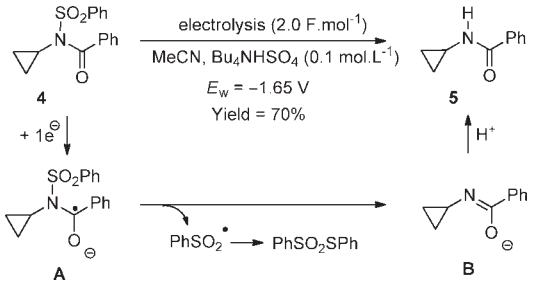


Figure 2. Cyclic voltammograms at a glassy carbon electrode in MeCN and Bu_4NHSO_4 (0.1 mol·L^{-1}), $v = 100$ mV·s^{-1} (···), in the presence of **1** (---), $c = 3 \times 10^{-3}$ mol·L^{-1}, and in the presence of **4** (—), $c = 3 \times 10^{-3}$ mol·L^{-1}.

Based on the strong difference between the electronic distributions predicted by DFT calculations, we embarked upon cyclic voltammetry studies to determine the influence of the benzoyl moiety on the redox behavior of **4** compared to **1** (Figure 2). The cyclic voltammogram of **4** shows two irreversible reduction processes with cathodic peak potentials at $E_{p,c} = -1.60$ V and $E_{p,c} = -2.31$ V (vs SCE). Compared to the cyclic voltammogram of **1**, the presence of the benzoyl substituent in **4** involves an additional reduction process at −1.60 V (vs SCE).

In order to determine the nature of this process, bulk electrolysis of **4** was conducted under constant cathodic potential at −1.65 V on a mercury pool cathode. After passing 2.0 F·mol^{-1}, we were delighted to observe the clean removal of the benzenesulfonyl group to afford the desired amide **5** in 70% yield after flash chromatography without any trace of the ring-opening product. In line with DFT calculations and electrochemical analysis, a mechanistic pathway is proposed (Scheme 3). The first reduction involves the transfer of one electron to the benzoyl moiety (formation of the radical anion **A**). The benzenesulfonyl

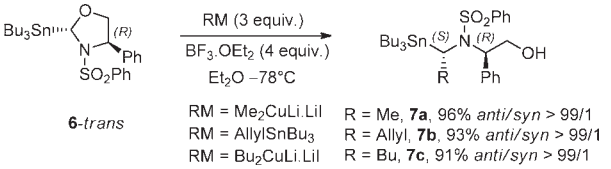
Scheme 3. Electrochemical Desulfonylation of **4**



radical is then eliminated via β-fragmentation to form enolate **B** which can undergo protonation to lead to **5**. Furthermore, GC-MS analysis of the crude reaction mixture indicated the presence of $PhSO_2SPh$ as a byproduct due to dimerization of the benzenesulfonyl radical in reductive conditions.[5] The second reduction process at -2.31 V corresponds to the reductive cleavage of the benzoyl group.

With this hypothesis in hand, we decided to extend the concept to more challenging substrates such as enantioenriched *N*-benzenesulfonyl α-aminoorganostannanes. These compounds are important for the stereocontrolled synthesis of enantioenriched nitrogen-containing compounds via Sn/Li transmetalation[6] or Stille cross-coupling.[7] Recently, we have developed the preparation of such compounds[8] and found that ring opening of *N*-benzene-sulfonyl-2-tributylstannyl-1,3-oxazolidine **6**-*trans* affords the corresponding tributylstannyl-α-amino alcohols **7a**−**c** in high yields and with excellent *anti* selectivity (*anti*/*syn* > 99/1) (Scheme 4).[9]

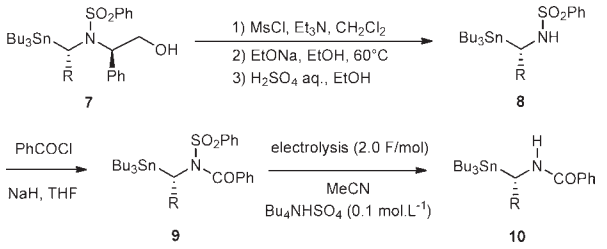
Scheme 4. Synthesis of Compounds **7**



After cyclic voltammetry analysis exhibiting an irreversible two-electron process at $E_{p,c} = -2.19$ V (vs SCE),[10] the bulk electrolysis of **7b** conducted under constant cathodic potential at -2.22 V (vs SCE) on a mercury pool cathode did not afford the expected deprotected β-aminoalcohol due to a homolytic β-fragmentation of the primary formed aminyl radical.[10]

According to our strategy, the conversion of the α-aminoorganostannane compounds **7** into their *N*-benzoyl derivatives might prevent β-fragmentation of the tributylstannyl radical. We set about carrying out the cleavage of the phenylglycinol moiety in order to obtain the expected *N*-benzenesulfonyl secondary amines. This involved a three-step sequence leading to **8** in moderate to good yields (Table 1).[11] The sulfonamides **8** were then reacted with benzoyl chloride in THF to produce the corresponding *N*-benzenesulfonamides **9** in excellent yields (Table 1). The electrochemical behavior of compounds **9** were investigated using cyclic voltammetry. As observed for **4**, the cyclic voltammograms of **9** show two irreversible reduction processes near -1.60 and -2.30 V (vs SCE) respectively. Bulk electrolyses carried out on **9** at a less negative potential than that applied to **7** allowed the formation of *N*-benzoyl α-aminostannylated compounds **10** in good yields (Table 1).

Table 1. Preparation of Compounds **10**



entry	R	product, yield (%),[a] *R*/*S*[b]		
1	Me	**8a**, 50, 1/99	**9a**, 98, nd[c]	**10a**, 79, 43/57
2	Allyl	**8b**, 64, 0.5/99.5	**9b**, 93, nd[c]	**10b**, 75, 44/56
3	Bu	**8c**, 47, 0/100	**9c**, 98, 2/98	**10c**, 51, 38/62
4	Bu	*ent*-**8c**, 53, 99/1	*ent*-**9c**, 98, 100/0	*ent*-**10c**, 52, 61/39

[a] Isolated yields. [b] Determined by chiral HPLC (see Supporting Information). [c] nd = not determined (see Supporting Information).

According to our strategy, the conversion of the α-aminoorganostannane compounds **7** into their *N*-benzoyl derivatives might prevent β-fragmentation of the tributylstannyl radical. We set about carrying out the cleavage of the phenylglycinol moiety in order to obtain the expected *N*-benzenesulfonyl secondary amines. This involved a three-step sequence leading to **8** in moderate to good yields (Table 1).[11] The sulfonamides **8** were then reacted with benzoyl chloride in THF to produce the corresponding *N*-benzenesulfonamides **9** in excellent yields (Table 1). The electrochemical behavior of compounds **9** were investigated using cyclic voltammetry. As observed for **4**, the cyclic voltammograms of **9** show two irreversible reduction processes near -1.60 and -2.30 V (vs SCE) respectively. Bulk electrolyses carried out on **9** at a less negative potential than that applied to **7** allowed the formation of *N*-benzoyl α-aminostannylated compounds **10** in good yields (Table 1).

The β-fragmentation of the Sn−C bond was prevented, but unfortunately a significant epimerization at the α-stannyl stereogenic center was observed in every case. At first we considered that this epimerization was due to a reversible deprotonation at the α-position related to tin, but this assumption was ruled out by carrying out electrolysis of an enantiopure *N*-protected α-methyl benzylamide.[10]

Another explanation for epimerization occurring could be the reversible migration of the tributylstannyl group assisted by the anionic oxygen of intermediate **C** (Scheme 5). We also considered that protonation (affording the desired product) and epimerization could be two competitive processes with comparable kinetics. It was proposed that the

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(6) (a) Coeffard, V.; Beaudet, I.; Evain, M.; Le Grognec, E.; Quintard, J.-P. *Eur. J. Org. Chem.* **2008**, 3344–3351. (b) Coeffard, V.; Beaudet, I.; Quintard, J.-P.; Le Grognec, E. *Chirality* **2010**, *22*, 864–869.

(7) Kells, K. W.; Chong, J. M. *J. Am. Chem. Soc.* **2004**, *126*, 15666–15667.

(8) (a) Cintrat, J.-C.; Léat, V.; Parrain, J.-L.; Le Grognec, E.; Beaudet, I.; Toupet, L.; Quintard, J.-P. *Organometallics* **2004**, *23*, 943–945. (b) Cintrat, J.-C.; Leat-Crest, V.; Parrain, J.-L.; Le Grognec, E.; Beaudet, I.; Quintard, J.-P. *Eur. J. Org. Chem.* **2004**, 4251–4267. (c) Cintrat, J.-C.; Léat-Crest, V.; Parrain, J.-L.; Le Grognec, E.; Beaudet, I.; Toupet, L.; Quintard, J.-P. *Eur. J. Org. Chem.* **2004**, 4268–4279.

(9) Coeffard, V.; Le Grognec, E.; Beaudet, I.; Evain, M.; Quintard, J.-P. *J. Org. Chem.* **2009**, *74*, 5822–5838.

(10) For detailed information, see Supporting Information.

(11) Fains, O.; Vernon, J. M. *Tetrahedron Lett.* **1997**, *38*, 8265–8266.

Scheme 5. Epimerization of the Chiral Stannylated Intermediate **C** through Sn−O Interaction

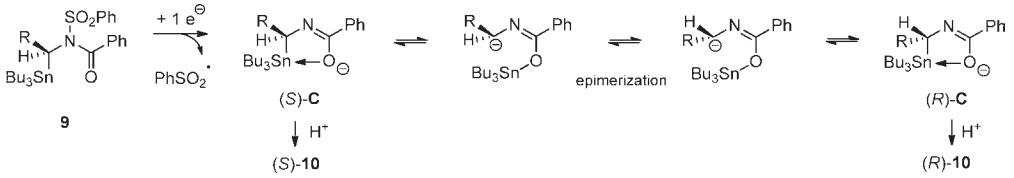
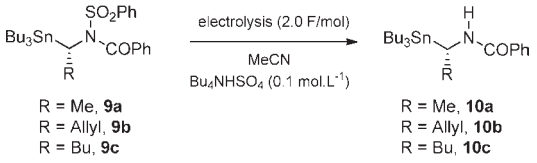


Table 2. Electrodesulfonylation of Compounds **9**



entry	compd	E_w (ΔE) (V)[a]	H_2O (%)	yield (%)	R/S[b]
1	*ent*-**9c**[c]	−1.67 (−0.06)	–	*ent*-**10c**,[c] 52	61/39
2	*ent*-**9c**	−1.70 (−0.06)	2	*ent*-**10c**, 55	70/30
3	*ent*-**9c**	**−1.67 (−0.05)**	**5**	***ent*-10c, 51**	**91/9**
4	*ent*-**9c**	−1.78 (−0.08)	10	*ent*-**10c**, 58	84/16
5	**9a**	−1.65 (−0.08)	5	**10a**, 56	5/95
6	**9b**	−1.77 (−0.08)	5	**10b**, 53	11/89

[a] E_w: potential applied for the electrolysis; $\Delta E = E_w - E_{p,c}$, difference between the potential applied for the electrolysis and the potential of the reduction peak. [b] Determined by chiral HPLC (see Supporting Information). [c] *ent*-**9c** and *ent*-**10c** are the enantiomers of **9c** and **10c** respectively.

addition of water in acetonitrile might increase the protonation kinetics and prevent the undesired epimerization occurring. We therefore examined the effect of water addition to *ent*-**9c**.[12] We observed a dramatic increase of the enantiomeric ratio by increasing the concentration of water from 2% H_2O (R/S = 70/30) to 5% H_2O (R/S = 91/9) (entries 2 and 3, Table 2).[13] It is worth noting that increasing the amount of water to 10% did not improve the R/S ratio (entry 4, Table 2). As a result, these conditions (CH_3CN/H_2O = 95/5) were subsequently applied to compounds **9a** (R = Me) and **9b** (R = allyl) allowing preparation of the corresponding enantioenriched stannylated benzoylamides (R/S = 5/95 and 11/89 respectively) (entries 5 and 6, Table 2).

Through a comprehensive study, we have extended the scope of the electrochemical reduction of sulfonamides. By using an additional benzoyl group placed on the nitrogen atom, an efficient deprotection can be achieved without ring opening of *N*-benzenesulfonyl cyclopropylamines. Epimerization of the chiral center can also be avoided in the case of α-methyl benzyl amines. Furthermore, when performed on highly sensitive enantioenriched α-tributylstannylsulfonamides, this electrodesulfonylation can be achieved preventing Sn−C β-fragmentation and minimizing epimerization of the α-amino stereogenic center by working in wet acetonitrile.

In summary, the electrochemical reduction of sulfonamides is a very efficient method even when highly sensitive substrates are involved and should find applications in multistep synthesis or in total synthesis.

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Supporting Information Available. Experimental procedures, NMR spectra and HPLC traces, DFT calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

(12) *ent*-**9c** is the enantiomer of **9c**.

(13) Addition of $LiClO_4$, Me_3SiCl or modulation of the reduction potential were also considered but without significant improvement on epimerization; see Supporting Information.

The authors declare no competing financial interest.