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Electrosynthesis of sulfonamides from DMSO and amines under mild conditions†

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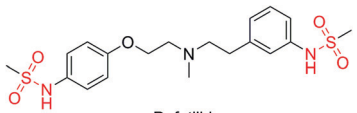
With DMSO as the solvent and the precursor of a $-SO_2Me$ unit at room temperature, a novel electrochemical oxidization and amination of DMSO with amines was developed for the synthesis of sulfonamides. Our investigations reveal that this transformation may involve a radical process and an electrochemical oxidization of DMSO.

Sulfonamide is an important structural motif, which widely exists in pharmaceuticals and bioactive compounds, such as anticonvulsants, HIV protease inhibitors, antiviral, antibacterial, anti-inflammatory and antitumor agents, and herbicides (Scheme 1).[1] Besides, sulfonamide, an easy removable protecting groups of amines, has played a significant role in the transformation of amines.[2] Until now, many methods have been developed to synthesize sulfonamides, including the direct reaction of amino compounds with sulfonyl chlorides[3] and metal catalyzed cross-coupling of sulfonamides with organic electrophiles,[4] or with arylboronic acids under oxidative conditions (Scheme 2).[5] Jiang and coworkers reported a direct aerobic oxidative coupling between sulfinate salts with amines to prepare sulfonamides.[6] Recently, Willis and Wu reported an elegant method to construct sulfonamides from cheap and commercially available amines and arylboronic acids in the presence of DABCO-bis(sulfur dioxide) or DABSO as a source of sulfur dioxide.[7] Though great progress had been made in this aera, there were still some drawbacks in the current methods, such as hazardous or expensive starting materials, stoichiometric amount of base or chemical oxidants, using a transition metal catalyst and so on. Therefore, a practical and eco-friendly method to synthesize sulfonamides under mild conditions was highly desirable.

DMSO can serve as not only a common solvent but also a multipurpose precursor for –Me,[8] –CN,[9] –CHO,[10] –SMe,[11] $-SO_2Me$,[12] and –O[13] units. Herein, we reported a novel and practical sulfonamide synthesis from DMSO and amines under electrochemical conditions.

Electrosynthesis, which employs electrons as traceless redox reagents, has been recognized as a green technology. In recent years, an electrochemical organic synthesis has attracted more and more attention due to its tunability over electron-transfer processes and friendliness to the environment.[14] Following our continuous interest on using DMSO as a synthon for organic transformations,[11,12,15] herein, we disclosed a novel and efficient electrochemical method to synthesize sulfonamides using DMSO as the starting material to provide the source of $-SO_2Me$ at room temperature (Scheme 2). To the best of our knowledge, this is the first example of the synthesis of sulfonamides using DMSO as the sulfur source.

N-Methyl-1-phenylmethanamine (**1a**) was chosen as a model substrate to examine the reaction conditions. Using KI as the supporting electrolyte, DMSO as the solvent and substrate, Pt plate as an anode and Ni plate as a cathode, *N*-methyl-*N*-benzylmethanesulfonamide **3a** was obtained in 81% isolated yield under 30 mA constant current for 8 h in an undivided cell (Table 1, entry 1). I^- ions were found to be crucial since no desired product was observed when KI was replaced by NH_4Br or n-Bu_4NBF_4 (Table 1, entries 2 and 3). In addition, Using NH_4I instead of KI, the yield of **3a** dropped significantly (Table 1, entry 4). Replacing DMSO with DMSO/H_2O (v/v = 4 : 1) or DMF/DMSO (v/v = 4 : 1), we could not detect the desired product **3a**, and a majority of dimers of **1a** was obtained (Table 1, entries 5 and 6). A Ni cathode was found to be important because no target product **3a** could be detected when the Ni electrode was replaced by a C cathode, with a low conversion of **1a** (Table 1, entry 7). Furthermore, using an inexpensive C plate



Dofetilide

Scheme 1 Drug with sulfonamide structure motif.

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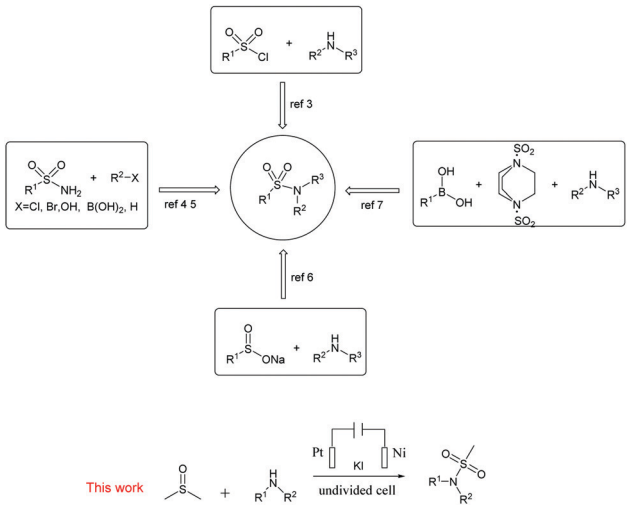
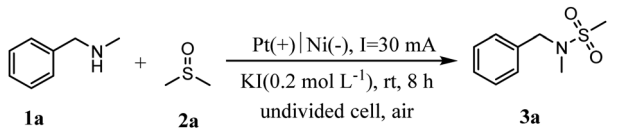


Scheme 2 Synthetic methods for sulfonamides.

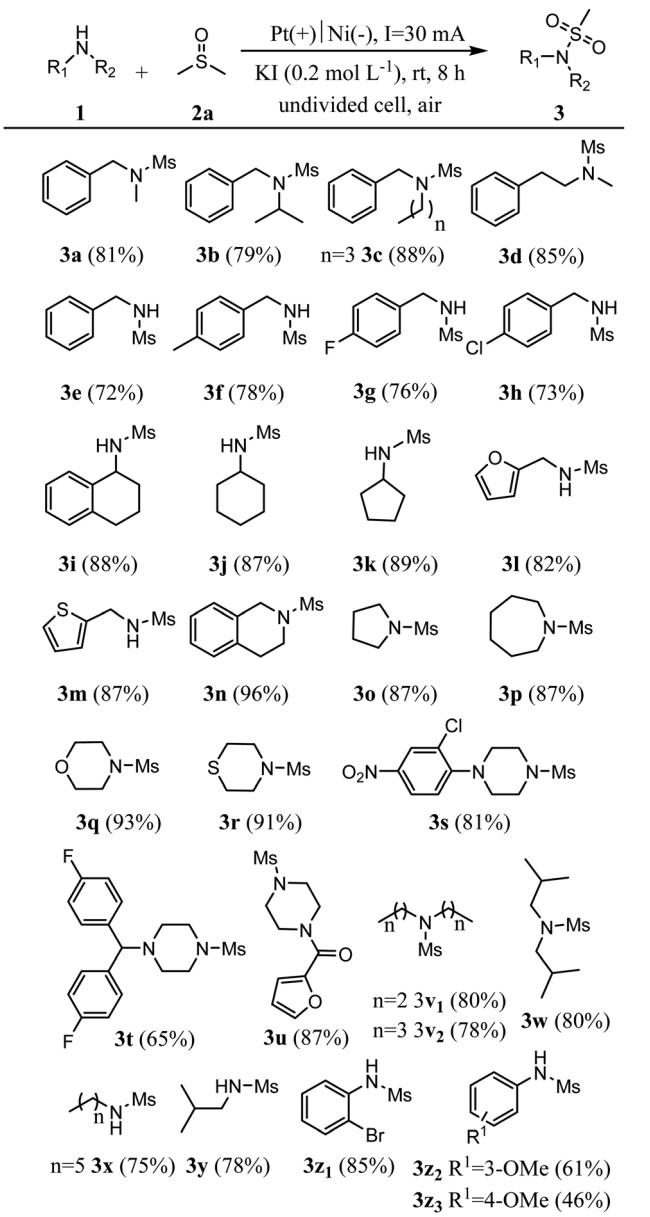
Table 1 Optimization of the reaction conditions[a]



Entry	Variation from the standard conditions	Yield[b]
1	None	86 (81%)[c]
2	NH_4Br instead of KI	n.d.
3	n-Bu_4NBF_4 instead of KI	n.d.
4	NH_4I instead of KI	Trace
5	DMSO/H_2O (v/v = 4 : 1) instead of DMSO	n.d.
6	DMF/DMSO (v/v = 4 : 1) instead of DMSO	n.d
7	Pt(+)|C(−) instead of Pt(+)|Ni(−)	n.r.
8	C(+)|Ni(−) instead of Pt(+)|Ni(−)	71%
9	20 mA instead of 30 mA	63%
10	10 mA instead of 30 mA	42%
11	5 mA instead of 30 mA	24%
12	No electricity	n.r.

[a] Pt plate (10 mm × 10 mm × 0.1 mm) anode, Ni plate (10 mm × 10 mm × 0.1 mm) cathode, constant current = 30 mA, **1a** (0.5 mmol), KI (0.2 mol L^{-1}), DMSO (5.0 mL), room temperature, 8 h, under air and an undivided cell. [b] Yield was analyzed by GC-MS with *n*-dodecane as an internal standard, n.d. = not detected, n.r. = no reaction. [c] Isolated yield.

Table 2 Scope of amine substrates[a]



[a] Conditions: **1** (0.5 mmol), DMSO (5 mL), 8 h, isolated yield based on amines.

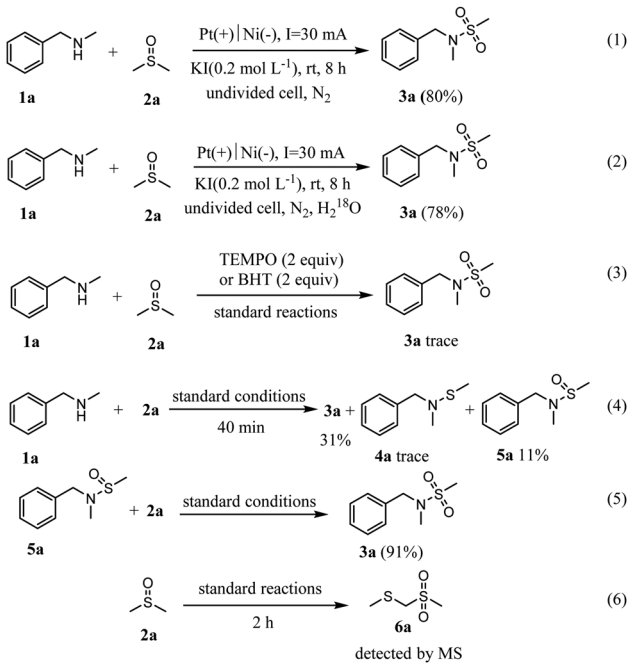
anode showed slightly reduced yield compared with the platinum plate anode (Table 1, entry 8). Moreover, a decreased current leads to lower reaction yields (Table 1, entries 9–11). Besides, the reaction could not take place without electricity (Table 1, entry 12).

Under the optimized reaction conditions, we further studied the scope of the reaction with different amines and the results are summarized in Table 2. Different aliphatic amines all show a good activity in those transformations. Steric hindrance on the nitrogen of benzylamine had a neglectable influence on this transformation (**3b**, **3c**). Besides, phenethylamine gave an excellent yield of the corresponding product (**3d**). A moderate yield of *N*-benzylmethanesulfonamide (**3e**) was obtained when benzylamine was used, which was due to its dimerization. Benzylamine with methyl, fluoro, and chloro groups on the aryl rings all gave moderate yields of the corresponding products (**3f–3h**). Cyclic secondary amines such as tetrahydroisoquinoline, pyrrolidine, morpholine, and thiomorpholine *etc.*, were compatible with those reactions, and were transformed into the corresponding products (**3n–3u**) in good yields. Aromatic amines such as 2-bromoaniline were suitable substrates to undergo this reaction in a good yield ($3z_1$). Notably, 3-methoxyaniline and 4-methoxyaniline could also be transformed into the corresponding products ($3z_2$–$3z_3$) in moderate yields.

In order to explore the reaction mechanism, several control experiments were carried out. The desired product **3a** was obtained in a good yield under the protection of N_2 gas

(Scheme 3, eqn (1)), which indirectly indicated that the oxygen atom of the sulfone group in **3a** did not come from air. No ^{18}O labeled product **3a** was obtained in the presence of $H_2{}^{18}O$ (Scheme 3, eqn (2)), suggesting that the oxygen atom of the sulfonamides **3a** did not originate from H_2O. Based on these experimental results, we deduced that DMSO provided all the oxygen atom of the sulfone group in **3a**. In addition, the desired product **3a** could only be obtained in a trace amount when adding radical inhibitor 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) or 2,6-di-*tert*-butyl-4-methylphenol (BHT) to the electrolytic system (Scheme 3, eqn (3)), indicating that the formation of **3a** presumably underwent a radical pathway. Within a reaction time of 40 minutes, *N*-benzyl-*N*,*S*-dimethylthiohydroxylamine (**4a**) and *N*-benzyl-*N*-methylmethanesulfinamide (**5a**) were detected by GC-MS (Scheme 3, eqn (4)). The intermediate **5a** could be isolated and its characterization was given in the ESI.† In addition, **5a** could be transformed to *N*-methyl-*N*-benzylmethanesulfonamide (**3a**) smoothly under the optimized conditions (Scheme 3, eqn (5)). This implies that **4a** and **5a** may be the intermediates in this conversion. Just DMSO in this standard reaction for 2 h, methyl((methylsulfonyl)methyl)sulfane (**6a**) can be detected, which means that DMSO can be transformed to CH_3SH under electrochemical conditions (Scheme 3, eqn (6)).[16]

Cyclic voltammetric (CV) experiments were executed to gain insight into the reaction process. In the blank experiment (Fig. 1a), no oxidation peak was observed. Adding KI, an obvious oxidation peak was observed at 1.47 V *vs.* Ag/AgCl (Fig. 1b). In the presence of **1a** and KI at the same time, a similar oxidation peak was observed (Fig. 1c), which was due to the electro-oxidation of I^- ions. Adding *n*-Bu_4NBF_4 to DMSO solvent, two obvious oxidation peaks were observed at 0.9 V and 1.5 V *vs.* Ag/AgCl, which were due to the electro-oxidations of DMSO (Fig. 1d). This result strongly indicated that DMSO could be oxidized under the electrochemical conditions.



Scheme 3 Control experiments.

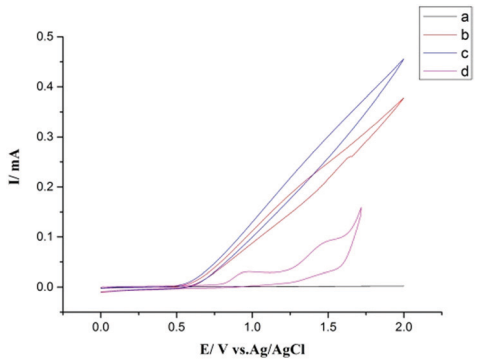
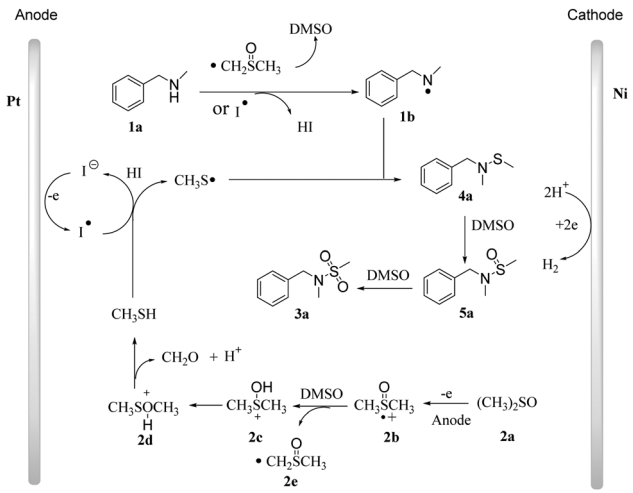


Fig. 1 Cyclic voltammograms of DMSO (10 mL) at room temperature. (a) Blank experiment; (b) KI (0.2 mol L^{-1}); (c) KI (0.2 mol L^{-1}) and *N*-methyl-*N*-benzylmethanesulfonamide **1a** (1 mmol); (d) DMSO (10 mL) and *n*-Bu_4NBF_4 (0.2 mol L^{-1}); with a GC disk working electrode, Pt counter electrode and Ag/AgCl reference electrode at 100 mV s^{-1} scan rate.



Scheme 4 Proposed reaction mechanism.

According to the above results, a plausible reaction mechanism was proposed in Scheme 4. Initially, the iodide ion was oxidized to an iodine radical in the Pt anode. Meanwhile, DMSO was electro-oxidized at the anode to form radical cation **2b**, which reacted with another molecule of DMSO to form dimethyl sulfoxonium cation **2c** and dimethyl sulfoxide radical **2e**.[17] The **2c** was rearranged to sulfenate ester **2d**, followed by decomposing to CH_3SH, CH_2O and H^+ ions.[17] Meanwhile **1a** was attacked by **2e** or an iodine radical to generate *N*-methyl-1-phenylmethanamine radical **1b**. In addition, the iodine radical attacked CH_3SH to give HI and MeS$^\bullet$.[18] And then, **1b** was captured by MeS$^\bullet$ to generate *N*-benzyl-*N*,*S*-dimethylthiohydroxylamine (**4a**), which was further oxidized by DMSO to form *N*-benzyl-*N*-methylmethanesulfinamide (**5a**).[12,19] And **5a** was further oxidized by DMSO to give the target product **3a**.[18] In the cathode, the cathodic reduction of H^+ ions led to hydrogen evolution.

In conclusion, a novel and efficient protocol for the synthesis of sulfonamides by an electrochemical oxidization and amination of DMSO was developed. The procedure presented a convenient method to generate methylthiyl radicals from DMSO at room temperature. The mechanism studies of these transformations supported an electrooxidation of DMSO pathway.

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Conflicts of interest

There are no conflicts to declare.

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