Methylene-bridged bis(benzimidazolium) salt as a highly efficient catalyst for the benzoin reaction in aqueous media

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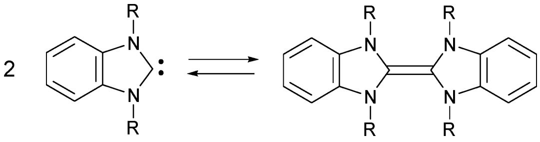
Benzoin reactions are catalyzed effectively by a methylene-bridged bis(benzimidazolium) salt to yield α-hydroxy ketones, and the reactions proceed in water as the aqueous medium under mild conditions.

Introduction

Since the discovery of stable carbenes in the last decade of the 20th century, *N*-heterocyclic carbenes (NHCs) have recently been receiving considerable attention for the catalysis of organic reactions.[1] Many reports on carrying out carbene-catalyzed reactions have been prepared, due to their ability to produce acyl anion equivalents.[2] This feature has been successfully exploited in numerous catalytic reactions, and NHCs also serve as nucleophilic catalysts in several important reactions such as the Stetter reaction,[3] the transesterification of alcohols,[4] and the cyanosilylation of aldehydes.[5] The α-hydroxycarbonyl group is an important synthon for the synthesis of natural products, industrial materials, and pharmaceutical materials. Among numerous synthetic strategies for introducing this moiety, the benzoin reaction and related additions are perhaps the most direct. Several nucleophilic carbenes derived from heterocyclic compounds have also been employed in this reaction as acyl anion synthons.[6] Unfortunately, these systems generally rely on high catalyst loading and frequently require long reaction times. Recently, the stability of the NHCs in water has been reported[7] and the importance of using NHCs for catalytic applications in water means they are beginning to play the catalytic roles in a number of catalytic processes. The use of water instead of organic solvents as a reaction medium is another approach to developing novel synthetic methodologies. Reports on aqueous reactions have become increasingly frequent; now, organic reactions in water have become one of the most exciting research fields.[8] Unique reactivity and selectivity that cannot be achieved under dry conditions are often observed in aqueous reactions due to the hydrophilic properties of water.[9] Carrying out reactions under aqueous conditions also provides advantages such as reduced pollution, lower costs, and greater simplicity in processing and handling. These factors are particularly important in an industry aiming at green and sustainable chemistry.

We have published[10] the benzoin reaction of benzaldehyde, and it is found that this reaction proceeds smoothly in water as the aqueous medium when *N,N*-didodecylbenzimidazolium salt and a base are employed. The precatalyst, with a base, catalyzes the benzoin reaction in water in 99% yield after 20 h at room temperature. This result indicates that the NHC derived from a benzimidazolium salt with long aliphatic side chains on the nitrogen atoms in the imidazole ring is effectively stabilized in water and plays an important role in micelle formation.

These results have motivated us to obtain more efficient precatalysts for the benzoin reaction in water as the aqueous medium. In our attempts to develop new precatalysts for the benzoin reaction in aqueous media, the key point is the construction of a more effective hydrophobic field in water. Therefore, we have focused on the equilibrium of carbene–ylid. The so-called "Wanzlick equilibrium"[11] demonstrates that benzimidazolium salts with sterically less demanding substituents such as methyl or ethyl moieties favor the formation of a tetraaminoethylene body, whereas sterically demanding substituents shift the equilibrium toward the free carbene (Scheme 1).



Scheme 1 The "Wanzlick equilibrium" of carbene–ylid.

Results and discussion

Based on the above report, we have designed and synthesized the methylene-bridged bis(benzimidazolium) salt **1a** as a novel precatalyst in the benzoin reaction. The treatment of **1a** with a base yields dicarbene **2**. Dicarbene **2** is expected to function as the constructor of the hydrophobic field in water. Moreover, based on the "Wanzlick equilibrium", dicarbene **2** is expected to form a more effective hydrophobic reaction field in an aqueous medium when tetraaminoethylene **3** is generated (Scheme 2). Starting from *N*-methylbenzimidazole, precatalyst **1a** is prepared easily by refluxing with 1,12-dibromododecane in acetonitrile in good yield.

First, we examined the benzoin reaction of benzaldehyde in water with the methylene-bridged bis(benzimidazolium) salt **1a** in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (pK_a; 12.0) as the base. Benzaldehyde (10 mol) was added to the solution of precatalyst **1a** (20 mol%) in 10 mL of H_2O, and DBU (40 mol%) was added to the resultant emulsion at room temperature with vigorous stirring. As a result, the benzoin was obtained in an almost quantitative yield within 15 min (Scheme 3).

In comparison with the previously reported 1,3-didodecylbenzimidazolium bromide,[10] which is found to be a good precatalyst for the benzoin reaction in water, it becomes clear that

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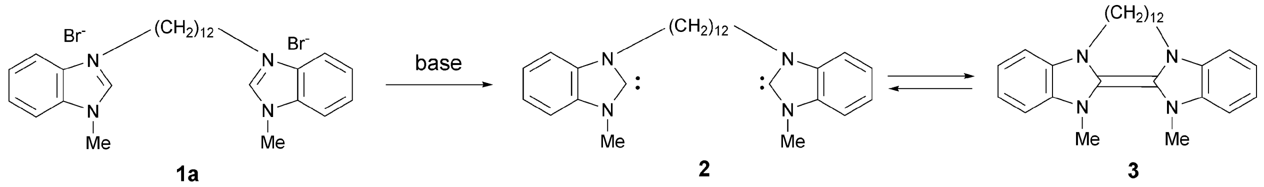
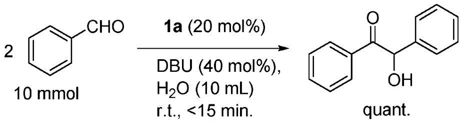
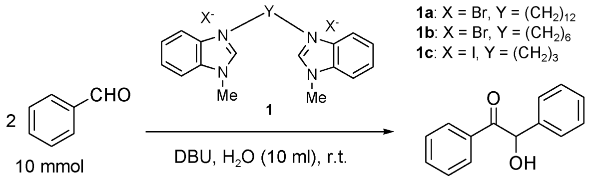


Scheme 2 Methylene-bridged bis(benzimidazolium) salt **1a** and the "Wanzlick equilibrium" of dicarbene **2** derived from **1a**.



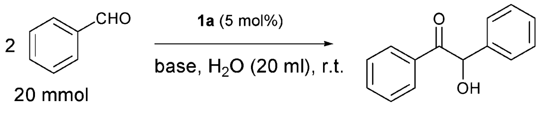
Scheme 3 Benzoin reaction catalyzed by the methylene-bridged bis(benzimidazolium) salt **1a** in water.

Table 1 Benzoin reaction catalyzed by methylene-bridged bis-(benzimidazolium) salts in aqueous medium



Catalyst						
1	X	Y	Cat. (mol%)	DBU (mol%)	Time/h	Yield (%)
a	Br	$(CH_2)_{12}$	20	60	0.5	100
a	Br	$(CH_2)_{12}$	2	6	24	91
b	Br	$(CH_2)_6$	20	60	1.5	71
b	Br	$(CH_2)_6$	2	6	24	50
c	I	$(CH_2)_3$	20	60	1.5	59
c	I	$(CH_2)_3$	2	6	24	11

Table 2 Comparison of the base employed in the benzoin reaction catalyzed by a methylene-bridged bis(benzimidazolium) salt **1a** in water



Base[a]	Time/h	Yield (%)
DBU	1.5	97
DBU	24	93
TEA	1.5	34
TEA	24	95
NaOH	24	93

[a] DBU: 0.75 mmol, TEA: 1.5 mmol, NaOH: 0.75 mmol.

Table 3 Catalytic loading of **1a** with a base in the self-condensation reaction of benzaldehyde in water

Base	Cat. **1a** (mol%)	Time/h	Yield (%)
DBU	20	1.5	100
DBU	5	1.5	97
DBU	3	1.5	86
DBU	2	2.5	68
DBU	2	24	91
DBU	1	8	40
DBU	1	24	46
TEA	5	24	95
TEA	2	24	94
TEA	1	24	89
TEA	0.5	36	92
TEA	0.3	48	84

the new methylene-bridged bis(benzimidazolium) salt **1a** is able to accelerate the reaction rate and act as a powerful precatalyst for the benzoin reaction in water as the aqueous medium.

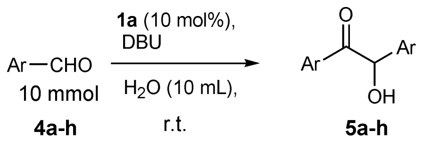
Next, we examined the influence of the length of the methylene bridge in the precatalyst **1** against the catalytic activity for the benzoin reaction in pure water. To compare the effects of the length of the methylene bridge, (hexane-1,6-diyl)- and (1,3-propan-diyl)bisbenzimidazolium salts[12] were examined. The results are summarized in Table 1. From the results, it is clear that the benzoin yield improved with an increase in the number of carbon atoms of the methylene bridge. The hydrophobic part of the precatalyst certainly plays an important role in the formation of the hydrophobic field.

The variation in the base required for the formation of the dicarbene was also investigated. In this benzoin reaction, DBU, TEA (pK_a; 10.7), and NaOH were employed as bases (Table 2). They were effective at deprotonating the methylene-bridged bis(benzimidazolium) salt in a self-condensation reaction. The superiority of **1a** in the benzoin reaction in water is also proved in the catalytic loading as shown in Table 3. A low loading (0.3 mol%) of **1a** with TEA resulted in 84% yield of benzoin. In the case of 0.5 mol% loaded precatalyst **1a** with TEA, the benzoin reaction proceeded in an almost quantitative yield. In contrast, when precatalyst **1a** was used with DBU, a low loading (1 mol%) of **1a** resulted in a decrease in the yield of benzoin. This appears to indicate that a strong base such as DBU causes the partial decomposition of **1a**. The precise mechanism of the deactivation of the catalyst was not investigated.

The preparation of various benzoins by the self-condensation of aromatic aldehydes catalyzed by **1a** was examined. The results are summarized in Table 4. In the presence of **1a** and DBU, the condensation of fluoro (**4a**), chloro (**4b**), bromo (**4c**), methoxyl (**4d**), and methyl (**4e**) *para*-substituted benzaldehydes proceeded to give the corresponding benzoins in good yields. Similar results were obtained in the self-condensation reaction of arenecarbaldehydes furan-2-carbaldehyde (**4f**), thiophene-2-carbaldehyde (**4g**) and naphthalene-1-carbaldehyde (**4h**).

The reusability of precatalyst **1a** in water was briefly investigated. In the general procedure of this reaction system, benzoin was obtained by filtration followed by washing with water several times. The filtrate obtained from the benzoin reactions was recycled. The resulting catalyst-containing filtrate was subject to the next run of the benzoin reaction by charging with the

Table 4 Benzoins **5a–h** prepared by the self-condensation of aromatic aldehydes **4a–h** in the presence of precatalyst **1a** in water



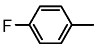
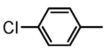
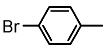
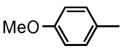
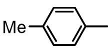
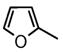
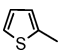
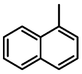
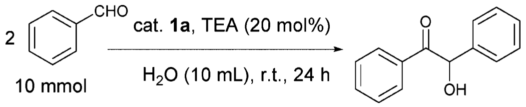
Aldehyde			
4	Ar	Time/h	5a; yield (%)
a		1.5	95
b		20	80
c		20	81
d		1.5	83
e		1.5	83
f		1.5	86
g		1.5	79
h		20	65

Table 5 Reuse of precatalyst **1a** in the benzoin reaction of benzaldehyde in the presence of TEA



Reuse number	Yield (%)
0	100
1	97
2	86
3	68
4	91
5	40

benzaldehyde under the same conditions. In this reaction, TEA was employed as the base. The results are summarized in Table 5. These results indicate that precatalyst **1a** is reusable for a moderate number of recyclings. However, an increase in the number of reuses causes a decrease in the yield of benzoin. The current challenge is to obtain an increase in the number of reuses that are effective.

Conclusions

In conclusion, we have presented a highly efficient benzoin reaction in water as an aqueous medium catalyzed by the dicarbene derived from the long chain methylene-bridged bis(benzimidazolium) salt. Benzoin is obtained in moderate to excellent yields for various combinations of precatalyst **1a** and base, without further purification. Precatalyst **1a** is easy to prepare, stable, and easy to handle. Moreover, **1a** is efficient for the synthesis of α-hydroxy ketones derived from various aromatic aldehydes in aqueous media under mild basic conditions. In these cases, the use of organic solvents as cosolvents is not required in order to overcome the low solubility of the substrates in pure water. The superior characteristic that must be mentioned specially is the acceleration of the reaction rate of the benzoin reaction in water even when the precatalyst is loaded in low volume. This unique characteristic proves that an efficient hydrophobic reaction field is constructed in water. Its utility also apparently increases from the viewpoint of green and sustainable chemistry. Considering these results, it can be thought that precatalyst **1a** is an interesting and exciting candidate for the development of catalysts for new C–C bond formation reactions due to its ability to produce acyl anion equivalents in water as an aqueous medium.

Experimental

NMR spectra were recorded on a JOEL ECA-500 (^{1}H at 500 MHz and ^{13}C at 126 MHz) NMR spectrophotometer. Chemical shifts are expressed in ppm downfield from Me_4Si (^{1}H, $\delta = 0.00$) as an internal standard, and coupling constants are reported in Hz. Routine monitoring of reactions was performed by TLC, using Kieselgel 60 F_{254} precoated aluminium sheets, commercially available from Merck. IR spectra were recorded on a Shimadzu IR Prestige-21. FAB mass spectra were recorded on a JEOL JMS-700 spectrometer. Column chromatography was performed with silica gel 60 N (Kanto). Melting points were recorded on a Yazawa BY-1 and were uncorrected.

1,12-Bis((1-methylbenzimidazolium)-3-yl)dodecane dibromide (1a)

N-Methylbenzimidazole (6.6 g, 50 mmol) was dissolved in acetonitrile (100 mL) and to the solution was added 1,12-dibromododecane (8.4 g, 25 mmol). The mixture was refluxed for 24 h. After cooling, the solvent was evaporated under reduced pressure and the residue was recrystallized to give **1a** (12.5 g, 84%). ^{1}H-NMR (DMSO-d_6): 9.72 (2H, s), 8.02 (4H, m), 7.68 (4H, m), 4.45 (4H, t, $J = 6.9$ Hz), 4.06 (6H, s), 1.86 (4H, m), 1.24 (16H, m); ^{13}C-NMR (DMSO-d_6): 142.70, 131.92, 131.05, 126.58, 113.72, 113.60, 46.63, 33.35, 29.07, 28.98, 28.75, 28.64, 25.87; IR (neat): 2920, 1571, 1465, 1355 (cm^{-1}); FAB-MS: 511 [M − Br]$^+$; Mp: 193–194 °C.

1,6-Bis((1-methylbenzimidazolium)-3-yl)hexane dibromide (1b)

N-Methylbenzimidazole (6.6 g, 50 mmol) was dissolved in acetonitrile (100 mL) and to the solution was added 1,6-dibromohexane (6.1 g, 25 mmol). The mixture was refluxed for 28 h. After cooling, the solvent was evaporated under reduced pressure and the residue was recrystallized to give **1b** (10.2 g, 81%). ^{1}H-NMR (DMSO-d_6): 9.77 (2H, s), 8.04 (4H, m), 7.69 (4H, t, $J = 3.2$ Hz), 4.48 (4H, t, $J = 6.9$ Hz), 4.07 (6H, s), 1.97 (4H, m), 1.37 (4H, s); ^{13}C-NMR (DMSO-d_6): 142.87, 132.07, 131.18, 126.75, 113.89, 113.75, 46.68, 33.52, 28.70, 25.49; IR (neat): 2929, 1570, 1456, 1271, 1220 (cm^{-1}); FAB-MS: 427 [M − Br]$^+$; Mp: 283–285 °C.

Typical procedure for the benzoin reaction catalyzed by methylene-bridged bis(benzimidazolium) salt 1

Benzaldehyde (2.12 g, 20.0 mmol) was added to water (20 mL). To the mixture was added methylene-bridged bis(benzimidazolium) salt **1** and an appropriate base was added. The reaction mixture was stirred vigorously at room temperature. The benzoin was filtered, washed with water and dried in the open air. In the case of unsatisfactory purity, purification by column chromatography (SiO_2, hexane–AcOEt = 5 : 1) was employed.

Typical procedure for the self-condensation of aromatic aldehyde (4) catalyzed by 1,12-bis((1-methylbenz-imidazolium)-3-yl)-dodecane dibromide (1a)

Aromatic aldehyde **4** (10.0 mmol) was added to water (10 mL). To the mixture was added **1a** (10 mol%) and DBU (20 mol%) was added. The reaction mixture was stirred vigorously at room temperature. The benzoin **5** was filtered, washed with water and dried in the open air. In the case of unsatisfactory purity, purification by column chromatography (SiO_2, hexane–AcOEt = 5 : 1) was employed.

The structures of the benzoins **5a**, **5c** were confirmed by comparison of their spectral data with those reported in the literature.[13] The structures of the benzoins **5b**, **5d–h** were confirmed by spectral data, and by comparison of the melting points with those of authentic samples reported in the literature.[14]

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