

Efficient and mild benzoin condensation reaction catalyzed by simple 1-*N*-alkyl-3-methylimidazolium salts

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Abstract—The benzoin reaction, catalyzed by simple 1-*N*-alkyl-3-methylimidazolium salt-based ionic liquid via carbene intermediate, to give the α -hydroxyl ketone proceeds in CH_2Cl_2 under mild conditions.

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The formation of carbon–carbon bond is one of the most fundamental reaction for the construction of a molecular framework.¹ In past decades, several carbon–carbon bond-forming reactions have been discovered and their applications in organic chemistry have also been well documented in the literature.² One such reaction family is exemplified by the benzoin reaction, and it has been recognized as one of the promising methods for the preparation of a variety of α -hydroxyl ketones since 1903.³ The reaction is usually carried out in basic media and promoted by toxic cyanide ion. A key intermediate in this reversible reaction is nitrile-stabilized carbanion.^{3,4} It has been shown subsequently that functional thiazolium salts, in combination with bases, also catalyze the benzoin reaction of aldehyde in impressive results.⁵ Surprisingly, to our knowledge, there are no examples of simple 1-*N*-alkyl-3-methylimidazolium salt-catalyzed carbon–carbon bond-forming benzoin reactions of aldehydes.

In these years, imidazolium salts-based ionic liquids have been shown to be of great promise as attractive alternatives to conventional solvents.⁶ Ionic liquids are being used as green solvents with unique properties such as wide liquid range, good solvating ability, tunable

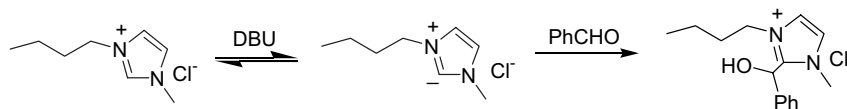
polarity, high thermal stability and so forth. As a result of their green credentials and potential to enhance rates and selectivities, ionic liquids based on imidazolium salts are finding increasing applications in organic synthesis.⁷ Herein we first reported the development of a family of organic catalyst with ionic liquids leading to an efficient benzoin condensation reaction under mild conditions.

However, Aggarwal et al.⁸ reported that imidazolium salts can react with aldehydes under basic conditions to yield adduct 3 and further transformation of the product did not occur in Baylis–Hillman reaction (Scheme 1). This finding showed that imidazolium salts-based ionic liquids were inert solvents under mildly basic conditions, and evidently, simple 1-*N*-alkyl-3-methylimidazolium salts cannot be used as a catalyst in benzoin condensation and other reaction.⁹ However, we found that a simple imidazolium ion can catalyze the benzoin condensation reaction of benzaldehyde using inorganic base under mild conditions.

In our initial work, the benzoin condensation reaction of benzaldehyde was found to proceed efficiently when 1-*N*-alkyl-3-methylimidazolium bromides and CH_2Cl_2 were employed. As shown in Table 1, the benzoin reactions of benzaldehyde could be catalyzed by BMIMBr and EMIMBr efficiently (entries 3–4). A subsequent solvent screen revealed that low-polarity solvents led to higher yield, with CH_2Cl_2 providing the best results, and the reaction did not occur or reacted slowly in water, THF and CH_3CN . Room temperature ionic

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Scheme 1. Reaction of ionic liquid with benzaldehyde demonstrated by Aggarwal et al.⁸

Table 1. Benzoin condensation reactions of benzaldehyde catalyzed by imidazolium salts-based ILs

Entry ^a	Solvent	Catalyst	Base	Time (h)	Yield/% ^b
1	THF	BMIMBr	NaOH	24	Trace
2	THF	BMIMBr	K ₂ CO ₃	24	20
3	CH ₂ Cl ₂	BMIMBr	K ₂ CO ₃	24	40
4	Toluene	BMIMBr	K ₂ CO ₃	24	32
5	CH ₂ Cl ₂	BMIMBr	Et ₃ N	48	0
6	H ₂ O	BMIMBr	K ₂ CO ₃	48	0
7	CH ₃ CN	BMIMBr	K ₂ CO ₃	24	0
8	CH ₃ OH	EMIMBr	K ₂ CO ₃	24	Trace
9	CH ₂ Cl ₂	BMIMPF ₆	K ₂ CO ₃	24	0
10	Toluene	BMIMPF ₆	K ₂ CO ₃	24	0
11	CH ₂ Cl ₂	BMIMBF ₄	K ₂ CO ₃	24	0
12	CH ₂ Cl ₂	BMIMBr	K ₂ CO ₃	12	76
13	CH ₂ Cl ₂	EMIMBr	K ₂ CO ₃	12	86

^a Standard reaction condition: 1 mmol benzaldehyde, 10 mol % imidazolium salts/K₂CO₃ (1/1.1, entries 1–11) or 50 mol % imidazolium salts/K₂CO₃ (1/1.1, entries 12–13), 3 mL of solvent, room temperature.

^b Determined by GC analysis.¹³

liquid (BMIMPF₆) has no catalytic reactivity in this benzoin condensation reaction (entries 9–10).

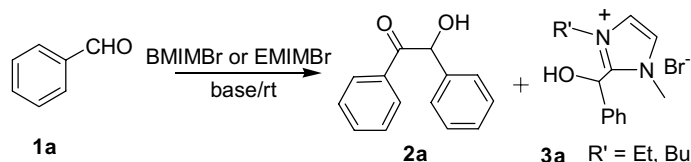
In such reactions, only a very small amount of the ionic liquid is converted into the carbene (ylide) and so the transformation usually goes slowly.¹⁰ To accelerate the rate of benzoin reaction, 0.5 equiv imidazolium salt was used as a catalyst and an excellent yield was obtained in shorter time (Table 1, entries 12–13), and trace carbene intermediate **3a** was also obtained (Scheme 2).

Under optimized conditions, the reactivity of a series of similar substrates to α -hydroxyl ketones was examined.¹² As shown in Table 2, the benzoin reaction of various substituted aldehydes including electron rich derivatives in CH₂Cl₂ were all completed within 20 h at room temperature. The aryl aldehyde substrates containing chloride and methyl moieties or even those substrated with *ortho*-positioned side chain afforded the desired α -hydroxyl ketones in high yields. As expected, alkyl aldehyde gave lower yield as compared to aryl aldehyde. For *n*-butylaldehyde, there are no acyloin products, but α,β -unsaturated aldehyde was obtained in high yield. The benzoin reactions of 4-nitrobenzaldehyde and *ortho*-methoxyl benzaldehyde were consider-

ably slow and the yield was very low. The results (entries 5–8) shown using the above mentioned substrates were converted to some by-products in the presence of inorganic base.

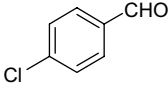
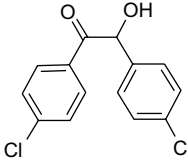
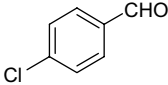
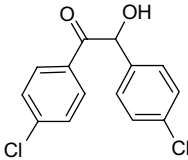
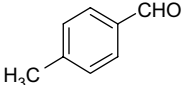
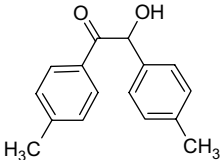
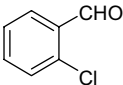
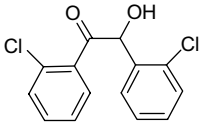
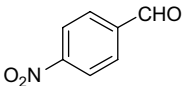
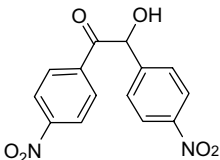
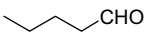
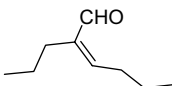

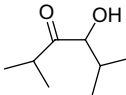
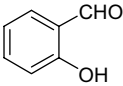
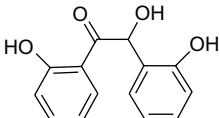
Although a large amount of ionic liquid salt (50 mol % EMIMBr) was used in this benzoin condensation reaction, the ionic liquid salt could be reduced to about 10 mol % using different procedure. In this improved study, the benzaldehyde (10 mmol) was added in the solution of EMIMBr (191 mg, 1 mmol), K₂CO₃ (152 mg, 2.2 mmol), 5 mL of CH₂Cl₂ in five portions every 18 h. After the completion, the desired product was obtained in 76% (isolated yield). The improved procedure could be performed to other aldehydes and resulted in high isolated yields in most cases.

Based on the above results, the possible mechanism of the benzoin condensation reaction is shown in Scheme 3, at the first, the carbene (ylide) can be derived from deprotonation of the imidazolium salt by a weak base. The initial addition of the ylide to aldehyde under the influence of a base resulted in the production of intermediate **D**, which was determined by ¹H NMR spectra. Similar to the mechanism of a thiazolium salt-catalyzed benzoin condensation,¹¹ the addition of intermediate **D**



Scheme 2. Benzoin condensation reactions of benzaldehyde catalyzed by imidazolium salts-based ILs.

Table 2. Benzoin condensation reactions of various aldehydes catalyzed by EMIMBr

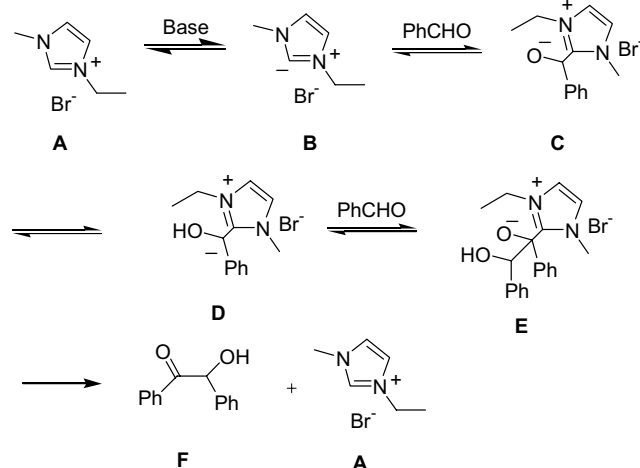
$ \begin{array}{c} \text{R-CHO} \\ \text{1} \end{array} \xrightarrow[\text{CH}_2\text{Cl}_2/\text{rt}/20\text{h}]{\text{ionic liquid catalyst}} \begin{array}{c} \text{O} \quad \text{OH} \\ \parallel \quad \\ \text{R-C-C-R} \\ \text{2} \end{array} \quad \text{Catalyst} = \begin{array}{c} \text{R}'\text{-N} \begin{array}{c} \diagup \diagdown \\ \text{C} \quad \text{C} \end{array} \text{N}^+ \\ \\ \text{Br}^- \end{array} + \begin{array}{c} \text{R}'\text{-N}^+ \begin{array}{c} \diagup \diagdown \\ \text{C} \quad \text{C} \end{array} \text{N} \\ \\ \text{HO-C-R} \end{array} \text{Br}^- $			
Entry ^a	Aldehyde	Product	Yield/% ^b
1			75
2			70 ^c
3			71
4			69
5			Trace
6			85 ^d
7			40
8			0

^a Standard reaction condition: 1 mmol benzaldehyde, 50 mol % EMIMBr/K₂CO₃ (1/1.1), 3 mL of CH₂Cl₂, room temperature.^b Determined by GC analysis.^c The reaction was run for 8 h.^d The yield of aldol product.

to aldehyde resulted in the conversion of the corresponding benzoin.

As described above, ionic liquid salts based on simple 1-*N*-alkyl-3-methylimidazolium salt catalyzed the benzoin

condensation reaction to give the α-hydroxyl ketone is reported for the first time. This provides a new insight for the catalytic utility of imidazolium salts-based ionic liquids but also an opportunity for extending the study of organic catalyst. The present reaction with its mild



Scheme 3. Mechanism of simple imidazolium salt (EMIMBr) catalyzed benzoin condensation reaction.

reaction conditions opens a novel green entry to synthesis of α -hydroxyl ketone by simple procedure. Finally, the successful application of very cheap catalysts bodes well for the development of asymmetric benzoin reaction. Current efforts are focused on the synthesis of chiral imidazolium-based catalyst and its application in this benzoin condensation reaction.

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12. General procedure: EMIMBr (191 mg, 1 mmol), aldehyde (2 mmol), K_2CO_3 (152 mg, 1.1 mmol), 3 mL of CH_2Cl_2 and a magnetic stir bar were combined. This mixture was stirred at room temperature. After the completion, this mixture was diluted with CH_2Cl_2 and washed with water. The organic layer was dried over anhydrous Na_2SO_4 and the yield was determined by GC analysis. The organic layer was filtered, concentrated in vacuo and purified by flash chromatography on silica gel. All products are identified by GC/MS and their 1H NMR were identical to authentic samples.
13. The GC yields in Tables 1 and 2 ignored the consuming amount of aldehyde which reacted with ionic liquid to yield trace carbene intermediate.