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Water-Accelerated Aldol Reaction of Ketene Silyl Acetals with Carbonyl Compounds

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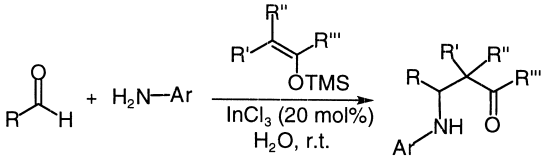
Abstract—The aldol reactions of ketene silyl acetals with reactive aldehydes proceed smoothly in water to afford the corresponding aldol products in good yields.

Introduction

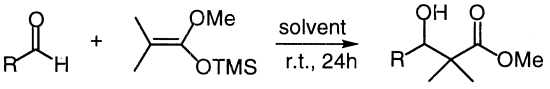
Aldol reactions in water at ambient temperature in the absence of Lewis acid catalysis or any special activation pose a great challenge for organic chemists.[1–6] The first aldol reaction in water using carbonyl compounds and silyl enol ethers without Lewis acid catalysis has been elegantly demonstrated to be feasible by Lubineau.[5] Unfortunately, the aldol reaction in pure water without special activation afforded the product in low yield.[6] In this paper, we demonstrate that various reactive aldehydes can react with ketene silyl acetals in water at ambient temperature without Lewis acid catalysis or special activation to afford the corresponding aldol product in moderate to good yields.

Results and Discussion

Recent studies from our group have shown that Mannich-type reactions of imines and silyl enol ethers or ketene silyl acetals in water proceed smoothly to afford the corresponding β-amino carbonyl compounds in the presence of indium trichloride, a well-established water-stable Lewis acid (Eq. (1)).[7] These successful results encouraged us to investigate the role of indium trichloride by monitoring the reaction using NMR. Furthermore, to investigate the relative reactivity of imine versus aldehyde in water, we carried out the Mannich reaction of 2-pyridine carboxaldehyde and aniline with ketene silyl acetal **1** in D_2O. It was found that ketene silyl acetal **1** selectively reacts with imine in the presence of indium trichloride to afford the β-amino carbonyl compounds in good yields. To our surprise, in the absence of any Lewis acid, the aldol reaction of 2-pyridine carboxaldehyde with ketene silyl acetal **1** proceeded smoothly in D_2O at room temperature to afford the aldol product quantitatively after 6 h (Fig. 1). The absence of resonances corresponding to ketene silyl acetal **1** is due to its insolubility in water. This unexpected result prompted us to further investigate the aldol reaction of ketene silyl acetal **1** with various aldehydes in pure water at ambient temperature in the absence of Lewis acid catalysis or any special activation (Eq. (2)). The results are shown in Table 1.



(1)



(2)

1 **2**

For comparison purposes, we also carried out the aldol reaction of 2-pyridine carboxaldehyde with ketene silyl acetal **1** in various solvents (Table 1, entries 1–3). Of special interest is that the aldol reaction of 2-pyridine carboxaldehyde proceeded smoothly to afford the product in very good yield when carried out in water (Table 1, entry 3). The reaction carried out in organic solvents afforded the aldol product in much lower yield (Table 1, entries 1 and 2). Therefore, various aldehydes were reacted with ketene silyl acetal **1** in water. As shown in Table 1, except for benzaldehyde, the reactions proceeded smoothly to afford the corresponding aldol products in moderate to high yields. Of special interest is the high yields observed for all the reactive aldehydes. Even in the case of methyl glyoxylate[8] which prefers to exist in the hydrate form in water, the aldol product was obtained in good yield (entry 7).

Of mechanistic interest is that the addition of pyridine,

Keywords: water-accelerated aldol reaction; ketene silyl acetal; carbonyl compounds.

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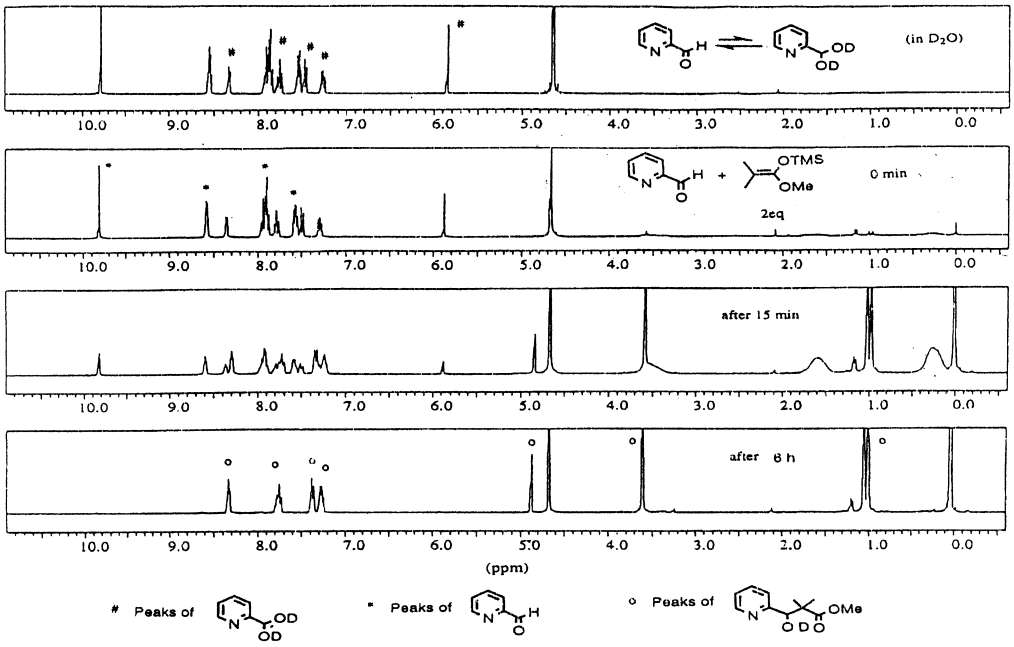
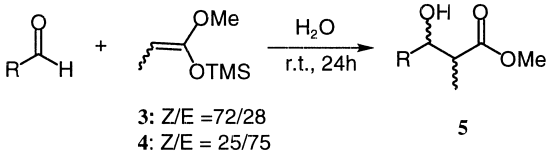


Figure 1.

DMAP, 2,6-di-*tert*-butylpyridine, 1,4-diazabicyclo-[2,2,2] octane or quinidine in the reaction of benzaldehyde does not increase the yield of the aldol product. This result rules out the possibility of the involvement of the nitrogen atom. At this moment, we do not know whether this aldol reaction proceeds via direct addition of silyl ketene acetal to aldehyde or desilylation of the silyl ketene acetal in water followed by the aldol reaction. Although the true mechanism of this reaction is still unknown, the yield of this aldol reaction is dependent on the reactivity of the aldehyde.

Next, we investigated the simple diastereoselectivity of this aldol reaction using ketene silyl acetal **3** and **4** with various aldehydes in water (Eq. (3)). The results are detailed in Tables 2 and 3.



(3)

Similarly, in all cases, the reactions proceeded smoothly to afford the corresponding aldol products in moderate to high yields. Unfortunately, only low to moderate diastereoselectivities were observed in all cases. Therefore, at this moment, it is difficult to come up with a transition state to explain these observed stereochemistries.

Table 1. The reaction of ketene silyl acetal **1** with various aldehydes in water

Entry	RCHO	Solvent	Product	Yield (%)
1	2-Pyridinecarboxaldehyde	THF	**2a**	26
2	2-Pyridinecarboxaldehyde	CH_2Cl_2	**2a**	23
3	2-Pyridinecarboxaldehyde	H_2O	**2a**	95
4	Benzaldehyde	H_2O	**2b**	20
5	2-Furaldehyde	H_2O	**2c**	50
6	3-Pyridinecarboxaldehyde	H_2O	**2d**	95
7	Methyl glyoxylate	H_2O	**2e**	70

Conclusions

In summary, we have found that the Mukaiyama-aldol reaction using ketene silyl acetals with aldehydes in water can afford the aldol products even without the use of Lewis acid or special activation. This untapped territory of reaction carried out in water without the use of metal complex and organic solvent remains to be explored. The use of chiral silicon containing silyl ketene acetals to investigate the mechanism as well as to develop an asymmetric version of this reaction is in progress.

Table 2. The reaction of ketene silyl acetal **3** with various aldehydes in water

Entry	RCHO	Yield (%)	*syn*/*anti*[a]
		5a–5d	
a	2-Pyridinecarboxaldehyde	95	35/65
b	3-Pyridinecarboxaldehyde	76	42/58
c	2-Furaldehyde	42	54/46
d	Methyl glyoxylate	63	43/57

[a] Relative stereochemistry determined based on similarity.[9]

Table 3. The reaction of ketene silyl acetal **4** with various aldehydes in water

Entry	RCHO	Yield (%)	*syn*/*anti*[a]
		5a–5d	
a	2-Pyridinecarboxaldehyde	84	33/67
b	3-Pyridinecarboxaldehyde	83	36/64
c	2-Furaldehyde	48	46/54
d	Methyl glyoxylate	58	47/53

[a] Relative stereochemistry determined based on similarity.[9]

Experimental

General methods and materials

NMR spectra were recorded on a Bruker ACF 300 NMR. MS spectra were obtained with a Hewlett–Packard 5890A gas chromatograph. HR-mass spectra (EI) were obtained with V.G. Micromass 7035. IR spectra were measured with a Perkin–Elmer 1600 FTIR spectrometer. Column chromatography was performed on silica gel, Merck grade 60 (40–63 μm particle size). All the solvents were distilled before use. Silyl ketene acetals were prepared according to the references or purchased from Fluka. All the aldehydes were distilled before use. Indium trichloride were purchased (Aldrich) and used directly.

Representative procedure

2-Pyridinecarboxaldehyde (1 mmol, 103 mg) was added to the suspension of ketene silyl acetal **1** (2 mmol, 366 mg) in water (5 mL). The ultimate suspension was stirred for 24 h at ambient temperature. The reaction mixture was extracted with ethyl acetate (3×50 ml). The combined organic solvent was washed with brine (1×), dried over anhydrous magnesium sulfate, and the solvent evaporated in vacuo. Purification of crude product by flash chromatography (hexane/ethyl acetate=6:1) gave the expected product as a colorless oil in excellent yield (95%, 198.94 mg); R_f (20% ethyl acetate/hexane) 0.2.

Methyl 3-hydroxy-2,2-dimethyl-3-(2-pyridyl) propanoate (2a). Colorless oil, yield 95%, ^{1}H NMR ($CDCl_3$): δ (ppm) 8.39–8.37 (1H, m, pyr), 7.57–7.51 (1H, m, pyr), 7.17–7.05 (2H, m, pyr), 4.88 (1H, s, *CH*OH), 3.58 (3H, s, O*Me*), 1.06 (3H, s, *Me*), 0.97 (3H, s, *Me*); ^{13}C NMR ($CDCl_3$) δ (ppm) 177.00, 158.42, 147.82, 135.98, 122.55, 121.92, 76.90, 51.63, 48.20, 20.67, 20.60; IR (thin film): 1726.6, 1258.2 cm^{-1}; MS (*m*/*z*, relative intensity) 209 (4), 178 (42), 132 (46), 108 (100), 78 (65), 52 (47), 27 (20); HRMS: calcd. for $C_{11}H_{15}NO_3$ 209.1052, found 209.1075.

Methyl 3-hydroxy-2,2-dimethyl-3-phenylpropanoate (2b). Colorless oil, yield 20%; ^{1}H NMR δ (ppm) 7.27 (5H, s, Ph), 4.86 (1H, s, *CH*OH), 3.68 (3H, s, O*Me*), 3.31 (1H, br, CH*OH*), 1.12 (3H, s, *Me*), 1.07 (3H, s, *Me*); ^{13}C NMR δ (ppm) 177.96, 140.02, 127.58, 127.55, 127.51, 78.44, 51.88, 47.68, 22.70, 19.00; IR (thin film): 1721.8, 1257.0, 704.9 cm^{-1}; MS (*m*/*z*, relative intensity) 208 (4), 119 (34), 102 (85), 43 (100), 27 (45); HRMS: calcd. for $C_{12}H_{16}O_3$ 208.1099, found 208.1118.

Methyl 3-(2-furyl)-3-hydroxy-2,2-dimethylpropanoate (2c). Known.[10]

Methyl 3-hydroxy-2,2-dimethyl-3-(3-pyridyl) propanoate (2d). Colorless oil; yield 95%; ^{1}H NMR δ (ppm) 8.33–8.28 (2H, m, pyr), 7.71 (1H, d, *J*=8.0 Hz, pyr), 7.25–7.20 (1H, m, pyr), 5.84 (1H, s, CH*OH*), 4.97 (1H, s, *CH*OH), 3.66 (3H, s, O*Me*), 1.15 (3H, s, *Me*), 1.04 (3H, s, *Me*); ^{13}C NMR δ (ppm) 176.90, 148.11, 147.77, 136.65, 135.38, 122.61, 75.31, 51.61, 47.72, 21.48, 19.02; IR (thin film): 1726.9, 1264.2 cm^{-1}; MS (*m*/*z*, relative intensity) 209 (2), 178 (4), 150 (16), 108 (100), 87 (74), 41 (41), 27 (28); HRMS: calcd. for $C_{11}H_{15}O_3N$ 209.1052, found 209.1072.

Dimethyl 3-hydroxy-2,2-dimethylbutane-1,4-dioate (2e). Colorless oil; yield 70%; ^{1}H NMR δ (ppm) 4.36 (1H, d, *J*=6.6 Hz, *CH*OH), 3.78 (3H, s, O*Me*), 3.72 (3H, s, O*Me*), 3.19 (1H, d, *J*=6.6 Hz, CH*OH*), 1.26 (3H, s, *Me*), 1.18 (3H, s, *Me*); ^{13}C NMR δ (ppm) 175.93, 173.52, 75.59, 52.62, 52.14, 46.71, 21.82, 20.40; IR (thin film): 1729.7, 1263.3 cm^{-1}; MS (*m*/*z*, relative intensity) 131 (64), 99 (66), 43 (100), 29 (32).

Methyl 3-hydroxy-2-methyl-3-(2-pyridyl)propanoate (5a). Mixture of two isomers; colorless oil; yield 95%, 84% (*syn*) ^{1}H NMR δ (ppm) 8.53–8.52 (1H, m, pyr), 7.72–7.66 (1H, m, pyr), 7.37–7.32 (1H, m, pyr), 7.23–7.18 (1H, m, pyr), 5.18 (1H, d, *J*=4.2 Hz, *CH*OH), 4.40 (1H, br, CH*OH*), 3.69 (3H, s, O*Me*), 3.07–2.94 (1H, m, *CH*Me), 1.03 (3H, d, *J*=7.3 Hz, CH*Me*); ^{13}C NMR δ (ppm) 175.18, 159.84, 148.17, 136.42, 122.28, 120.61, 73.13, 51.61, 45.58, 10.02; (*anti*) ^{1}H NMR δ (ppm) 8.53–8.52 (1H, m, pyr), 7.72–7.66 (1H, m, pyr), 7.37–7.32 (1H, m, pyr), 7.23–7.18 (1H, m, pyr) 4.86 (1H, d, *J*=6.6 Hz, *CH*OH), 4.40 (1H, br, CH*OH*), 3.66 (3H, s, O*Me*), 3.07–2.94 (1H, m, *CH*Me), 1.1 (3H, d, *J*=7.0 Hz, CH*Me*); ^{13}C NMR δ (ppm) 175.18, 159.96, 148.46, 136.51, 122.54, 121.29, 75.22, 51.48, 46.20, 13.42, IR (thin film): 1731.0, 1196.3 cm^{-1}; MS (*m*/*z*, relative intensity) 195 (0.5), 162 (40), 117 (92), 108 (100), 52 (100), 27 (75); HRMS: calcd. for $C_{10}H_{13}O_3N$ 195.0895, found 195.0905.

Methyl 3-hydroxy-2-methyl-3-(3-pyridyl)propanoate (5b). Mixture of two isomers; colorless oil; yield 76, 83%; (*syn*) ^{1}H NMR δ (ppm) 8.42–8.37 (2H, m, pyr), 7.73–7.70 (1H, m, pyr), 7.31–7.23 (1H, m, pyr), 5.08 (1H, d, *J*=4.9 Hz, *CH*OH), 3.63 (3H, s, O*Me*), 2.87–2.73 (1H, m, *CH*Me), 1.16 (3H, d, *J*=7.3 Hz, CH*Me*); ^{13}C NMR δ (ppm) 175.31, 148.63, 147.40, 137.93, 134.15, 123.16, 71.57, 51.63, 46.63, 11.15; (*anti*) ^{1}H NMR δ (ppm) 8.42–8.37 (2H, m, pyr), 7.73–7.70 (1H, m, pyr), 7.31–7.23 (1H, m, pyr), 4.79 (1H, d, *J*=8.7 Hz, *CH*OH), 3.72 (3H, s, O*Me*), 2.87–2.73 (1H, m, *CH*Me), 0.98 (3H, d, *J*=7.0 Hz, CH*Me*); ^{13}C NMR δ (ppm) 175.46, 148.63, 148.08, 137.70, 134.51, 123.45, 73.54, 51.73, 47.03, 13.85; IR (thin film): 1731.6 cm^{-1}; MS (*m*/*z*, relative intensity) 195 (3), 164 (4), 135 (3), 108 (100), 88 (53), 57 (44), 27 (21) HRMS: calcd. for $C_{10}H_{13}O_3N$ 195.0895, found 195.0913.

Methyl 3-(2-furyl)-3-hydroxy-2-methylpropanate (5c). Mixture of two isomers; colorless oil; yield 42, 48%; (*syn*) ^{1}H NMR δ (ppm) 7.38–7.35 (1H, m, furyl), 6.34–6.27 (2H, m, furyl), 5.01 (1H, br, *CH*OH), 3.73 (3H, s, *OMe*), 3.16 (1H, br, CH*OH*), 3.07–2.93 (1H, m, *CH*Me), 1.21 (3H, d, *J*=7.2 Hz, CH*Me*); ^{13}C NMR δ (ppm) 175.85, 154.25, 141.92, 110.20, 106.71, 68.86, 51.96, 44.10, 11.67; (*anti*) ^{1}H NMR δ (ppm) 7.38–7.35 (1H, m, furyl), 6.34–6.27 (2H, m, furyl), 4.80–4.76 (1H, m, *CH*OH); 3.69 (3H, s,O*Me*), 3.07–2.93 (1H, m, *CH*Me), 1.80 (1H, br, CH*OH*), 1.09 (3H, d, *J*=7.2 Hz, CH*Me*); ^{13}C NMR δ (ppm) 175.21, 154.09, 142.34, 110.20, 107.54, 69.77, 51.96, 44.61, 14.17; IR (thin film): 1734.5 cm^{-1}; MS (*m*/*z*, relative intensity) 184 (44), 135 (12), 97 (100), 57 (61), 27 (36); HRMS: calcd. for $C_9H_{12}O_4$ 184.0736, found 184.0723.

Dimethyl 2-hydroxy-3-methylbutane-1,4-dioate (5d). Mixture of two isomers; colorless oil; yield 63, 58%; (*syn*) ^{1}H NMR δ (ppm) 4.62 (1H, d, J=3.5 Hz, *CH*OH), 3.82 (3H, s, O*Me*), 3.80 (3H, s, O*Me*), 3.08–3.00 (1H, m, *CH*Me), 1.78 (1H, br, CHO*H*), 1.30 (3H, d, J=7.3 Hz, CH*Me*); ^{13}C NMR δ (ppm) 173.64, 173.58, 72.48, 52.67, 51.97, 43.16, 13.06; (*anti*) ^{1}H NMR δ (ppm) 4.28 (1H, d, J=3.2 Hz, *CH*OH), 3.74 (3H, s, O*Me*), 3.69 (3H, s, O*Me*), 2.99–2.90 (1H, m, *CH*Me), 1.78 (1H, br, CHO*H*), 1.17 (3H, d, J=7.3 Hz, CH*Me*); ^{13}C NMR δ (ppm) 173.64, 173.58, 71.47, 52.78, 52.12, 42.98, 10.63; IR (thin film): 1731.7, 1213.0 cm^{-1}; MS (*m*/*z*, relative intensity) 176 (0.5), 159 (1), 117 (97), 85 (100), 57 (98), 29 (87); HRMS: calcd. for $C_7H_{12}O_5$ 176.0684, found 176.0674.

Acknowledgements

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