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Original article

Ultrasound improves the synthesis of 5-hydroxymethyl-2-mercapto-1-benzylimidazole as a base compound of some pharmaceutical products

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Abstract

Application of ultrasound in synthesis appears to be a promising alternative for high-value chemicals and pharmaceuticals. This work describes the results of investigations carried out towards the synthesis of 5-hydroxymethyl-2-mercapto-1-benzylimidazole (HMMBI) in the presence of ultrasound (sono-synthetic) and in the absence of ultrasound (control method). Instead of mixing for long time in control method, the mixture was sonicated indirectly with 500 kHz and directly with 20 kHz apparatus. In some experiments the yield of the reaction was optimized by suitable manipulation of conditions such as temperature, vapor pressure of the solvent, ultrasonic intensity, and contact time. In control method, the yield of the reaction was increased by increasing the temperature but in sono-synthetic method, the thermal dependency was different in the range of temperature studied (7–25 °C). Kinetic results at 7 °C indicate that the yield of the reaction was reached to 90% after half an hour sonication but in control method it was reached to 70% after 72 h under the same conditions. Therefore, it is possible to reach a high yield of product under proper conditions of sonication.

Keywords: Sono-synthesis; 5-Hydroxymethyl-2-mercapto-1-benzylimidazole; Cavitation; Sonication

1. Introduction

Ultrasound as an efficient means of activation in synthetic chemistry has been employed for decades with varied success [1–6]. This method not only enhances the mechanical effects in heterogeneous processes, but it also induces new reactivities which leading to the formation of unexpected chemical species. What makes sonochemistry unique is the remarkable phenomenon of cavitation. The cavitation process consists of the creation, growth and implosive collapse of cavity. The bubble collapse in liquid results in an enormous concentration of energy from the conversion of kinetic energy of liquid motion into heating of contents of the bubble [7,8]. Extreme temperatures and pressures occur within the bubbles during cavitational collapse [9]. These extreme conditions lead to a diverse set of applications of ultrasound such as maximizing rate of the reaction, changing the reaction pathway, increasing reactivity of materials in organic synthesis, and so on.

HMMBI and its derivatives are the base compounds for the synthesis of a wide range of drugs which have an important role in medicinal chemistry [10–12]. For example 1,4-dihydro-2,6-dimethyl-4-(2-alkylthio-1-benzyl-5-imidazolyl)-3,5-pyridine-dicarboxylic acid esters are evaluated as calcium antagonists on guinea-pig ileal smooth muscle [13–15] and 9-[1-benzyl-5-(alkylsulfonyl)-1H-2-imidazolyl]perhydro-1,8-acridinediones has been found as possible effective activators at the ATP sensitive K^+ channel [16–19]. There is another new drug in the epilepsies therapy which is 2-(2-alkylthio-1-benzyl-5-imidazolyl)1-2,3,4-threehydro-5-imino-1,3,4-thiadiazole [20]. There are many different structures in diverse pharmacological activity that can be prepared from the compound selected for this work. One of the classical

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methods for the synthesis of HMMBI is stirring of benzylamine hydrochloride with 1, 3-dihydroxyacetone dimmer and potassium thiocyanate for 72 h. In this study for decreasing the contact time and increasing the yield, we investigated the sono-synthesis of HMMBI as a new method for this compound and compared the results with control method.

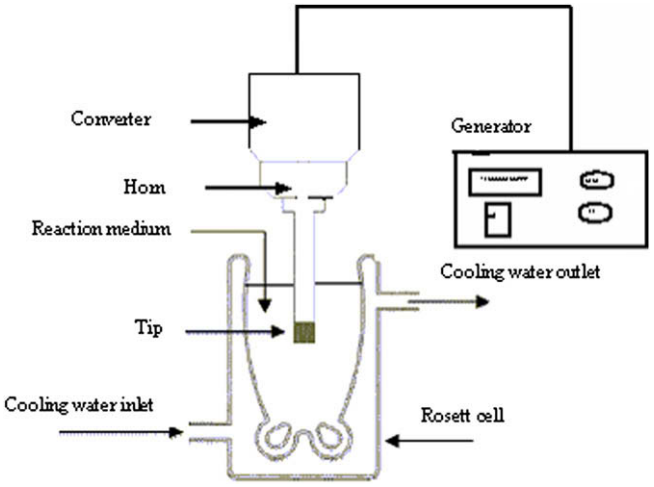
2. Experimental

2.1. Apparatus

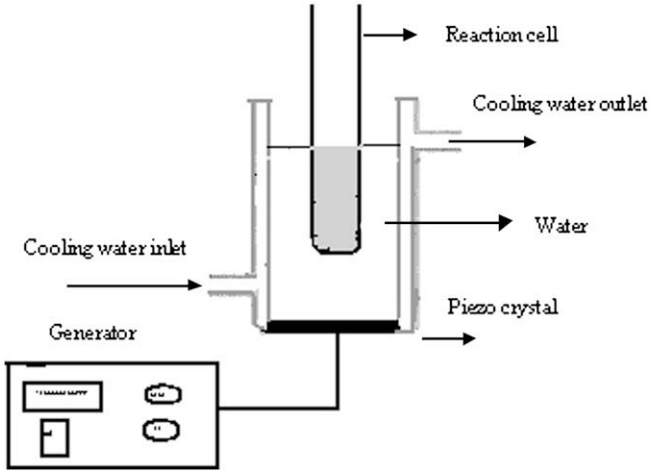
The irradiation of solution was carried out by two ultrasonic equipments working at 20 kHz and 500 kHz separately. Schemes 1 and 2 demonstrate the set up used in this work. The melting points were determined in open capillary tubes by an Electrothermal IA 9000 melting point apparatus. The H NMR spectra were recorded on a Bruker 100-MHz instruments using tetramethylsilan (TMS) as an internal standard. The mass spectra were determined with Shimadzu GCMS-QD 1000 EX instrument (70 eV).

2.2. Procedure

In control method the reaction was proceed by adding 1, 3-dihydroxyacetone dimmer 4.6 mmol (0.42 g) (99%, Merck), potassium thiocyanate 6.9 mmol (0.68 g) (99%, Merck) and benzylamine hydrochloride 6.5 mmol (0.94 g) (salt of benzylamine reaction with concentrated chloric acid in butanol solvent) to a mixture of glacial acetic acid (1 ml) (98%, Merck) and 1-butanol 6.5 ml (99%, Merck) as a solvent. The produced white suspension was stirred for 72 h. Then by adding water-de-ionized (1 ml), the mixture was filtered and the solid phase washed with water-de-ionized (3 ml) and ether (3 ml), respectively [10]. The product was HMMBI as a pure compound. In sono-synthetic method instead of stirring, the mixture was sonicated for different length of times. The resulting solid was filtered, washed with water-de-ionized (4 ml) and then ether (3 ml), respectively. The structure of this compound was studied by different methods. Scheme 3 demonstrates the preparation of the mentioned compound by the formula.



Scheme 1. Experimental setup for 20 kHz apparatus.



Scheme 2. Experimental setup for 500 kHz apparatus.

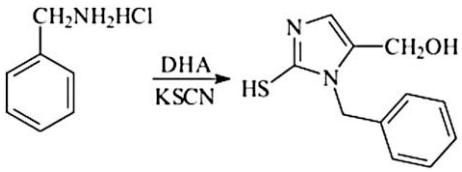
3. Results and discussion

3.1. Same product with two different methods

The compound of HMMBI produced by control and sono-synthetic methods was analyzed with different methods. The H NMR and the Mass spectrum of the final product was the same in both methods. In addition, the melting point and the TLC were also confirmed the similarity of the mentioned compound produced by the two different methods.

3.2. Synthesis under control and indirect sonication (500 kHz)

In control method, the synthesis was normally carried out at different temperatures to give HMMBI. In sono-synthesis the solution was sonicated indirectly by 500 kHz apparatus at different temperatures. The synthesis of this compound was studied at temperatures 7, 13, and 25 °C. The sono-synthetic method was behaved differently than control method by changing the temperature. Fig. 1 shows the different effects of temperature on the yield of HMMBI in both methods. In control method with increasing the temperature, the yield was also increased. This is attributed to the higher collisions of reactants at higher temperature which lead to the higher yield. In contrast, in the presence of ultrasound (sono-synthetic



Scheme 3. Formula for the synthesis of 5-hydroxymethyl-2-mercapto-1-benzylimidazole.

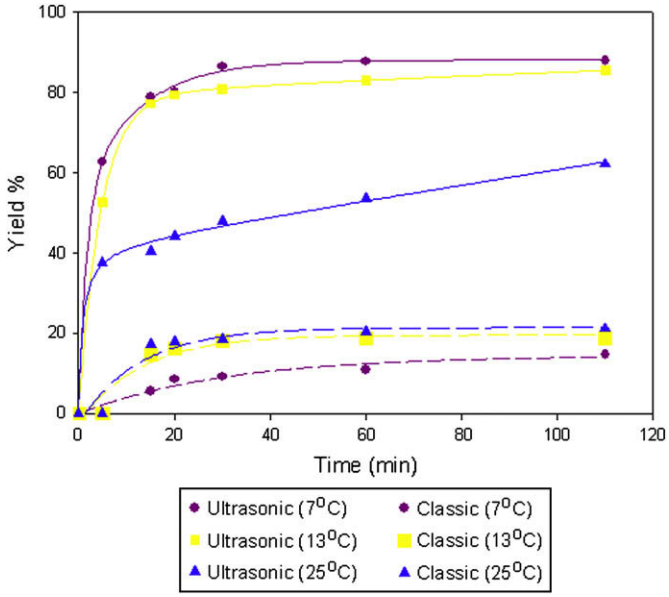


Fig. 1. The yield of 5-hydroxymethyl-2-mercapto-1-benzylimidazole versus contact time at different temperatures in classic and indirect sonication (500 kHz).

method) by increasing the temperature the yield of the reaction was decreased. Contrary to the chemical reactions in general, in some cases an increase in the ambient reaction temperature results in an overall decrease in the sonochemical effect. This behavior could be explained by the cavitation process. As the reaction temperature is raised, the equilibrium vapor pressure of the system is also increased. This leads to the reduction of critical conditions produced during the cavitation process and therefore the sonochemical effects are reduced at higher temperatures. For each system there is an optimum temperature which the effect of cavitation process is higher than the other temperatures. For this system, the highest difference of the yield between control and sonicated method was achieved at about 7 °C (Fig. 2).

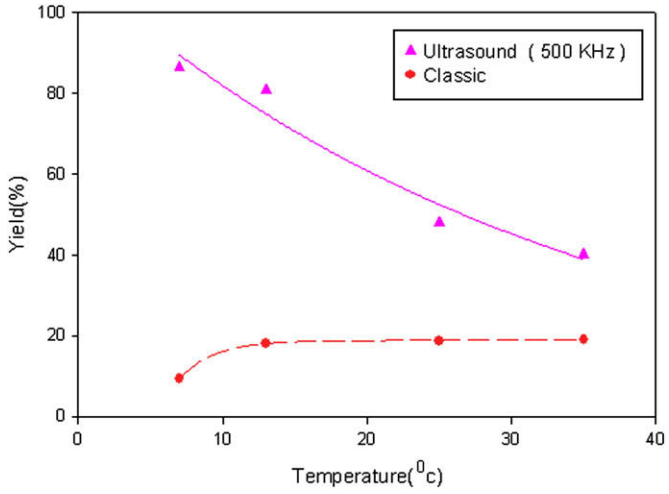


Fig. 2. The yield of 5-hydroxymethyl-2-mercapto-1-benzylimidazole versus temperature in classic and indirect sonication (500 kHz) for 30 min.

3.3. Synthesis under direct sonication (20 kHz)

The frequency of ultrasound has a significant effect on the sonochemical reactions [21,22]. This effect is related to the cavitation process which influences the critical size of the cavitation bubble and the collapse time. At very high frequencies, the cavitational effects are reduced.

There was a possibility to sonicate directly the solution for synthesis of HMMBI by 20 kHz apparatus. In indirect sonication (500 kHz), the acoustic power deliver to the solution was lower than the direct sonication (20 kHz) and in addition, the reflection and absorption of acoustic wave by the wall of the reactor immersed into the liquid medium reduces the acoustic intensity. Fig. 3 shows the yield of the reaction versus contact time at different temperatures under direct sonication of solution by 20 kHz. The yield was higher in direct sonication than indirect one, especially at lower temperature (7 °C). This could be related to the higher intensity and the harsher conditions produced during the cavitation process in lower frequency. In addition, the most pertinent effects of ultrasound on liquid–solid systems are mechanical which are attributed to the asymmetric cavitation. Shock waves are produced during the cavitation process and lead to microscopic turbulences within interfacial films surrounding nearby solid particles, also referred to as microstreaming [23]. This phenomenon increases the mass-transfer of the film, thus increasing the intrinsic mass-transfer coefficient, as well as possibly thinning the film. Hagenson and Doraiswamy [24] obtained evidence of a twofold increase in the intrinsic mass-transfer coefficient when modeling experimental data obtained for the synthesis of dibenzyl sulfide in the presence and absence ultrasound. The shock waves produced by the cavitation increase the momentum of solid powders in solution, causing them to collide with great force. Then, the particles are fractured upon collision, leading to an overall decrease in the average particle size. Suslick et al. [25] have also estimated the speed of the microjets to be 100 m/s in aqueous solution; and this lead to

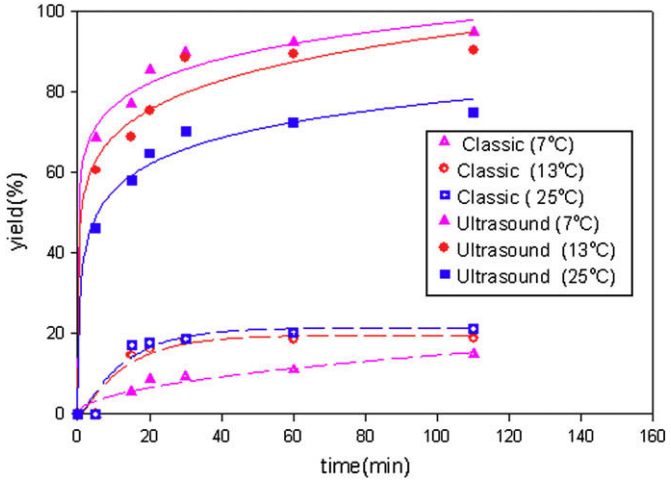


Fig. 3. The yield of 5-hydroxymethyl-2-mercapto-1-benzylimidazole versus contact time at different temperatures in classic and in direct sonication (20 kHz).

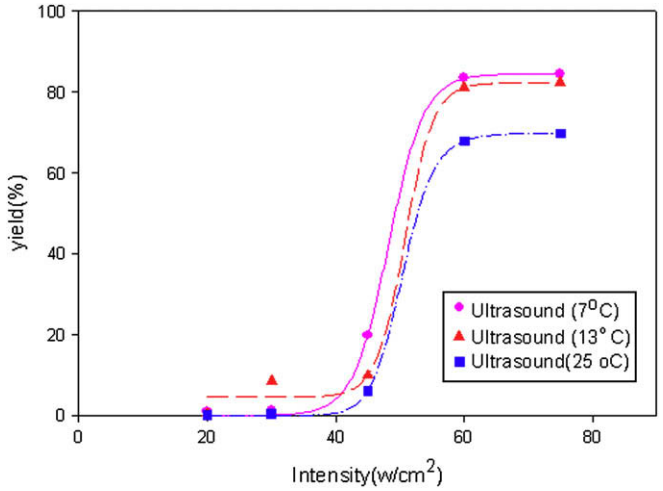


Fig. 4. The yield of 5-hydroxymethyl-2-mercapto-1-benzylimidazole versus intensity for 30 min direct sonication (20 kHz) at different temperatures in *n*-butanol as a solvent.

pitting and erosion of the surface, in addition to the well-known cleaning effects associated with ultrasound. These behaviors of ultrasound in heterogeneous systems could be very effective in enhancement of the mentioned reaction.

3.4. Synthesis under different acoustic powers

According to Fig. 4, the effect of acoustic power and temperature on the synthesis of this compound was studied in the range of 20–75 (W) acoustic power. The length of sonication for all the samples was 30 min. The yield was negligible in the range of 20–40 W. This is due to the low power which is less than the threshold power for this process. There is a sharp increase in the yield in the range of 40–60 W which is above the threshold power. The acoustic power over 60 W has a negligible effect on the yield of the reaction. The best result was obtained in low temperature and high acoustic power.

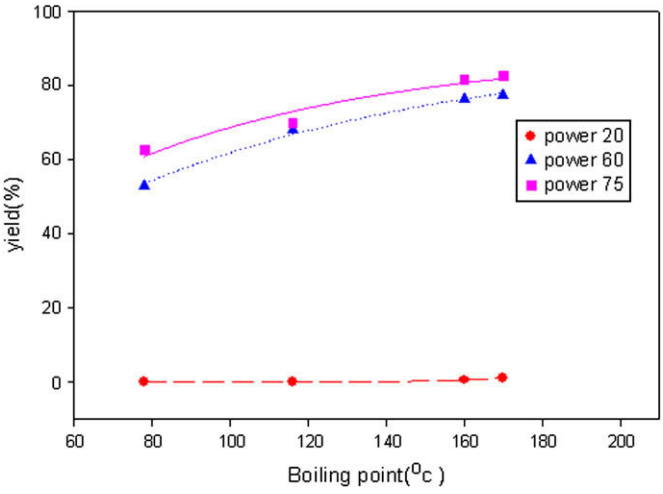


Fig. 5. The yield of 5-hydroxymethyl-2-mercapto-1-benzylimidazole versus boiling point of different solvents for 30 min direct sonication (20 kHz) at 13 °C.

Table 1
Comparison of the yields of 5-hydroxymethyl-2-mercapto-1-benzylimidazole for the classic and indirect sonication (500 kHz)

Temperature (°C)	Ultrasound (500 kHz) indirect (30 min) (%)	Classic (30 min) (%)
7	86	9
13	81	18
25	48	19

3.5. Synthesis with different solvents

The reaction was carried out with four different solvents (ethanol, *n*-butanol, *n*-cyclohexanol, and 2-octanol with boiling point of 78, 116, 160, 170 °C, respectively) under the same conditions. The results indicated that the yield of the reaction was also dependent on the kind of the solvent. As it was shown in Fig. 5, the yield of the reaction was increased by increasing the boiling point of the solvent. In general, the cavities are more readily formed when using a solvent with a high vapor pressure or low boiling point. In contrary, the cavitation process produces harsher conditions when using a solvent with a high boiling point. According to the results, it could be concluded that the harsher conditions produced in solvents with higher boiling point is preferred than the more readily formation of the cavity. In addition, Fig. 5 also confirms that higher power applied to the solvent with higher boiling points is more favorable to reach the higher yield.

3.6. Comparison of the results

Synthesis of HMMB was carried out under different conditions. Tables 1 and 2 summarize the yield of the reaction in control and sono-synthetic method with indirect sonication (500 kHz) and direct sonication (20 kHz) for 30 min. In indirect sonication (500 kHz), the yield was enhanced by approximately 9.4 times at 7 °C and 2.6 times at 25 °C with respect to the control method. Under the same conditions with direct sonication (20 kHz), the best results were obtained at lower temperature (7 °C) which ultrasound enhanced the yield to about 9.7 times. At higher temperature (25 °C) the yield enhanced to about 3.8 times in the presence of ultrasound.

4. Conclusion

The synthesis of HMMBI was carried out by control and sono-synthetic methods under different conditions. The most important point is that with sonication under proper

Table 2
Comparison of the yields of 5-hydroxymethyl-2-mercapto-1-benzylimidazole for the classic and direct sonication (20 kHz)

Temperature (°C)	Ultrasound (20 kHz) direct (30 min) (%)	Classic (30 min) (%)
7	90	9
13	88	18
25	70	18

conditions, it is possible to achieve a high yield in a short period of time. Ultrasound enhanced the yield of HMMBI to about 10 times under mild conditions.

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