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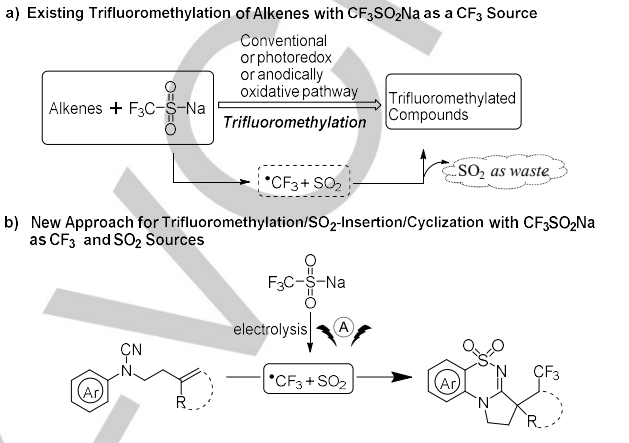
CF_3SO_2Na Acted as a Bifunctional Reagent: Electrochemical Trifluoromethylation of Alkenes Accompanied by SO_2-Insertion to Access Trifluoromethylated Cyclic *N*-Sulfonylimines

*Zheng Li,[+] Lingcong Jiao,[+] Yunhai Sun, Zeying He, Zhonglin Wei, Wei-Wei Liao**

Abstract: *An unprecedented electrochemical trifluoromethylation/SO_2-insertion/cyclization process has been achieved in an undivided cell in an atom-economic fashion. The protocol relies on tandem cyclization of N-cyanamide alkenes by using Langlois reagent as CF_3 and SO_2 sources under direct anodically oxidative conditions, in which two C−C bonds, two C-X bonds (N-S and S-C) and two rings were formed in a single operation. This transformation enabled efficient construction of various trifluoromethylated cyclic N-sulfonylimines from readily accessible materials.*

Decoration small molecules with trifluoromethyl (CF_3) group has gained growing attentions both from industrial and academic communities, due to the unique physical properties of trifluoromethylated compounds such as lipophilicity, bioavailability and metabolic stability and their frequent occurrence in pharmaceuticals, agrochemicals and performance materials. [1] As a consequence, development of efficient and practical protocols to rapidly access trifluoromethylated molecules continues to be highly demanded. [2]

The trifluoromethylation of alkenes with the simultaneous formation of C−C or C−X bonds represents one of the most practical and powerful strategies for preparing acyclic or cyclic trifluoromethyl-containing building blocks for bioactive compounds. [2b-2i] Various either electrophilic (e.g., Umemoto's reagent or Togni's reagents) or nucleophilic trifluoromethylating reagents (e.g., Langlois' reagent and Baran's reagent) enabled a diversity of trifluoromethylation of alkene transformations in which most of them were based on a radical mechanism, to access structurally diverse trifluormethylated molecules. Owing to recent remarkable advances on photoredox [2h-2i] and electrochemical approaches, [3a-3b] the trifluoromethylation of alkenes can be performed environmental-friendly by avoiding the utilization of stoichiometric quantities of chemical oxidants or reductants and the generation of hazardous waste. [3c-3i, 4] Sodium trifluoromethanesulfinate (Langlois reagent), which is an inexpensive, bench-stable, and easily handled trifluoromethyl source, has been regarded as an attractive trifluoromethylating reagent and received more attention. [5] In particular, since Baran and co-workers' pioneer contribution on the radical



Scheme 1. Existing and new approach for trifluoromethylation of alkenes with CF_3SO_2Na.

trifluoromethylation of heterocycles under direct electrolytic conditions, [6] electrochemically oxidative difunctionalization of alkenes involving the simultaneous formation of C−CF_3 and C−O, C-N, C-C bonds has aroused as a highly attractive strategy to streamline the access for CF_3-containing compounds by employing readily available trifluoromethanesulfinates as the radical precursors. [3] However, all of trifluoromethanesulfinates-based reagents acted exclusively as a sole CF_3 source regardless of conventional oxidative, photoredox or electrochemical pathway, and the concomitantly generated SO_2 was discarded as a waste (Scheme 1a).

Recently, rapidly developed protocols on the preparation of sulfonyl compounds by means of SO_2-insertion have drawn increasing attention. [7] In particular, the incorporation of in situ

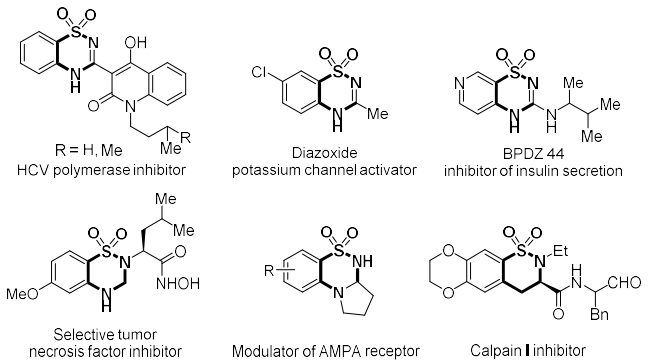


Figure 1. Selective examples of bioactive and synthetically useful molecules containing six-membered cyclic *N*-sulfonylimine-related motifs.

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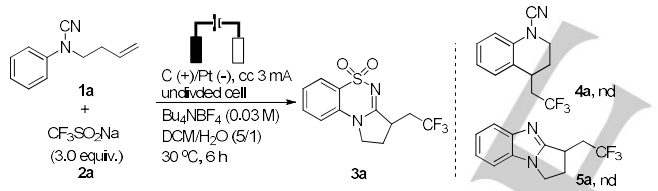
generated sulfur dioxide from surrogates into the organic frameworks in aminosulfonylative reactions *via* a radical pathway afforded an attractive strategy to construct a series of sulfonamides, [8] which are valuable structural motifs in medicinal and agrochemical agents. [9] Among them, Wu *et al.* have reported direct vicinal difunctionalization of alkynes through trifluoromethylation (or difluoroalkylation) and aminosulfonylation by employing fluorinating reagent, alkynes, sulfur dioxide of surrogates and hydrazines *via* an insertion of sulfur dioxide under catalyst-free or photoinduced conditions. [10] Inspired by the advances of radical trifluoromethylation and the insertion of sulfur dioxide and environmentally friendly nature of electrochemical organic synthesis due to its tunability over electron transfer processes and use of electrons as traceless reagents, [11] we envision that readily available CF_3SO_2Na may act as a bifunctional reagent, namely, both as a radical ($\bullet CF_3$) source and a sulfating reagent (SO_2) in a tandem cyclization of *N*-cyanamide alkene process under direct anodically oxidative conditions (Scheme 1b), which could extremely extend the application of Langlois reagent on efficient construction of fluorinated molecules with advanced sulfonyl complexities by concomitant incorporation of *in situ* generated trifluoromethyl and sulfur dioxide in an atom economical fashion. Herein, we report the application of this strategy on the electrochemical preparation of six-membered cyclic *N*-sulfonylimine derivatives bearing CF_3 units in an undivided cell, which are both synthetically useful [12] and medicinally important (Figure 1), [13] in an environment-friendly manner.

Table 1: Selected optimization of reaction conditions. [a]



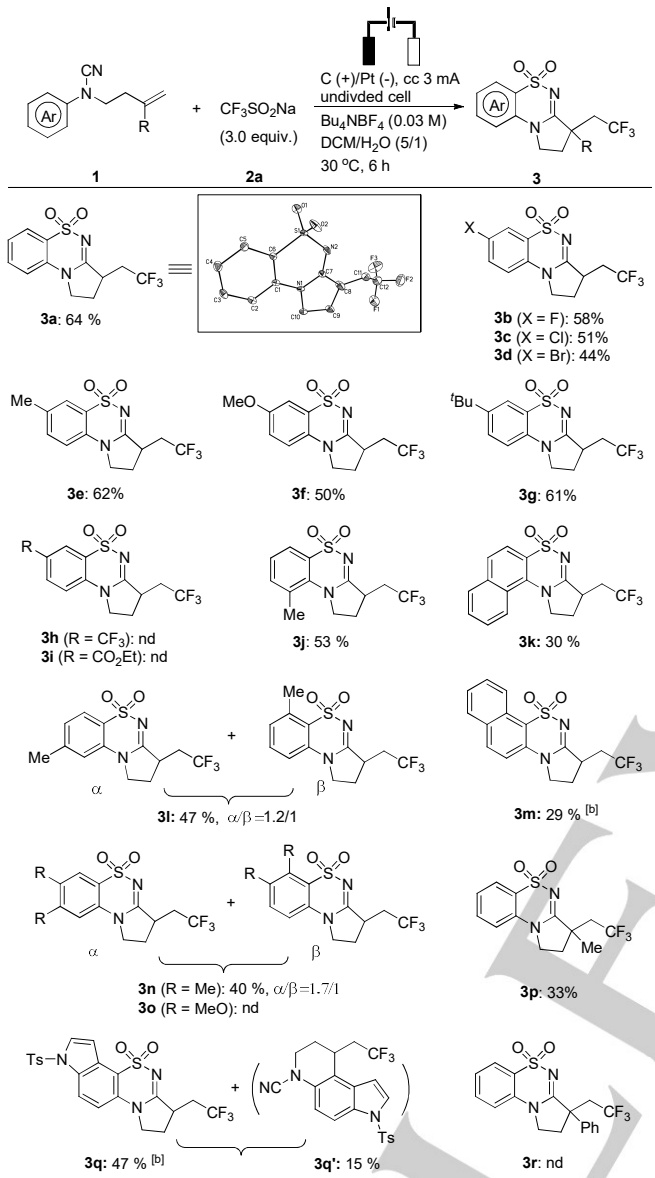
Entry	Deviation from standard conditions	Yield (%) [b]
1	none	66 (64)
2	1.5 mA, 12 h	61
3	6 mA, 3 h	53
4	under nitrogen atmosphere	61
5	CF_3SO_2Na (2.0 equiv.)	48
6	$(CF_3SO_2)_2Zn$ (1.5 equiv.)	56
7	No electricity	nd

[a] Reaction conditions: **1a** (0.3 mmol), **2a** (0.9 mmol), Bu_4NBF_4 (0.3 mmol) and DCM/H_2O (5/1) (c = 0.03 *M*) in an undivided cell with graphite rod anode (Φ 6 mm), Pt plate cathode (10 × 10 × 0.1 mm), constant current = 3.0 mA, 30 °C, 6 h. 2.2 F/mol. [b] Determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as the internal standard. Isolated yield in parenthesis.

Initially, *N*-(but-3-en-1-yl)-*N*-phenylcyanamide **1a** was chose as the model substrate to evaluate the feasibility of the electrochemical trifluoromethylation/SO_2-insertion/cyclization process using Langlois reagent (**2a**) as possible CF_3 and SO_2 sources in an undivided cell.[14] After extensive screening of reaction conditions, we found that anodically electrolyzing **2a** and cyanamide **1a** bearing a terminal alkene moiety as the radical acceptor at 30 °C in a cosolvent of DCM/H_2O = 5/1, including Bu_4NBF_4 as electrolyte and C(+)/Pt(-) as the electrodes with a constant electric current of 3 mA for 6 h, led to the formation of cyclic *N*-sulfonylimine **3a** concomitantly incorporating both trifluoromethyl and SO_2 moieties in 64% isolated yield as the sole product (Table 1, entry 1). In this case, two C−C bonds, two C-X bonds (N-S and S-C) and two rings were formed with Langlois reagent (**2a**) as CF_3 and SO_2 sources in a single operation. The lower electricity and long reaction time gave the similar result to that of the reaction with 3 mA and 6 hours, while the high electricity led to a reduced yield (Table 1, entries 2-3). Inert atmosphere was not essential, since the outcome of electrochemical reaction was not improved under nitrogen atmosphere (Table 1, entry 4). The reduced amount of **2a** resulted in the deteriorative production of **3a** (Table 1, entry 5). Zinc(II) bis(trifluoromethanesulfinate) ($Zn(SO_2CF_3)_2$, Baran's reagent) can also serve as CF_3 and SO_2 sources to deliver the desired product **3a** with comparable efficacy (Table 1, entry 6). In addition, control experiment suggested that electricity was indispensable (Table 1, entry 7) (see the SI for full detailed). Notably, other possibly cyclic compounds such as **4a** or **5a** *via* alternatively possible radical pathway were not observed.

With the optimized reaction conditions in hand, the substrate scope of this tandem electrosynthesis was investigated (Table 2). First, we examined a diverse range of *N*-aryl cyanamides **1** bearing unactivated terminal alkene moiety. A broad range of substituents on the aromatic ring system of cyanamides, such as *para*-fluoro, *para*-chloro, *para*-bromo, *para*-methyl, *para*-methoxy and *para*-*t*-butyl were well tolerated and afforded both CF_3 and SO_2 incorporated cyclic *N*-sulfonylimines **3b-3g** in this transformation. However, cyanamides **1** bearing strong electronic withdrawing groups such as CF_3 and CO_2Et on the *para*-position of aromatic ring, failed to give any desired products (**3h-3i**). Both *ortho*- or *meta*-substitution of the aromatic ring system of cyanamides were tolerated (**3j**, **3l**), and *meta*-substituted analogue afforded a 1.2:1 mixture of regioisomers (**3l**). Disubstituted cyanamides were also evaluated, and *N*-(3,4-dimethylphenyl) cyanamide gave the desired product **2n** with regioselectivity 1.7/1, while the expected tandem reaction of 3,4-dimethoxyl analogue with **2a** did not occur (**3o**) with the recovery of the most of starting material. Besides, either *N*-*α*- or *β*-naphthyl substituted cyanamides can also serve as suitable substrates to furnish the desired trifluoromethyl cyclic *N*-sulfonylimines (**3k**, **3m**) as sole regioisomers. Notably, heterocyclic moiety like 5-substituted indole was amenable to this electrochemical transformation, and the desired product **3q** can obtained in moderate yield with high regioselectivity along with small amount of by-product **3q'** which may stem from the trifluoromethylation/cyclization without SO_2-insertion. *N*-Aryl cyanamides **1** bearing disubstituted alkene moiety were also evaluated, and *N*-(3-methylbut-3-en-1-yl)-*N*-phenylcyanamide gave the desired product **3p** in 33% yield, while phenyl-substituted analogue did not react with **2a** to give the desired cyclic sulphonamide (**3r**) under the optimized reaction conditions. The structure of trifluoromethylated cyclic *N*-sulfonylimine was unambiguously confirmed by single crystal X-ray analysis of compound **3a**.

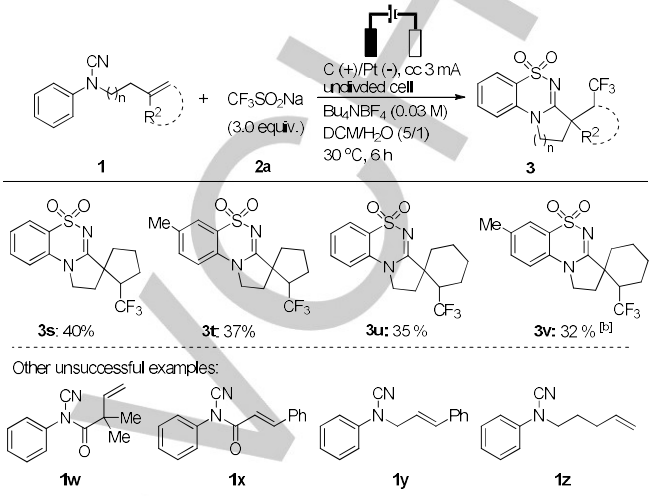
Table 2: Substrates scope. [a]



[a] Reaction conditions: **1** (0.3 mmol), **2a** (0.9 mmol), Bu_4NBF_4 (0.3 mmol) and DCM/H_2O (5/1) (c = 0.03 *M*) in an undivided cell with graphite rod anode (Φ 6 mm), Pt plate cathode (10 × 10 × 0.1 mm), constant current = 3.0 mA, 30 °C, 6 h. Isolated yields. [b] Constant current = 5.0 mA, 30 °C, 6 h.

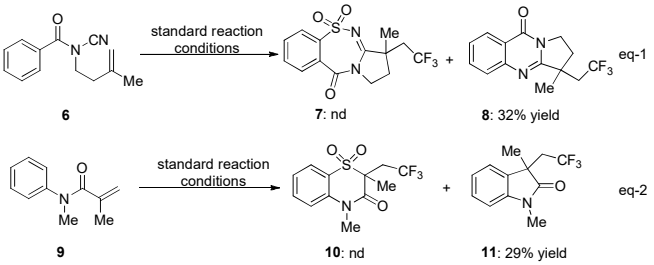
Besides, to our delight, the electrolytic trifluoromethylation/SO_2-insertion/cyclization tandem sequence was applicable to *N*-aryl cyanamides **1** containing unactivated internal alkene moiety under the standard reaction conditions. By virtue of Langlois reagent (**2a**) as a bifunctional reagent, trifluoromethylated *N*-sulfonylimines **3s-3v** incorporating spiro-cyclic moieties can be readily assembled from *N*-aryl cyanamides **1** containing cyclopentene and cyclohexene moieties as sole diastereoisomers (Table 3). Further investigations revealed that this tandem sequence was susceptive to the substitution and the length of the linkage between *N* and alkenyl moieties of cyanamides. For examples, *N*-(2, 2-dimethylbut-3-enoyl) substituted cyanamide (**1w**), *N*-cinnamoyl

Table 3: Substrates scope. [a]

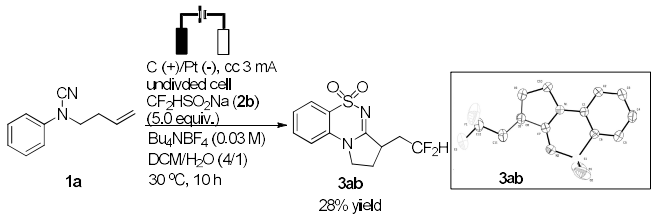


[a] Reaction conditions: **1** (0.3 mmol), **2a** (0.9 mmol), Bu_4NBF_4 (0.3 mmol) and solvent (c = 0.03 *M*) in an undivided cell with graphite rod anode (Φ 6 mm), Pt plate cathode (10 ×10 × 0. 1 mm), constant current = 3.0 mA, 30 °C, 6 h. [b] Constant current = 5.0 mA, 30 °C, 6 h.

substituted cyanamide (**1x**), *N*-cinnamyl substituted cyanamide (**1y**) or *N*-(pent-4-en-1-yl)- substituted cyanamide (**1z**) cannot participate in this tandem electrochemical cyclization to afford the desired products, while *N*-benzoyl substituted cyanamide **6** delivered CF_3-substituted quinazolinone **8** in 32% yield instead of *N*-sulfonylimine **7** with SO_2-insertion (eq-1), which can also prepared from copper-catalyzed trifluoromethylation/cyclization of **6** by using Togni's reagent. [14a] In addition, cyanamide moiety seemed to be pivotal to this electrolytic sequence, since electrochemical reaction between *N*-arylacrylamide **9** with CF_3SO_2Na (**2a**) furnished trifluoromethylated oxindole **11** instead of CF_3-incorporated cyclic *N*-sulfonylimine **10** under the current electrolysis conditions (eq-2).[3e, 3g-3h]

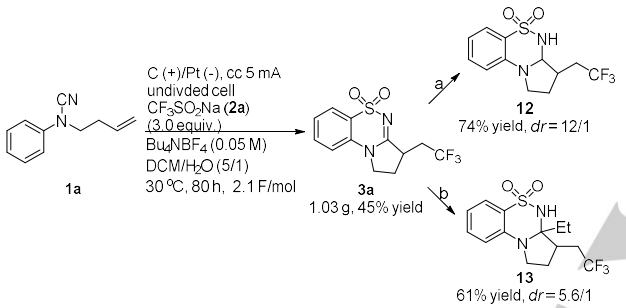


Besides, this electrochemical approach was also applicable to difluoromethylation/SO_2-insertion/cyclization sequence, which was exemplified by the reaction between **1a** and sodium difluoromethanesulfinate **2b**. The desired difluoromethylated cyclic *N*-sulfonylimine **3ab** can be obtained in 28% yield under the slightly modified reaction conditions.



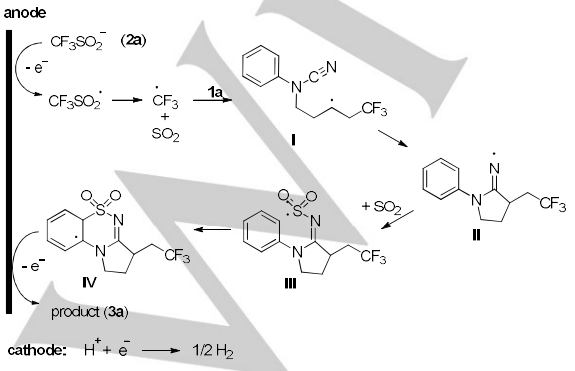
Scheme 2. Electrochemical difluoromethylation/SO_2-insertion/cyclization sequence of **1a** and **2b**.

To evaluate the potential application of this protocol, the electrolytic reaction of **1a** (7.5 mmol, 1.29 g) with **2a** could be performed on a gram scale with acceptable yield (1.03 g, 45%) (Scheme 3).[15] On the other hand, cyclic *N*-sulfonylimine **3a** could be readily converted to functionalized trifluoromethylated cyclic sulfonamides (**12** and **13**) by using $LiAlH_4$ and Grignard reagent respectively.



Scheme 3. Gram-scale experiment and synthetic transformations. Reaction conditions: (a) $LiAlH_4$, THF, 0 - 30 °C, 12 h; (b) EtMgBr, THF, 0 – 50 °C, 16 h.

On the basis of these studies, [15] a plausible mechanism was proposed for this electrochemical transformation with the exemplification of **1a** and **2a** in Scheme 4. The anodic oxidation of the trifluoromethanesulfinate anion produces the corresponding radical that decomposes to the CF_3 radical and SO_2 in a desulfurative manner. Attack of the CF_3 radical to the alkene moiety of cyanamide **1a**, results in C-radical intermediate **I**, which is cyclized by intramolecular addition of C-radical to cyano group to give iminyl radical **II**. The capture of SO_2 by iminyl radical intermediate **II** can deliver sulfonyl radical **III**, which undergoes further cyclization to give intermediate **IV**. Finally, further anodic oxidation followed by aromatization affords the corresponding product.



Scheme 4. Proposed mechanism.

In summary, we have developed an unprecedented electrochemical trifluoromethylation/SO_2-insertion/cyclization process in an undivided cell. By utilizing Langlois reagent as CF_3 and SO_2 sources, this protocol enabled efficient construction of various trifluoromethylated cyclic *N*-sulfonylimines from readily accessible materials in a single operation in an atom-economic fashion. The difluoromethylation/SO_2-insertion/cyclization sequence and synthetic application were also demonstrated. We are currently studying the application of this approach to other sulfonylative reactions.

Acknowledgments

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Conflict of interest

The authors declare no conflict of interest.

Keywords: Electrochemical reaction • trifluoromethylation • SO_2-insertion • cyclization • atom-economy

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[15] For the control experiments and cyclic voltammetry (CV) experiments, see the Supporting Information for details.

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Layout 2:

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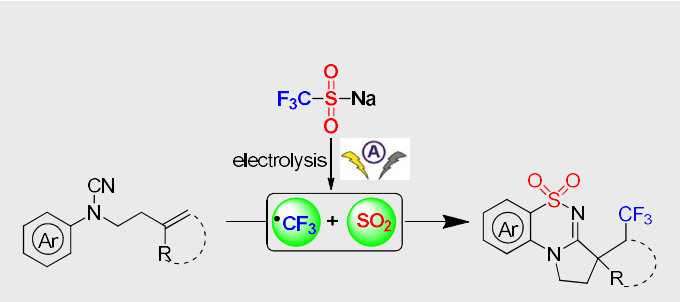

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CF_3SO_2Na Acted as a Bifunctional Reagent: Electrochemical Trifluoromethylation of Alkenes Accompanied by SO_2-Insertion to Access Trifluoromethylated Cyclic *N*-Sulfonylimines

Two birds with one stone: An electrochemical trifluoromethylation/SO_2-insertion/cyclization process is presented in an undivided cell in an atom-economic fashion. Various trifluoromethylated cyclic *N*-sulfonylimines can be readily accessed from readily available materials by using Langlois reagent as CF_3 and SO_2 sources in a single operation under direct anodically oxidative conditions.