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Benzoin reaction in water as an aqueous medium catalyzed by benzimidazolium salt

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Abstract—Benzoin reactions are catalyzed by *N*,*N*-dialkylbenzimidazole to yield α-hydroxy ketones; the reaction proceeds in water as an aqueous medium under mild conditions. The utility of these salts as pre-catalysts in these reactions has been demonstrated.
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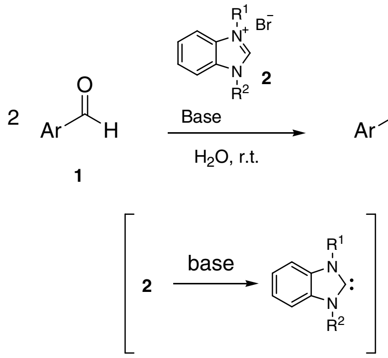
Recently, *N*-heterocyclic carbenes have received considerable attention in the catalysis of organic reactions.[1] There have been several reports dealing with carbene-catalyzed reactions due to their ability to produce acyl anion equivalents.[2] This feature has been successfully exploited in numerous catalytic reactions. The α-hydroxycarbonyl group is an important synthon for the synthesis of natural products, industrial materials, and pharmaceutical materials. Among the numerous synthetic strategies for introducing this moiety, the benzoin reaction and related additions remain, perhaps, the most direct. The benzoin reaction is catalyzed by the toxic cyanide ion in its traditional form.[3] Several nucleophilic carbenes are derived from heterocyclic compounds including thiazole,[4] triazole,[5] and imidazole,[6] which are also employed in this reaction as acyl anion synthons.

Breslow and Kool[7] reported the effect of inorganic salts on the rate of the cyanide-catalyzed benzoin reactions in aqueous media. The reaction is 200 times faster in water than in ethanol. Recently, the use of aqueous media in organic reactions has been extensively investigated for synthesis and also for exploiting hydrophobic effect.[8]

In our initial work,[9] the benzoin reaction was found to proceed efficiently when 1,3-dimethylbenzimidazolium iodide was employed as pre-catalyst in THF or methanol under basic condition. In another study, a simple 1-*N*-alkyl-3-methylimidazolium salt was demonstrated to catalyze the benzoin reaction via a carbene intermediate.[10] However, these pre-catalysts were ineffective for the benzoin reaction in water as an aqueous medium. However, we found that 1,3-dipropylbenzimidazolium bromide **2a** catalyzed the benzoin reaction in the presence of triethylamine (TEA) in water in 43% yield. This result encouraged us to investigate the limit and scope of benzimidazolium salts as pre-catalysts for the benzoin reaction in water.

We report herein that *N*-heterocyclic carbenes derived from benzimidazolium salts with one or two long aliphatic side chains at the nitrogen atoms in the imidazole ring catalyze the benzoin reaction to give α-hydroxy ketones **3** in water as an aqueous medium in moderate to excellent yields (Scheme 1).



Scheme 1. Benzoin reaction catalyzed by benzimidazolium salts **2** in water.

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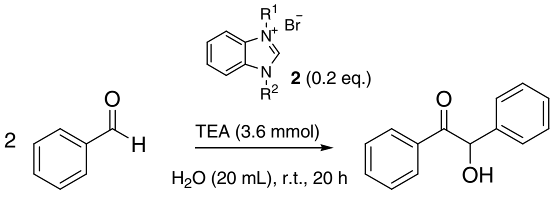


1a (20 mmol) **3a**

Scheme 2. Benzoin reaction of **1a** catalyzed by benzimidazolium salts **2** in water.

Table 1. Benzoin reaction catalyzed by benzimidazolium salts (**2a**–**g**) in the presence of TEA in water

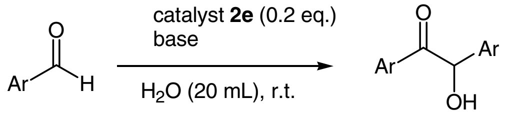
Catalyst			Yield (%)	**1a**: Recovery (%)
2	R^1	R^2		
a	$(CH_2)_2Me$	$(CH_2)_2Me$	43	22
b	Me	$(CH_2)_2Me$	45	15
c	Me	$(CH_2)_3Me$	76	—
d	Me	$(CH_2)_{11}Me$	99	—
e	$(CH_2)_{11}Me$	$(CH_2)_{11}Me$	98	—
f	Me	Me	—	80
g	Et	Et	—	73

First, we examined the benzoin reaction of benzaldehyde **1a** in water with benzimidazolium salts **2** in the presence of triethylamine (TEA) as a base; the reaction produces *N*-heterocyclic carbenes from benzimidazolium salt (Scheme 2). The results are summarized in Table 1. Pre-catalysts **2a**–**g** were easily prepared from benzimidazole with a suitable alkyl halide in the usual manner.

From the results, with an increase in the number of the carbon atoms of the N-substituent, it is clear that the benzoin yield improved. Between the two N-substituents of the benzimidazole ring, a good correlation is observed between the number of carbon atoms of the longer substituent and the benzoin yield. Based on the result, one of the important factors that contribute to the construction of the reaction field in an aqueous medium is considered to be a hydrophobic long N-alkyl chain. The hydrophobic tails in the pre-catalyst certainly play an important role in the micelle formation.

The preparation of various benzoins **3** by the self-condensation of aromatic aldehydes **1** catalyzed by benzimidazolium salt **2e** was examined (Scheme 3).[11]

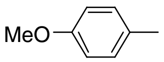
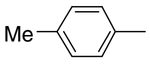
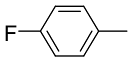
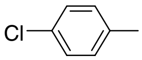
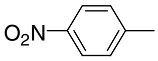
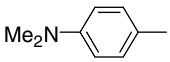
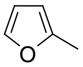
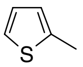
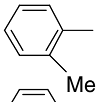
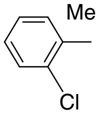
The results are summarized in Table 2. In the presence of **2e**, the benzoin reaction of fluoro, chloro, methyl, and methoxy *para*-substituted benzaldehydes proceeded to give the corresponding benzoins **3** in good yields, as shown in Table 2. The reaction of *p*-nitrobenzaldehyde **1f**, possessing a strong electron-accepting group, and *p*-*N*,*N*-dimethyl-aminobenzaldehyde **1g**, possessing a strong electron-donating group, failed to proceed in a manner similar to that with the cyanide ion.[12] In the case of *ortho*-substituted benzaldehydes **1j** and **k**, the reaction proceeded with difficulty in comparison with that of the *para*-substituted benzaldehydes because of the steric hindrance, although benzoins were obtained in low yields.



1b - k **3b - k**

Scheme 3. Benzoin reaction catalyzed by benzimidazolium salts **2e** in water.

Table 2. Benzoins **3b**–**k** prepared by the self-condensation of aromatic aldehydes **1b**–**k** (20 mmol) in the presence of pre-catalyst **2e** in water

1	Ar	Base[a]	Time (h)	Yield (%)
b		TEA DBU NaOH	20 20 20	39 79 76
c		TEA	20	70
d		TEA DBU	3 3	71 91
e		TEA	20	81
f		TEA DBU	20 20	— —
g		TEA DBU	20 20	— —
h		DBU	2	78
i		DBU	1	62
j		DBU	30	43
k		TEA	30	38

[a] TEA: 3.6 mmol, DBU: 3.3 mmol, NaOH: 12.5 mmol.

The variation of the base required for the formation of the carbene was also investigated. In this benzoin reaction, TEA (p*Ka*; 10.7), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (p*Ka*; 12.0), and NaOH were employed as bases. TEA and DBU were effective for deprotonating the benzimidazolium salt in a self-condensation reaction involving various aromatic aldehydes. NaOH was also found to be effective. However, in the case where NaOH is employed in a benzoin reaction in THF, it has been reported that NaOH tends to cause the benzoins formed in the reaction to precipitate as their sodium salts retards any further reaction.[13] In our examination, NaOH proved to be an excellent base, and there was no indication that the reaction was retarded by NaOH under our reaction conditions.

Next, we examined the turnover numbers (TONs) of **2e** in the self-condensation of **1a** (20 mmol) in water

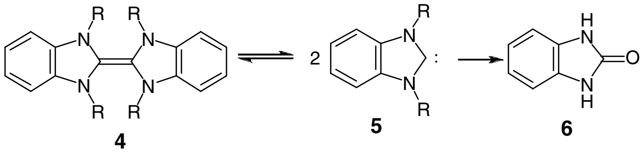
Table 3. TONs of 1,3-didodecylbenzimidazolium pre-catalyst **2e** in the self-condensation reaction of **1a** in water

2e (mmol)	**3a**: Yield (%)	**1a**: Recovery (%)	Turnover
0.02	—	77	—
0.04	—	94	—
0.06	68	13	113
0.1	98	Trace	98
0.2	96	Trace	48

(20 ml). In this reaction, NaOH (12.5 mmol) was employed as the base. The results are summarized in Table 3. The benzoin reaction proceeded quantatively in the case of 5 mol % loaded pre-catalyst **2e**. Low loading (0.3 mol %) of **2e** resulted in a 68% yield of benzoin **3a** and 13% recovery of **1a**. Moderate TONs suggest that the partial decomposition of a pre-catalyst proceeds concomitantly to yield an inactive catalyst. The so-called 'Wanzlick equilibrium'[14] demonstrates that benzimidazolium salts having sterically less demanding substituents like methyl or ethyl moieties favor the formation of tetraaminoethylene **4**, whereas sterically demanding substituents shift the equilibrium toward free carbene **5**. This report suggests that benzimidazolium salt **2e** tends to exist as a free carbene and hence the free carbene is likely to oxidize during a long reaction time (Scheme 4). In fact, the oxidized compound 1*H*-benzo[*d*]imidazol-2(3*H*)-one **6** was obtained from the reaction mixture of the benzoin reaction where pre-catalyst **2e** was used in water. The precise mechanism of the deactivation mechanism of the catalyst was not investigated.

The reusability of pre-catalyst **2e** in water was briefly investigated. The filtrate, obtained as described in a typical procedure for benzoin reactions[11] was recycled. The filtrate containing catalyst was employed for the next reaction. In this reaction, NaOH was employed as the base. The results are summarized in Table 4.

In conclusion, we have presented the first benzoin reaction in water as an aqueous medium, catalyzed by *N*-heterocyclic carbenzenes derived from the benzimidazolium salts with one or two long aliphatic side chains at the nitrogen atoms. α-Hydroxy ketones are obtained throughout in moderate to excellent yields without further purification. These catalysts are easy to prepare, stable, and easy to handle. Benzimidazolium salt **2e** is currently the most efficient pre-catalyst for the synthesis of α-hydroxy ketones in aqueous media under mild basic conditions. Moreover, its utility aparently increases from the viewpoint of green chemistry. This provides a new insight for the catalytic utility of benzimidazolium salts.



Scheme 4. The 'Wanzlick equilibrium' and the formation of 1*H*-benzo[*d*]imidazol-2(3*H*)-one **6** as deactivated pre-catalyst **2e**.

Table 4. Reuse of pre-catalyst **2e** (4 mmol) in the benzoin reaction of **1a** (20 mmol) in the presence of NaOH (12.5 mmol)

Reuse number	Time (h)	**3a**: Yield (%)
0	3	99
1	3	99
2	17	92
3	72	85

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11. *Typical procedure for benzoin reactions catalyzed by benzimidazolium salts, as exemplified for using* **2e** *as the pre-catalyst*: Benzaldehyde **1a** (2.12 g, 20.0 mmol) was added water (20 mL). To the mixture was added *N*,*N*-dialkylbenzimidazolium pre-catalyst **2e** (4.0 mmol) and 0.5 mL of triethylamine (3.6 mmol) was added under vigorous stirring. The reaction mixture was stirred for 20 h at room temperature. Benzoin **3a** was filtered, washed with water, and dried in open air. In the case of unsatisfied purity, the purification by column chromatography (SiO_2, hexane–AcOEt = 5:1) was employed.
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