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Electrically Driven N($_{sp^2}$)- C($_{sp^{2/3}}$) Bond Cleavage of Sulfonamides

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Research Article

Electrically Driven $N(_{sp}{}^{2})-C(_{sp}{}^{2/3})$ Bond Cleavage of Sulfonamides

Annica Wetzel and Alan M. Jones*

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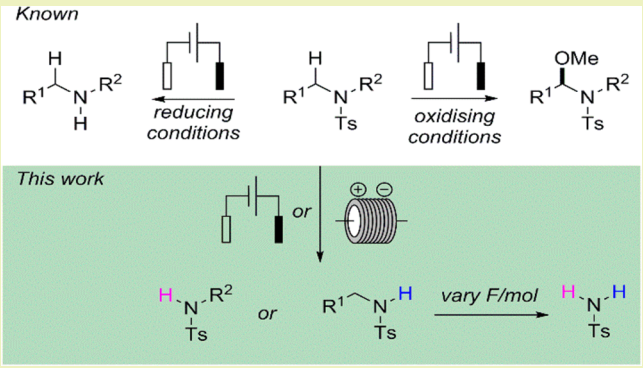
ABSTRACT: Sulfonamides are a privileged class of functional groups in medicinal chemistry and an important class of protecting groups in organic synthesis. We report the discovery and development of unexpected electrically driven $N(sp^2)-C(sp^2)$ and $N(sp^2)-C(sp^3)$ bond cleavage reactions alongside a dehydrogenative $C-O$ bond coupling reaction under batch and electroflow conditions. Intra-molecular trapping experiments with the diuretic hydrochlorothiazide gave insight into the intermediacy of an *N*-sulfonyliminium ion en route to the related drug metabolite, chlorothiazide. Using only electrons as the oxidant, this is a green and sustainable technological advancement for sulfonamide deprotection chemistry and drug metabolism studies.



KEYWORDS: *Electrosynthesis, Dealkylation, Sulfonamide, Oxidation, Shono, Dehydrogenative Coupling*

INTRODUCTION

The sulfonamide group is a prevalent and privileged functional group within the top 200 most-used drugs (Figure 1) and is

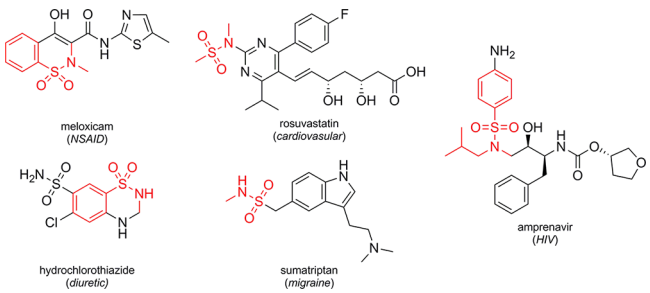


Figure 1. Examples of sulfonamide-containing drugs. Medication indication in parentheses.

encountered in many bioactive molecules.[1−3] Key to the sulfonamide group's bioactivity is its ability to form hydrogen bonds with target receptors in approximately 30% of all drugs ($pK_{BHX} = 1.0$); by contrast, it is also one of the weakest hydrogen bond acceptors.[4]

Furthermore, arylsulfonamides (e.g., tosyl-protected amines) are commonly encountered protecting groups for amines that are known to be capricious to deprotect using stoichiometric deprotection strategies.[5] During the course of our electrosynthetic research into the Shono-type modification of amides[6,7] and esters,[8] we became interested in developing routes to access drug metabolites through $C-X$ bond scission reactions.[9] The phase I metabolism of drug molecules containing alkylated heteroatoms (e.g., $C-N$) is an important clearance pathway in the body that determines drug dosing regimens and safety profiles and is of critical importance in drug development.[10,11]

Recent attention has been devoted to the synthesis[12] and late stage functionalization[13] of sulfonamides, including their *de novo* electrochemical synthesis.[14,15] Intriguingly, no overoxidation of the electrochemically prepared sulfonamides was observed during their synthesis.[14]

A survey of the known electrochemical behaviors of sulfonamides is shown in Scheme 1. Under reductive electrochemical conditions, the selective cleavage of the $N-S$ bond is

Scheme 1. Known Electrochemical Reactions of Sulfonamides and This Work

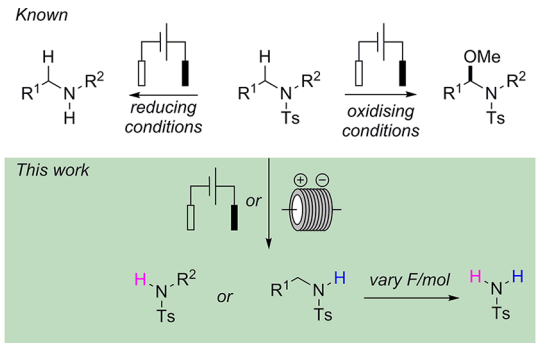


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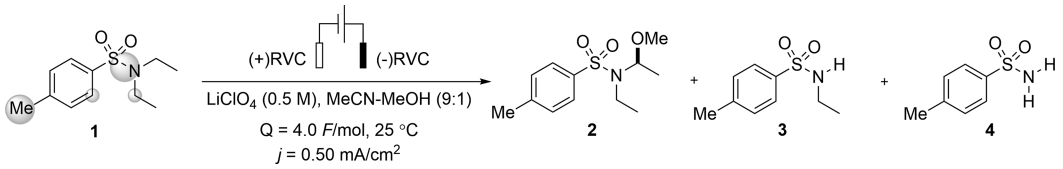
Table 1. Optimisation of the Conversion of 1 to 3 Rather than to the Expected Dehydrogenative Coupling Product 2



entry	deviation from above	conversion to 3 (%)[a]
1	none	>99
2	no electrolyte	0
3	no electricity	0
4	Bu_4NClO_4 instead of $LiClO_4$	<5
5	Et_4NTs instead of $LiClO_4$	<5

[a]Percentage conversion measured by ^{1}H NMR spectroscopy.

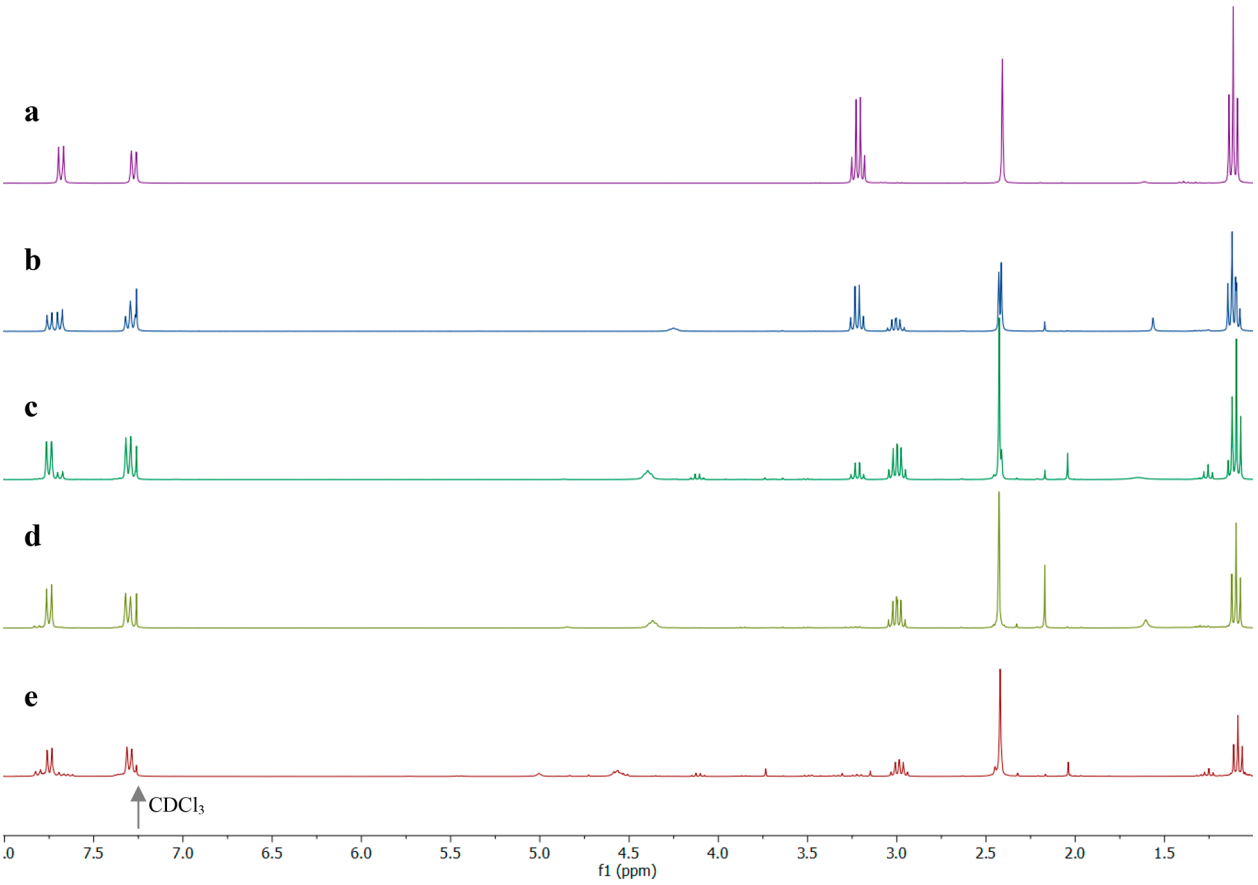


Figure 2. Step-wise formation of **3** by varying F/mol passed to **1** as monitored by ^{1}H NMR spectroscopy in $CDCl_3$. Key ^{1}H NMR spectra of (a) **1**, (b) **1** subjected to 1.0 F/mol, (c) **1** subjected to 2.0 F/mol, (d) **1** subjected to 3.0 F/mol, and (e) **1** subjected to 4.0 F/mol.

well documented as a mild tosyl deprotection strategy.[16−31] By contrast, under oxidizing electrochemical conditions, there are limited examples of Shono-type dehydrogenative couplings in sulfonamides compared to the well-studied tertiary amides.[32−42] To the best of our knowledge, a *C*−*N* bond cleavage reaction of a sulfonamide can only be achieved using conventional stoichiometric chemical routes.[43−49] Other electrochemical properties of sulfonamides[50] include its use as a directing and participating group for 1,5- and 1,6-cyclizations[51] and its use as a competent nucleophile in anodic oxidations.[52] Although the chemical removal of protecting groups attached to sulfonamides is known to reveal an *N*−H functional handle (e.g., *SEM, Bn, PMB, allyl,* ^{t}*Bu*),[53] to the best of our knowledge, the late-stage electrochemical oxidative cleavage of operationally inert $N(sp^2)-C(sp^{2/3})$ bonds (e.g., alkyl, aryl substituents) adjacent to a sulfonamide is unknown in this important class of compounds using a green methodology.

As part of our continuing electrosynthesis and drug metabolism program we considered whether $N(sp^2)-C(sp^{2/3})$ bond cleavage is possible in sulfonamides—this would lead to two advantages for (1) drug metabolism and discovery, e.g., mimicking Cyp-P_{450} dealkylation of sulfonamides, and (2) synthetic chemistry, e.g., enabling a new orthogonal deprotection strategy in sulfonamides.

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RESULTS AND DISCUSSION

Our initial investigations began with a survey of conditions on a model *N*-substituted *p*-toluenesulfonamide, **1** (Table 1). Model substrate **1** contains four potential electroactive moieties, namely, the aryl ring system; the *S*−*N* bond of the sulfonamide; and the *C*−*H* bonds adjacent to the sulfonamide nitrogen and aryl methyl group (gray spheres, inset).

Our initial exploration of the anodic oxidation of **1** considered the formation of the Shono-type dehydrogenative coupling product (**2**) and potential opportunity for *mono*-(**3**) or *di*-(**4**) *C*−*N* bond cleavage products and mixtures thereof. Sulfonamide **1** is an electroactive molecule with an E_{ox} = +1880 mV vs Ag/AgCl (Table S1).[54] Intriguingly, both the crude ^{1}H NMR spectra and isolated product did not contain the expected diagnostic Shono (*α*-methoxy or *α*-hydroxy) signals but instead had **3** as the major product.

Optimisation survey experiments are provided in the Supporting Information (Table S2);[54] briefly, changing the electrolyte from $LiClO_4$ was detrimental to conversion. Reticulated vitreous carbon (RVC) or graphite (C) electrodes are optimal over metals (Cu, Fe, Pt), and a reduction in yield was observed in a divided cell setup. A survey of charge transfer showed that 4.0 F/mol is optimal for high conversions of **1** and isolated yield of **3** (Figure 2). Higher charge transfers gave a secondary *C*−*N* bond cleavage reaction to **4**.

The ability to selectively dial-in the mono-, or double dealkylation product (**3** and **4**, respectively) was monitored by ^{1}H NMR spectroscopy. Near complete conversion of **1** to **3** can be seen after the passage of 3.0 F/mol of electrons (Figure 2c). The beginnings of the formation of **4** can be observed from 4.0 F/mol onward (Figure 2d). This demonstrated that **4** forms from **1** via **3** and not from a different mechanism. This is a markedly different reactivity to the related amide bond containing systems that stop further *C*−*N* bond scission after monodealkylation is accomplished.[9]

Furthermore, the reaction proceeds in flow using the commercially available Ammonite8 electroflow reactor.[55] In comparison to the batch process, a significant lowering of electrolyte loading was possible due to the 500 *μ*m interelectrode gap (5.0 mM $LiClO_4$). Using a retention time (t_r) of 10 min with a flow rate of 0.1 mL/min (reactor volume = 1.0 mL) led to the formation of **3** in 34% yield, from the first pass, with initial conditions of using a C anode and Fe cathode (*I* = 330 mA). Lowering the current to 28 mA enabled a comparable *j* of 0.5 mAcm^{-2} (*c.f.*, the optimized batch conditions) and an improved first pass yield of 89% (Faraday efficiency of 52%).[14]

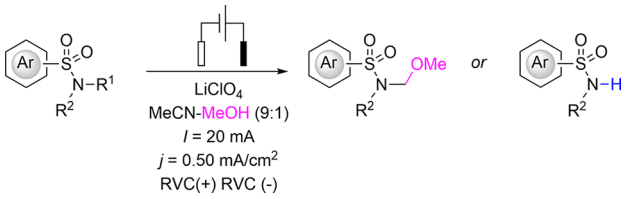
With the identification of optimal conditions in batch and flow, we probed the generality of the reaction with *N*-substituted sulfonamides, as shown in Table 2. Details of the preparation of key precursors are in the Supporting Information.[54]

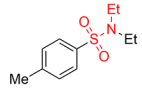
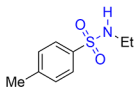
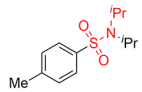
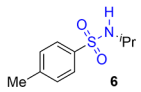
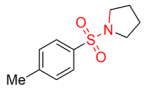
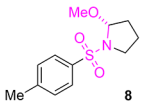
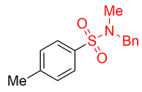
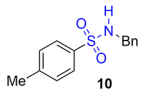
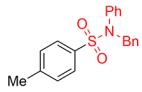
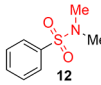
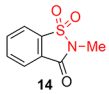
The optimized conditions for the monodealkylation of **1** delivered **3** (Table 1, entry 1) in a 88% yield under batch conditions and similar 89% yield under flow conditions with the added benefit of the reaction being complete in 10 min (*c.f.*, batch). Moving to a more hindered secondary isopropyl-containing substrate (entry 2) afforded **6** in modest 34−45% yield (batch vs flow, respectively). In an amide bond containing analogue removal of an isopropyl group is only possible with harsh trifluoroacetic acid conditions.[56]

A cyclic example was selected (entry 3) to further understand the mechanism, by potentially trapping *in situ* the analogous leaving group formed in the acyclic examples. In this instance, **7** instead dehydrogenatively *C*−*O* coupled in preference to the predicted *C*-*N* bond scission, in excellent conversion and good isolated yield. Subjecting **7** to an excess charge of 10.0 F/mol resulted in traces of what was tentatively assigned a double dehydrogenative coupled product, but no evidence of ring opening to an aldehyde-oxidation level product was observed.[57]

Differentially *N*,*N*′-substituted tertiary amide bond containing systems are reported to afford a 3:1 selectivity[58] for electrochemical dehydrogenative coupling of a methyl *C*−*H* bond over the benzyl *C*−*H* bond. To our surprise, in entry 4, complete regioselectivity for methyl *C*−*N* scission over the benzylic methylene bond was observed. To further understand this regioselectivity issue, an alternative *N*,*N*′-substituted system (entry 5) was expected to deliver exclusive debenzylation over dearylation; surprisingly, on multiple repeats exclusive dearylation was observed to afford **10**. A rationale for this outcome is

Table 2. Reaction Scope for the Single *C*−*N* Bond Cleavage Reaction on Tertiary Sulfonamides[a]



Entry	Compound	Q (*F*mol^{-1})	Conversion %	Product (isolated yield %)
1	 **1**	4.0	>99	 **3** flow (89%) **batch** (88%)
2	 **5**	4.0	60	 **6** flow (45%) **batch** (34%)
3	 **7**	4.0	>99	 **8** flow (50%) **batch** (55%)
4	 **9**	4.0	95	 **10** flow (70%) **batch** (60%)
5	 **11**	4.0	>99	**10** **batch** (75%)
6	 **12**	4.0	>99	**13** flow (84%) **batch** (80%)
7	 **14**	4.0	85	**15** **batch** (70%)

[a]Percentage conversion measured by ^{1}H NMR spectroscopy.

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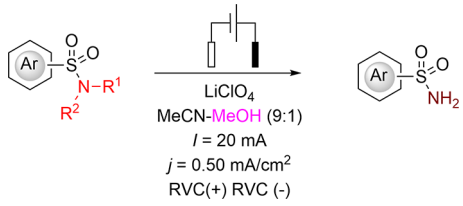
the stabilization of the *N*-centered radical onto the adjacent benzene system, leading to *C*−*N* bond cleavage.[59]

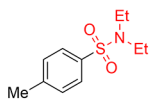
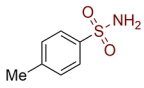
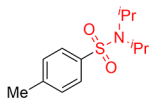
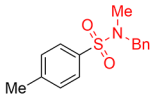
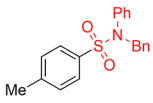
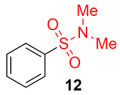
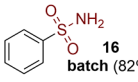
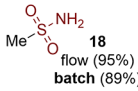
Replacing the tolyl group with a phenyl (entry 6) also enabled high conversions and isolated yield both in batch and flow. An *N*-methylated cyclic sulfonamide (entry 7) was readily converted to the artificial sweetner, saccharin (**15**), under batch conditions. The comparative flow experiment was not attempted due to limited solubility.

The additional passage of 4.0 F/mol of charge to selected products from the *mono* *C*−*N* scission products from Table 1 are shown in Table 2. Entries 1−3 show on tosyl sulfonamides a second *C*−*N* bond breaking event is possible in modest-to-good yields. In particular, the isopropyl group in entry 2 proved more challenging than a simple ethyl (entry 1) or benzyl group (entry 2). On a nontosyl sulfonamide a further methyl group could be cleaved with ease (entry 4) in batch and flow.

Table 3 demonstrates a range of tandem *C*−*N* bond breaking events with increase charge passed (8.0 F/mol). Entries 1 and 2 demonstrate on *N,N′*-symmetrical examples (diethyl, entry 1, and di*iso*propyl, entry 2) that both groups can be cleaved with control; again the steric bulk of the isopropyl group impaired the conversion and isolated yield. On nonsymmetrical *N,N′*-substituted examples (entries 3 and 4) the two groups can also be cleaved. From prior results (Tables 2 and 4), it is believed

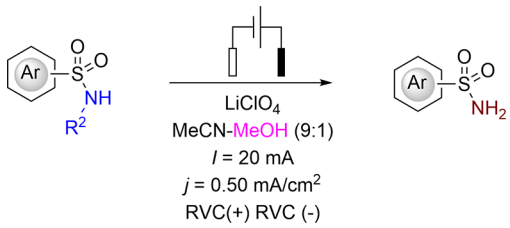
Table 3. Reaction Scope for the Double *C*−*N* Bond Cleavage Reaction on Tertiary Sulfonamides[a]

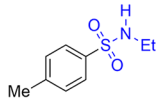
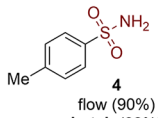
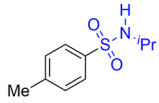
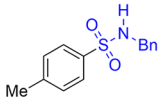
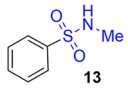
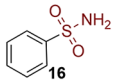


Entry	Compound	Q (*F*mol^{-1})	Conversion %	Product (isolated yield %)
1	 **1**	8.0	>99	 **4** **batch** (81%)
2	 **5**	8.0	70	**4** **batch** (44%)
3	 **9**	8.0	>99	**4** **batch** (62%)
4	 **11**	8.0	>99	**4** **batch** (58%)
5	 **12**	8.0	>99	 **16** **batch** (82%)
6	**17**	8.0	>99	 **18** flow (95%) **batch** (89%)

[a]Percentage conversion measured by ^{1}H NMR spectroscopy.

Table 4. Reaction Scope for the Single *C*−*N* Bond Cleavage Reaction on Secondary Sulfonamides[a]



Entry	Compound	Q (*F*mol^{-1})	Conversion %	Product (isolated yield %)
1	 **3**	4.0	>99	 **4** flow (90%) **batch** (82%)
2	 **6**	4.0	65	**4** **batch** (45%)
3	 **10**	4.0	72	**4** **batch** (64%)
4	 **13**	4.0	>99	 **16** flow (81%) **batch** (79%)

[a]Percentage conversion measured by ^{1}H NMR spectroscopy.

for entry 3 that the methyl group is cleaved in preference to the benzyl group, and for entry 4, the phenyl group is cleaved prior to the benzyl group. The double *C*−*N* scission is also possible in nontosyl sulfonamides (entries 5 and 6). In particular, an alkyl sulfonamide gave an excellent isolated yield after two cycles (entry 6).

We then sought to exploit the potential of the *C*−*N* bond scission reaction on drug molecules (Table 5). The *N*-substituted sulfonamide drugs begacestat (**19**), a *γ*-secretase inhibitor for Alzheimer's, and hydrochlorothiazide (HCTZ, **21**), a diuretic, were selected.[60] Under the standard conditions the *C*-*N* bond in **19** cleaved to afford **20** under batch conditions in a modest 59% yield. Despite **21** containing a cyclic system, we hypothesized a highly stabilized *N*-sulfonyl iminium ion would result, which, rather than dehydrogenative coupling (*c.f.*, **8**), might give insight into the reaction mechanism. Formation of **22** would give further credence to the mechanism being Shono-type in its initiation. To our delight, the well-known drug molecule chlorothiazide (CTZ, **22**) formed in near quantitative conversion and with a good isolated yield (71%).[61−65]

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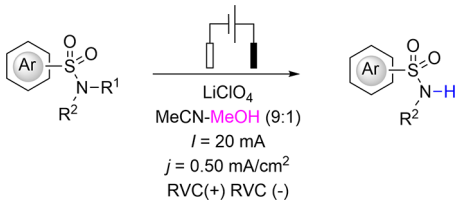
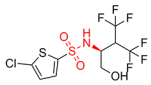
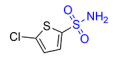
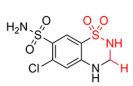
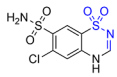
Table 5. Drug Molecule Screen for Selective *C*−*N* Bond Cleavage and Related Oxidative Metabolism Products[a]

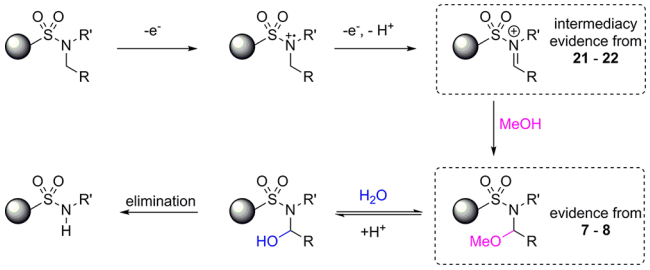


Entry	Compound	Q (*F*mol^{-1})	Conversion %	Product (isolated yield %)
1	 Begacestat **19**	4.0	75	 **20** batch (59%)
2	 HCTZ **21**	4.0	>99	 CTZ **22** batch (71%)

[a]Percentage conversion measured by ^{1}H NMR spectroscopy.

To further address the potential mechanism in operation, a control experiment was employed. Removal of methanol from the reaction conditions led to no appreciable dealkylation or dehydrogenative coupling products. Therefore, methanol was critical to both reaction outcomes. Furthermore, an electro-generated acid (EGA) from $LiClO_4$ generating "anhydrous" $HClO_4$ with adventious water from methanol near the electrode surface was speculated to be important. This could act as a Lewis acid to accelerate the decomposition of the Shono-type intermediates from the *N*-sulfonyl iminium ion intermediate. Recently, Aggrawal[34] has shown it is possible to convert an α-methoxy electrochemical product to an α-hydroxy compound under nonelectrosynthetic conditions and that these α-hydroxy compounds proved to be stable to further synthetic elaboration without degradation. Taken together, our results point toward the intermediacy of an electro-generated *N*-sulfonyl iminium species in operation intercepted by H_2O to afford the dealkylated products (Scheme 2).[9]

Scheme 2. Postulated Mechanism for the *C*−*N* Bond Cleavage Reaction in the Sulfonamide Class



SUSTAINABILITY MEASUREMENT

Electrosynthesis is inherently a green process, meeting the 12 principles of green chemistry.[66] The disclosed *C*−*N* bond breaking reaction will always be <100% efficient due to the loss of a fragment of the molecule (e.g., an alkyl group); even so, a typical transformation (e.g., **1** to **3**) has an atom economy of 88% and only electrons as the reagent. $LiClO_4$ as the electrolyte can be recovered by precipitation from diethyl ether, and the solvents could be theoretically recovered from the reactor. The key comparison is to the state-of-the-art conventional stoichiometric and catalytic methods of *C*−*N* bond breakage in sulfonamides,[43−49] where the electrochemical procedure removes the need for transition metals or stoichiometric reagents to achieve the desired dealkylated compound.

CONCLUSIONS

In summary, this work provides a mild, green, controllable, and complementary *N*−*C*(sp$^{2/3}$) bond cleavage reaction of sulfonamides without the need for stoichiometric chemical oxidants. By switching from reducing to oxidizing electro-synthetic conditions, alternative bonds on *N*,*N*′-substituted sulfonamides can be cleaved in sequence, with control, by varying the charge transferred under controlled current electrolysis. This new method holds promise as a general route to complement existing protecting group strategies and also late-stage functionalization of drug molecules to diversify or prepare drug metabolites.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acssuschemeng.0c00387.

Compound characterization, ^{1}H and ^{13}C NMR spectra, and voltammograms (PDF)

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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