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Electrochemical synthesis of sulfonamides from arenesulfonohydrazides or sodium *p*-methylbenzenesulfinate and amines

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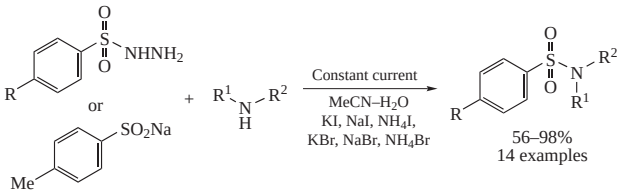
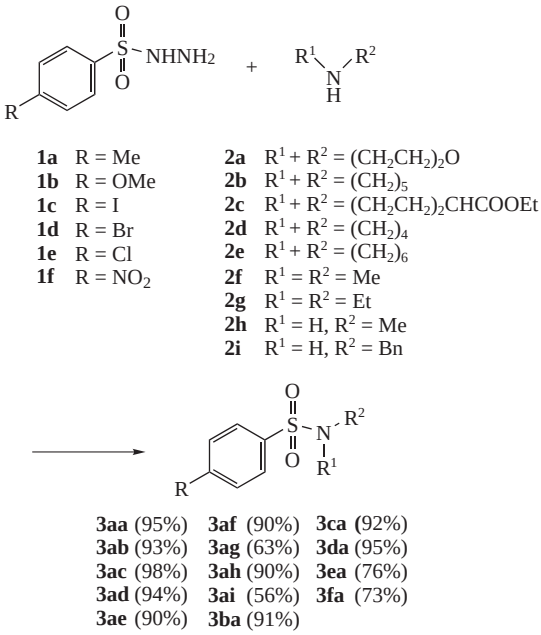
An efficient electrochemical synthesis of sulfonamides (yields 56–98%) from arenesulfonohydrazides or sodium *p*-methylbenzenesulfinate and amines was performed in an undivided cell with graphite anode and iron cathode in MeCN–H_2O medium using halides as redox mediators and supporting electrolytes.



Sulfonamides play an important role in the modern organic[1] and medicinal chemistry.[2,3] Sulfonamide moiety is widespread in natural and biologically active compounds.[4] Substances of this class possess antibacterial,[5,6] anticancer,[7,8] antiviral,[9] anticonvulsant,[10] anti-inflammatory,[11] and anti HIV protease activity.[12]

Traditionally sulfonamides are prepared by the reactions of sulfonyl chlorides with amines,[13–15] N-coupling of N-unsubstituted sulfonamides with alcohols,[16–18] organic halides,[19–21] arylboronic acids[22,23] and by transition metal catalyzed sulfonylation of hydrocarbons.[24,25] In the past years, transformations of sulfonyl azides[26,27] and oxidative S–N coupling[28–30] of arenesulfonohydrazides and sodium arylsulfinates using $CuBr_2$ and I_2/TBHP and TBAI/TBHP systems were documented.



Scheme 1 *Reagents and conditions*: molar ratio **1**:**2** was 1:1.5, NH_4Br in MeCN–H_2O, constant current, Fe cathode, graphite anode, 25–30 °C. In the designations of products **3** the first letter shows arenesulfonohydrazide **1** moiety, the second is amine **2** moiety. Isolated yields are given. For **3ag**: KBr was used. For **3ah** and **3ai**: molar ratios **1**:**2** were 1:3.

Redox processes with organic compounds are widely implemented using electrochemical techniques[31,32] by the following reasons: availability and low cost of electric current, variety of electrochemical reaction mechanisms and decrease in waste amounts.[33] The main idea of our work was the replacement of chemical oxidants applied for oxidative S–N coupling of arenesulfonohydrazides and sodium arylsulfinates with amines by anodic oxidation.

Electrolysis of arenesulfonohydrazides **1a–f** and amines **2a–i** at constant current density 35–40 mA cm^{-2} in an undivided cell with graphite anode and iron cathode affords the target sulfonamides **3** (Scheme 1).

Optimal reaction conditions were selected on the example of the synthesis of *p*-toluenesulfonomorpholide **3aa** from reactants **1a** and **2a** (Table 1).

Entries 1, 2 (see Table 1) show that the complete conversion of compound **1a** was achieved on passing 5 F mol^{-1} electricity.

Table 1 Electrochemical synthesis of sulfonamide **3aa** from *p*-toluenesulfonohydrazide **1a** and morpholine **2a**.[a]

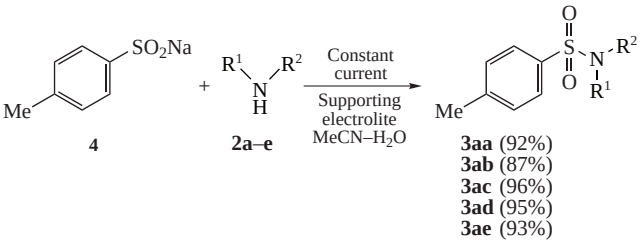
Entry	Molar ratio **1a**:**2a**	Supporting electrolyte	Electricity passed/ F per mole of **1a**	Isolated yield of **3aa** (%)
1	1:2	KI	3	62
2	1:2	KI	5	85
3	1:3	KI	5	79
4	1:1.5	KI	5	85
5	1:1	KI	5	75
6	1:1.5	NaI	5	92
7	1:1.5	NH_4I	5	90
8	1:1.5	KBr	5	91
9	1:1.5	NaBr	5	93
10	1:1.5	NH_4Br	5	95
11	1:1.5	NH_4Cl	5	96

[a] The solution of **1a** (300 mg, 1.61 mmol), **2a** (1.61–4.83 mmol) and electrolyte (0.8 mmol, 0.5 equiv. with respect to **1a**) in 30 ml of MeCN–H_2O (1:1) was electrolyzed at 25–30 °C under magnetic stirring.

Optimal molar excess of morpholine **2a** above **1a** is 1.5 (entry 4), providing 85% yield of **3aa** (*cf.* entries 3–5). Sulfonamide **3aa** was obtained in high yields using a wide range of supporting electrolytes: KI, NaI, NH_4I, KBr, NaBr, NH_4Br, and NH_4Cl (entries 4, 6–11), however the best results were achieved with NH_4Br and NH_4Cl (entries 10, 11). Mainly under optimized conditions of entry 10 compounds **3aa**–**3fa** were synthesized in 56 to 98% yields (see Scheme 1).†

In general, yields of sulfonamides **3aa**–**3fa** did not depend crucially on the nature of sulfonohydrazide **1** and amine **2**. The main condition for successful reaction using primary amines **2h** and **2i** was the use of threefold excess of amine **2**. Influence of the electron-withdrawing group in *p*-chloro- and *p*-nitro-substrates **1e** and **1f** is probably the reason of lower yields of the corresponding sulfonamides **3ea** and **3fa**. On using anilines as N-reagents, the formation of N-arylated sulfonamides was not observed.

Next, sodium *p*-methylbenzenesulfinate **4** was chosen as the S-reagent to prepare sulfonamides (Scheme 2).



Scheme 2

Optimization of *p*-toluenesulfonomorpholide **3aa** synthesis from **4** and **2a** showed that passing 5 F mol^{-1} electricity in the MeCN–H_2O solvent system with 1.5-fold molar excess of amine **2** afforded the desired sulfonamide **3aa** with the following yields in the case of corresponding supporting electrolyte: KI, 52%; NH_4Cl, 74%; NH_4Br, 92%; and NH_4I, 75%.

Under the optimized conditions with NH_4Br as the supporting electrolyte, representative sulfonamides (see Scheme 2) were obtained in good yields. In total, electrochemical synthesis with NH_4Br as the supporting electrolyte with high current density of 35–40 mA cm^{-2} affords sulfonamides **3aa**–**3ae** in 87–96% yields. Apparently, halide anions are electrochemically oxidized at the anode to molecular halides or hypohalites, which effectively oxidize the starting reactants. This makes possible to replace chemical oxidants with electric current in oxidative S–N coupling sulfonamide synthesis. It is important to note, that sulfonamides **3aa**–**3fa** are obtained in pure form and do not contain organic impurities according to NMR data. Analytically pure samples for determination of characteristics and evaluation of isolated product yields were obtained by recrystallization from ethanol.

In conclusion, effective and selective electrochemical synthesis of sulfonamides (yields 56–98%) from arenesulfonohydrazides or sodium *p*-methylbenzenesulfinate and amines in an undivided cell with graphite anode and iron cathode was developed. An advantage of this electrochemical process is the possibility of using high current density (35–40 mA cm^{-2}), which permits to carry out the synthesis fast and employ small electrodes surface (6–7 cm^2).

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2016.11.027.

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† *General procedure*. An undivided cell was equipped with a carbon plate anode (7.5 cm^2) and a Fe plate cathode (7.5 cm^2) and connected to a DC regulated power supply. The solution of corresponding amine **2** (1.5–4.83 mmol) in 30 ml MeCN–H_2O (1:1), arenesulfonohydrazide **1** (300 mg, 1.00–1.61 mmol) and supporting electrolyte KBr, NH_4Br (0.5–0.8 mmol; molar ratio to **1** was 1:2) were added to the cell. The mixture was electrolyzed with constant current (35–40 mA cm^{-2}) at 25–30 °C under magnetic stirring. Then the solvent was removed under reduced pressure (10–20 Torr). The residue was diluted with EtOAc (50 ml) and washed with brine (2 × 8 ml) and water (2 × 8 ml), dried over Na_2SO_4, and concentrated under reduced pressure (10–20 Torr). Then it was purified by recrystallization from ethanol.

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