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Mukaiyama aldol reaction using ketene silyl acetals with carbonyl compounds in ionic liquids

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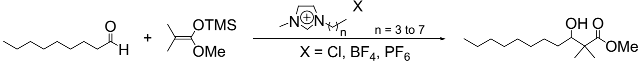
Abstract—Mukaiyama aldol reactions using ketene silyl acetals with various aldehydes proceed smoothly in ionic liquids to afford the corresponding aldol products in moderate yields.

The Mukaiyama aldol reaction is one of the most important reactions in organic synthesis.[1,2] Although the Mukaiyama aldol reaction has been extensively studied, the Mukaiyama aldol reaction at ambient temperature in the absence of Lewis acid catalysis or any special activation continues to pose a great challenge for organic chemists.[3] Recently our group has developed a water-accelerated Mukaiyama aldol reaction using ketene silyl acetals.[3d] Using this method, Mukaiyama aldol reactions can proceed in water at ambient temperature without any Lewis acid catalysis or special activation to afford the corresponding aldol products in moderate to good yields. However, this reaction only works with reactive aldehydes. No reaction was observed with aliphatic aldehydes. Therefore, a more general method that could work with a wide variety of aldehydes is highly desirable. In this paper, we report Mukaiyama aldol reactions in ionic liquids, which proceeded smoothly with various aldehydes including aliphatic aldehydes at ambient temperature without Lewis acid catalysis or special activation.

Ionic liquids have attracted great attention because of their potential use as 'green solvents'.[4,5] Recently, our group has reported the asymmetric Mannich-type reaction in 1-*R*-3-methylimidazolium based ionic liquids.[6] In this study, the Mukaiyama aldol product, as compared to the Mannich product, increases with the increase in the carbon chain length of the ionic liquids. These findings, coupled with the highly polar nature of these solvents, encouraged us to investigate further the effect of ionic liquids in Mukaiyama aldol reactions.

The Mukaiyama aldol reaction of nonyl aldehyde and 1-methoxy-2-methyl-1-trimethylsilyloxypropene was carried out at room temperature using different ionic liquids.[7] As shown in Table 1, the Mukaiyama aldol reaction proceeded to afford the product. As predicted, ionic liquids with long cation carbon chain length afforded better yields of the aldol products (entries 3, 5, and 7). In addition, the [Cl$^-$]-type ionic liquids were the preferred solvent systems (entries 6 and 7).



Next, we investigated the reaction of 1-methoxy-2-methyl-1-trimethylsilyloxypropene with various aldehydes using [omim][Cl$^-$] ($n = 7$). The results are shown in Table 2. In all cases, the products were obtained in moderate to good yields. It is important to note that even unreactive aldehydes such as aliphatic (entries 2, 3, and 9) and aromatic aldehydes (entries 8, 10, and 11) reacted with the ketene silyl acetal to afford the products in good yields.[8]

Keywords: Mukaiyama aldol reaction; ionic liquids.

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Table 1. Investigation of Mukaiyama aldol reaction using various ionic liquids

Entry	Ionic liquid	Yield[a] (%)
1	[bmim][PF_6^-], $n = 3$	4
2	[hmim][PF_6^-], $n = 5$	6
3	[omim][PF_6^-], $n = 7$	12
4	[bmim][BF_4^-], $n = 3$	8
5	[hmim][BF_4^-], $n = 5$	29
6	[hmim][Cl^-], $n = 5$	50
7	[omim][Cl^-], $n = 7$	51

[a] Isolated yield of aldol product.

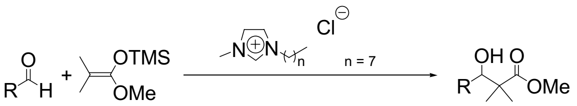
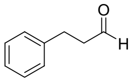
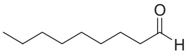
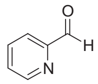
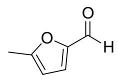
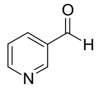
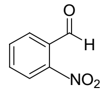
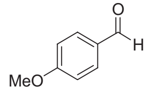
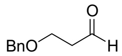
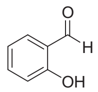
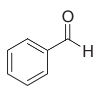
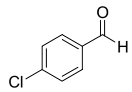


Table 2. Mukaiyama aldol reaction using [omim][Cl^-] with various aldehydes

Entry	Aldehyde	Yield[a] (%)
1		50
2		51
3		53[b]
4		58
5		59[b]
6		60
7		62
8		63
9		68
10		72
11		74

[a] Isolated yield of aldol product.

[b] Including TMS protected aldol product.

In summary, we have developed a general Mukaiyama aldol reaction using ionic liquids as solvent at room temperature without any Lewis acid or/and other special activation. This method works with a wide variety of aldehydes. The mild reaction conditions and the simplicity of the reaction procedure will certainly attract interest among organic chemists. The combinatorial synthesis of other ionic liquids for this aldol reaction, the development of an asymmetric version and the application of this method for the synthesis of complex molecules are in progress.

Acknowledgements

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7. Representative experimental procedure: A mixture of benzaldehyde (1 mmol) and 1-methoxy-2-methyl-1-trimethylsilyloxypropene (1.1 mmol) in the ionic liquid (0.5 mL) was stirred at room temperature for 6 h. Another 1.1 mmol of 1-methoxy-2-methyl-1-trimethylsilyloxypropene was added subsequently and the reaction mixture was allowed to stir at room temperature for 12 h. After that, 2 mL of 1 M HCl was added and the product was then extracted with diethyl ether. The combined organic phases were

washed with brine and dried over anhydrous $\mathrm{Na_2SO_4}$. The solution was then concentrated in vacuo followed by the purification using flash silica gel chromatography. ^{1}H NMR (300 MHz): δ 7.32–7.28 (m 5H, Ph), 4.90 (d, $J = 3.81$, 1H, $\mathrm{C}H\mathrm{OH}$), 3.73 (s, 3H, $\mathrm{OC}H_3$), 3.05 (d, $J = 3.81$, 1H, $\mathrm{CHO}H$), 1.15 (s, 3H, $\mathrm{C(C}H_3\mathrm{)(CH_3)}$), 1.12 (s, 3H, $\mathrm{C(CH_3)(C}H_3\mathrm{)}$) ppm; ^{13}C NMR (75.4 MHz): 178.0, 148.0, 127.6, 126.6, 127.5, 78.5, 51.9, 47.7, 22.8, 19.0 ppm; FTIR (KBr, neat): 1721.8, 1257.0, 704.9 cm^{-1}; HRMS (EI): calculated ($\mathrm{C_{12}H_{16}O_3}$, [$\mathrm{M^+}$]): 208.1099, found: 208.1103.

8. At this stage we do not have a explanation for either why the reaction proceeds with unreactive aldehydes or why the reaction proceeds without any Lewis acid or/and other special activation. ^{1}H NMR, ^{13}C NMR, FTIR, and mass spectrometry were used to confirm the structures of the other products.