L-Proline-Catalyzed One-Pot Three-Component Reaction for the Synthesis of β-Alkoxy Ketones

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Abstract: β -Alkoxy ketones were prepared by a one-pot threecomponent reaction of aliphatic aldehydes, ketones, and alcohols catalyzed by L-proline. Steric effects on the reaction were studied with substituted ketones, aldehydes, and alcohols, and the results indicate that reactions employing methyl ketones, α -unsubstituted aliphatic aldehydes and methanol produce the β -alkoxy ketones in the best yields when L-proline is used as the catalyst. The reaction mechanism is discussed.

Key words: β -alkoxy ketones, aldehydes, alcohols, one-pot reaction, aldol reactions, Mannich addition

The direct aldol reaction is a highly efficient tool for the construction of β -hydroxy ketone moieties in organic synthesis.¹ β-Hydroxy ketones and their alkylated derivatives, β -alkoxy ketones, are very important in the synthesis of polyoxygenated subunits in natural product synthesis.¹ While β -hydroxy ketones may be synthesized by a direct aldol reaction, β -alkoxy ketones have to be obtained indirectly. For example, a Mukaiyama aldol-type reaction of a silvl enol ether and an acetal or ketal is one of the most useful methods for the synthesis of β -alkoxy ketones.^{2,3} These compounds may also be obtained by alkylation of the corresponding β -hydroxy ketones with the use of enol ethers,⁴ or by nucleophilic addition of alcohols to enones, catalyzed by phosphines or metals.⁵⁻⁷ Alternatively, they may be obtained by reaction of alkoxycarbenium ions with silyl enol ethers,⁸ or of aldehydes with an enol acetate and alcohols in the presence of N-bromosuccinimide and tin(II) chloride.9 Although there are several methods available, all the above procedures require some special preformed substrates. Direct synthesis of β -alkoxy ketones from the readily available ketones and aldehydes still remains a challenge in organic synthesis. During our studies on direct aldol reactions,¹⁰ we accidentally observed an unprecedented direct formation of β -alkoxy ketones when an aldehyde, a ketone, and an alcohol react in the presence of L-proline. In this paper, we wish to report our results of this novel proline-catalyzed one-pot synthesis of β -alkoxy ketones.

To understand why L-proline-catalyzed direct aldol reactions produce poor enantioselectivity in water,¹¹ we studied the L-proline-catalyzed reaction of hydrocinnamaldehyde and acetone in methanol, a protic solvent similar

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to water. To our surprise, the isolated product from this reaction was not the expected aldol product; instead, we obtained the corresponding β -methoxy ketone **1a** as the major product. This interesting one-pot transformation prompted us to pursue this new reaction further, and the results are summarized in Table 1.

As is evident in Table 1, the L-proline-catalyzed threecomponent reaction yields β -alkoxy ketones 1 as the major products, while some percentage of the enone products 2 could also be isolated, as in proline-catalyzed direct aldol reactions. In the reactions of hydrocinnamaldehyde and acetone in methanol (Table 1, entry 1), ethanol (entry

Table 1L-Proline-Catalyzed Reaction between Aldehydes andAcetone in Various Alcohols^a



		1 a –j		2a–r	
Entry	\mathbf{R}^1	\mathbb{R}^2	Time (h)	(h) Yield ^b (%)	
				1	2
1	$(CH_2)_2Ph$	Me	5	71 (1a)	22 (2 a)
2	$(CH_2)_2Ph$	Et	24	61 (1b) ^c	30 (2a)
3	$(CH_2)_2Ph$	Bn	24	50 (1c)	32 (2 a)
4	(CH ₂) ₄ Me	Me	5	70 (1d) ^c	25 (2b)
5	(CH ₂) ₄ Me	Et	24	64 (1e) ^c	27 (2b)
6	(CH ₂) ₄ Me	Bn	24	52 (1f)	34 (2b)
7	(CH ₂) ₅ Me	Me	5	69 (1g) ^c	26 (2c)
8	(CH ₂) ₇ Me	Me	5	71 (1h)	23 (2d)
9	<i>i</i> -Pr	Me	48	53 (1i)	31 (2e)
10	Су	Me	48	44 (1j)	46 (2f)
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^a Conditions: aldehyde (5.0 mmol), acetone (20.0 mmol), alcohol (25.0 mL), L-proline (5.0 mmol), r.t.

^b Yields of isolated products after chromatographic purification.

^c All new compounds were characterized by ¹H and ¹³C NMR spectroscopy and elemental analysis.

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2), and benzyl alcohol (entry 3), the yield of the corresponding β -alkoxy ketone product **1** decreases with increasing alcohol alkyl chain length, while the amount of enone 2 formed remains steady. No β -alkoxy ketone 1 formed when the reaction was performed in secondary or tertiary alcohols (data not shown). A similar trend was also observed with hexan-1-al as the substrate (Table 1, entries 4-6). Nevertheless, the length and steric encumbrance of the aliphatic chain of the aldehyde has little effect on the formation of β -alkoxy ketone **1**, as heptan-1-al (Table 1, entry 7) and nonan-1-al (entry 8) gave the corresponding β -alkoxy compounds **1** in methanol in yields similar to that from hexan-1-al (entry 4). Increasing the steric hindrance about the α -position of the aldehyde led to a slight decrease in the yields of alkoxy ketones 1 (Table 1, entries 9, 10). On the other hand, aromatic aldehydes did not produce the corresponding β -alkoxy ketones 1 under these reaction conditions; the normal aldol products were obtained instead (data not shown).

The reaction of hydrocinnamaldehyde with various ketones was also studied, and the results are collected in Table 2. The reaction of butan-2-one (Table 2, entry 1) was highly regioselective. Only β -alkoxy ketone **3a** was isolated, and none of the other possible regioisomers formed. It is worth noting that **3a** is the product of the less stable enolate intermediate, i.e. it is a kinetic product. This result is totally different from a similar proline-catalyzed aldol reaction, where the kinetic product is always a minor product.11 Similarly, the reaction of acetol with hydrocinnamaldehyde (Table 2, entry 2) also regioselectively yielded the kinetic product of the corresponding β -alkoxy compound 3b. Other methyl ketones, such as acetonylacetone (Table 2, entry 3), cyclopropyl methyl ketone (entry 4), and acetophenone (entry 5) also participate in this reaction. However, ketones without methyl substituents, e.g., cyclohexanone, do not participate in this reaction (data not shown).

Besides L-proline, some other proline derivatives may also be used as catalysts for this reaction (Table 3). For example, both L-prolinamide (Table 3, entry 2) and (*S*)-5pyrrolidin-2-yl-1*H*-tetrazole¹² (entry 3) catalyze the threecomponent reaction of hydrocinnamaldehyde, acetone, and methanol with lower efficiency compared with L-proline. However, the zinc–L-proline complex, which is a good catalyst for the direct aldol reaction,^{11b,11c} does not catalyze this reaction (Table 3, entry 4). L-Proline appears to be the best catalyst for this reaction (Table 3, entry 1). It should be pointed out that, even with all these optically active catalysts, no enantioselectivity was observed in this three-component reaction.

In the normal direct aldol reaction, proline reacts with the ketone to form an enamine intermediate, which then attacks the aldehyde to form the aldol product.^{11,13} In the current case, the alkoxy ketone formation from the corresponding aldol product is excluded, since substitution of the aldol hydroxy group by the alcohol does not take place under the reaction conditions. Furthermore, acetophenone, a particularly sluggish substrate for such an en
 Table 2
 L-Proline-Catalyzed Reaction between Hydrocinnamaldehyde and Methyl Ketones in Methanol^a



^a Conditions: hydrocinnamaldehyde (5.0 mmol), ketone (10.0 mmol), MeOH (25 mL), L-proline (5.0 mmol), r.t.

^b Yields of isolated products after chromatographic purification.

^c All new compounds were characterized by ¹H and ¹³C NMR spectroscopy and elemental analysis.

^d Calculated from the ¹H NMR spectrum; inseparable from self-aldol product of hydrocinnamaldehyde (ca. 30%).

^e The reaction was performed under reflux.

Table 3 One-Pot Synthesis of β -Alkoxy Ketone **1a** Catalyzed by
Various Pyrrolidine Derivatives^a



Entry	Catalyst	Time (h)	Yield ^b (%)	
			1a	2a
1	L-proline	5	71	22
2	L-prolinamide	12	31	16
3	(S)-5-pyrrolidin-2-yl-1H-tetrazole	12	44	10
4	(L-proline) ₂ Zn	24	_	_

^a Conditions: hydrocinnamaldehyde (5.0 mmol), acetone (20.0 mmol), MeOH (25 mL), catalyst (5.0 mmol), r.t.

^b Yields of isolated products after chromatographic purification.

amine formation, participates in this three-component reaction (Table 2, entry 3). Therefore, the mechanism of this three-component reaction must be different from that of the direct aldol reaction. On the basis of the experimental data, we propose the mechanism shown in Scheme 1. Thus, the aldehyde reacts with L-proline to form an iminium intermediate A, which is then attacked by methanol (Scheme 1, pathway a) to generate intermediate **B**, which is in equilibrium with intermediate C. Nucleophilic attack of intermediate C by the enol of the ketone generates the expected alkoxy ketone product 1 with the cleavage of the catalyst. Since the reaction relies on the attack of the ketone enol on intermediate C (or A for the formation of the enone, vide infra), a sterically less hindered enol should react much faster, so that the kinetic product prevails. This mechanism can explain why only methyl ketone can participate in the reaction, since only these ketones can form the least sterically demanding enol.

Similar arguments can be used to explain why the reaction yield drops when the alcohol molecule becomes bulkier. The reason why the zinc-proline complex cannot act as a catalyst for such a reaction is probably its inability to form the iminium intermediate **A**. We did not obtain any asymmetric induction in this reaction. Some possible reasons may include the following: (a) the addition of methanol to **A** is not enantioselective; (b) the solvent methanol interferes with hydrogen-bond directing effects; and (c) enol addition to **C** is an S_N1-type mechanism.

As for the enone generated as a minor product in this reaction, we have independently verified that it is neither due to the elimination of methanol from compound **1** (Scheme 1), nor due to the dehydration of the corresponding aldol product (data not shown), since both **1** and the aldol product are stable under the reaction conditions. The mechanism that involves a Mannich reaction, followed by elimination (Scheme 1, pathway *b*) is proposed to account for its formation: The iminium intermediate **A** is attacked by the enol of the ketone to generate the intermediate **D**. Elimination of L-proline from **D** gives the enone product. List and co-workers have employed a similar mechanism to explain the enone formation in a proline-catalyzed reaction of aldehydes and acetone.¹⁴

In conclusion, we have developed a simple one-pot methodology for the preparation of β -alkoxy ketones from aliphatic aldehydes, ketones, and alcohols. The reaction is highly regioselective when unsymmetrical methyl ketones are used. Besides its mechanistic interest, this method is very useful for the laboratory synthesis of this type of compound because of the use of easily accessible starting materials and the simple operation.

¹H NMR and ¹³C NMR spectra were recorded on a GE (300 MHz) spectrometer, with CDCl₃ used as solvent. IR spectra were recorded on a Bruker Vector 22 spectrophotometer. Elemental analyses were conducted by Desert Analytics Laboratory, Arizona.

β-Alkoxy Ketones 1 and 3; General Procedure

To a soln of the aldehyde (5.0 mmol) and the ketone (20.0 mmol) in anhyd MeOH (25.0 mL) at r.t. was added L-proline (575 mg, 5.0 mmol). The reaction mixture was stirred at r.t. for the time indicated in Table 1 or Table 2. The solvent was then removed under reduced pressure and the concentrated mixture was dissolved in Et_2O (25.0 mL). The precipitated L-proline (>95% recovery) was filtered and washed with Et_2O (20.0 mL). The filtrates were combined and concentrated under reduced pressure. The crude products thus obtained were purified by flash column chromatography (silica gel, hexane– EtOAc) to afford compounds 1 (or 3) and 2 (or 4). Characterization data for the new compounds are presented below (except for 4d, which could not be separated by column chromatography).

4-Ethoxy-6-phenylhexan-2-one (1b)

Liquid.

IR (neat): 2928, 1710, 1092 cm⁻¹.

¹H NMR (300 MHz, CDCl₃): δ = 7.10–7.25 (m, 5 H), 3.76 (m, 1 H), 3.45 (q, *J* = 7.0 Hz, 2 H), 2.58–2.72 (m, 3 H), 2.44 (dd, *J* = 15.6, 5.1 Hz, 1 H), 2.11 (s, 3 H), 1.71–1.79 (m, 2 H), 1.12 (t, *J* = 7.0 Hz, 3 H). ¹³C NMR (75 MHz, CDCl₃): δ = 207.1, 141.8, 128.4, 128.3, 125.7, 75.1, 64.7, 48.7, 36.3, 31.6, 31.1, 15.6.

Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.10; H, 9.42.



Scheme 1 Proposed mechanism for the formation of β -alkoxy ketones in the three-component one-pot reaction catalyzed by proline

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4-Methoxynonan-2-one (1d) Liquid.

IR (neat): 1707, 1157 cm⁻¹.

¹H NMR (300 MHz, CDCl₃): δ = 3.60 (m, 1 H), 3.25 (s, 3 H), 2.60 (dd, *J* = 15.8, 7.8 Hz, 1 H), 2.39 (dd, *J* = 15.8, 4.5 Hz, 1 H), 2.11 (s, 3 H), 1.22–1.46 (m, 8 H), 0.82 (t, *J* = 6.5 Hz, 3 H).

¹³C NMR (75 MHz, CDCl₃): δ = 207.2, 77.3, 56.7, 48.3, 33.9, 31.9, 30.9, 24.7, 22.6, 13.9.

Anal. Calcd for $C_{10}H_{20}O_2$: C, 69.72; H, 11.70. Found: C, 69.65; H, 11.76.

4-Ethoxynonan-2-one (1e)

Liquid.

IR (neat): 1714, 1121 cm⁻¹.

¹H NMR (300 MHz, CDCl₃): δ = 3.66 (m, 1 H), 3.35–3.46 (m, 2 H), 2.60 (dd, *J* = 15.6, 7.5 Hz, 1 H), 2.38 (dd, *J* = 15.6, 5.1 Hz, 1 H), 2.10 (s, 3 H), 1.21–1.42 (m, 8 H), 1.07 (t, *J* = 6.9 Hz, 3 H), 0.81 (t, *J* = 5.6 Hz, 3 H).

 ^{13}C NMR (75 MHz, CDCl₃): δ = 207.5, 75.8, 64.7, 48.9, 34.6, 32.0, 31.2, 25.0, 22.7, 15.6, 14.0.

Anal. Calcd for $C_{11}H_{22}O_2$: C, 70.92; H, 11.90. Found: C, 70.74; H, 11.79.

4-Methoxydecan-2-one (1g)

Liquid.

IR (neat): 1710, 1155 cm⁻¹.

¹H NMR (300 MHz, CDCl₃): δ = 3.54 (m, 1 H), 3.20 (s, 3 H), 2.55 (dd, *J* = 15.8, 7.5 Hz, 1 H), 2.34 (dd, *J* = 15.8, 4.5 Hz, 1 H), 2.06 (s, 3 H), 1.16–1.39 (m, 10 H), 0.76 (t, *J* = 5.9 Hz, 3 H).

¹³C NMR (75 MHz, CDCl₃): δ = 207.1, 77.3, 56.7, 48.3, 33.9, 31.8, 30.9, 29.3, 25.1, 22.6, 14.0.

Anal. Calcd for $C_{11}H_{22}O_2$: C, 70.92; H, 11.90. Found: C, 70.62; H, 11.72.

5-Methoxy-7-phenylheptan-3-one (3a) Liquid.

IR (neat): 2931, 1710, 1079 cm⁻¹.

¹H NMR (300 MHz, CDCl₃): δ = 7.21–7.37 (m, 5 H), 3.79 (m, 1 H), 3.40 (s, 3 H), 2.67–2.81 (m, 3 H), 2.47–2.56 (m, 3 H), 1.86 (q, *J* = 7.7 Hz, 2 H), 1.10 (t, *J* = 7.2 Hz, 3 H).

¹³C NMR (75 MHz, CDCl₃): δ = 209.5, 141.8, 128.3, 128.2, 125.7, 76.8, 56.9, 46.9, 37.1, 35.9, 31.5, 7.7.

Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.16; H, 9.47.

1-Hydroxy-4-methoxy-6-phenylhexan-2-one (3b) Liquid.

IR (neat) : 3515, 2921, 1713, 1094 cm⁻¹.

¹H NMR (300 MHz, CDCl₃): δ = 7.11–7.26 (m, 5 H), 4.19 (d, J = 4.5 Hz, 2 H), 3.66 (m, 1 H), 3.28 (s, 3 H), 3.07 (br s, 1 H, OH), 2.57–2.67 (m, 3 H), 2.44 (dd, J = 15.0, 4.5 Hz, 1 H), 1.73–1.89 (m, 2 H).

¹³C NMR (75 MHz, CDCl₃): δ = 208.3, 141.4, 128.5, 128.3, 126.1, 76.8, 69.3, 57.1, 43.4, 35.6, 31.4.

Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.11; H, 8.05.

7-Methoxy-9-phenylnonane-2,5-dione (3c) Liquid.

IR (neat): 2930, 1727, 1172 cm⁻¹.

¹H NMR (300 MHz, CDCl₃): δ = 7.09–7.24 (m, 5 H), 3.65 (m, 1 H), 3.27 (m, 3 H), 2.46–2.74 (m, 8 H), 2.12 (s, 3 H), 1.74 (m, 2 H).

¹³C NMR (75 MHz, CDCl₃): δ = 207.5, 206.6, 141.8, 128.3, 125.8, 76.6, 56.9, 47.4, 37.3, 36.9, 35.8, 31.4, 29.9.

Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 73.16; H, 8.57.

1-Cyclopropyl-3-methoxy-5-phenylpentan-1-one (3d) Liquid.

IR (neat): 2928, 1715, 1095 cm⁻¹.

¹H NMR (300 MHz, CDCl₃): δ = 7.09–7.25 (m, 5 H), 3.68 (m, 1 H), 3.30 (s, 3 H), 2.81 (dd, *J* = 15.6, 6.6 Hz, 1 H), 2.53–2.71 (m, 3 H), 1.87–1.92 (m, 1 H), 1.73–1.81 (m, 2 H), 0.96–1.01 (m, 2 H), 0.79–0.85 (m, 2 H).

¹³C NMR (75 MHz, CDCl₃): δ = 208.9, 141.9, 128.5, 128.3, 125.8, 76.8, 57.0, 48.0, 36.2, 31.6, 21.3, 10.9.

Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.59; H, 8.67.

1-Hydroxy-6-phenylhex-3-en-2-one (4b)

Liquid.

IR (neat): 3518, 2902, 1704 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): $\delta = 7.10-7.27$ (m, 5 H), 6.92 (dt, J = 16.2, 6.9 Hz, 1 H), 6.09 (d, J = 16.2 Hz, 1 H), 4.33 (d, J = 3.0

Hz, 2 H), 3.25 (br s, 1 H, OH), 2.75 (t, J = 7.7 Hz, 2 H), 2.53 (q, J = 7.3 Hz, 2 H). ¹³C NMR (75 MHz, CDCl₃): δ = 197.8, 147.9, 140.2, 128.5, 128.2,

126.4, 126.3, 66.4, 34.3 (2C).

Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.78; H, 7.48.

9-Phenylnon-6-ene-2,5-dione (4c)

Liquid.

IR (neat): 2926, 1707 cm⁻¹.

¹H NMR (300 MHz, CDCl₃): δ = 7.14–7.28 (m, 5 H), 6.87 (dt, J = 16.3, 6.8, 1 H), 6.11 (d, J = 16.3, 1 H), 2.67–2.81 (m, 6 H), 2.43 (m, 2 H), 2.17 (s, 3 H).

¹³C NMR (75 MHz, CDCl₃): δ = 207.7, 198.8, 146.7, 140.9, 130.7, 128.8, 128.6, 126.5, 37.1, 34.6, 34.4, 33.8, 30.3.

Anal. Calcd for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88. Found: C, 77.86; H, 7.76.

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