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Neat benzoin condensation in recyclable room-temperature ionic liquids under ultrasonic activation

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Abstract—A new method for the benzoin condensation is proposed in imidazolium-based ionic liquids as solvents/catalysts. The use of a 30 kHz ultrasonic irradiation as activation method provides a quantitative yield of benzoin in 1-octyl-3-methyl-imidazolium bromide without degrading the ionic medium which can be-reused at least three times with no loss of activity.

Over the past decade, room temperature ionic liquids (RTILs) have emerged as a new class of stable and inert solvents. Indeed, this family of ionic moieties presents several interesting properties compared to classical molecular solvents. They exhibit at least high thermal stability, high polarity due to their ionic nature and a great ability to solubilize polar and non-polar organic compounds.[1] Moreover, their immiscibility with some molecular solvents and their very low vapor pressure make them very good solvents for both extraction and recyclability.[2] The use of ionic liquids as solvents for chemical transformations is also of a topical interest in academia and industry according to the 12 principles ruling Green Chemistry.[3] Moreover, together with the substitution of common molecular solvents, non conventional activation methods have emerged as powerful tools to decrease reaction times and to enhance reactivity, mainly ultrasound and microwave irradiations. Ultrasound can enhance or promote chemical reaction, mass transfer and offer potential for shorter reaction cycles and less extreme physical conditions. Sonochemistry, the devoted name of ultrasound chemistry, arises from acoustic cavitation which is the formation, the growth and implosive collapse of bubbles in a liquid. Cavitational collapse produces intense local heating (5000 K), high pressures (~1000 atm), and enormous heating and cooling rates ($>10^{10}$ K × s^{-1}). Acoustic cavitation provides a unique interaction of energy and matter, giving rise to an unusual mechanism for generating high-energy chemistry.[4] Suslick et al. studied the ultrasonic irradiation of organic liquids and established that, as long as the total vapor pressure is low enough to allow an effective bubble collapse, almost all organic liquids generate free radicals when they undergo an ultrasonic irradiation. Unusual reactivity patterns have then been observed during ultrasonic irradiation, including the initiation of homogeneous catalysis at a low ambient temperature, with rate enhancements greater than 100,000-fold.[5]

In addition, several physical effects occur such as mass transport, size reduction of particles or efficient micromixing. These very specific conditions can be of great interest for chemical reactions especially in biphasic systems as for instance aromatic substitutions[6] or rearrangements.[7] In sonochemistry, the use of high-vapor pressure solvents is not interesting since their incorporation in collapsing bubbles can lead either to their decomposition, allowing side-reaction or 'vaporous' cavitation that produces lower temperature and pressure conditions during the collapse. Consequently, the use of room-temperature ionic liquids (RTILs) can be especially powerful in sonochemistry as their low vapor pressure avoid them going into cavitation bubbles. Thus, RTILs have already been utilized in sono-assisted organic reactions such as Suzuki and Heck[8,9] coupling, Diels–Alder cyclisation[10] or even for the synthesis of RTILs.[11]

In this way, benzoin condensation is a well-known synthetic organic reaction leading to very attractive

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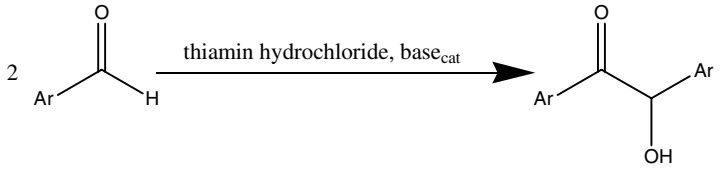
α-hydroxy-carbonyls. These compounds are very interesting building blocks to access to several natural compounds[12] by following the overall reaction described in Scheme 1.

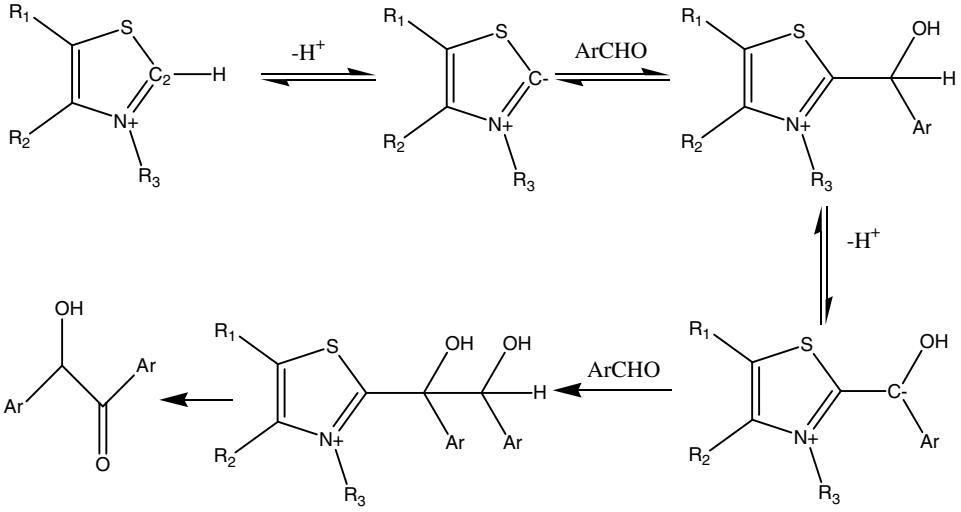
The key-step of the mechanism is the inversion of polarity of the C_2 carbonyl via an acyl-anion. According to this, various catalysts have been successfully used, such as thiamin,[13] triazolium,[14] heteroazolium carbens,[15] cyanide anion,[16] metallophosphites[14] or thiazolium salts.[17] In his pioneering work about this reaction, Breslow gave a mechanism catalyzed by thiazolium salts and base as co-catalyst,[18] the generally admitted mechanism being given here below (Scheme 2).

As this pathway is driven by an ionic mechanism, the beneficial effects brought by ultrasound are hypothetically of physical nature. Indeed, the high viscosity of RTILs avoids or disturbs heterogeneous systems to be efficient under conventional mechanical stirring. The use of ultrasound might lead to an enhanced microemulsion and therefore to an enhanced process by breaking the heterogeneity of the system. We recently described a microwave-assisted benzoin condensation in RTILs.[19] This methodology gives very interesting results for very short reaction times and for 2% amount of catalyst as described in Scheme 3.

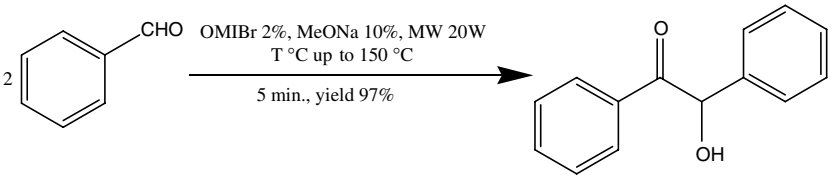
Microwave dielectric heating is very dependent on the polarity of the irradiated medium. The more polar the mixture is, the higher and faster the heating is. Because of their exclusive ionic nature, RTILs absorb strongly microwaves. In our microwave methodology for benzoin condensation, the main drawback is the very polar nature of the RTIL catalysts which does not only imply the swift and efficient heating of the reaction but also the problematic degradation of the ionic liquid itself. Consequently, the ionic medium cannot be recycled when this methodology is used. Thus, a brownish and decomposed ionic liquid was obtained after extraction when it was used as well as catalyst and solvent. It was so necessary to change the activation method and, in this present article, ultrasounds were chosen as activation methods for benzoin condensation in view of RTIL recycling.



Scheme 1. Benzoin condensation catalyzed by thiamin hydrochloride.



Scheme 2. Breslow's mechanism for benzoin condensation.



Scheme 3. Microwave-assisted benzoin condensation with 3-octyl-1-methyl-imidazolium bromide (OMIBr) as catalyst.

Table 1. Benzoin condensation under ultrasonic activation with a 2% ratio RTIL catalyst

Entry[a]	RTIL catalyst	Frequency (kHz)	Reaction time(s)[b]	Yield[c] (%)
1	OMIBr	30	30	64
2	OMIBr	500	60	28
3	OMIBr	1600	20	54
4	OMIOTf	30	20	24
5	$OMIPF_6$	30	30	45

[a] General procedure: 100 mmol of benzaldehyde; 10 mol % MeONa; 2% RTIL; no solvent; 80 °C.
[b] Reaction stopped after natural precipitation of the mixture.
[c] GC–MS yield.

On the first stage, benzoin condensation is performed without solvent and with different RTILs as catalysts so as to keep the conditions described in recently published microwave method. Different frequencies and RTILs were tested but for all of them natural precipitation of the medium was observed after less than 1 min as shown in Table 1.

These first results give significant information about the reaction system. First of all, benzoin condensation succeeds with relatively good yields compared to the very short time of reaction. In addition, the reaction occurs more easily when, for the same 1-octyl-3-methyl-imidazolium cation, bromide (Br^-) is used as a counter anion. This phenomenon was already observed in previous works,[19,20] and was ascribed to the steric hindrance due to the size of the anion precluding the reaction on the C_2 carbon of the imidazolium ring. An influence of the ultrasonic frequency on the yield of reaction is also observed. It is well-known that low-frequency ultrasound produces harsher physical effects on the irradiated heterogeneous midfield than does high-frequency one.[21] In other words, the stirring of the mixture is more efficient with lower frequencies. This might explain the higher yield of the reaction done under 30 kHz in spite of interference other parameters such as acoustic power or the geometry of the different reactors interfere. However, a geyser of liquid is observed for a 1600 kHz irradiation. This physical effect seems to be sufficient to mix the whole system since 54% benzoin are obtained. Nevertheless, the precipitation of the system is very problematic in both cases. Indeed, by precipitating, the solid benzoin reflects the ultrasonic wave.[22] This reflection implies a very quick overheating of the ultrasonic piezo-electric probe leading to its destruction. This problem can be overcome by diluting or solubilizing the medium with a solvent, as our objective was to perform a green benzoin condensation using a recyclable RTIL catalyst, we avoided the use of common molecular volatile organic compounds (VOC's). We then drastically increased the amount of RTIL, using it as well as catalyst and solvent. These experiments are described in Table 2.

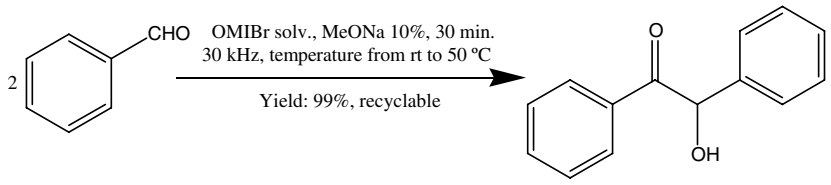
The results in Table 2 show that a gradual increase of temperature occurs along the 30 min reaction time. This phenomenon is probably due to the inadequate diffusion of the ultrasonic waves in such a viscous midfield which implies its heating, even with a temperature regulation system. The reaction was then begun at room-temperature so as to avoid this quick over-heating of the system. It can also be quoted that the reaction occurs quantitatively in OMIBr but not in the other ionic liquids tested, which confirms the hypothesis that bulky anions block the C_2 of imidazolium. Nevertheless, this hypothesis does not fit for OMICl. Actually, as the bromide anion is bulkier than chloride one, the steric effect should be more important for OMIBr so it shall not work as well as OMICl. This is obviously not the case since only 23% of benzoin is obtained with OMICl as shown in entry 4. This poor yield can be explained by the degradation of the ionic medium OMICl during the ultrasonic irradiation. This degradation was already described by Suslick et al.[23] when 1-butyl-3-methyl-imidazolium moieties are used under sonication. It is generally admitted that reagents having an important vapor pressure are able to vaporize and then can go into the cavitation bubbles in which high temperature and pressure catalyze the reaction. As RTILs have a neglectable vapor pressure, they cannot follow this path. However, Suslick et al. demonstrated that temperature and pressure reached during the collapse are high enough to decompose pure ionic liquids in the surrounding shell of the cavitation bubbles at the liquid–gas interface. By controlling our final mixture by GC–MS, degradation is observed only when 1-octyl-3-methyl-imidazolium chloride (OMICl) is used and not for the other ionic liquids tested. Moreover, the presence of 1-chlorooctane in the reactional medium is very problematic since it can deactivate sodium methoxide with a reaction of β-H-elimination between 1-chlorooctane and sodium methoxide.

Consequently, only OMIBr is reactive and stable enough to catalyze benzoin condensation in the conditions described in Table 2. The influence of the frequency on the reaction is comparable to those described in Table 1 with a drastically lower yield with a high frequency son-

Table 2. Ultrasound-assisted benzoin condensation in RTILs as solvent–catalyst

Entry[a]	Solvent	Temperature (°C)	Frequency (KHz)	Reaction time (min)	Yield[b] (%)
1	OMIBr	From rt to 50	30	30	99
2	OMIBr	From rt to 50	500	30	0
3	OMIBr	From rt to 50	1600	30	7
4	OMICl	From rt to 50	30	30	23[c]
5	$OMIPF_6$	From rt to 50	30	30	0
6	$OMIBF_4$	From rt to 50	30	30	0
7	OMIOTf	From rt to 50	30	30	0

[a] General procedure: 5 mmol of benzaldehyde; 10 mol % MeONa; 10 mL RTIL; temperature from rt to 50 °C after 30 min.
[b] GC–MS yield.
[c] Degradation is observed.



Scheme 4. Ultrasound-assisted benzoin condensation in OMIBr as solvent–catalyst.

Table 3. Effect of recycling on ultrasound-assisted benzoin condensation

Entry[a]	Solvent	Temperature (°C)	Frequency (KHz)	Recycling	Yield[b] (%)
1	OMIBr	From rt to 50	30	—	99
2	OMIBr	From rt to 50	30	First recycling	99
3	OMIBr	From rt to 50	30	Second recycling	97
4	OMIBr	From rt to 50	30	Third recycling	97

[a] General procedure: 5 mmol of benzaldehyde; 10 mol % MeONa; 40°C; 30 min, mechanical stirring.
[b] GC–MS yield.

ication. Thus, no geyser effect is observed for a 1600 kHz irradiation probably because of the density of the ionic medium when used as a dual catalyst/solvent. The yield of benzoin for this frequency is consequently drastically lower than when only 2% of ionic liquid are used (see Table 1). As there is no other difference between Table 1, entry 3 and Table 2, entry 3 but this geyser effect (same reactor, same frequency, same volume of liquids), it tends to prove that the geyser observed only when 2% of RTIL are used is responsible of the quite high yield observed on Table 1, entry 3. Actually, a three-phase midfield is observed since the ionic liquid phase remains between the sodium methoxide solid below and benzaldehyde in the upper phase. It is so very important to have a very efficient stirring in order to solve this problem of heterogeneity. As comparison, experiments have been performed in the same conditions under mechanical stirring in silent conditions without any conversion of benzaldehyde. In fact, mechanical stirring is not efficient enough to break the heterogeneity of the system since two phases (benzaldehyde/ionic liquid) are observed all reaction long. As optimal conditions are now obtained for ultrasound-assisted benzoin condensation, some recycling experiments were run to valorize the overall process. The reaction studied is shown in Scheme 4.

One of the most interesting property of ionic liquids is their ease of recycling. Indeed, most of the organic products can be distilled from ionic liquids as RTILs have very large liquid range compared to organic compounds. For this recycling, the solubility properties of OMIBr are advantageously used. Actually, as OMIBr is soluble in water but not in diethylether, the final mixture is poured into water and benzoin is then extracted with diethylether. Water is evaporated under vacuum and OMIBr is then re-used for benzoin condensation. The results of benzoin condensation operated with recycled OMIBr are summarized in Table 3. Three recycling cycles were performed.

The results in Table 3 show that after three recycling of OMIBr, no significant loss of activity is observed, confirming the OMIBr's recycling ability. It is to our best knowledge the first time that room temperature ionic liquids are recycled for benzoin condensation.[24]

In this letter, we showed that the use of low-frequency ultrasound is of great interest in performing benzoin condensation. 1-Octyl-3-methyl-imidazolium bromide can be used as very efficient solvent–catalyst for this reaction and low-frequency ultrasound is an adequate activation method to break the problematic heterogeneity of this triphasic system. By using 1-octyl-3-methyl-imidazolium bromide as solvent/catalyst, quantitative yield was observed under a 30 kHz ultrasonic irradiation for only a 30 min ultrasonic irradiation. Furthermore, no loss of activities are observed even after three recycling of the RTIL meaning that these conditions do not or significantly degrade the ionic medium. At last, the use of water as a recycling agent makes the overall process approach Green Chemistry.

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References and notes

1. Welton, T. *Chem. Rev.* **1999**, *99*, 2071–2083.
2. Examples of recyclable process in the recent literature: (a) Meshram, H. M.; Reddy, P. N.; Vishnu, P.; Sedashir, K.; Yadav, J. S. *Tetrahedron Lett.* **2006**, *47*, 991–995; (b) Gong, H.; Cai, C.; Yang, N.; Yang, L.; Fan, Q. *J. Mol. Catal. A-Chem.* **2006**, *249*, 236–239.
3. *Green chemistry: Theory and Practice*; Anastas, P. T., Warner, J. C., Eds.; Oxford University Press: New York, 1998.
4. Suslick, K.; Schubert, P.; Goodale, J. *J. Am. Chem. Soc.* **1981**, *103*, 7342–7344.
5. Suslick, K.; Goodale, J.; Schubert, P.; Wang, H. *J. Am. Chem. Soc.* **1983**, *105*, 5781–5785.
6. Villemin, D.; Alloum, A. B. *Synth. Commun.* **1990**, *20*, 925–932.

7. Harrowven, D. C.; Dainty, R. F. *Tetrahedron Lett.* **1996**, *37*, 7659–7660.
8. Rajagopal, R.; Jarigote, D. V.; Srinivasan, K. V. *Chem. Commun.* **2002**, *6*, 616–617.
9. Deshmukh, R. R.; Rajagopal, R.; Srinivasan, K. V. *Chem. Commun.* **2001**, *17*, 1544–1545.
10. Bravo, J. L.; Lòpez, I.; Cintas, P.; Silvero, G.; Arévalo, M. J. *Ultrason. Sonochem.* **2006**, *13*, 408–414.
11. Léveque, J.-M.; Luche, J.-L.; Pétrier, C.; Roux, R.; Bonrath, W. *Green Chem.* **2002**, *4*, 357–360.
12. Linghu, X.; Potnick, J.; Johnson, J. *J. Am. Chem. Soc.* **2004**, *126*, 3070–3071.
13. Ukai, T.; Tanaka, R.; Dokawa, T. *J. Pharm. Soc. Jpn.* **1943**, 296–300.
14. Knight, R. L.; Leeper, F. J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1891–1893.
15. Chan, A.; Scheidh, K. A. *Org. Lett.* **2005**, *7*, 905–908.
16. Kuebrich, J. P.; Schowen, R. L.; Wang, M.-S.; Lupes, M. E. *J. Am. Chem. Soc.* **1971**, *93*, 1214–1220.
17. Davis, J. H., Jr.; Forrester, K. J. *Tetrahedron Lett.* **1999**, *40*, 1621–1622.
18. Breslow, R. *J. Am. Chem. Soc.* **1958**, *80*, 3719–3726.
19. Estager, J.; Léveque, J.-M.; Turgis, R.; Draye, M. *J. Mol. Catal. A-Chem.* **2006**, *256*, 261–264.
20. Xu, L.; Gao, Y.; Yin, J.; Li, L.; Xiu, C. *Tetrahedron Lett.* **2005**, *46*, 5317–5320.
21. *Synthetic Organic Sonochemistry*; Luche, J.-L., Ed.; Plenum Press: New York, 1998.
22. *Sonochemistry: The Uses of Ultrasound in Chemistry*; T. J. Mason, Ed.; Royal Society of Chemistry, 1990.
23. Falnnigan, D. J.; Hopkins, S. D.; Suslick, K. S. *J. Organomet. Chem.* **2005**, *690*, 3513–3517.
24. *Typical procedure for ultrasound-assisted benzoin condensation with 1-octyl-3-methyl-imidazolium bromide*: In a 10 mL reactor, reagents are introduced as followed: 0.03 g of sodium methoxide (0.5 mmol), 9 mL of OMIBr and 0.5 mL of benzaldehyde (5 mmol). The mixture is irradiated by 30 kHz ultrasound for 30 min., temperature naturally increasing from room temperature to 50 °C. The mixture is then poured in 13 mL of water and organic products are extracted 8 times with 15 mL of diethylether. The yields of products were calculated based on GC–MS analysis. Ether and water are then removed from the RTIL under vacuum at 80 °C so as to recycle the ionic medium.