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An investigation of the catalytic potential of mono- and dicationic imidazolium N-heterocyclic carbenes in the benzoin condensation

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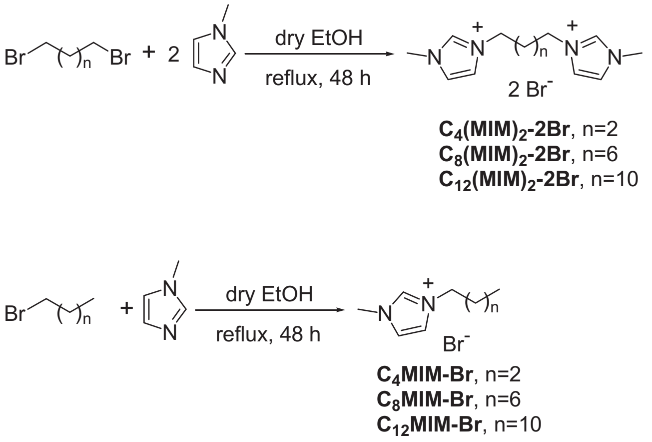
ABSTRACT

The catalytic potential of imidazolium salts in the benzoin condensation was investigated. Various aromatic aldehydes were tested in the benzoin condensation under the optimised protocol to afford α-hydroxyketones using N-heterocyclic carbenes derived from mono- and dicationic imidazolium salts. The products were obtained in good yields within short reaction times. Dicationic imidazolium salts with a long aliphatic chain between the imidazole rings were found to be more effective pre-catalysts for the benzoin condensation in comparison to the corresponding monocationic salts having the same aliphatic chain length.

N-Heterocyclic carbenes (NHCs) have attracted considerable interest in recent years as effective organocatalysts. They are generated in situ from azolium salts such as thiazolium, imidazolium and triazolium salts in the presence of weak bases and are used successfully in important reactions.[1] 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.[2] The key step of the reaction is a polarity inversion of the electrophilic carbonyl carbon. Traditionally, umpolung at the carbonyl carbon in the benzoin condensation is accomplished by using toxic cyanide anions. After the first report by Ukai,[3] who used thiamine as a pre-catalyst, various NHCs have been used to promote the reaction effectively. The use of pre-catalysts such as thiazolium, triazolium, imidazolium and benzimidazolium 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.[4]

Dicationic imidazolium salts have been investigated widely for their ionic liquid[5] and complex formation[6] properties, but, as far as we know, there are few reports on the use of dicationic azolium salts as pre-catalysts in benzoin condensation.[7] Hence, our interest focused on an investigation of the effect of dicationic NHCs in this reaction. This paper describes the use, for the first time, of dicationic imidazolium salts with long aliphatic chains between the imidazolium rings as NHC precursors in the acyloin condensation. These dicationic imidazolium salts show considerable catalytic potential when compared with monocationic imidazolium salts with long aliphatic chains, and they are also important for green chemistry.

Mono-[C_nMIM-Br] and dicationic [$C_n(MIM)_2$-2Br] imidazolium salts were obtained by refluxing *N*-methylimidazole with mono- and dibromoalkanes in dry EtOH for 48 h according to the literature procedure[8] (Scheme 1). The structures of the products were determined from their spectroscopic data which was in accord with those in the literature.[5a–c,8] The dicationic imidazolium salt [$C_6(BzIM)_2$-2Br] was prepared as a new chiral salt from 1-[(1*S*)-1-



Scheme 1. Synthesis of the mono- and dicationic imidazolium salts.

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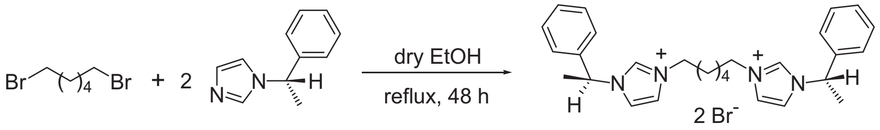
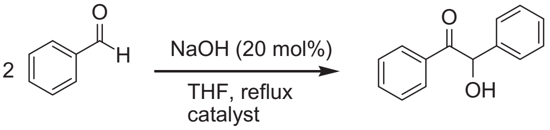


$C_6(BzIM)_2$-2Br

Scheme 2. Synthesis of 1,6-bis[3-(1*S*)-1-phenylethylimidazolium-1-yl]hexane dibromide.

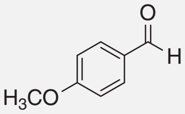
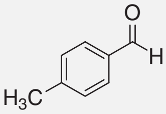
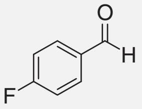
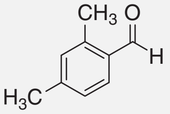
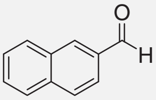
Table 1
Comparison of the catalytic activities of 1,*n*-bis(3-methylimidazolium-1-yl)alkane dibromides [$C_n(MIM)_2$-2Br] and 1-methyl-3-alkyl-1*H*-3-imidazolium bromides [C_nMIM-Br]



Catalyst (mol %)	Time (min)	Yield[a] (%)	Catalyst (mol %)	Time (min)	Yield[a] (%)
$C_4(MIM)_2$-2Br (1.0)	24	82	C_4MIM-Br (1.0)	31	76
$C_4(MIM)_2$-2Br (0.5)	45	73	C_4MIM-Br (0.5)	50	65
$C_4(MIM)_2$-2Br (0.25)	67	67	C_4MIM-Br (0.25)	72	63
$C_4(MIM)_2$-2Br (0.1)	75	61	C_4MIM-Br (0.1)	84	54
$C_4(MIM)_2$-2Br (0.05)	91	55	C_4MIM-Br (0.05)	103	46
$C_8(MIM)_2$-2Br (1.0)	19	86	C_8MIM-Br (1.0)	27	78
$C_8(MIM)_2$-2Br (0.5)	39	78	C_8MIM-Br (0.5)	42	71
$C_8(MIM)_2$-2Br (0.25)	56	73	C_8MIM-Br (0.25)	66	69
$C_8(MIM)_2$-2Br (0.1)	68	63	C_8MIM-Br (0.1)	75	57
$C_8(MIM)_2$-2Br (0.05)	87	58	C_8MIM-Br (0.05)	101	54
$C_{12}(MIM)_2$-2Br (1.0)	15	96	C_{12}MIM-Br (1.0)	21	84
$C_{12}(MIM)_2$-2Br (0.5)	27	82	C_{12}MIM-Br (0.5)	33	79
$C_{12}(MIM)_2$-2Br (0.25)	38	77	C_{12}MIM-Br (0.25)	45	72
$C_{12}(MIM)_2$-2Br (0.1)	57	68	C_{12}MIM-Br (0.1)	64	65
$C_{12}(MIM)_2$-2Br (0.05)	74	62	C_{12}MIM-Br (0.05)	87	53

[a] Isolated yield.

Table 2
Synthesis of the acyloins

Aldehyde	$C_4(MIM)_2$-2Br		$C_8(MIM)_2$-2Br		$C_{12}(MIM)_2$-2Br	
	Time (min)	Yield[a] (%)	Time (min)	Yield[a] (%)	Time (min)	Yield[a] (%)
	155	65	135	75	120	82
	215	72	190	77	170	84
	200	80	165	85	125	90
	230	65	200	72	180	79
	100	76	85	87	60	95

[a] Isolated yield.

phenylethyl]-1*H*-imidazole which was itself rapidly obtained from (*S*)-α-methylbenzylamine (Scheme 2) using the literature procedure.[9] The structure of this compound was established from its IR and ^{1}H NMR spectra as well as by elemental analysis.[10]

The potential of the dicationic imidazolium salts in benzoin condensations was investigated by using benzaldehyde as the substrate and 1 mol % of $C_8(MIM)_2$-2Br as the catalyst. To determine the optimum conditions, the use of solvents such as acetonitrile, THF and dichloromethane, and various bases including potassium carbonate, triethylamine and sodium hydroxide was tested. It was found that THF was the best solvent with respect to the reaction rate, and NaOH was the best base for the deprotonation of the dicationic imidazolium salts in the studied reaction. Although it had been reported[5d] that NaOH causes precipitation of the acyloins formed in the reaction as their sodium salts and retards further reaction, in our study the formed benzoin remained in solution in all our experiments. Under the same conditions, the $C_4(MIM)_2$-2Br salt gave a lower yield with a longer reaction time, whereas $C_{12}(MIM)_2$-2Br gave the highest yield and the shortest reaction time. Monocationic imidazolium salts with the same aliphatic chain length (C_nMIM-Br) were also investigated as pre-catalysts for comparison with their dicationic analogues. The bisimidazolium salts needed shorter reaction times and gave higher yields than the monocationic salts. This can be interpreted as a result of the increased number of active centres which could enhance the catalytic activity. Different salt concentrations were also examined for all of the catalysts. The results are summarised in Table 1, and show that 1 mol % of the catalyst gave the best results in terms of the percentage yield and short reaction times. The activity of the bisimidazolium salts was also investigated for the benzoin condensation of several aromatic aldehydes. In these reactions, 1 mol % of the catalyst was used[11] and it was observed that the yields and reaction times were reasonably good (Table 2).

The chiral salt, $C_6(BzIM)_2$-2Br, was also investigated for the benzoin condensation of benzaldehyde (80% yield, 100 min) and *p*-methylbenzaldehyde (74% yield, 120 min) to investigate its catalytic and enantiomeric induction potential. Although the yields and reaction times were good, the products did not show any optical activity.

In conclusion, dicationic imidazolium salts with long aliphatic chains between the imidazole rings were found to be more effective pre-catalysts for the benzoin condensation in comparison with the monocationic salts having the same aliphatic chain length. The condensation yields and reaction times improve with an increase in the number of carbon atoms between the *N*-atoms. These catalysts can be easily prepared and handled, they are stable, and their use instead of toxic cyanide ions is important from the viewpoint of green chemistry.

Acknowledgement

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10. *Spectroscopic data for $C_6(BzIM)_2$-2Br*: IR (neat): ν 3030, 2981, 2935, 2859, 1652, 1536, 1495, 1454, 1382, 762, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.32–1.41 (m, 4H, CH_2), 1.79–1.97 (m, 4H, CH_2), 1.96 (d, J = 7.2 Hz, 6H, CH_3), 4.22–4.27 (m, 4H, N–CH_2), 5.78–5.83 (q, J = 7.2 Hz, 2H, CH), 7.28–7.47 (m, 10H, ArH), 7.53 (br s, 2H, ArH), 7.64 (br s, 2H, ArH), 9.07 (s, 2H, ArH) ppm. Anal. Calcd for $C_{28}H_{36}Br_2N_4$ (588.41): C, 57.15; H, 6.17; N, 9.52. Found: C, 56.98; H, 6.32; N, 9.60.
11. *Typical procedure for a benzoin condensation*: To a solution of the aldehyde (1 mmol) in THF (25 mL), the catalyst (1 mol %) and NaOH (20 mol % in 3 mL of H_2O) were added, and the mixture was heated under reflux for the appropriate amount of time to complete the reaction, as indicated by TLC. After solvent evaporation, the resulting solid was dissolved in H_2O, and extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extract was dried ($MgSO_4$), and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc) or recrystallized from EtOH.