Novel Synthesis of Mafenide and Other Amino Sulfonamides by Electrochemical Reduction of Cyano Sulfonamides

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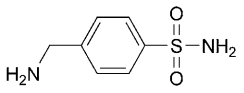
Both aliphatic and aromatic amino sulfonamides such as mafenide (**1a**) were synthesized in good yields (80–86%) by direct electrochemical hydrogenation of the corresponding nitriles in an *undivided* cell containing a Ni cathode, a Pt anode, and *Raney* Ni as catalyst (*Table 1*). The reaction can be performed without external supply of pressurized gas by *in situ* generation of H_2. Slightly elevated temperatures (45°) and low current densities (10 mA/cm^2) are favorable conditions for this type of electrochemical nitrile hydrogenation. Our synthetic protocol does not require high-pressure equipment or chemical hazards, is environmentally very friendly, and more economical than traditional methods. The concentration of adsorbed H$^{\cdot}$ radicals on the catalyst surface can be easily controlled by adjusting the electric potential, which may lead to improved product selectivity and, at the same time, reduces the risk of explosion and fire.

Introduction. – Amino sulfonamides are important synthetic organic compounds that often exhibit antibacterial and antifungal activities [1][2]. Therefore, some of these compounds are called 'sulfa medicines', one example being mafenide (**1a**), which is being used in the treatment of acute burns [3]. The synthesis of amino sulfonamides from the corresponding nitriles by (catalytic) reduction is very important. In this process, primary amines are obtained, which form a large group of compounds widely used in pharmaceuticals and agrochemicals [4]. Nitrile reduction is also very important both in synthetic [5] and industrial [6] chemistry. *Miller et al.* have synthesized several amino sulfonamides by catalytic reduction of cyano compounds, nitro sulfonamides, or *N*-acyl derivatives [1].



Mafenide (**1a**)

One great advantage of *electrochemical* reduction is the fact that they are ecologically very friendly. Since there is a 'mass-free' electron transfer between an electrode and a substrate, there is typically no need for waste disposal [7]. So, *Krishnan et al.* [8][9], and *Song* and *Pintauro* [10] have studied the electrochemical reduction of nitriles with different metal-block electrodes in a divided cell. However, the use of a *divided* cell substantially increased production costs, and the system was impractical

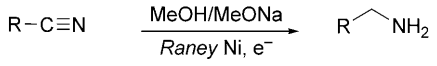
to be further developed for commercial applications. To develop a more-convenient and commercially useful synthetic method for the preparation of amino sulfonamides from nitriles, it would, thus, be highly desirable to find a high-yielding system based on an *undivided* cell for performing electrochemical hydrogenation.

In this paper, we present, for the first time, an electrochemical technique that involves a combination of *in situ* electrochemical generation of pure H_2 adsorbed on *Raney* Ni as the catalyst in an undivided cell equipped with a Ni cathode and a Pt anode.

Results and Discussion. – Electrolysis was carried out under anhydrous conditions in MeOH/MeONa to avoid nitrile hydrolysis [11]. The use of compressed H_2 gas was circumvented by electrolytic generation of H_2 as reducing agent. The selective reduction of the biologically relevant nitriles **2a**–**f** was performed in an undivided cell containing a Ni cathode, a Pt anode, and *Raney* Ni as catalyst at various temperatures (*Table 1*) and current densities (*Table 2*). In the absence of catalyst, the electrochemical hydrogenation of compounds **2** resulted in only poor yields (15–20%) of the amines **1** due to non-productive evolution of H_2 gas.

The best conditions in terms of yield were slightly elevated temperature (45°) and low current density (10 mA/cm^2). The reactions at the cathode mainly include hydrogenation and H_2 evolution, which alters the product yield. These results suggest that elevated temperatures accelerate the reduction of nitriles to a greater extent than the formation and evolution of H_2 from electrochemically generated, adsorbed H$^{\bullet}$ radicals. In turn, with increasing current density, H_2 evolution increased; hence, low current densities are favorable.

Table 1. *Influence of Temperature on the Yield of Electrochemically Generated Amino Sulfonamides.* All reactions were performed at a current density of 10 mA/cm^2.



2 **1**

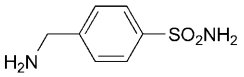
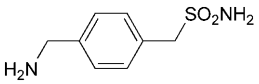
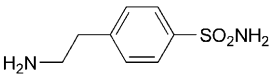
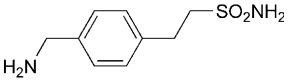
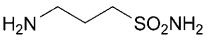
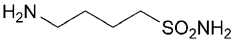
Series	Product (**1**) $H_2N–CH_2–R$	Isolated yield [%]				
		5°	15°	25°	35°	45°
a		60	69	75	81	85
b		59	67	71	80	83
c		62	71	77	81	86
d		61	65	72	74	80
e		57	67	74	78	81
f		61	69	71	76	83

Table 2. *Influence of Current Density on the Yield of Electrochemically Generated Amino Sulfonamides.* All reactions were performed at 25°.

Entry	Current density [mA/cm^2]	Isolated yield [%]					
		1a	**1b**	**1c**	**1d**	**1e**	**1f**
1	10	75	71	77	72	74	71
2	25	70	64	71	67	70	64
3	50	63	59	63	60	62	56

From a mechanistic point of view, the observed increase in product yields is the result of the competition between the two above reactions. Electrochemical hydrogenation of an organic substance proceeds *via* the formation of adsorbed H$^\bullet$ interacting with the organic substrate approaching from solution. When reductions are carried out in the presence of *Raney* Ni as catalyst, H^+ is abstracted from MeOH, and then takes up one electron. The resulting atomic H$^\bullet$ gets adsorbed on the catalyst surface, and then reacts with a CN group to form the desired CH_2NH_2 function according to *Eqns. 1* and *2*:

$$MeOH + e^- \rightarrow H^\bullet_{ads} + MeO^- \quad (1)$$

$$4\ H^\bullet_{ads} + R{-}C{\equiv}N \rightarrow R{-}CH_2NH_2 \quad (2)$$

According to the above mechanism, we assume that the actual reduction of the CN function takes place by the adsorbed, electrochemically generated, catalyst-activated H-atoms, rather than by direct electron transfer between the substrate and the electrode.

Experimental Part

Electrochemical Hydrogenation. All reactions were carried out in an undivided cell containing a Ni cathode and a Pt anode (2×2 cm each). Through a soln. of the nitrile **2** (10 mmol) [1][12][13] in anh. MeOH (40 ml) containing MeONa (0.1 mol) and freshly prepared *Raney* Ni (1.0 g) [14], O_2-free N_2 gas was bubbled for 10–15 min. Then the soln. was electrolyzed at const. current density (10 mA/cm^2) until 4 F/mol of electricity were consumed. Then, the mixture was transferred to a round-bottom flask, and the solvent was evaporated. The residue was treated with 10% aq. HCl, and the aq. layer was extracted with Et_2O. The aq. soln. was made strongly alkaline by addition of NaOH and extracted with Et_2O (3×25 ml). The combined org. extract was dried (Na_2SO_4) and concentrated under reduced pressure to afford the appropriated amino sulfonamides **1**. For yields, see *Table 1*.

4-(Aminomethyl)benzenesulfonamide (**1a**). M.p. 147–149° (lit. m.p. 151–152° [1]). IR (KBr): 1124, 1335, 2231, 3327 cm^{-1}. ^{1}H-NMR ($CDCl_3$): $\delta = 3.36$ (*s*, CH_2); 3.9 (br. *s*, NH_2); 6.41 (br. *s*, SO_2NH_2); 7.26 (*d*, 2 arom. H); 7.73 (*d*, 2 arom. H). Anal. calc. for $C_7H_{10}N_2O_2S$ (186.23): C 45.15, H 5.40, N 15.04; found: C 45.17, H 5.38, N 15.07.

1-[4-(Aminomethyl)phenyl]methanesulfonamide (**1b**). M.p. 159–161° (lit. m.p. 160.5–162.0° [1]). IR (KBr): 1127, 1337, 3325 cm^{-1}. ^{1}H-NMR ($CDCl_3$): $\delta = 3.18$ (*s*, ArCH_2N); 3.8 (br. *s*, CH_2NH_2); 4.78 (*s*, ArCH_2S); 6.38 (br. *s*, SO_2NH_2); 7.08 (*d*, 2 arom. H); 7.12 (*d*, 2 arom. H). Anal. calc. for $C_8H_{12}N_2O_2S$ (200.26): C 47.98, H 6.08, N 13.99; found: C 47.95, H 6.07, N 13.96.

4-(2-Aminoethyl)benzenesulfonamide (**1c**). M.p. 145–147° (lit. m.p. 147.5–149.0° [1]). IR (KBr): 1136, 1341, 3331 cm^{-1}. ^{1}H-NMR ($CDCl_3$): $\delta = 2.77$ (*t*, ArCH_2); 2.91 (*t*, CH_2N); 3.6 (br. *s*, CH_2NH_2); 6.24 (br. *s*, SO_2NH_2); 7.29 (*d*, 2 arom. H); 7.74 (*d*, 2 arom. H). Anal. calc. for $C_8H_{12}N_2O_2S$ (200.26): C 47.98, H 6.03, N 13.98; found: C 48.01, H 6.01, N 13.95.

2-[4-(Aminomethyl)phenyl]ethane-1-sulfonamide (**1d**). M.p. 172–174°. IR (KBr): 1129, 1331, 3329 cm^{-1}. ^{1}H-NMR ($CDCl_3$): $\delta = 3.23$ (*t*, ArCH_2C); 3.69 (*t*, SO_2CH_2); 3.76 (br. *s*, CH_2NH_2); 3.89 (*s*, ArCH_2-N); 6.31 (br. *s*, SO_2NH_2); 7.24 (*d*, 2 arom. H); 7.76 (*d*, 2 arom. H). Anal. calc. for $C_9H_{14}N_2O_2S$ (214.29): C 50.44, H 6.59, N 13.07; found: C 50.46, H 6.56, N 13.09.

3-Aminopropane-1-sulfonamide (**1e**). M.p. (HCl salt) 155–157° (lit. m.p. 159–160° [1]). IR (KBr): 1119, 1334, 3328 cm^{-1}. ^{1}H-NMR ($CDCl_3$): $\delta = 2.04$ (*m*, SCH_2CH_2); 2.58 (*t*, CH_2N); 2.9 (br. *s*, CH_2NH_2); 3.30 (*t*, SCH_2); 6.36 (br. *s*, SO_2NH_2). Anal. calc. for $C_3H_{10}N_2O_2S$ (138.19): C 26.07, H 7.29, N 20.27; found: C 26.09, H 7.27, N 20.29.

4-Aminobutane-1-sulfonamide (**1f**). M.p. (HCl salt) 124–125° (lit. m.p. 127–129° [1]). IR (KBr): 1121, 1329, 3342 cm^{-1}. ^{1}H-NMR ($CDCl_3$): $\delta = 1.59$ (*m*, CH_2CH_2N); 1.79 (*m*, CH_2CH_2S); 2.4 (br. *s*, CH_2NH_2); 2.71 (*t*, CH_2N); 3.38 (*t*, CH_2S); 6.30 (br. *s*, SO_2NH_2). Anal. calc. for $C_4H_{12}N_2O_2S$ (152.22): C 31.56, H 7.95, N 18.40; found: C 31.59, H 7.93, N 18.38.

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