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Electrochemical Imination of Sulfoxides Using *N*-Aminophthalimide

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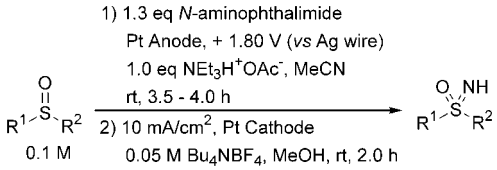
ABSTRACT



A novel electrochemical sulfoxide imination process is described. Our approach starts with a highly selective nitrene transfer from *N*-aminophthalimide to a variety of sulfoxides. This oxidative treatment is followed by reductive N–N bond cleavage under the controlled current conditions, which leads to a range of parent NH sulfoximines. In addition to solving the challenging problem of removing the *N*-phthalimido group, the overall process avoids the use of toxic oxidants and metal additives.

The general interest in the chemistry of sulfoximines dates back to the work of Whitehead and Bentley[1] in the 1950s, when they found that the sulfoximine of methionine is the compound produced when wheat flour is treated with nitrogen trichloride. Methionine sulfoximine is still the most studied biologically active sulfoximine and has been identified as a selective inhibitor of γ-glutamylcysteine synthase which catalyses the rate-limiting step in glutathione biosynthesis.[2] Buthionine sulfoximine was shown to restore the sensitivity of cancer tumors resistant to melphalan.[3] Other sulfoximines have been studied as antibiotics, antithrombotics, and tumor metastasis inhibitors.[4]

Sulfoximines have also attracted the attention of synthetic chemists, largely due to the pioneering work by Johnson.[5,6] The versatile chemistry of sulfoximines is made possible by the presence of amphoteric nitrogen, acidic α-protons, and a stereogenic sulfur atom (Figure 1). The ability of sulfoximines to stabilize adjacent carbanions (thus allowing C−C bond formation with carbon electrophiles) as well as to serve as leaving groups in reactions with nucleophiles led Trost to refer to them as "chemical chameleons" for asymmetric synthesis.[7]

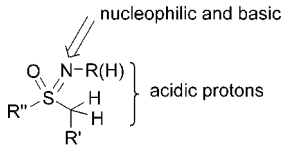


Figure 1. The sulfoximine functional group.

A number of routes to sulfoximines have been developed.[5,6d,e] A variety of oxidants can be used for the oxidative imination of sulfoxides, e.g., hydrazoic acid (HN_3, generated in situ by reaction of NaN_3 with concentrated H_2-

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SO_4),[8] *N*-amino-substituted compounds with $Pb(OAc)_4$,[9] TsN_3,[10] *N*-tosylimino phenyl iodinane and catalytic CuOTf [11a] or $Cu(OTf)_2$,[11b] $BocN_3$ with $FeCl_2$,[12] *o*-mesitylene sulfonyl hydroxylamine (MSH),[13] and *tert*-butyl hypochlorite with aromatic amines.[14] All of these processes involve toxic oxidants and/or metal additives. Here we demonstrate an alternative method for making sulfoximines using electrochemistry that avoids metal-based reagents, catalysts, and stoichiometric oxidants.

Electrochemical reactions involve electron transfer in the Helmholtz layer at the electrode−solution interface.[15] Highly reactive intermediates can be generated under very mild conditions, such as ambient temperatures, normal pressure, and often in non-halogenated solvents.[16] As opposed to conventional chemical reactions, in which stoichiometric amounts of reductants or oxidants are used, direct electrochemical reductions/oxidations of substrates utilize practically mass-free electrons as the only reagents. In this sense, electrochemistry is frequently referred to as one of the prototypical green technologies of the future.[17]

In our effort to develop general electrochemical solutions to the selective functionalization of organic molecules, we recently found a practical process for olefin aziridination with *N*-aminophthalimide.[18] The development of this reaction was based on a logical emulation of metal-based selectivity and accomplished the replacement of the conventional method that calls for excess $Pb(OAc)_4$. We suggested that there must be a possibility to develop a set of guidelines for emulating a variety of metal-based redox processes via optimization of reaction conditions with the goal of maximizing the difference in overpotentials between the reacting molecules. This Letter extends electrochemical oxidative methodology to sulfoximine synthesis. Furthermore, this contribution underscores the facility with which the N−N bond can be cleaved using electrochemistry.

In our previous study[18] we found that oxidation of olefins on platinum anode is kinetically disfavored over the oxidation of *N*-aminophthalimide. This phenomenon of overpotential appears to be the key factor for the successful nitrene transfer to olefins. At the outset of the present study, we compared the redox behavior of *N*-aminophthalimide and sulfoxides using cyclic voltammetry (CV). The CV of *N*-aminophthalimide (0.01 M in acetonitrile) on a platinum electrode shows two irreversible one-electron oxidation processes with anodic peak potentials at +1.35 V and +1.68 V (vs Ag/AgCl).[18] At the second peak potential of +1.68 V, tetramethylene sulfoxide (0.01 M in acetonitrile) produces an anodic current of −7.52 μA, which is considerably smaller than the current recorded for *N*-aminophthalimide (−152 μA). This indicates that the background oxidation of sulfoxides on a platinum electrode is kinetically sluggish, paving the way to direct electrochemical nitrogen transfer to sulfoxides. It should be emphasized that the nature of the electrode material is crucial to the success of the reaction. The CV of tetramethylene sulfoxide (0.01 M in acetonitrile) on a glassy carbon electrode shows two irreversible oxidation processes with peak potentials at +1.64 V and +1.82 V and a much higher anodic current (−272 μA) than that of *N*-aminophthalimide at +1.68 V. Thus, bulk electrolysis of tetramethylene sulfoxide in the presence of *N*-aminophthalimide on a graphite anode gave tetramethylene sulfone as the major product with no evidence of sulfoximine formation.

On the platinum anode, the electrolysis conditions were similar to those of aziridination.[18] A small excess of *N*-aminophthalimide relative to the sulfoxide was used. The electrolysis was performed in a divided cell using a silver wire as a pseudo-reference electrode, which was calibrated against the ferrocene/ferricinium couple in the electrolysis medium (E_{pa} = 0.47 V, E_{pc} = 0.30 V). No special precautions to exclude moisture or air were taken. The reaction was stopped when the cell current dropped to less than 5% of its original value. Table 1 illustrates the substrate scope of this process. For sulfoxide **2d** (entry 4), no aziridination product was observed, indicating the possibility of achieving chemoselective nitrene transfer to the sulfoxide moiety.[19] There was no evidence for the background formation of sulfone byproduct. Furthermore, the electrochemical nitrene transfer is stereospecific. An enantiomerically enriched (93% ee of the *R*-enantiomer) sample[20] of **1b** was electrolyzed under the same conditions as above. The ee value measured by HPLC for the product sulfoximine **2b** was the same (97%) within experimental error, and the X-ray crystallographic analysis (anomalous dispersion) showed retention of configuration,[21] indicating that no racemization occurred during the nitrene transfer process.

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(19) Attempted oxidative imination of sulfides (resulting in sulfimines) using the same methodology was not successful. Due to the less positive oxidation potential of sulfides compared to *N*-aminophthalimide, a mixture of products consisting mainly of sulfoxide and sulfoximine was obtained.

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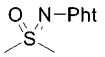
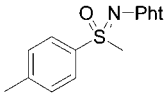
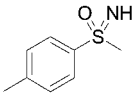
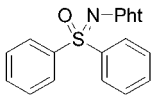
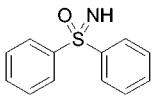
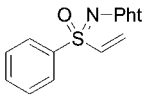
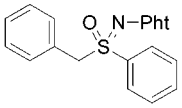
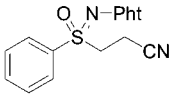
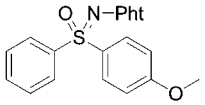
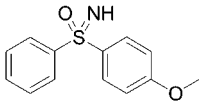
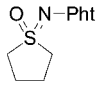
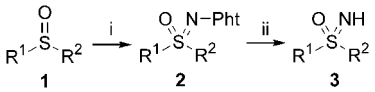
Table 1. Electrochemical Synthesis of Sulfoximines and N−N Bond Cleavage

Entry	Sulfoximine **2** (yield, %)	Sulfoximine **3** (yield, %)
1	 **2a** (76)	 **3a** (62)
2	 **2b** (62)	 **3b** (83)
3	 **2c** (83)	 **3c** (81)
4	 **2d** (70)	-- [a]
5	 **2e** (86)	-- [a]
6	 **2f** (81)	-- [a]
7	 **2g** (88)	 **3g** (52)
8	 **2h** (75)	 **3h** (64)

[a] Starting material decomposed.

Various methods for removal of the *N*-bound substituent to generate "free" sulfoximine **3** have been reported in the literature. The detosylation with concentrated sulfuric acid is often used but is complicated by a considerable loss of material.[22] An alternative way of detosylation is the sodium anthracenide method introduced by Johnson but it only works for the dialkyl-substituted sulfoximines.[23] In comparison, the removal of the *N*-Boc group is performed under mild conditions. Recently Bolm et al. developed procedures for the $TiCl_4$- or $AlCl_3$-catalyzed deprotection of *N*-Boc group in the synthesis of chiral benchrotrenes.[24] However, no deprotection liberating the "free" sulfoximines **3** from the *N*-phthalimido derivatives **2** is described in the literature. We have found that electrolysis of **2** in methanol with water as a proton source under galvanostatic conditions (Scheme 1)

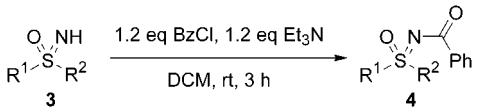
Scheme 1. Electrosynthesis of Sulfoximines and N−N Bond Cleavage[a]



[a] (i) +1.80 V (vs Ag wire), platinum anode, 1.3 equiv of *N*-aminophthalimide, 1.0 equiv of $NEt_3H^+OAc^-$, rt, 3.5−4.0 h. (ii) 10 mA/cm^2, platinum cathode, MeOH, 0.05 M $Bu_4N^+BF_4^-$, rt, 2.0 h.

gave the desired products in good yields for the dialkyl- and diaryl-substituted sulfoximines. A small excess of electricity (2.4 F, theoretical charge 2.0 F) was passed in order to ensure complete conversion of the starting material. For some alkyl−aryl-substituted sulfoximines (i.e., **2d**, **2e**, and **2f**), decomposition of the starting material was observed, resulting in complicated product mixtures. Isolation by flash chromatography (silica gel, hexane/EtOAc eluent) was sufficient to afford pure product except in the case of **2a** where separation of **3a** from supporting electrolyte (Bu_4NBF_4) was problematic. In this instance, we utilized a benzoylation procedure (Scheme 2) by treating the crude product **3a** with benzoyl

Scheme 2. Benzoylation of Sulfoximines **3**



a: $R^1 = R^2 = Me$
b: $R^1 = Ph$, $R^2 = (4\text{-MeO})Ph$

chloride and triethylamine to afford isolable sulfoximine **4a** in 92% overall yield. The same strategy was used to transform the unstable compound **3g** to **4g** in 77% overall yield.

In summary, we have extended our electrochemical nitrogen transfer methodology[18] to the synthesis of sulfoximines. This finding underscores the rational approach that bypasses the requirement for stoichiometric amounts of toxic oxidants and metal additives in organic redox reactions. We have also demonstrated that the chemically "impossible" [6e] removal of the *N*-phthalimido group in sulfoximines can be

(21) X-ray data for *R*-**2b** (recrystallized from toluene): $C_{16}H_{14}N_2O_3S$, MW = 314.35, colorless prismatic crystal, crystal size 0.30 × 0.12 × 0.10 mm^3, orthorhombic, space group $P2_12_12_1$, a = 7.9615(2) Å, b = 9.9599(2) Å, c = 38.3334(10) Å, V = 3039.68(13) Å^3, Z = 8, d_{calc} = 1.374 g/cm^3, $F(000)$ = 1312, μ = 0.227 mm^{-1}, T = 150(1) K, 12041 reflections collected, 6335 independent reflections, R = 0.0614, R_w = 0.0936, GOF on F^2 = 1.022.

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readily achieved by electrochemistry. This methodology may also be used for the deprotection of the *N*-phthalimido aziridines[18] and is within the scope of our future studies. We are also aiming at the adaptation of these methodologies into our recently developed parallel electrosynthesis platform.[25]

Acknowledgment. We thank the National Science and Engineering Research Concil (NSERC), Canada Foundation for Innovation, ORDCF, and the University of Toronto for financial support. Andrei Yudin is a Cottrell Scholar of Research Corporation. We also thank Ms. Leslie Fradkin and Dr. Alan Lough for their help in the X-ray crystal structure determination.

Supporting Information Available: Experimental procedures and characterization data for the sulfoximines; X-ray data of compound *R*-**2b** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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