An investigation of the catalytic potential of potassium cyanide and imidazolium salts for ultrasound-assisted synthesis of benzoin derivatives

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Abstract A rapid, highly efficient and mild green synthesis of benzoin was performed using substituted benzaldehyde catalyzed by KCN and imidazolium salts in EtOH/H2O under ultrasonic activation. The products were obtained in good yields within short reaction times with N,N'-dialkylimidazolium salts, which were found to be more effective pre-catalysts at room temperature for benzoin condensation in comparison to corresponding cyanide ion in heating method. This simple method affords benzoin derivatives at room temperature in short reaction times with high yield and purity.

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1. Introduction

The formation of carbon–carbon bond is one of the most fundamental reaction for the construction of a molecular framework (Trost, 1991; Basavaiah et al., 2003). 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 (Sammelson and Kurth, 2003; Huddleston and Krische, 2003; Gibson and Stevenazzi, 2003; Moreno-Mañas and Pleixats, 2003). Among these reactions, the benzoin condensation is an important method for the formation of carbon–carbon bonds starting from aldehydes giving α-hydroxycarbonyl compounds, which are interesting building blocks for the synthesis of natural and pharmaceutical compounds (Iwamoto et al., 2006; Konosu et al., 1991).

After the first report by Wöhler and Liebig who used cyanide as a pre-catalyst in 1832 (Wöhler and Liebig, 1832), various catalysts have been used to promote the benzoin condensation reaction effectively. Breslow in 1958 first recognized that the N-heterocyclic carbenes (NHCs) could also serve all these roles similar to that of cyanide ion in benzoin condensation (Breslow, 1958), and NHCs are better nucleophiles and leaving groups than cyanide. Nevertheless, the discovery of stable carbenes by Arduengo in 1991 (Arduengo et al., 1991) provided the access to develop a variety of NHC catalysts for benzoin condensation (Mavis et al., 2010; Baragwanath et al., 2009; Toole et al., 2011).
The use of NHCs such as thiazolium (Knight and Leeper, 1998), triazolium (Enders and Han, 2008), imidazolium (Orsini et al., 2009) and benzimidazolium (Pesch et al., 2004) salts has resulted in steady improvements of the yields and selectivities. Different reaction conditions have been studied to obtain milder and simpler methods for the benzoin condensation (Storey and Williamson, 2005; Xu et al., 2005). A number of recent reports however, have described efficient imidazole based carbene catalysts with the advantage of trivial catalyst synthesis, and increased stability over other heterocyclic systems (Orlandi et al., 2003). There still appears a need to introduce novel methods to permit better selectivity under milder conditions and with easy work-up procedures. Ultrasonic irradiation has been considered as a clean and useful protocol in organic synthesis during the last three decades, compared with traditional methods, the procedure is more convenient. A large number of organic reactions can be carried out in higher yield, shorter reaction time or milder conditions under ultrasonic irradiation (Safari and Moshtael Arani, 2011; Safari et al., 2010; Estager et al., 2007).

Herein, we wish to report the synthesis of symmetrical and unsymmetrical benzoin derivatives using potassium cyanide and imidazolium salts in ethanol-water binary mixtures under ultrasound (Scheme 1).

We found that the imidazolium salts efficiently catalyze the benzoin condensation of aldehydes in the presence of a base. Hence, our interest focused on an investigation of the effect of tricationic and dicationic NHCs in this reaction under ultrasound. These tricationic and dicationic imidazolium salts show considerable catalytic potential when compared with monocationic imidazolium salts and toxic cyanide anions. This paper describes for the first time, the use of tricationic imidazolium salts in the acyloin condensation under ultrasound. This simple method affords benzoin derivatives at room temperature in short reaction times with high yield and purity.

2. Experimental

2.1. Materials and instruments

In a typical procedure, chemicals were purchased from Merck chemical company. The N,N'-dialkylimidazolium salts were prepared using the published procedure (Estager et al., 2002; Bonhôte et al., 1996; Tulloch et al., 2000). 1H NMR (400 MHz) and 13C NMR (100 MHz) spectra were recorded on a Bruker DPX-400 Avance spectrometer. Tetramethyl silane (TMS) was used as an internal reference. IR spectra were obtained on a Magna-550 Nicolet instrument. Vibrational transition frequencies were reported as wave numbers (cm−1), and band intensities designated as weak (w), medium (m) and strong (s). A mass spectrum was recorded by a QP-1100EX Shimadzu spectrometer. Sonication was performed in a UP 400S ultrasonic processor equipped with a 3 mm wide and 140 mm long probe, which was immersed directly into the reaction mixture. The operating frequency was 30 kHz and the output power was 0–400 W through manual adjustment. UV spectra were recorded on a Hitachi 200–20 spectrometer using spectrophotometric grade ethanol (Baker). Melting points were obtained with a micro melting point apparatus (Electrothermal, Mk3) and are uncorrected.

2.2. General procedure for synthesis of a–m

2.2.1. KCN-catalyzed benzoin condensation under ultrasound irradiation

General procedure for synthesis of a–h: To synthesize the symmetrical benzoins, a solution of 1 mmol of benzaldehyde and 1 mmol of potassium cyanide (96–98 %) is mixed in water-ethanol mixtures (water:ethanol, 1:5 v/v). This reaction was completed under ultrasound irradiation at 80 °C for the appropriate amount of time to complete the reaction. The completion of reaction was monitored by TLC (petroleum ether:ethyl acetate, 4:1 v/v). The reaction mixture was cooled and the product was collected by vacuum filtration and washed thoroughly with water. The product was recrystallized from ethanol.

General procedure for synthesis of i–m: To synthesize the unsymmetrical benzoins, 1 mmol of donor benzaldehyde, 1 mmol of acceptor benzaldehyde, and 1 mmol of potassium cyanide are mixed in water-ethanol mixtures (water:ethanol, 1:5 v/v). This reaction was completed under ultrasound irradiation at 80 °C. The completion of reaction was monitored by TLC (petroleum ether:ethyl acetate, 4:1 v/v). The reaction mixture was cooled and the product was collected by vacuum filtration and washed thoroughly with water. The product was recrystallized from ethanol.

2.2.2. Imidazolium salts-catalyzed benzoin condensation under ultrasound irradiation

Three N,N'-dialkylimidazolium salts, [EtMeIm]Br, [C6H4(CH2ImMe)2]Br2 and [C6Me3(CH2ImMe)3]Br3 were prepared according to reported procedures in the literature (Iwamoto et al., 2006; Kankala et al., 2011; Knight and Leeper, 1998; Sannemson and Kurth, 2001) (Scheme 2).

General procedure for synthesis of a–h: To a solution of the 1 mmol aldehyde in water-ethanol mixtures (water:ethanol, 1:5 v/v), 1 mol % catalyst and 20 mol % NaOH in 3 mL of H2O were added, and the mixture was exposed to ultrasonic irradiation at room temperature for the appropriate amount of time to complete the reaction. The completion of reaction was monitored by TLC (petroleum ether:ethyl acetate, 4:1 v/v). The reaction mixture was cooled and the product was collected by vacuum filtration and washed thoroughly with water. The product was recrystallized from ethanol.

Scheme 1 Preparation of benzoin with cyanide and imidazolium salts under ultrasound irradiation.
collected by vacuum filtration and washed thoroughly with water. The product was recrystallized from ethanol.

**General procedure for synthesis of i–m:** To a solution of the 1 mmol of donor benzaldehyde, 1 mmol of acceptor benzaldehyde, in water–ethanol mixtures (water:ethanol, 1:5 v/v), 1 mol % catalyst and 20 mol % NaOH in 3 mL of H2O were added, and the mixture was exposed to ultrasonic irradiation at room temperature for the appropriate amount of time to complete the reaction. The completion of reaction was monitored by TLC (petroleum ether:ethyl acetate, 4:1 v/v). The reaction mixture was cooled and the product was collected by vacuum filtration and washed thoroughly with water. The product was recrystallized from ethanol.

The structure of these compounds has been investigated using different methods of spectroscopy and spectrometry: UV, 1H NMR, 13C NMR, IR and MS.

### 2.3. Spectral data

#### 2.3.1. Compound (a), benzoin

**UV** (CH3OH) \(\lambda_{\text{max}}\): 320, 283 nm; 1H NMR (400 MHz, CDCl3) \(\delta\): 4.5 (1H, d, OH, J = 6 Hz), 5.9 (1H, d, CH, J = 6 Hz), 7.28 (1H, m, CH), 7.35 (4H, m, CH), 7.41 (3H, t, CH, J = 7.6 Hz) ppm; 13C NMR (100 MHz, DMSO-d6) \(\delta\): 78 (CH), 127.81 (CH), 128.58 (CH), 128.70 (CH), 129.14 (CH), 129.17 (CH), 133.56 (C), 133.91 (C), 139.07 (C), 200 (CO) ppm; IR (KBr, \(\nu_{\text{max}}\) cm\(^{-1}\)): 3379, 3415 (OH, s), 1678 (CO, s), 1450, 1308 (NO2, s), 750 (C–H, s); MS (70 Ev, EI) \(m/z = 213 (M^+ + 1), 212 (M^+)\), 195, 107, 77.

#### 2.3.2. Compound (b), 4,4′-dimethoxybenzoin

**UV** (CCl4) \(\lambda_{\text{max}}\): 270 nm; 1H NMR (400 MHz, DMSO-d6) \(\delta\): 2.21 (3H, s, CH₃), 2.30 (3H, s, CH₃), 5.88 (1H, b, OH), 6 (1H, s, CH), 7.09 (2H, d, CH, J = 7.2 Hz), 7.251 (4H, d, CH, J = 10.8, 8.8 Hz), 7.85 (2H, d, CH, J = 6.8 Hz) ppm; 13C NMR (100 MHz, DMSO-d6) \(\delta\): 21.2 (CH₂), 21.7 (CH₂), 75.8 (CH), 124.77 (C), 127.35 (CH), 128.09 (CH), 129.85 (CH), 135.96 (C), 136.08 (C), 141.58 (C), 198 (CO) ppm; IR (KBr, \(\nu_{\text{max}}\) cm\(^{-1}\)): 3456 (OH, s), 1676 (CO, s), 1450, 1580 (C=C, m), 830 (==C–H, s); MS (70 Ev, EI) \(m/z = 240 (M^+)\), 223, 121, 119, 91.

#### 2.3.3. Compound (c), 3,3′-dimethoxybenzoin

**UV** (CH3OH) \(\lambda_{\text{max}}\): 239 nm; 1H NMR (400 MHz, CDCl3) \(\delta\): 2.27 (3H, s, CH₃), 2.31 (3H, s, CH₃), 4.56 (1H, s, OH), 5.88 (1H, s, CH), 6.90–7.63 (8H, m, CH) ppm; 13C NMR (100 MHz, CDCl3) \(\delta\): 19.39 (CH₃), 20.17 (CH₃), 69.21 (CH), 124.41 (CH), 126.91 (CH), 127.22 (CH), 128.03 (CH), 128.87 (CH), 129.15 (CH), 130.56 (CH), 131.37 (CH), 135.71 (C), 138.03 (C), 140.49 (C), 142.13 (C), 196.24 (CO) ppm; IR (KBr, \(\nu_{\text{max}}\) cm\(^{-1}\)): 3220–3550 (OH, m), 1685 (CO, s), 1480, 1620 (C=C, m), 690, 780 (==C–H, s); MS (70 Ev, EI) \(m/z = 241 (M^+ + 1), 240 (M^+)\), 223, 121, 119, 91.

#### 2.3.4. Compound (d), 4,4′-dimethoxynitrobenzoin

**UV** (CCl4) \(\lambda_{\text{max}}\): 345, 260 nm; 1H NMR (400 MHz, DMSO-d6) \(\delta\): 3.88 (6H, s, CH₃), 3.9 (6H, s, CH₃), 6.44 (2H, s, CH), 6.51 (1H, s, CH), 7.32 (2H, d, CH, J = 8.4 Hz), 7.34 (2H, d, CH, J = 4.8 Hz), 7.97 (2H, d, CH, J = 8.4 Hz) ppm; 13C NMR (100 MHz, DMSO-d6) \(\delta\): 75.51 (CH₃), 74.36 (CH), 113.5 (CH), 120.29 (C), 128.49 (CH), 130.78 (C), 131 (CH), 158.16 (C), 162.84 (C), 195.65 (CO) ppm; IR (KBr, \(\nu_{\text{max}}\) cm\(^{-1}\)): 3465, 3258 (OH, s), 1645 (CO, s), 1400–1488 (C=C, m), 1667 (==C–H, m); MS (70 Ev, EI) \(m/z = 272 (M^+)\), 255, 137, 135, 107, 77.

#### 2.3.5. Compound (e), 4,4′-dibromo-3,3′-dimethoxybenzoin

**UV** (CCl4) \(\lambda_{\text{max}}\): 325, 280 nm; 1H NMR (400 MHz, DMSO-d6) \(\delta\): 4.83 (1H, s, OH), 6.17 (1H, s, CH), 7.21 (2H, m, CH), 7.37 (2H, d, CH, J = 8.42 Hz), 7.43 (2H, m, CH), 7.5 (2H, d, CH, J = 8.4 Hz) ppm; 13C NMR (100 MHz, DMSO-d6) \(\delta\): 74.36 (CH), 122.27 (C), 122.57 (C), 127.37 (C), 126.78 (CH), 130.84 (CH), 131.65 (CH), 138.14 (C), 195.65 (CO) ppm; IR (KBr, \(\nu_{\text{max}}\) cm\(^{-1}\)): 3396, 3258 (OH, s), 1645 (CO, s), 1400–1488 (C=C, m), 1667 (==C–H, m); MS (70 Ev, EI) \(m/z = 370 (M^+)\), 353, 188, 186, 77.
(2H, d, CH, J = 8.8 Hz), 7.81 (2H, d, CH, J = 8.4 Hz), 10.3 
(2H, s, OH) ppm; 13C NMR (100 MHz, DMSO-d6) δ: 55.874 
(CH3), 56.11 (CH3), 99 (CH), 107 (CH), 118.84 (C), 126.82 
(CH), 155.76 (C), 141 (C), 162.22 (C), 187.57 (CO) ppm; 
IR (KBr, v_{max}, cm⁻¹): 3160-3470 (OH, m), 1270, 7\(\frac{2}{2}\) (CH), 115.34 (CH), 122.50 (C), 126.49 (CH), 128.02 (CH), 
129.43 (CH), 130.17 (CH), 132.96 (CH), 133.27 (C), 138.13 
(C), 139.61 (C), 197.17 (CO) ppm; IR (KBr, v_{max}, cm⁻¹): 
3400 (OH, s), 1650 (CO, s), 1400, 1560 (C=C, m), 1100, 
1280 (C=O, s), 780, 840 (C=H, s); MS (70 Ev, EI) m/z 
= 322 (M⁺ + 2), 320 (M⁺), 185, 135, 77.

2.3.13. Compound (m), 4-methoxybenzoin

UV (CCL₄) λ_{max}: 345, 280 nm; 1H NMR (400 MHz, DMSO-d6) 
δ: 3.78 (3H, s, OCH₃), 4.68 (1H, s, OH), 5.96 (1H, s, CH), 6.85 
(1H, d, CH, J = 8.4 Hz), 7.26 (1H, d, CH, J = 8.4 Hz), 7.31 
(1H, d, CH, J = 8.8 Hz), 7.33 (1H, d, CH, J = 8.0, 7.8 Hz), 
7.91 (2H, t, CH, J = 8.0 Hz) ppm; 13C NMR (100 MHz, DMSO-d6) 
δ: 55.43 (CH₃), 75.77 (CH), 131.92 (CH), 126.26 (C), 127.69 (CH), 128.41 (CH), 131.94 (CH), 139.61 (C), 197.17 (CO) ppm; IR 
(KBr, v_{max}, cm⁻¹): 3430–3520 (OH, m), 1675 (CO, s), 1450, 1600 
(C=C, m), 1120, 1300 (C=O, s), 770, 830 (C=H, s); MS (70 Ev, EI) 
m/z = 242 (M⁺), 135, 107, 77.

3. Results and discussion

Benzen condensation is a well-known synthetic organic reaction 
leading to very attractive a-hydroxy-carbonyls. Liebig in 
1832 first discovered the benzoin condensation catalyzed by 
cyanine salts (Wöhler and Liebig, 1832). Cyanide ion can serve 
four distinct roles, namely, (i) high nucleophilic activity, (ii) 
facilitating the proton transfer, (iii) ability to stabilize the 
negative charge in active aldehyde intermediate, and (iv) ability to 
depart finally (Kankala et al., 2011). Later, Breslow in 1958 first 
recognized that the NHCs could also serve all these roles similar 
to that of cyanide ion in benzoin condensation (Breslow, 
1958), and NHCs are better nucleophiles and leaving groups 
than cyanide (Chan and Scheidt, 2005; Mavis et al., 2010).

In our initial work, the benzoin condensation consists in the 
treatment of an aromatic aldehyde with potassium cyanide, 
usually in aqueous ethanolic solution under ultrasound irradiation 
at 80 °C. By the use of one mole of each of two different aromatic 
aldehydes, it is possible to prepare many unsymmetrical 
benzoins. The reaction is not applicable to all aromatic 
aldehydes. The condensation is affected greatly by the nature 
of the substituents in the aromatic nucleus. Many substituted 
benzaldehydes either do not react or yield products other than 
benzoins. In order that an aldehyde may form a symmetrical 
benzoin it must possess not only a relatively unsaturated car- 
boxyl group but also a mobile hydrogen atom. Two aldehydes, 
either of which forms a symmetrical benzoin, may form an 
unsymmetrical benzoin if one aldehyde is an acceptor and the 
other a donor of a hydrogen atom. Benzaldehyde, which is 
both an acceptor and a donor, readily forms a benzoin. For 
instance, 4-methylaminobenzaldehyde does not form a 
symmetrical benzoin. However, it condenses with benzalde- 
hyde, acting as a donor, to yield an unsymmetrical benzoin 
(i). Benzaldehyde by contrast usually acts as an acceptor when 
it reacts with other aldehyde to form unsymmetrical benzoins. 
Two different aldehydes might be expected to yield a mixture 
of two symmetrical benzoins and unsymmetrical benzoins, 
but only a single unsymmetrical benzoin usually is isolable. 
The second unsymmetrical benzoin may be formed when the 
reactivity of the two aldehydes is similar (Schowen and 
Kuebner, 1971; Buck and Ide, 1932).

The results in Table 1 show that benzoin condensation suc- 
ceeds with relatively good yields compared to the very short
time of reaction. This phenomenon is due to the inadequate diffusion of the ultrasonic waves and heating method. Thereinafter, we considered the effect of imidazolium salts on the benzoin condensation at room-temperature so as to avoid this heating of the system. We found that an imidazolium ion can catalyze the benzoin condensation reaction of benzaldehyde using inorganic base under ultrasonic at room-temperature.

As shown in Table 2, the benzoin reactions of benzaldehyde could be catalyzed by [EtMeIm]Br, [C₆H₄(CH₂ImMe)₂]Br₂ and [C₆Me₃(CH₂ImMe)₃]Br₃ efficiently. The potential of the monocationic, dicaticonic and tricationic imidazolium salts in benzoin condensations was investigated by using 1 mol benzaldehyde as the substrate and 1 mol % of imidazolium salts as the catalyst. To determine the optimum conditions, the use of various bases including potassium carbonate, triethylamine and sodium hydroxide was tested. It was found that NaOH was the best base for the deprotonation of the imidazolium salts in the studied reaction. The trisimidazolium and bisimidazolium salts needed shorter reaction times and gave higher yields than the monocationic salts and cyanide ion. This can be interpreted as a result of the increased number of active centers which could enhance the catalytic activity. Different salt concentrations were also examined for all of the catalysts. The results are summarized in Table 2, and show that 1 mol % of the catalyst gave the best results in terms of the percentage yield and short reaction times.

In this Letter, we showed that the use of low-frequency ultrasound is of great interest in performing benzoin condensation. N,N'-Dialkyl imidazolium bromide can be used as a very efficient catalyst for this reaction and ultrasound is an adequate activation method to break the problematic thermal heating method.
4. Conclusion

In this paper, we have developed the catalytic potential of imidazolium salts and cyanide ion in the benzoin condensation under ultrasound irradiation at room temperature and heating method respectively. The imidazolium salts needed shorter reaction times and gave higher yields than the monocatic ions and cyanide ion. This procedure can be used as a replacement for conventional thermal synthetic methodology, allowing rapid access for the synthesis of natural and pharmaceutica compounds.

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