

# Solventless and swift benzoin condensation catalyzed by 1-alkyl-3-methylimidazolium ionic liquids under microwave irradiation

Julien Estager, Jean-Marc Lévêque\*, Raphaël Turgis, Micheline Draye

Laboratoire de Chimie Moléculaire et Environnement, ESIGEC, Université de Savoie, 73376 Le Bourget du Lac CEDEX, France

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## Abstract

A solventless benzoin condensation was performed with several imidazolium-based ionic liquids as catalysts under microwave irradiation. The process enables the formation of  $\alpha$ -hydroxy- $\alpha$ -phenylacetophenone with good yield (up to 97%) and purity in a very short time. Moreover, the work-up only requires the use of water, giving a green touch to the overall process.

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## 1. Introduction

Non-traditional cleavage becomes available by reversing the alternative donor–acceptor reactivity pattern imposed by heteroatoms. This inversion of normal reactivity, described as “umpolung”, is a powerful strategy in organic chemistry that provides unconventional access to important material [1]. Especially attractive are catalytic processes, the best known example of which is the benzoin condensation [2], in which carbonyl polarity is inverted via an intermediate that functions as acyl anions equivalents. The  $\alpha$ -hydroxy carbonyls that result from benzoin or acyloin condensations are desirable building blocks and include a structural motif that is common among natural products [3].

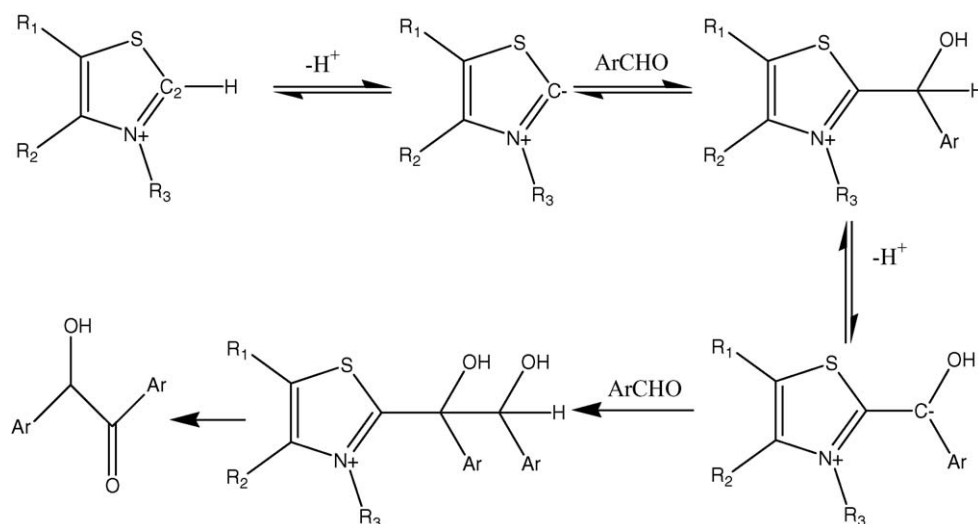
Breslow, in a pioneering application of NMR, pointed out the catalyst role of thiazolium compound for the self condensation of benzaldehyde to benzoin and proposed a mechanism, depicted in Scheme 1, that was unexpected but generally admitted [4]. This carbonyl polarity inversion has been realized catalytically with thiamin [5], triazolium [6], heteroazolium carbens [7], cyanide anion [8], metallophosphites [3], halide room temperature ionic liquids (RTILs) [9]. An other example is given with imidazolium-based salts which have much higher melting point

than 100 °C, upper limit admitted to be considered as RTILs [10].

These last years, RTILs have become a very attractive alternative to conventional solvents [11]. Because of their negligible vapor pressure, they are used as green solvents. In addition, their wide liquid range, tunable polarity or good solvating ability make them very interesting in organic synthesis [12]. Even if Aggarwal et al. proved that imidazolium based ionic liquids can react with benzaldehyde under basic conditions [13], these compounds are used since very recently for the benzoin condensation because of the poor acidity of C2 hydrogen compared to thiazolium or triazolium salts [14]. Nevertheless, imidazolium-based RTILs remain the most common and accessible ionic liquids. Consequently, the aim of this work was to find a process or a method to take advantage of the remarkable properties of these compounds in order to enlarge their application field, by enhancing their reactivity using non-conventional activation methods such as ultrasound and microwave.

Because of its low time consumption, microwave irradiation is considered as a green activation method. It offers also considerable advantages over conventional heating in term of rate enhancement and selectivity in a wide range of organic reactions [15]. Moreover, RTILs efficiently absorb microwave energy [16] because of their high polarity. This property should greatly accelerate reaction rates in RTILs when they are used as solvents and/or catalysts. This work describes an eco-friendly benzoin

\* Corresponding author. Tel.: +33 479758824; fax: +33 479759410.  
E-mail address: [jean-marc.leveque@univ-savoie.fr](mailto:jean-marc.leveque@univ-savoie.fr) (J.-M. Lévêque).



Scheme 1. Breslow et al. mechanism of thiazolium-catalyzed benzoin condensation.

condensation where RTILs are used as catalysts and microwaves as an activation method in a solvent free system.

## 2. Results and discussion

Recently, Xu et al. described for the first time the use of imidazolium-based RTILs as catalysts for benzoin condensation [14]. Even if this reaction occurs in mild conditions, the reaction requires 12 h while using a large amount of RTIL (50%) in an organic solvent, usually dichloromethane. Under microwave irradiation, the use of low boiling-point solvents, and especially halogenated ones, is inadequate because of the very fast temperature increase that becomes quickly problematic. In our work, we substituted the molecular organic solvent by RTILs that have a large liquid range and stability. A temperature increase in such solvent is also very important under microwave activation, which is very interesting for the reaction. As a consequence, RTILs were used both as catalyst and solvent. Scheme 2 describes the benzoin condensation under microwave irradiation in 1-octyl-3-methylimidazolium bromide (OMIBr) as solvent–catalyst and with MeONa as base. OMIBr was chosen as it is liquid at room temperature and on the other hand it is one of the most common, accessible and cheapest ionic liquid. Moreover, the first attempts were done in the presence of Et<sub>3</sub>N, weaker but hindered base compared to MeONa. None of the tested ionic liquids led to valuable yield of benzoin. Ionic liquids are known as non-dissociated ion pairs [17], we then postulated that a steric hindrance was induced by the size of the counter-anion. Higher the size of the

Table 1

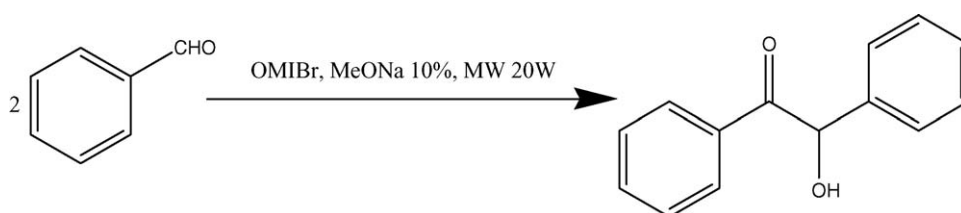
Benzoin condensation with 1-octyl-3-methyl imidazolium bromide (OMIBr) as solvent and catalyst under microwave irradiation  $P = 20$  W,  $T$  up to  $150$  °C

Entry <sup>a</sup>	OMIBr (mol.%)	Reaction time (min)	Isolated yield (%)
1	90	3	56
2	40	3	74
3	20	4	83

<sup>a</sup> Standard reaction condition: 22 mmol benzaldehyde, 10 mol.% MeONa,  $x$ % OMIBr (entries 1–3), temperature up to  $150$  °C, 20 W microwave irradiation.

counter-anion is, higher the corresponding steric hindrance is. MeONa is used since it is quite a stronger base than Et<sub>3</sub>N and it is small enough to avoid the potential steric hindrance due to the proximity between the imidazolium ring and the anion. The first results are described in Table 1.

These first results are very stimulating even if ionic liquid decomposition is observed. Actually, some retro synthesis products are observed such as 1-methylimidazole or 1-bromooctane. This side-reaction is probably due to a nucleophilic attack of the bromide anion [18], on the alkyl chain of the imidazolium. In addition, some traces (about 4%) of deoxybenzoin are observed for entries 1 and 2. We thus optimized the RTIL concentration that seemed to be the key of this side reaction. The results show that the RTIL decomposition is in inverse ratio to its concentration. The initial concentration was then decreased and the RTIL was used as a simple catalyst. This behavior is probably due to the specific MW irradiation because RTILs are high microwave absorbing and decreasing their presence decreases as well the



Scheme 2. Benzoin condensation under microwave irradiation in 1-octyl-3-methylimidazolium bromide (OMIBr) as solvent–catalyst and with MeONa as base.

Table 2  
Solvent free benzoin condensation catalysed by imidazolium ionic liquids

Entry	Catalyst	Solvent	Activation method	Time (min)	Yield (%) <sup>c</sup>
1 <sup>a</sup>	OMIBr 10%	None	MW 20 W up to 150 °C	4	80
2 <sup>a</sup>	OMIBr 5%	None	MW 20 W up to 150 °C	5	80
3 <sup>a</sup>	OMIBr 2%	None	MW 20 W up to 150 °C	5	79
4 <sup>b</sup>	OMIBr 2%	None	Thermal 150 °C	5	74
5 <sup>a</sup>	OMICl 2%	None	MW 20 W up to 150 °C	5	86
6 <sup>b</sup>	OMICl 2%	None	Thermal 150 °C	5	77
7 <sup>a</sup>	BMIBr 2%	None	MW 20 W up to 150 °C	5	79
8 <sup>b</sup>	BMIBr 2%	None	Thermal 150 °C	5	70
9 <sup>a</sup>	BMICl 2%	None	MW 20 W up to 150 °C	5	97
10 <sup>b</sup>	BMICl 2%	None	Thermal 150 °C	5	70

<sup>a</sup> General procedure: 22 mmol of benzaldehyde; 10 mol.% MeONa, 150 °C.

<sup>b</sup> General procedure: 22 mmol of benzaldehyde; 10 mol.% MeONa, temperature up to 150 °C, 20 W microwave irradiation.

<sup>c</sup> Isolated yield.

MW absorbed energy, leading to a lower decomposition. Since less chemicals are used, this reaction becomes not only cheaper but greener. Experiments performed in halide RTILs are summarized in Table 2. All microwave experiments were compared to mechanical stirring under thermal activation.

Even if our first objective was to use RTILs as solvent and catalyst, it is possible to drastically reduce the amount of OMIBr for an even better yield in a neat system (entries 1–3). Moreover, this reaction gives also suitable results under thermal activation. Anyway, even if the results under microwave irradiation are slightly better, the gain in saving up energy is very appreciable. It is also important to quote that our work-up is also very competitive according to green chemistry concepts as a solvent-less system has been developed.

The final mixture is poured into cold water in which benzoin alone precipitates. The target product can be obtained by a simple filtration. Under optimized conditions, almost quantitative yield of benzoin is synthesized in 5 min for 2% of catalyst. It is to our knowledge the fastest conditions for an imidazolium based ionic liquid, requiring the lowest amount of catalyst and leading to the best yield in literature. Finally, this present process agrees with several concepts of the green chemistry since it requires a very small amount of catalyst, uses an eco-friendly activation with microwave, does not require any solvent except

the reagent itself with water as extraction medium. Recycling of the RTILs is presently on progress in our laboratory. In this aim, it would be advantageous to modify the physical properties of the RTIL catalyst and carry out the reaction with an hydrophobic RTIL. According to the literature, benzoin condensation only works out with halide imidazolium-based RTILs when a thermal heating is used [14]. We applied our microwave conditions to several hydrophilic and hydrophobic ionic liquids and the results are described and compared to thermal activation in Table 3 (Scheme 3).

Table 3 shows that the yields are lower than those obtained with halide imidazolium catalysts. Nevertheless, it is to our knowledge the first example of benzoin condensation with non-halide imidazolium-based ionic liquids. In addition, reaction yields are higher and more selective under microwave than under thermal conditions. Actually, for thermal activated reactions, several by-products are observed such as benzoic acid or ethanone, 2-(benzoyloxy)1,2-diphenylethanone. A 20-W irradiation appears to be high enough to overpass the activation barrier of benzoin condensation. Once again, this method is very attractive in term of energy consumption. Moreover, an anion effect is shown for the reaction since yields are highly dependant on the nature of the ionic liquid's anion. This observation shows that the microwave irradiation directly acts on the RTIL catalyst – or

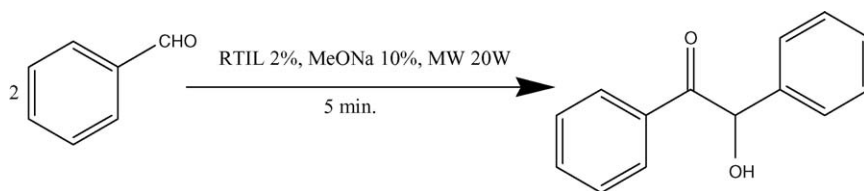
Table 3  
Solvent free benzoin condensation with not-halide ionic liquids

Entry <sup>a</sup>	Catalyst 2 (mol.%)	Activation method	Yield (%) <sup>b</sup>	Benzoic acid (%) <sup>c</sup>	Ethanone, 2-(benzoyloxy) 1, 2-diphenylethanone (%) <sup>c</sup>
1	OMIOTf	Thermal 150 °C	18	26	0
2	OMIOTf	MW 20 W up to 150 °C	70	0	0
3	OMIPF <sub>6</sub>	Thermal 150 °C	13	61	12
4	OMIPF <sub>6</sub>	MW 20 W up to 150 °C	65	0	0
5	OMINTf <sub>2</sub>	Thermal 150 °C	6	0	0
6	OMINTf <sub>2</sub>	MW 20 W up to 150 °C	55	0	0
7	OMIBF <sub>4</sub>	Thermal 150 °C	0	0	0
8	OMIBF <sub>4</sub>	MW 20 W up to 150 °C	29	0	0
9	BMICF <sub>3</sub> CO <sub>2</sub>	Thermal 150 °C	5	0	0
10	BMICF <sub>3</sub> CO <sub>2</sub>	MW 20 W up to 150 °C	76	0	0

<sup>a</sup> General procedure: 22 mmol of benzaldehyde; 10 mol.% MeONa, 2 mol.% RTIL, 150 °C (oil bath) or temperature up to 150 °C 20 W microwave irradiation; reaction time, 5 min.

<sup>b</sup> Isolated yield.

<sup>c</sup> Based on GCMS yield.



Scheme 3. Benzoin condensation with not-halide RTIL.

on the RTIL/aldehyde intermediate – and not only on the sodium methylate or on the benzaldehyde precursor. In addition, the fact that yields are influenced by the nature of the RTIL proves that imidazolium-based ionic liquids are tunable not only in term of physical properties but also in terms of chemical reactivity.

### 3. Conclusion

In summary, this work reports an eco-friendly benzoin condensation catalyzed by imidazolium-based ionic liquids. It requires a very short reaction time and is very attractive in term of energy consumption since microwave irradiation is used. Furthermore, it is very economic in term of solvent utilization since this reaction occurs without any solvent and the final product is extracted with water. This method gives very good results for chloride and bromide imidazolium-based ionic liquids catalysts but is also possible with non-halide RTILs. Efforts are presently focused on the optimization of the temperature and reaction time in order to apply our process on benzoin condensation catalyzed by chiral imidazolium-based ionic liquids.

### 4. Experimental

General procedure: under a flow of argon, 0.12 g of MeONa (2.2 mmol), 0.44 mmol of RTIL and 2.25 mL of benzaldehyde (22 mmol) are combined. The mixture was stirred under microwave irradiation for about 5 min until temperature reaches 150 °C (Prolabo Synthewave 401). A yellow powder is obtained and washed until it turns white. Then the product is dried in an oven at 95 °C for 1 h and then weighted. The purity of the final products was determined by GCMS and their <sup>1</sup>H NMR were identical to commercial samples.

<sup>1</sup>H NMR (Bruker 300 MHz AMX): δ 7.93 (d, 2H, *J* = 8 Hz) 7.57–7.27 (m, 7H) 5.97 (d, 1H, *J* = 5 Hz) 4.57 (d, 1H, *J* = 6 Hz).

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