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# Ultrasound assisted synthesis of imidazolium salts: An efficient way to ionic liquids

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ABSTRACT

In this study a straightforward and efficient approach concerning synthesis of 1,3-diazole derivatives under ultrasound (US) irradiation as well as under conventional thermal heating (TH) is presented. *N*-alkylation under US irradiation may be considered environmentally friendly in terms of higher yields, smaller amounts of solvent used and an overall energy efficiency due to a substantial reduction of reaction times. A comparative study of ultrasound *vs.* conventional conditions has been performed. Overall, the use of US proved to be more efficient than TH. A possible explanation concerning the different behavior of imidazole and benzimidazole in the *N1*-alkylation reactions under US irradiation was proposed.



## 1. Introduction

Ultrasound (US) irradiation has gained popularity in organic chemistry in the past decade as a viable reaction alternative to conventional thermal heating (TH). It already offers a versatile and facile pathway in a large variety of syntheses [1–11]. Compared with conventional TH, US irradiation brings a substantial decrease of reaction time, improved yields and high purity of compounds as well as simplicity in handling and processing. Also, an increased selectivity and lower costs of US procedure is a powerful reason for the use of this alternative. At the same time, by using small amounts of solvents and generating fewer side products, the reactions under US irradiation could be considered environmentally friendly [12].

Imidazole and its derivatives have demonstrated fascinating potential applications for medicinal chemistry, these including anticancer activity [13,14], anti-HIV [15,16], antibacterial and antifungal activity [17,18] and drugs for treatment of cardiovascular diseases [19,20]. Moreover, imidazolium salts are potent room temperature ionic liquids of current great interest in industry [21,22].

A major drawback in the synthesis of ionic liquids is that reactions involved in both imidazole quaternization (first generation of ionic liquids) and anion metathesis (second generation of ionic liquids) are excessively time consuming. Under conventional TH, the synthesis of the first generation of imidazolium-based ionic liquids can take from a few hours in the case of bromides up to a few days for the chlorides. Given the attractive properties of these compounds, finding an alternative way for improving their synthesis becomes an important target. Microwave-assisted preparation of first generation ionic liquids in solvent [23] or under solvent-free conditions [24], was hence addressed, starting with 2001. US technology was also used prior in preparation of first generation ionic liquids [25]. The classic method used for anion metathesis requires 24–48 h, large amounts of solvents for purification and a few hours of drying under high vacuum. This procedure being also time-consuming, the effort of several research groups was focused to adapt non-conventional methods to synthesize second generation of the ionic liquids [26,27]. Other literature data reported *one-pot* synthesis of various imidazolium based second generation ionic liquids using classical [28], ultrasound [29], and a combination of the microwave and ultrasound conditions [30].

In previous research work within the imidazole area, we have presented several contributions concerning the synthesis of imidazolium salts [31,32]. Their potential practical applications such as anticancer agents [33] and ionic liquids [34] were also investigated by us. In continuation of our work in this area [31–34], we focus on developing a straightforward, efficient and environmentally friendly method for preparation of imidazolium and benzimidazolium salts, under US irradiation and conventional TH.

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## 2. Method

### 2.1. Apparatus and analysis

All reagents and solvents were purchased from commercial sources and used without further purification. Melting points were recorded on a MEL-TEMP II apparatus in open capillary tubes and are uncorrected. Analytical thin-layer chromatography was performed with commercial silica gel plates 60 $F_{254}$ (Merck) and visualized under UV light. The NMR spectra were recorded on a Bruker Avance 400 DRX spectrometer operating at 400 MHz for $^{1}H$ and 100 MHz for $^{13}C$, or on a Bruker Avance III 500 MHz spectrometer operating at 500 MHz for $^{1}H$ and 125 MHz for $^{13}C$. The following abbreviations were used to designate chemical shift multiplicities: s = singlet, d = doublet, dd = doublet of doublet, t = triplet, m = multiplet. Chemical shifts were reported in delta ($\delta$) units, part per million (ppm) and coupling constants ($J$) in Hz. Infrared (IR) data were recorded as films on potassium bromide (KBr) pellets on a FT-IR Shimadzu Prestige 8400s spectrophotometer. The microanalyses were in satisfactory agreement with the calculated values: C, ±0.15; H, ±0.10; N, ±0.30. Ultrasound assisted reactions were carried out using Bandelin Ultrasound reactor (Sonopuls GM 3200), with a nominal power of 200 W and a frequency of 20 kHz. The booster horn SH 213 G was fixed tightly to the ultrasonic converter. The titanium flat probe tip TT13 (diameter: 12.7 mm; length: 7 mm) was fixed tightly to the booster horn. The titanium probe tip was immersed in the used solvent.

Compound **3a** was initially synthesized by Makaev [22]. Synthesis and optical spectral characteristics of compounds **5a-f** and **5′a-c**were first reported by us [31,32].

### 2.2. General procedure for N-alkylation under TH and US irradiation

#### 2.2.1. General procedure for the synthesis of N1-alkylated imidazole derivatives 3a-d andN1-alkylated benzimidazole derivatives 3′a-d under conventional TH and US irradiation

50 mmol of imidazole derivative (as indicated in Table 1), 0.2 mL triethylamine and 50 mmol acrylic acid derivative were dissolved in 60 mL toluene. The mixture was refluxed using an oil bath for 26 h (for **3a-d**) and 36 h (**3′a-d**). After the completion of the reaction (TLC), the solvent was removed under vacuum and the obtained imidazole derivatives were separated with a good grade of purity. For further purification this derivatives can be crystallized (if solid) from an appropriate solvent. Analytically pure samples were obtained after 48 h of drying in vacuum oven at 60 °C under reduced pressure.

Under US irradiation, 5 mmol of imidazole derivative (as indicated in Table 1), 0.02 mL triethylamine and 5 mmol acrylic acid derivative (as indicated in Table 1) in 4 mL solvent [toluene (for obtaining **3a-d**) and dimethylformamide (DMF) (for obtaining **3′a-d**X)], were placed in the reaction vessel and exposed to US irradiation for an appropriate time as is presented in Table 3. Once the irradiation cycle was completed, the reaction tube was removed from the reactor, and processed as indicated above for TH.

**Table 1**
Amounts of imidazole and acrylic acid derivatives involved in the synthesis of *N1*-alkylated imidazole derivatives.

| Compound | Imidazole derivative | | Acrylic acid derivative | |
|---|---|---|---|---|
| | TH (g) | US (g) | TH (g/mL) | US (g/mL) |
| **3a** | Imidazole | | Acrylonitrile | |
| | 3.40 | 0.34 | 2.65/3.25 | 0.27/0.33 |
| **3b** | Imidazole | | Ethyl acrylate | |
| | 3.40 | 0.34 | 5.00/5.45 | 0.50/0.55 |
| **3c** | Imidazole | | Methyl acrylate | |
| | 3.40 | 0.34 | 4.30/4.50 | 0.43/0.45 |
| **3d** | Imidazole | | Acrylamide | |
| | 3.40 | 0.34 | 3.55 | 0.36 |
| **3′a** | Benzimidazole | | Acrylonitrile | |
| | 5.90 | 0.59 | 2.65/3.25 | 0.27/0.33 |
| **3′b** | Benzimidazole | | Ethyl acrylate | |
| | 5.90 | 0.59 | 5.00/5.45 | 0.50/0.55 |
| **3′c** | Benzimidazole | | Methyl acrylate | |
| | 5.90 | 0.59 | 4.30/4.50 | 0.43/0.45 |
| **3′d** | Benzimidazole | | Acrylamide | |
| | 5.90 | 0.59 | 3.55 | 0.36 |

#### 2.2.2. General procedure for the N1-alkylation of imidazole under US irradiation in the presence of a radical scavenger, TEMPO

Under US irradiation, 5 mmol of imidazole (0.34 g), 0.02 mL triethylamine, 5 mmol acrylonitrile (0.27 g, 0.33 ml) and 7.5 mmol 2,2,6,6-Tetramethylpiperidin-1-yl)oxy (TEMPO) (1.17 g) in 4 mL toluene were placed in the reaction vessel and exposed to US irradiation for 2 h. After two hours of US irradiation, the GC–MS shows 12% conversion of the imidazole to the desired product **3a**.

#### 2.2.3. General procedure for the synthesis of imidazolium salts 5a-l and benzimidazolium salts 5′a-l under conventional TH and US irradiation

10 mmol of *N1*-alkylated imidazole derivative (as listed in Table 2) was dissolved in 20 mL of acetone. A solution of 12 mmol activated halogeno-derivative in 10 mL of acetone was added drop wise under stirring. The reaction mixture was then refluxed using an oil bath, for appropriate time as is presented in Table 5. The obtained salt was filtered under vacuum and washed with 5 mL of diethyl ether. For future purification these salts can be crystallized from an appropriate solvent. Analytically pure samples were obtained after 48 h of drying in vacuum oven at 60 °C and reduced pressure.

Under US irradiation, 5 mmol of imidazole derivative (as indicated in Table 2) and 6 mmol of activated halogeno-derivative (as indicated in Table 2) in 10 mL of acetone, were placed in the reaction vessel and exposed to US irradiation for an appropriate time, as is presented in Table 5. The reaction vessel was cooled to 20 °C using a circulating bath in order to prevent the acetone evaporation. Once the irradiation cycle was completed, the reaction tube was removed from the reactor, and processed as indicated above for TH.

The structure of compounds was proved by elemental and spectral analysis [IR, MS, $^{1}H$ NMR, $^{13}C$ NMR, 2D-COSY, 2D-HETCOR (HMQC), long range 2D-HETCOR (HMBC)], and were in accordance with the proposed structure (Scheme 1).

*2.2.3.1. 3-(1H-imidazol-1-yl)propanenitrile (**3a**).* Transparent liquid; 5.875 g, 97% using TH; 0.588 g, 97% using US; IR (KBr): $\bar{\nu}$/cm$^{-1}$: 3099, 3068, 3039 (C–$H_{arom}$), 2983, 2972 (C–$H_{aliph}$), 2250 (CN), 1512, 1456, 1419 (C–$C_{arom}$); $^{1}H$ NMR (400 MHz, $CDCl_3$): $\delta_{ppm}$: 2.82 (2H: $H_7$, t, $J_{6,7}$ = 6.4 Hz), 4.25 (2H: $H_6$, t, $J_{6,7}$ = 6.4 Hz), 7.03 (1H: $H_5$, s), 7.09 (1H: $H_4$, s), 7.56 (1H: $H_2$, s); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta_{ppm}$: 20.55 ($C_7$), 42.41 ($C_6$), 116.89 ($C_5$), 118.79 (CN group), 130.23 ($C_4$), 137.08 ($C_2$); Anal. calcd. $C_6H_7N_3$: C, 59.49; H, 5.82; N, 34.69; Found: C, 59.44; H, 5.79; N, 34.77.

*2.2.3.2. Ethyl 3-(1H-imidazol-1-yl)propanoate (**3b**).* Transparent liquid; 8.241 g, 98% using TH; 0.824 g, 98% using US; IR (KBr): $\bar{\nu}$/cm$^{-1}$: 3110, 2981 (C–$H_{arom}$), 2939 (C–$H_{aliph}$), 1720 (C=$O_{ester}$), 1506, 1446, 1398 (C–$C_{arom}$), 1284, 1193 (C–O–C); $^{1}H$ NMR (400 MHz, $CDCl_3$): $\delta_{ppm}$: 1.22 (3H: $H_9$, t, $J_{8,9}$ = 7.2 Hz, $CH_3$ from $OC_2H_5$), 2.75 (2H: $H_7$, t, $J_{6,7}$ = 6.4 Hz), 4.12 (2H: $H_8$, q, $J_{8,9}$ = 7.2 Hz, $CH_2$ from $OC_2H_5$), 4.24 (2H: $H_6$, t, $J_{6,7}$ = 6.4 Hz), 6.95 (1H: $H_5$, s), 7.00 (1H: $H_4$, s), 7.50 (1H: $H_2$, s); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta_{ppm}$: 14.09 ($C_9$, $CH_3$ from $OC_2H_5$), 36.11 ($C_7$), 42.29 ($C_6$), 60.98 ($C_8$, $CH_2$ from $OC_2H_5$), 118.97 ($C_5$), 129.39 ($C_4$), 137.30 ($C_2$), 170.55 ($CO_{ester}$);

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