Amine-Catalyzed Aldol Condensation in the Presence of Lithium Perchlorate

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Abstract: A catalytic aldol condensation in the presence of lithium perchlorate and tertiary amines is described giving pure products in high yields. The aldol condensation can be performed even in the presence of hydrated lithium perchlorate.

Key words: aldol reactions, aldehydes, ketones, catalysis, amines





 α,β -Unsaturated carbonyl compounds, diarylylidene or dialkylidene carbonyl compounds, are very important precursors in the perfume industry,¹ for bioactive pyrimidines,² as agrochemicals, and as liquid crystal polymers.³ Moreover, α , β -unsaturated carbonyl compounds are important structural elements in the curcumin family of natural products which exhibit certain anti-cancer properties.⁴ They were used in the indium-catalyzed synthesis of substituted vinylcyclopropanones⁵ or the goldcatalyzed alkylation of indoles.⁶ Many of these substances are widely used as ligands in palladium-catalyzed coupling processes,⁷ moreover, some of these ligands are extremely expensive.⁸

Recently, several methods appeared describing the synthesis of arylidene- or alkylideneketones. Several metal salts were employed as reagents in these reactions,⁹ however, often higher temperatures and long reaction times are necessary for complete conversion and hence formation of byproducts increased. In addition, most of these reactions were accompanied by low chemoselectivity, also self-condensations were observed rather than cross-aldol condensations, which caused problems in their purification.

During our ongoing studies of aldol processes in the presence of LiClO₄¹⁰ we developed a very mild, easy, and catalytic process for the synthesis of arylidene and alkylidene carbonyl compounds, which we describe herein.

While investigating aldol addition processes, we observed that ketones and aldehydes react in the presence of LiClO₄ and catalytic amounts of tertiary amines to yield aldol condensation products. The reaction was carried out neat in the presence of 10 mol% Et₃N at room temperature (Scheme 1).

In order to test the catalytic potential of this transformation we reacted acetone and benzaldehyde with different ratios of LiClO₄ and Et₃N (Table 1). Excellent yields were achieved even when the amounts of Et₃N and LiClO₄ were

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Table 1	Reactions of Benzaldehyde with Acetone in the Presence
of LiClO ₄	and Et ₃ N ^a

Entry	LiClO ₄ (mol%) ^b	$Et_3N \ (mol\%)^b$	Time	Yield (%)
1	100	10	2 min	94
2	50	10	2 min	89
3	20	10	2 h	87
4	10	10	16 h	96
5	100	1	24 h	91
6	100 ^c	10	17 h	95

^a Procedure A.

^b Relative to benzaldehyde.

° LiClO₄·3H₂O.

reduced. Dibenzylacetone was isolated in up to 91% yield in the presence of 1 mol% Et₃N (Table 1, entry 5).

To ensure complete conversion, relatively long reaction times, 16–24 hours at room temperature, were required. Initial experiments were carried out in the presence of anhydrous LiClO₄; however, later we realized the outcome of the reaction was not influenced by water: even with a two-phase system quantitative yields were obtained (Table 1, entry 6, 0.5 mL of water added).



Scheme 2

With optimized conditions in hand (anhyd $LiClO_4$, r.t.) we began to study the scope of the reaction (Scheme 2). Initially we carried out the reaction with benzaldehyde and varied the ene component (Table 2). As discussed above, the reaction of benzaldehyde with acetone is very fast and quantitative; the same is true for the reaction of benzalde-

Table 2 Reaction of Benzaldehyde with a Range of Ketones in thePresence of $LiClO_4$ and Et_3N^a

Entry	R^1	\mathbb{R}^2	Compd	Yield (%)
1	Н	Н	2a	94
2	-(CH ₂) ₂ -		2b	91
3	-(CH ₂) ₃ -		2c	93
4	Н	Me	$2d^{b}$	48
5	Me	Me	$2e^{b}$	45
6	ОН	Н	2f	-
7	OMe	Н	2g	-
8	ОН	ОН	2h	-
9	OAc	OAc	2i	_

^a General Procedure A.

^b General Procedure B.

hyde with cyclopentanone and cyclohexanone: quantitative yields were obtained within three minutes at room temperature. Highly substituted acetone derivates required longer reaction times or additional heating to force the reaction to go to completion (General Procedure B, for compounds 2d and 2e). Oxygen-substituted acetone derivatives were unsuitable for these reactions. None of the expected products could be detected in reactions with hydroxyacetone, dihydroxyactone, diacetoxyacetone, or methoxyacetone (Table 2, entries 6–9); products derived from acetalization were isolated.



Scheme 3

Table 3 Reactions of a Range of Aldehydes with Acetone in thePresence of $LiClO_4$ and Et_3N^a

Entry	R	Compd	Time	Yield (%)
1	$p-NO_2C_6H_4$	4 a	30 min	62
2	p-ClC ₆ H ₄	4b	4 min	94
3	<i>p</i> -MeOC ₆ H ₄	4c	5 min	92
4	3,4-(MeO) ₂ C ₆ H ₃	4d	4 d	50
5	p-HOC ₆ H ₄	4e	2 d	_
6	C ₆ H ₅ CH=CH-	4f	30 min	57
7	c-Hex	$4g^{b}$	4 d	12
8	<i>i</i> -Pr	4h	4 d	97

^a General Procedure A.

^b General Procedure B.



Next, we tested the range of aldehydes applicable to this transformation with acetone employed as the ene component in every reaction (Scheme 3, Table 3). Aromatic aldehydes **3a**, **3b**, **3c**, and **3f** reacted under these conditions to give the expected unsaturated ketones **4a**, **4b**, **4c**, and **4f**. The reactions were very fast and quantitative (with the exception of cinnamaldehyde **3f**, ca. 60%). Even aliphatic enolizable aldehydes reacted under these conditions, isobutyraldehyde **3h** reacted with acetone to give compound **4h** in quantitative yields. As expected, *p*-hydroxybenzaldehyde **3e** did not react under these conditions (Table 3, entry 5).



Scheme 4

Table 4Reactions of a Range of Aldehydes with Cyclopentanonein the Presence of $LiClO_4$ and Et_3N^a

Entry	R	Compd	Time	Yield (%)
1	$p-NO_2C_6H_4$	5a	1 min	74
2	p-ClC ₆ H ₄	5b	4 min	97
3	<i>p</i> -MeOC ₆ H ₄	5c	1 min	100
4	3,4-(MeO) ₂ -C ₆ H ₃	5d	4 d	100
5	p-HOC ₆ H ₄	5e	4 d	-
6	C ₆ H ₅ CH=CH	5f	3 min	90
7	c-Hex	5g	24 h	95
8	<i>i</i> -Pr	5h	4 d	100

^a General Procedure A.

Finally, we reacted a range of aldehydes with cyclopentanone as the ene component and found cyclopentanone to be an even better ene component than acetone (Scheme 4, Table 4). Overall, reactions were faster, yields were higher, and the range of suitable aldehydes increased, in particular, the reactions of both 3,4-dimethoxybenzaldehyde (3d; compare Table 3, entry 4 with Table 4, entry 4) and cyclohexylcarboxyladehyde (3g; compare Table 3, entry 7 with Table 4, entry 7) were much improved. As expected, p-hydroxybenzaldehyde 3e did not react at all under these conditions (Table 4, entry 5). Also the self-condensation of cyclopentanone was very slow, after a reaction time of 11 days at room temperature cyclopentylidenecyclopentanone was obtained in 70% yield. This is in contrast with the acetone series (Table 3), where we did not observe self-condensation of acetone.

In conclusion, we have demonstrated convincingly that LiClO_4 and amines can be used as catalysts in aldol condensation processes. This method works even in the pres-

ence of enolizable aldehydes resulting in quantitative yields. The mild, very rapid, and clean performance of these reactions is an advantage over previously described procedure. Products were obtained with a high degree of purity and no chromatographic procedures were necessary for further purification. Analytically pure compounds were obtained by one recrystallization of the crude reaction mixture.

Aldehydes were distilled before use. Products were purified by recrystallization (CH_2Cl_2) with the exception of **2e** (flash chromatography, hexane–EtOAc, 8:2). LiClO₄ was dried at 120 °C in vacuo for 10 h before use.¹¹

¹H NMR and ¹³C NMR spectra were recorded at 300 and 75 MHz, respectively, in CDCl₃, on a AC-300 spectrometer. Chemical shifts are given in ppm. TLC was carried out with Merck Silica Gel 60 F_{254} TLC plates. Yields are not optimized and are relative to the amount of aldehyde.

General Procedure A

To a solution of LiClO₄ (1.1 g, 10 mmol), aldehyde (10 mmol), and ketone (5 mmol), Et₃N (0.14 mL, 1 mmol) was added. The reaction mixture was stirred at r.t. and monitored by TLC. When the reaction was complete a sat. aq solution of NH₄Cl (30 mL) was added and the resulting mixture was extracted with CH₂Cl₂ (100 mL). The organic layer was dried over MgSO₄ and the solvent was removed in vacuo to give the crude product.

General Procedure B

To a solution of LiClO₄ (1.1 g, 10 mmol), aldehyde (10 mmol), and ketone (5 mmol) in toluene (10 mL), Et₃N (0.14 mL, 1 mmol) was added. The reaction mixture was refluxed and monitored by TLC. When the reaction was complete a sat. aq solution of NH₄Cl (30 mL) was added and the resulting mixture was extracted with CH₂Cl₂ (100 mL). The organic layer was dried over MgSO₄ and the solvent was removed in vacuo to give the crude product.

(1*E*,4*E*)-Dibenzylideneacetone (2a)^{9h}

¹H NMR: δ = 7.75 (d, *J* = 16.0 Hz, 2 H), 7.61 (m, 4 H), 7.42 (m, 6 H), 7.09 (d, *J* = 16.0 Hz, 2 H).

¹³C NMR: δ = 189.0, 143.4, 134.9, 130.6, 129.0, 128.5, 125.5.

Dibenzylidenecyclopentanone (2b)9g

¹H NMR: δ = 7.60–7.58 (m, 6 H), 7.45–7.35 (m, 6 H), 3.12 (s, 4 H). ¹³C NMR: δ = 188.1, 144.4, 142.3, 133.3, 128.5, 127.5, 126.7, 22.6.

Dibenzylidenecyclohexanone (2c)¹⁰

¹H NMR: δ = 7.67–7.11 (m, 12 H), 2.78–2.66 (m, 4 H), 1.63–1.51 (m, 2 H).

¹³C NMR: δ = 190.1, 136.9, 136.2, 136.0, 130.5, 128.7, 128.5, 28.5, 23.0.

(1E)-2-Methyl-1,5-diphenylpenta-1,4-dien-3-one $(2d)^{12}$

¹H NMR: δ = 7.62–7.20 (m, 13 H), 2.26 (d, *J* = 1.5 Hz, 3 H).

¹³C NMR: δ = 192.6, 143.3, 138.6, 138.4, 135.9, 135.0, 134.5, 130.3, 129.7, 128.8, 128.4, 128.2, 121.8, 13.7.

2,4-Dimethyl-1,5-diphenylpenta-1,4-dien-3-one (2e)¹³

¹H NMR: δ = 7.48–7.36 (m, 12 H), 2.07 (d, *J* = 1.1 Hz, 6 H). ¹³C NMR: δ = 195.7, 149.9, 137.4, 130.0, 128.7, 128.4, 128.1, 10.9. (1*E*,4*E*)-1,5-Bis(4'-nitrophenyl)penta-1,4-dien-3-one (4a)^{9h} ¹H NMR: δ = 8.27 (d, *J* = 15.6 Hz, 2 H), 7.90 (d, *J* = 7.6 Hz, 4 H), 7.69 (m, *J* = 8.2 Hz, 4 H), 7.27 (d, *J* = 15.6 Hz, 2 H). ¹³C NMR: δ = 189.2, 149.5, 142.5, 142.2, 131.0, 131.4, 125.4.

(1*E*,4*E*)-1,5-Bis(4'-chlorophenyl)penta-1,4-dien-3-one (4b)^{9h} ¹H NMR: δ = 7.69 (d, *J* = 15.9 Hz, 2 H), 7.57 (d, *J* = 8.5 Hz, 4 H), 7.42 (t, *J* = 5.8 Hz, 4 H), 6.98 (d, *J* = 15.9 Hz, 2 H).

¹³C NMR: δ = 189.3, 142.7, 136.1, 133.5, 129.5, 129.2, 125.1.

(1*E*,4*E*)-1,5-Bis(4'-methoxyphenyl)penta-1,4-dien-3-one (4c)^{9h} ¹H NMR: $\delta = 7.70$ (d, J = 15.8 Hz, 2 H), 7.54 (m, J = 8.5 Hz, 4 H), 6.94 (d, J = 15.8 Hz, 2 H), 6.90 (d, J = 7.2 Hz, 4 H), 3.81 (s, 6 H).

¹³C NMR: δ = 204.3, 160.0, 140.5, 128.4, 126.8, 121.9, 112.7, 53.7.

(1E,4E)-1,5-Bis(3',4'-dimethoxyphenyl)penta-1,4-dien-3-one $(4d)^{14}$

¹H NMR: δ = 7.61 (d, *J* = 15.8 Hz, 2 H, =CH), 7.12 (dd, *J* = 1.9, 8.3 Hz, 2 H, *o*-Ph), 7.06 (d, *J* = 1.9 Hz, 2 H, *m*-Ph), 6.88 (d, *J* = 15.8 Hz, 2 H, =CH), 6.80 (d, *J* = 8.3 Hz, 2 H, *o*-Ph), 3.86 (s, 6 H, OMe), 3.84 (s, 6 H, OMe).

 ^{13}C NMR: δ = 188.6, 151.3, 149.2, 143.0, 127.8, 123.6, 123.1, 111.1, 109.8, 56.0, 55.9.

(1*E*,3*E*,6*E*,8*E*)-1,9-Diphenylnona-1,3,6,8-tetraen-5-one (4f)¹⁵

¹H NMR: δ = 7.51–7.44 (m, 6 H), 7.38–7.29 (m, 6 H), 6.95 (d, J = 8.8 Hz, 4 H), 6.56 (d, J = 14.9 Hz, 2 H).

 13 C NMR: δ = 189.0, 143.0, 141.5, 136.1, 129.2, 129.0, 128.8, 127.2, 127.0.

MS: m/z (%) = 286 (67), 258 (18), 195 (28), 128 (100), 91 (42), 77 (49), 51 (31).

(1*E*,4*E*)-Dicyclohexylideneacetone (4g)

IR (KBr): 2923, 1728, 1664, 1631, 1611, 1333, 1313, 1276, 983 $\rm cm^{-l}.$

¹H NMR: δ = 6.81 (dd, *J* = 6.8, 15.8 Hz, 2 H), 6.25 (dd, *J* = 1.1, 15.8 Hz, 2 H), 2.20–1.05 (m, 22 H).

¹³C NMR: δ = 190.3, 152.7, 126.2, 40.8, 31.8, 25.9, 25.7.

HRMS: *m*/*z* calcd for C₁₇H₂₆O (M⁺): 246.1984; found: 246.1985

(3*E*,6*E*)-2,8-Dimethylnona-3,6-dien-5-one (4h)¹⁶

¹H NMR: $\delta = 6.85$ (dd, J = 15.7, 6.4 Hz, 2 H), 6.26 (dd, J = 15.8, 1.5 Hz, 2 H), 2.47 (qd, J = 6.8, 1.5 Hz, 2 H), 1.06 (d, J = 6.8 Hz, 12 H, Me).

¹³C NMR: δ = 190.2, 153.9, 125.7, 31.1, 21.2.

MS: m/z (%) = 166 (13), 124 (15), 97 (97), 56 (50), 43 (71), 71 (100).

2,5-Bis(4'-nitrobenzylidene)cyclopentanone (5a)^{9g}

¹H NMR: δ = 8.32–8.26 (m, 4 H), 7.76–7.69 (m, 4 H), 7.63 (s, 2 H, =CH), 3.18 (m, 4 H).

¹³C NMR: δ = 196.6, 148.5, 143.0, 142.7, 133.0, 131.9, 125.2, 27.4

2,5-Bis(4'-chlorobenzylidene)cyclopentanone (5b)^{9g}

¹H NMR: δ = 7.47–7.45 (m, 6 H), 7.35–7.33 (m, 4 H), 3.00 (m, 4 H). ¹³C NMR: δ = 195.9, 137.5, 135.4, 134.2, 132.7, 131.8, 129.1, 26.4.

2,5-Bis(4'-methoxybenzylidene)cyclopentanone (5c)9g

¹H NMR: δ = 7.59–7.51 (m, 6 H), 6.97–6.89 (m, 4 H), 3.83 (s, 6 H, OMe), 3.06 (m, 4 H).

¹³C NMR: δ = 196.3, 160.5, 135.3, 133.3, 132.5, 128.7, 114.3, 55.4, 26.4.

2,5-Bis(3',4'-dimethoxybenzylidene)cyclopentanone (5d)¹⁷

¹H NMR: δ = 7.55 (s, 2 H), 7.22 (dd, *J* = 1.9, 8.3 Hz, 2 H), 7.12 (d, *J* = 1.9 Hz, 2 H), 6.92 (d, *J* = 8.3 Hz, 2 H), 3.92 (s, 12 H), 3.10 (s, 4 H).

¹³C NMR: δ = 196.1, 150.3, 148.9, 135.4, 133.7, 129.0, 124.6, 113.4, 111.2, 56.0, 55.9, 26.5.

2,5-Bis(3'-phenylallylidene)cyclopentanone (5f)^{9d}

¹H NMR: δ = 7.49 (d, *J* = 7.0 Hz, 4 H), 7.38–7.26 (m, 8 H), 6.97 (d, *J* = 6.8 Hz, 4 H), 2.90 (s, 4 H).

 ^{13}C NMR: δ = 188.7, 141.3, 139.8, 136.6, 132.7, 129.0, 128.8, 127.2, 124.7, 23.9.

MS: m/z (%) = 312 (80), 286 (42), 105 (82), 77 (77), 51 (37), 91 (100).

2,5-Dicyclohexylidenecyclopentanone (5g)¹⁸

¹H NMR: δ = 6.44 (d, *J* = 9.4 Hz, 2 H), 2.55 (s, 4 H), 2.21–2.08 (m, 2 H, CH), 1.73–1.54 (m, 8 H), 1.31–1.04 (m, 12 H).

¹³C NMR: δ = 195.7, 142.1, 137.2, 38.7, 31.6, 25.8, 25.5, 23.2.

MS: *m*/*z* (%) = 272 (100), 229 (15), 177 (73), 41 (61).

2,5-Diisobutylidenecyclopentanone (5h)

IR (KBr): 2872, 2731, 2670, 1708, 1644, 1465, 1385, 1167, 962 $\rm cm^{-1}.$

¹H NMR: δ = 6.43 (d, J = 9.8 Hz, 2 H), 2.55 (s, 4 H, CH₂), 2.52–2.37 (m, 2 H, CH), 0.98 (d, J = 6.8 Hz, 12 H, Me).

¹³C NMR: δ = 195.8, 143.8, 136.7, 28.9, 23.0, 21.6.

MS: *m*/*z* (%) = 192 (42), 177 (74), 43 (100).

HRMS: *m/z* calcd for C₁₃H₂₀O (M⁺): 192.1514; found: 192.1515.

2-Cyclopentylidenecyclopentanone¹⁹

¹H NMR: δ = 2.68 (m, 2 H), 2.52 (m, 2 H), 2.28 (m, 2 H), 2.23 (m, 2 H), 1.85 (m, 2 H), 1.66 (m, 4 H).

¹³C NMR: δ = 206.9, 158.3, 127.9, 39.7, 34.3, 32.5, 29.6, 27.0, 25.3, 20.1.

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