# An Efficient Combined Electrochemical and Ultrasound Assisted Synthesis of Imidazole-2-Thiones

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**Abstract:** The electrochemical reduction of 1,3-dialkylimidazolium ionic liquids gave the corresponding N-heterocyclic carbenes that, after reaction with elemental sulfur and ultrasound irradiation, yielded 1,3-dialkylimidazole-2-thiones in very high yields. The reaction is very clean, produces no side-products and avoids the use of any other added reagent.

**Keywords:** electrochemistry; imidazole-2-thiones; imidazole2-ylidenes; ionic liquids; sulfur

Imidazole-2-thiones are important molecules used in the pharmaceutical and chemical industry. They are, in fact, important drugs. In particular, methimazole (I) and carbimazole (II) (Figure 1) are the most commonly used drugs for treatment of hyperthyroidism,<sup>[1]</sup> as they block thyroid hormone biosynthesis by inhibiting the thyroid peroxidase (TPO)-catalyzed iodination of tyrosine residues in thyroglobulin. Methimazole derivatives can be utilized as inhibitors of cell adhesion in cell adhesion-mediated pathologies.<sup>[2]</sup>

Moreover, they have been used as efficient catalysts in cross-linking reactions between polymers with pendent anhydrides and polymers with hydroxy or epoxy functionality.<sup>[3]</sup> Imidazole-2-thiones have been



also used as complexing agents in electroless plating solutions.  $\ensuremath{^{[4]}}$ 

More recently, these heterocycles have been employed as precursors of ionic liquids in entirely halide-free forms, by oxidative desulfurization with benzoyl peroxide.<sup>[5]</sup> In fact, one of the major problems in the use of ionic liquids is their purity, due mainly to halide impurities that derive from the non-exhaustive anion exchange in their synthesis.

Since the first synthesis of 1-substituted imidazole-2-thiones was established by Marckwald in 1889,<sup>[6]</sup> by the reaction of a isothiocyanate with an amino acetal, many synthetic routes to this important class of compounds have been described.

There are two main strategies of synthesis: a cyclization of linear thioureas and the sulfurization of Nheterocyclic carbenes. Matsuda and co-workers<sup>[7]</sup> carried out the synthesis of 1-substituted imidazole-2-thiones by cyclization of a substituted thiourea in a onepot reaction between an isothiocyanate and amino acetal in toluene, with concentrated HCl, at 110 °C for 1–3 h; Schreiner and co-workers,<sup>[5]</sup> instead, synthesized these compounds by thioureidation of *N*-butylglycinate and subsequent reduction with sodium borohydride (55% yield from ethyl *N*-butylglycinate). N-Substituted imidazole-2-thiones have been also synthesized by the electrochemically induced cyclization of phenacyl azide thiosemicarbazones, on a mercury cathode.<sup>[8]</sup>

The alternative way for the synthesis of these compounds is the one patented by Arduengo,<sup>[9]</sup> that is, the reaction of sulfur with an N-heterocyclic carbene, obtained by reaction of a strong base with an imidazolium salt, either in methanol over a period of 24 h, or in solventless conditions in 20 h, obtaining imidazole-2-thiones in high yields. The same reaction has been carried out by O. Yang and co-workers,<sup>[10]</sup> with BuLi in THF at -78 °C or with EtMgBr, in THF at room temperature; in this case the yields in thiones are 40–

Figure 1. Structures of drugs methimazole and carbimazole.

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84%. Also Lei and co-workers<sup>[11]</sup> used an imidazolium salt for the synthesis of thiones, by reaction with potassium thioacetate or thiocyanate, under solventless conditions and under microwave irradiation, obtaining 1,3-disubstituted imidazole-2-thiones in 35–70% yields.

Herein we report the first example of the reaction of an electrogenerated N-heterocyclic carbene with elemental sulfur accelerated by ultrasound irradiation, yielding imidazole-2-thiones in very high yields and short times.

The electrochemical reduction of a 1,3-substituted imidazolium ion is a monoelectronic process that leads to the formation of the corresponding carbene and dihydrogen (Scheme 1).<sup>[12]</sup>



Scheme 1. Electrochemical reduction of imidazolium salts.

This methodology for the generation of carbenes permits one to avoid the use of strong bases and the formation of by-products<sup>[13]</sup> (the imidazolium salt, an ionic liquid, acts as solvent, as supporting electrolyte and as reagent, needing no other compound in the electrolytic cell). This singlet carbene<sup>[14]</sup> can behave as a base or a nucleophile.<sup>[15]</sup> When reacting with elemental sulfur, it acts as nucleophile, opening the eight-membered ring of sulfur and probably giving a linear intermediate (Scheme 2) (an analogous mechanism has been reported in the case of the reaction between elemental sulfur and phosphonium ylides).<sup>[16]</sup>

As at the end of the reaction all eight atoms of sulfur have been used,  $S_7$  can re-enter the reaction and go on till all sulfur atoms are used.

Our first attempt to synthesize thiones used BMIM BF<sub>4</sub> (1-butyl-3-methylimidazolium tetrafluoroborate) (**1a**) as starting ionic liquid, 1.0 Faraday per mol of S and the experimental conditions used in our previous papers regarding the electrochemical generation of carbene,<sup>[17]</sup> that is, a divided cell, N<sub>2</sub> atmosphere, room temperature, platinum electrodes and galvano-static conditions ( $I=30 \text{ mA cm}^{-2}$ ). At the end of the

electrolysis, elemental sulfur was added to the catholyte and the mixture left under stirring at room temperature. After two hours, the corresponding thione **2a** was isolated in 35% yield (after extraction with diethyl ether) (Table 1, run 1).

As the literature reports that this reaction requires long times,<sup>[9]</sup> in order to accelerate it we tried to furnish heat. As reported in Table 1, run 2, this "expedient" gave no result (34% yield in **2a**).

An increase in the number of Faradays per mol of S increased the yield (45% at 2.0 F/mol, run 4), but not to a satisfactory value, while diminishing the concentation of sulfur from 2 mmol in 1.5 mL to 1 mmol in the same volume (run 5) gave the same result, leaving the ionic liquid cleaner (and so more easily reusable). To try to increase the yield, we combined various factors, following the reaction Scheme reported in Scheme 3.



Scheme 3. General Scheme of reaction.

 $\Delta$  is the heat furnished to the system at the end of the electrolysis and after the addition of sulfur, while US stands for ultrasound irradiation; we tried with heat (runs 7 and 8) with good results (73 and 88% yields), and with ultrasound irradiation, that gave the best results (runs 9–12).<sup>[18]</sup>

Having established that 10 min of ultrasound irradiation were sufficient to obtain a complete conversion (run 11), we tried to establish if a lower amount of electricity was sufficient, but with negative results (runs 16 and 17); we also checked the influence of the counter ion of BMIM in this reaction. The anion has an appreciable effect on this synthesis, but the yields remain always high (78–99%, runs 11 and 13–15), the fluorinated ones being the best.

Last, this reaction was extended to imidazolium ionic liquids containing different substituents on the nitrogen atoms, and in all cases the yields of isolated thiones were very high (runs 18–22 and 24), with the



Scheme 2. Hypothesis for mechanism.

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**Table 1.** Electrochemical reduction of ionic liquids (ILs) **1a**- $\mathbf{k}$ ,<sup>[a]</sup> followed by the addition of elemental sulfur.<sup>[b]</sup> Energy was supplied to the catholyte (heat, or ultrasound irradiation US<sup>[c]</sup>) for a time *t* (see Scheme 3).

Run	<b>1</b> , R <sup>[d]</sup>	<b>1</b> , anion	F/mol of S	⊿ or US	Irrad. time	<b>2</b> [%] <sup>[e]</sup>
1 <sup>[f]</sup>	<b>1a</b> , C <sub>4</sub>	$\mathrm{BF_4}^-$	1.0	_	2 h	<b>2a</b> , 35 <sup>[10]</sup>
$2^{[f]}$	<b>1a</b> , C <sub>4</sub>	$BF_4^-$	1.0	60°C	2 h	<b>2a</b> , 34
3 <sup>[f]</sup>	<b>1a</b> , C <sub>4</sub>	$\mathrm{BF_4}^-$	1.5	-	2 h	<b>2a</b> , 41
4 <sup>[f]</sup>	<b>1a</b> , C <sub>4</sub>	$\mathrm{BF_4}^-$	2.0	-	2 h	<b>2a</b> , 45
5	<b>1a</b> , C <sub>4</sub>	$BF_4^-$	2.0	_	2 h	<b>2a</b> , 46
6	<b>1a</b> , C <sub>4</sub>	$\mathrm{BF_4}^-$	2.0	-	20 h	<b>2a</b> , 35
7	<b>1a</b> , C <sub>4</sub>	$\mathrm{BF_4}^-$	2.0	60°C	20 h	<b>2a</b> , 73
8	<b>1a</b> , C <sub>4</sub>	$\mathrm{BF_4}^-$	2.0	100°C	20 h	<b>2a</b> , 88
9	<b>1a</b> , C <sub>4</sub>	$BF_4^-$	2.0	US	30 min	<b>2a</b> , 99
10	<b>1a</b> , C <sub>4</sub>	$\mathrm{BF_4}^-$	2.0	US	20 min	<b>2a</b> , 99
11	<b>1a</b> , C <sub>4</sub>	$BF_4^-$	2.0	US	10 min	<b>2a</b> , 99
12	<b>1a</b> , C <sub>4</sub>	$\mathrm{BF_4}^-$	2.0	US	5 min	<b>2a</b> , 78
13	<b>1b</b> , C <sub>4</sub>	$MeSO_4^-$	2.0	US	10 min	<b>2a</b> , 81
14 <sup>[g]</sup>	<b>1c</b> , C <sub>4</sub>	$PF_6^-$	2.0	US	10 min	<b>2a</b> , 99
15	<b>1d</b> , C <sub>4</sub>	I-	2.0	US	10 min	<b>2a</b> , 92
16	<b>1a</b> , C <sub>4</sub>	$BF_4^-$	1.0	US	10 min	<b>2a</b> , 51
17	<b>1a</b> , C <sub>4</sub>	$\mathrm{BF_4}^-$	1.5	US	10 min	<b>2a</b> , 72
18	<b>1e</b> , C <sub>2</sub>	$\mathrm{BF_4}^-$	2.0	US	10 min	<b>2e</b> , 99 <sup>[10]</sup>
19	<b>1f</b> , C <sub>6</sub>	$\mathrm{BF_4}^-$	2.0	US	10 min	<b>2f</b> , 99
20 <sup>[h]</sup>	<b>1g</b> , C <sub>8</sub>	$\mathrm{BF_4}^-$	2.0	US	10 min	<b>2g</b> , 99 <sup>[9b]</sup>
21 <sup>[h]</sup>	<b>1h</b> , C <sub>10</sub>	$\mathrm{BF_4}^-$	2.0	US	10 min	<b>2h</b> , 99
22 <sup>[i]</sup>	1i, PhCH <sub>2</sub>	$\mathbf{BF}_4^{-}$	2.0	US	10 min	2i, <sup>[j]</sup> 75 <sup>10</sup>
23 <sup>[i]</sup>	<b>1j</b> , Allyl	Cl <sup>-</sup>	2.0	US	10 min	<b>2j</b> , <sup>[k]</sup> 57 <sup>[10]</sup>
24	1k, HOEt	$\mathrm{BF_4}^-$	2.0	US	$10 \min$	<b>2k</b> , 86 <sup>[10]</sup>

- [a] Divided cell, Pt electrodes (apparent area: ca. 1 cm<sup>2</sup>), room temperature, N<sub>2</sub> atmosphere, galvanostatic conditions (30 mA/cm<sup>2</sup>), catholyte: 1.5 mL IL **1a-k**, anolyte: 0.5 mL IL **1a-k**.
- <sup>[b]</sup> 1 mmol (if not otherwise stated) of  $S_8$  was added at the end of the electrolysis to the catholyte.
- <sup>[c]</sup> 22.5 kHertz.
- <sup>[d]</sup> C<sub>4</sub>: *n*-butyl; HO-Et: 2-hydroxyethyl; C<sub>2</sub>: ethyl; C<sub>6</sub>: *n*-hexyl; C<sub>8</sub>: *n*-octyl; C<sub>10</sub>: *n*-decyl.
- <sup>[e]</sup> Yields are based on starting sulfur.
- <sup>[f]</sup> 2 mmol of  $S_8$  were used.
- <sup>[g]</sup> During this electrolysis it was necessary to add BMIM BF<sub>4</sub> into the anodic compartment as the anodic process (oxidation of PF<sub>6</sub><sup>-</sup> to PF<sub>5</sub> and F) led to the formation of a foam that lowered very much the conductivity of the anolyte.
- <sup>[h]</sup> This electrolysis was carried out at 50 °C, due to the high viscosity of this ionic liquid.
- <sup>[i]</sup> This electrolysis was carried out at 80 °C, due to the melting point of this ionic liquid.
- [i] The work-up of this electrolysis led to a less efficient extraction of 2i from the catholyte due to the fact that IL 1i is solid at room temperature.
- <sup>[k]</sup> 1-Methylimidazole was obtained in this case, due to a deallylation reaction.

exception of 1-allyl-3-methylimidazole-2-thione (run 23) that was isolated in 57% yield. In this case, 1-methylimidazole was also isolated from the cathodic mixture, due to a de-allylation reaction that probably occurred during the electrolysis.

As one of the characteristics that renders ionic liquids interesting solvents is their recyclability, the catholyte relative to run 11 of Table 1 was kept under reduced pressure at room temperature for 30 min (to eliminate the residues of diethyl ether) after having extracted 1-butyl-3-methylimidazole-2-thione, and then reused for an electrolysis. This procedure was carried out for four times, and in all cases very high yields of **2a** were obtained (as reported in Table 2), confirming the important role of this kind of solvent in modern chemistry.

**Table 2.** Recycle of BMIM BF<sub>4</sub> in the synthesis of 1-butyl-3-methyl-1*H*-imidazole-2(3H)-thione **2a**.<sup>[a]</sup>

Cycle	1 <sup>[b]</sup>	2	3	4	5
% <b>2a</b>	99	99	99	99	95

<sup>[a]</sup> Electrolysis conditions as in Table 1, run 11.

<sup>[b]</sup> Same electrolysis of Table 1, run 11, reported for a useful comparison.

In conclusion, we have carried out a combined electrochemical and ultrasound assisted synthesis of 1,3disubstituted imidazole-2-thiones by cathodic reduction of an imidazolium ionic liquid (that behaves as solvent, supporting electrolyte and reagent), yielding the corresponding carbene. The reaction of this electrogenerated carbene with elemental sulfur, induced by ultrasound irradiation, gave 1,3-disubstituted imidazole-2-thiones in very high yields. The use of a solvent with very low vapour pressure, along with the possibility of its recycle without any loss of reactivity, renders this synthesis environmental friendly.

## **Experimental Section**

Constant current electrolyses were carried out using a glass two-compartment home-made cell. Anolyte (*ca.* 0.5 mL) and catholite (*ca.* 1.5 mL) were separated through a glass disk (porosity 4). The electrode apparent surface areas were  $1.0 \text{ cm}^2$  for the cathodic Pt spiral (99.9%) and 0.8 cm<sup>2</sup> for the anodic Pt spiral (99.9%). The current density was  $30 \text{ mA/cm}^2$ .

Preparative electrolyses were carried out at room temperature, under nitrogen atmosphere, using IL **1** as anolyte and catholyte. After the consumption of the number of Faradays per mol of sulfur reported in Table 1, the current was switched off and elemental sulfur was added to the catholyte (see Table 1, note b). The mixture was kept at room temperature, or at 60°C, or at 100°C for the required time (Table 1). Otherwise, it was submitted to ultrasound irradiation (22.5 kHz, 100 W). The catholyte was extracted with diethyl ether (10 mL) for three times, the solvent was removed under reduced pressure and the residue was analyzed by <sup>1</sup>H NMR. Yields were based on starting sulfur. When the purity of the corresponding thione **2** was not acceptable, the residue was purified by flash chromatography (*n*-hexane/ethyl acetate = 7/3), affording the corresponding pure **2**. All known compounds gave spectral data in accordance with the ones reported in the literature.

#### **Recycle of IL 1a**

After the extraction of product 2a from the solution, the catholyte was kept under vacuum at room temperature for 30 min to eliminate diethyl ether residues, then it was used as catholyte for the following electrolysis, adding 1 mmol of new IL in replacement of the one converted in thione.

**1-Hexyl-3-methyl-1***H***-imidazole-2(3***H***)-thione (2f):** Brown oil; <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>):  $\delta$ =6.64 (s, 2H), 3.96 (t, 2H, *J*=7.4 Hz), 3.56 (s, 3H), 1.74–1.67 (m, 2H), 1.32–1.20 (m, 6H), 0.83 (app. t, 3H, *J*=6.3 Hz); <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>):  $\delta$ =162.0, 117.5, 116.4, 48.0, 35.0, 31.3, 28.8, 26.1, 22.4, 13.9; EI-MS, *m*/*z*=200 (6%, M<sup>+</sup>+2), 198 (57%, M<sup>+</sup>), 169 (5%), 165 (100%), 141 (10%), 114 (27%); anal. calcd. for C<sub>10</sub>H<sub>18</sub>N<sub>2</sub>S: C 60.56, H 9.15, N 14.12; found: C 60.58, H 9.18, N 14.09.

**1-Decyl-3-methyl-1***H***-imidazole-2(3***H***)-thione (2h):** Brown oil; <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>):  $\delta = 6.63$  (s, 2H), 3.95 (t, 2H, J = 7.3 Hz), 3.55 (s, 3H), 1.74–1.66 (m, 2H), 1.26–1.19 (m, 14H), 0.81 (app. t, 3H, J = 6.3 Hz); <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>):  $\delta = 162.0$ , 117.4, 116.4, 48.0, 34.9, 31.8, 29.4, 29.4, 29.2, 29.1, 28.8, 26.5, 22.6, 14.0. EI-MS: m/z = 254 (29%, M<sup>+</sup>), 221 (100%), 128 (9%), 141 (10%), 114 (24%); anal. calcd. for C<sub>14</sub>H<sub>26</sub>N<sub>2</sub>S: C 66.09, H 10.30, N 11.01; found: C 66.12, H 10.33, N 10.99.

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