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Efficient organocatalyzed solvent-free selective synthesis of conjugated enones

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ABSTRACT

A series of conjugated dienones and enones were synthesized by a reaction of both conjugated and simple aldehydes, respectively, with 1,3-dicarbonyl compounds and aldehydes under solvent-free conditions at room temperature in the presence of 10 mol % of L-proline as catalyst. The selective formation of one isomer was observed exclusively with most of the 1,3-dicarbonyl compounds and aldehydes. The most commonly formed xanthene derivative from the cyclic diketones is inhibited with our protocol, with the exclusive formation of conjugated dienones only.

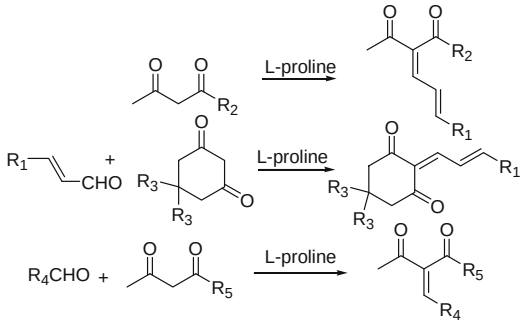
α,β-Enones are synthetically important organic molecules, which are generally used as substrates for Morita–Baylis–Hilmann reactions,[1] addition to carbonyl groups and conjugated double bonds.[2] On the other hand, conjugated enones are versatile synthones[3] and significant substrates for Diels–Alder reactions and 1,4-addition.[4] These compounds are generally synthesized by the aldol and Knoevenagel condensation,[5] the Horner–Wadsworth–Emmons reaction,[6] and isomerization of α,β-ynones,[6c] among which the Knoevenagel condensation is of great significant value. These condensations are generally carried out in the presence of base,[7] acids[8] and solvent-free conditions[9] under microwave[10] or infra red irradiation.[11] However, these methods suffer from numerous limitations such as harsh reaction conditions, use of hazardous solvents, and requirement of high temperatures, to name a few. Although the reaction can be carried out under catalyst-free conditions, the yields of the condensed products were low.[12]

While the Knoevenagel condensations are generally carried out with active methylene compounds such as β-ketoesters, cyanoacetates, malononitriles, the reaction with β-diketones is less reported.[13] This is because the 1,3-diketones have an inherent tendency to form a stable cyclic enol, which makes it less reactive than other active methylene compounds. Furthermore, a very recent report[14] of 1,3-diketones as the Knoevenagel substrate faces the drawbacks of much longer times and smaller yields.

In continuation of our work with new synthetic methodologies,[15] we report a mild and environmentally-benign protocol for the selective synthesis of an *E*-isomer of the conjugated enones using a catalytic amount of either amines or amino acids. Among these, L-proline was found to be the best at room temperature and has a very short reaction time as shown in Scheme 1.

Initially, we screened a variety of amines as well as amino acids for effective catalytic activity as shown in Table 1. Benzoyl acetone, an unsymmetric diketone, and cinnamaldehyde were taken as the model substrates. Among the screened catalysts, 10 mol % of L-proline was found to be the most effective as the reaction was completed within a very short time.

The incapability of the protocol to furnish one pure isomer selectively in ethanol, forced us to find a suitable solvent system in order to get the optimum yield of one isomer selectively. Hence, another set of reactions was performed with cinnamaldehyde and benzoyl acetone in various solvents in the presence of a catalytic amount of L-proline as shown in Table 2. The observations indicate that one selective isomer was obtained exclusively under the



Scheme 1. Synthesis of conjugated dienone system.

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Table 1
Screening of catalyst[a]

Entry	Catalyst (10 mol %)[b]	Time (h) [min]	Yield[c] (%)
1	Benzyl amine	10	60
2	Pyridine	8	65
3	Adenine	6	75
4	Pyridine dicarboxylic acid	5	82
5	Lysine	4	74
6	Aniline	2	80
7	L-Histidine	3	70
8	L-Cysteine	3	83
9	L-Proline	[40]	90

[a] Reaction was carried out with cinnamaldehyde (1 mmol) and benzoyl acetone (1.1 mmol).
[b] All the reactions were performed in ethanol.
[c] Yields refer to the isolated yield.

Table 2
Screening of solvents[a]

Entry	Solvents (3 ml)	Time (min)	*E*:*Z*[b]	Yield[c] (%)
1	Dichloromethane	35	65:35	90
2	Chloroform	40	60:40	88
3	Acetonitrile	30	71:29	75
4	Ethanol	40	80:20	88
5	—	10	100:0	87

[a] Reaction was carried out with cinnamaldehyde (1 mmol) and benzoyl acetone (1.1 mmol).
[b] The ratio found from NMR.
[c] Yields refer to the isolated yield.

solvent-free condition indicating that the solvent assists in the cis–trans isomerization of the condensed products.

Upon finding the optimal condition, a set of reactions were carried out with a variety of 1,3-dicarbonyl compounds (Table 3, entries 1c–4c). The two unsaturated aldehydes chosen were crotonaldehyde (**a**) and cinnamaldehyde (**b**), respectively. The reaction with β-ketoesters (Table 3, entries 1c–3c), considered the classical Knoevenagel substrates, and with aldehydes furnished the desired conjugated enones **1ad**–**3ad** and **1bd**–**3bd** in excellent yields.[16]

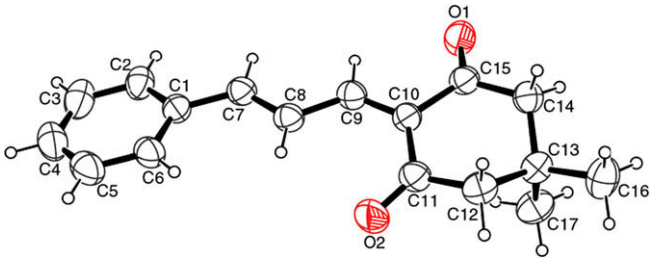


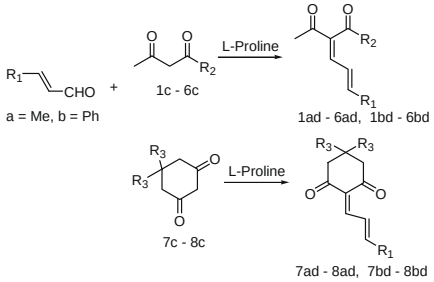
Figure 1. Single crystal XRD for compound **8bd**.

All the products were obtained selectively as *E*-isomers with the exception of allyl acetoacetate (Table 3, entry 4c) which gave a mixture of both *E* and *Z* isomers **4ad**–**bd** with an *E*-isomer in the predominant form. Next, we carried out the reaction with a variety of both acyclic and cyclic 1,3-diketones (Table 3, entries 5c–8c). It is to be noted that the reported Knoevenagel reaction[13a] with cyclic diketones and β-carbonyl compounds generally furnishes xanthene derivatives as the reaction further proceeds after the condensation to give a Michael product. However, our protocol gave the conjugated dienone **5ad**–**8ad** and **5bd**–**8bd** exclusively in good yields without a further Michael reaction.

The structure of **8bd** was further confirmed by single crystal XRD as depicted in Figure 1.

With these results in hand, we tried to explore the reaction of both aliphatic and aromatic unconjugated aldehydes (Table 4, en-

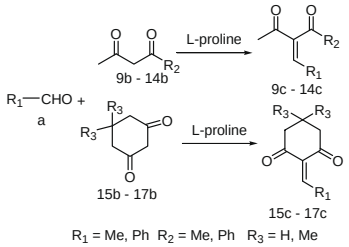
Table 3
Reaction of α,β-unsaturated aldehydes with 1,3-dicarbonyl compounds



Entry	1,3-Dicarbonyl compounds (c)	Products	Time (min)	Yield[a,b] [*E*:*Z* ratio] (%)
1	R_2 = OMe	**1ad**	15	80
		1bd	15	80
2	R_2 = OEt	**2ad**	15	84
		2bd	15	91
3	R_2 = $OCMe_3$	**3ad**	15	72
		3bd	10	83
4	R_2 = OCH_2–CH=CH_2	**4ad**	15	74 [60:40]
		4bd	15	81 [80:20]
5	R_2 = Me	**5ad**	15	85
		5bd	10	90
6	R_2 = Ph	**6ad**	15	79
		6bd	10	87
7	R_3 = H	**7ad**	10	85
		7bd	10	93[c]
8	R_3 = Me	**8ad**	10	81
		8bd	10	92[c]

[a] Yields refer to isolated yield.
[b] All the compounds were characterized by NMR, mass, and elemental analyses.
[c] The crude products were recrystallized from ethanol and analyzed directly without further purification.

Table 4
Reaction of aldehydes with 1,3-dicarbonyl compounds



Entry	Aldehyde (a)	1,3-Dicarbonyl compounds (b)	Time (min)	Yield[a,b] (%)
9	R_1 = Ph	R_2 = Me	30	85
10	R_1 = *p*-Br–C_6H_4	R_2 = Me	20	89
11	R_1 = *p*-NO_2–C_6H_4	R_2 = Me	20	83
12	R_1 = *p*-OMe–C_6H_4	R_2 = Ph	35	67
13	R_1 = Ph	R_2 = Ph	30	72
14	R_1 = Cyclohexyl	R_2 = Me	40	71
15	R_1 = Cyclohexyl	R_3 = Me	20	76
16	R_1 = Ph	R_3 = H	20	85
17	R_1 = *p*-Br–C_6H_4	R_3 = Me	20	88

[a] Yields refer to isolated yield.
[b] All the compounds were characterized by NMR, mass, and elemental analyses.

tries 9a–17a) with 1,3-diketones (Table 4, entries 9b–17b). Interestingly, the reactions took a considerably longer time for completion as compared to the conjugated aldehydes as shown in Table 4. The reaction gave Knoevenagel products **9c**–**17c** exclusively with the formation of an *E*-isomer. The aldehydes with both electron-withdrawing and electron-donating groups underwent the reaction smoothly. However, the yields obtained with electron-donating aldehydes were smaller and had a longer reaction time. The aliphatic aldehyde also gave the α,β-unsaturated products **14c** and **15c** in good yields without undergoing further isomerization[17] to β,α-unsaturated ones, inspite of the presence of α-hydrogens in aliphatic aldehydes.

In conclusion, we have devised a simple and efficient environmentally-benign protocol for the solvent-free synthesis of conjugated dienones with the formation of *E*-isomer selectively within a short reaction time at room temperature. The formation of a single isomer selectively, without any side products, which is a major drawback faced with other reported methods, is a major asset of our protocol. Another notable advantage is the retardation of the Michael reaction of the synthesized Knoevenagel products from cyclic diketones. Taking account of these advantages, our clean protocol should contribute toward the realm of synthetic organic chemistry.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.12.036.

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Chem. Lett. Rev. **2008**. doi: 10.1080/17518250802403774.; (d) Goswami, P. *Syn. Commun.* **2008**, in press.

16. *General procedure for the Knoevenagel condensation*: A mixture of 1,3-dicarbonyl compound (1.1 mmol), aldehydes (1 mmol), and L-proline (10 mol %) was mixed in a mortar under solvent-free conditions. After the completion of the reaction as indicated by Thin Layer Chromatography (TLC), ethyl acetate was added to the crude reaction mixture. The reaction mixture in ethyl acetate was added to water for the removal of the catalyst. The organic layer was separated, dried over anhydrous Na_2SO_4 and evaporated under a vacuum. The crude products were purified by column chromatography (hexane:ethyl acetate 1:9). The purified products were analyzed by spectral analyses.Spectroscopic data for selected compounds:*5,5-Dimethyl-2-(3-phenyl-allylidene)-cyclohexane-1,3-dione (**8bd**)*: ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm):1.07 (s, 6H), 2.53 (s, 2H), 2.54 (s, 2H), 7.34 (d, J = 15.2 Hz, 1H), 7.38–7.39 (m, 3H), 7.59–7.62 (m, 2H), 7.78 (d, J = 12.0 Hz, 1H), 8.35 (dd, J = 12.0 Hz, J = 15.6 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm): 28.70(2C), 30.24, 52.52, 54.22, 125.73, 128.93(2C), 129.16(2C), 131.12(2C), 135.80, 151.43, 153.59, 198.12, 199.17. Anal. Calcd For $C_{17}H_{18}O_2$: C, 80.28; H, 7.13. Found: C, 80.09, H, 7.28.*2-(3-Phenyl-allylidene)-cyclohexane-1,3-dione (**7bd**)*: ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm): 2.03 (pent, J = 6.8 Hz, 2H), 2.63 (t, J = 6.8 Hz, 2H), 2.64 (t, J = 6.8 Hz, 2H), 7.34 (d, J = 15.2 Hz, 1H), 7.38–7.39 (m, 3H), 7.60–7.62 (m, 2H), 7.80 (d, J = 12.0 Hz, 1H), 8.33 (dd, J = 12.0 Hz, J = 15.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm): 18.35, 38.93, 40.55, 125.88, 129.02(2C), 129.24(2C), 130.74, 131.21, 135.87, 152.14, 153.66, 198.45 199.48. Anal. Calcd for $C_{15}H_{14}O_2$: C, 79.62; H, 6.24. Found: C, 79.50; H, 6.37.*2-Acetyl-5-phenyl-penta-2,4-dienoic acid methyl ester (**1bd**)*: ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm): 2.39 (s, 3H), 3.90 (s, 3H), 7.09 (d, J = 15.2 Hz, 1H), 7.26 (dd, J = 11.6 Hz, J = 15.2 Hz, 1H), 7.34–7.37 (m, 3H), 7.44 (d, J = 11.6 Hz, 1H), 7.49–7.51 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm): 27.83, 52.15, 123.56, 127.91(2C), 128.89(2C), 130.04, 132.09, 135.52, 145.08, 146.01, 166.73, 195.57. Anal. Calcd for $C_{14}H_{14}O_3$: C, 73.03; H, 6.13. Found: C, 73.24; H, 6.24.*2-Acetyl-hexa-2,4-dienoic acid ethyl ester (**2ad**)*: ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm): 1.34 (t, J = 6.8 Hz, 3H), 1.92 (d, J = 6.8 Hz, 3H), 2.33 (s, 3H), 4.32 (q, J = 6.8, 2H), 6.39 (pent, J = 6.8 Hz, 1H), 6.54 (dd, J = 11.6 Hz, J = 14.8 Hz, 1H), 7.20 (d, J = 11.6 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz):δ (ppm): 14.37, 19.45, 27.86, 61.39, 127.76, 131.49, 144.78, 145.91, 166.65, 195.81. Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found: C, 66.09; H, 7.88.

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