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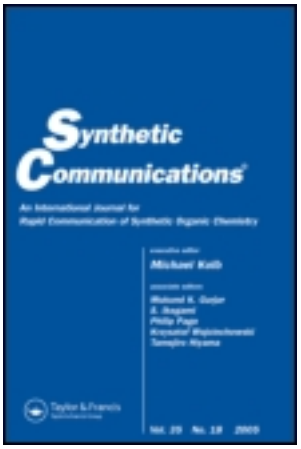

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Natural α-Amino Acid L-Lysine-Catalyzed Knoevenagel Condensations of α,β-Unsaturated Aldehydes and 1,3-Dicarbonyl Compounds

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NATURAL α-AMINO ACID L-LYSINE–CATALYZED KNOEVENAGEL CONDENSATIONS OF α,β-UNSATURATED ALDEHYDES AND 1,3-DICARBONYL COMPOUNDS

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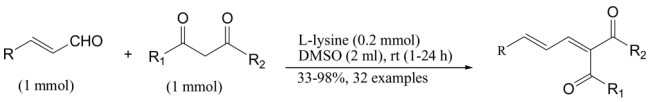
GRAPHICAL ABSTRACT



R = aryl, alkyl; R_1, R_2 = aryl, alkyl, ethoxy

Abstract *Knoevenagel condensations of α,β-unsaturated aldehydes and 1,3-dicarbonyl compounds were catalyzed by primary natural amino acid L-lysine. The reactions were carried out at room temperature in dimethylsulfoxide. It provides a facile entry to a wide variety of α,β,γ,δ-unsaturated dicarbonyl compounds.*

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Keywords 1,3-Dicarbonyl compound; Knoevenagel condensation; L-lysine; α,β-unsaturated aldehyde

INTRODUCTION

Knoevenagel condensation is the reaction between an aldehyde or ketone and an active methylene compound.[1,2] It has been widely used to form C-C bonds.[3] Especially, the Knoevenagel condensations between α,β-unsaturated aldehydes and 1,3-dicarbonyl compounds generate useful α,β,γ,δ-unsaturated dicarbonyl compounds,[4] which are versatile synthons[5–7] and significant substrates for Diels–Alder reactions and 1,4-additions.[8–13] However, there are only a few examples of Knoevenagel condensations involving α,β-unsaturated aldehydes, and most of them either gave poor yields[14–16] or required drastic temperatures.[17,18] Furthermore, the Knoevenagel condensations involving 1,3-diketones often face the drawbacks of longer reaction times or lesser yields than other methylene active compounds[3,19,20] because 1,3-diketones have an inherent tendency to form stable cyclic enols.

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Therefore, development of a mild and high-yielding Knoevenagel condensation of α,β-unsaturated aldehydes with 1,3-dicarbonyl compounds is still a desirable and challenging goal.

On the other hand, α-amino acids as cheap and environmentally benign catalysts have been widely used in organic synthesis.[21–26] However, amino acid–catalyzed Knoevenagel condensations are relatively few, and among them L-proline is the most used acid. With regard to the great success of secondary amino acid L-proline,[8,27] it is somewhat surprising that the primary amino acids remain largely unexplored. Therefore, the potential of primary amino acids as catalysts in Knoevenagel condensation still deserves exploration. We recently reported primary amino acid L-tryptophan as a catalyst in Knoevenagel condensations of aldehydes with acetylacetone and ethyl acetoacetate.[28] Herein, we report another primary natural amino acid, L-lysine, as a catalyst in Knoevenagel condensations between various α,β-unsaturated aldehydes and a wide range of 1,3-dicarbonyl compounds. The reaction is operationally simple, mild, and high yielding. A wide variety of α,β,γ,δ-unsaturated dicarbonyl compounds were prepared using this method, and among them there are 12 new compounds. X-ray crystal analysis was used to determine the structures.

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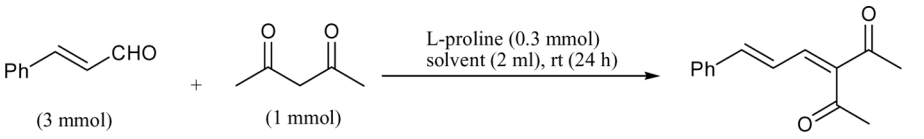
RESULTS AND DISCUSSION

In our initial study, to examine the solvent effect on amino acid–catalyzed Knoevenagel condensation, the reaction between cinnamaldehyde and acetyl acetone catalyzed by 30 mol% L-proline was selected as a model reaction (Table 1). The excess of cinnamaldehyde and long reaction time (24 h) were provided to guarantee relatively good yields. The reaction in H_2O gave a poor yield of 26% (Table 1, entry 1). It is probably because of the insolubility of cinnamaldehyde and acetyl acetone in H_2O. Both tetrahydrofuran (THF) and CH_2Cl_2 were found to give poor yields (Table 1, entries 2 and 3). Dimethylformamide (DMF) and solvent-free conditions gave modest yields (Table 1, entries 4 and 5). The reaction in dimethylsulfoxide

Table 1. Knoevenagel condensation between cinnamaldehyde and acetyl acetone in different solvents



Entry	Solvent	Yield (%)[a]
1	H_2O	26
2	THF	31
3	CH_2Cl_2	48
4	DMF	58
5	Solvent-free	60
6	DMSO	97

[a]Refers to yield of isolated product after flash chromatography.

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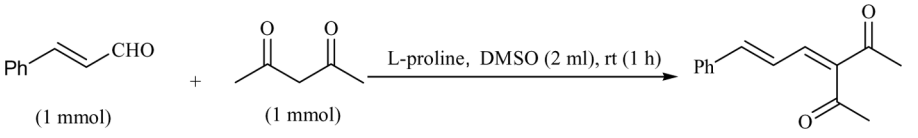
(DMSO) provided the best yield of 97% (Table 1, entry 6). Therefore, DMSO was chosen as the optimized solvent for the Knoevenagel condensation.

Next, to find out the proper catalyst loading, 10, 20, 30, and 40 mol% of L-proline were used to catalyze the condensation between cinnamaldehyde and acetyl acetone (Table 2). A loding of 20 mol% of L-proline was determined as optimal.

With the chosen solvent and catalyst loading in hand, we screened 20 natural α-amino acids (Table 3). We found that several amino acids can catalyze the Knoevenagel condensation efficiently. L-Proline gave a good yield of 89%, which ranked second (Table 3, entry 19). Basic amino acid L-lysine showed the best result of 93% yield (Table 3, entry 20), and basic amino acid L-arginine gave a moderate yield of 64% (Table 3, entry 17). The results of L-lysine and L-arginine led us to assume that the alkalinity of the amino acid is essential for good catalytic activity. However, basic amino acid L-histidine, which contains an imidazole, gave a yield of only 6% (Table 3, entry 5). Meanwhile, L-tryptophan, which contains an indole, gave a good yield of 72% (Table 3, entry 18). As we all know, the imidazole is more alkaline than indole. Those results convinced us that the alkalinity of amino acid should not be the factor of catalytic activity. Interestingly, the structurally similar amino acids L-asparagine and L-glutamine showed enormously different activities (Table 3, entries 16 and 7). No better results were obtained for other tested amino acids. The reaction without catalyst was also carried out, which gave only 7% yield (Table 3, entry 21). The experiments showed that some amino acids are indeed catalysts, and among them L-lysine is the most efficient one.

Based on this investigation, a series of α,β-unsaturated aldehydes and 1,3-dicarbonyl compounds were catalyzed by L-lysine (20 mol%) in DMSO (Table 4). The reactions gave the corresponding α,β,γ,δ-unsaturated dicarbonyl compounds in moderate to excellent yields. It was observed that electronic factors of aromatic α,β-unsaturated aldehydes played a crucial role. Better yields were obtained in the presence of electron-donating substituents (Table 4, entries 7–16) than the electron-withdrawing substituents (Table 4, entries 17–27), and some by-products were observed for the latter. This is probably due to the further Michael or Knoevenagel reactions of the products (α,β,γ,δ -unsaturated dicarbonyl compounds)

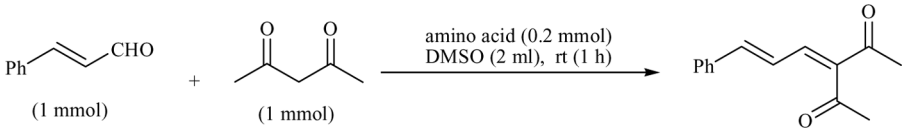
Table 2. Effect of catalyst loading on the Knoevenagel condensation



Entry	L-proline (mol%)	Yield (%)[a]
1	10	76
2	20	89
3	30	90
4	40	90

[a]Refers to yield of isolated product after flash chromatography.

Table 3. Various amino acids used as catalysts for Knoevenagel condensation



Entry	Amino acid	Yield (%)[a]
1	L-Isoleucine	2
2	L-Tyrosine	3
3	L-Aspartate	4
4	L-Glutamate	5
5	L-Histidine	6
6	L-Alanine	7
7	L-Glutamine	8
8	L-Leucine	9
9	L-Valine	10
10	L-Phenylalanine	12
11	L-Threonine	13
12	Glycine	15
13	L-Methionine	33
14	L-Cysteine	34
15	L-Serine	35
16	L-Asparagine	58
17	L-Arginine	64
18	L-Tryptophan	72
19	L-Proline	89
20	L-Lysine	93
21	No amino acid	7

[a]Refers to yield of isolated product after flash chromatography.

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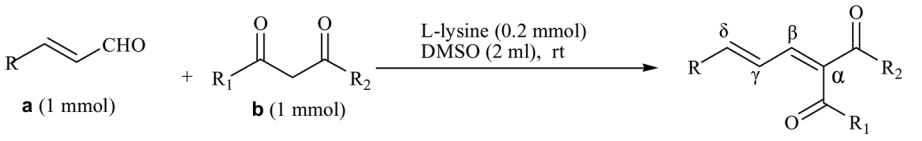
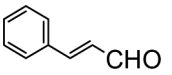
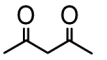
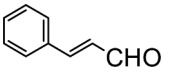
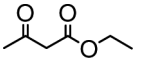
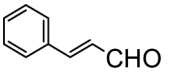
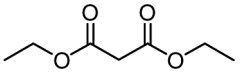
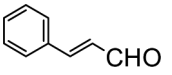
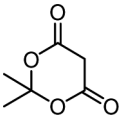
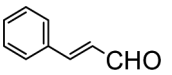
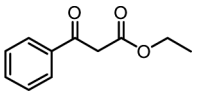
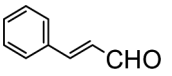
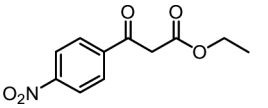
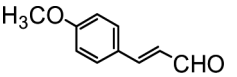
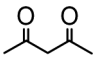
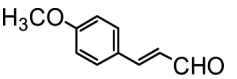
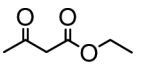
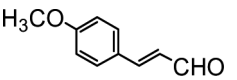
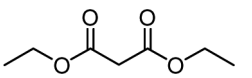
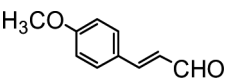
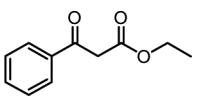
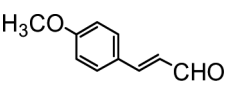
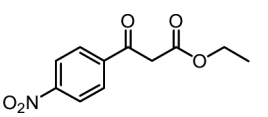
with 1,3-dicarbonyl compounds. The electron-withdrawing groups increase the activity of the α,β,γ,δ-unsaturated dicarbonyl compounds, which facilitates these side reactions. We tried to identify some by-products but failed to purify them. Besides the effect of aldehydes, 1,3-dicarbonyl compounds also played an important role. Knoevenagel condensations of diethyl malonate with *p*-methylcinnamaldehyde or *p*-fluorocinnamaldehyde (Table 4, entries 14 and 25) and *p*-nitrobenzoylacetic acid ethyl ester with *p*-chlorocinnamaldehyde or *p*-fluorocinnamaldehyde (Table 4, entries 22 and 27) gave relatively poor yields because of the incomplete reactions. Prolonged reaction times did not improve the yields. The Meldrum's acid progressed with poor yields because of the instability of the products (Table 4, entries 4 and 20). Ethyl acetoacetate gave all products as *E* and *Z* configuration isomers. *Z* and *E* refer to the newly formed double bond between α-C and β-C (Table 4). The configurations were determined by NMR in comparison with reported cinnamaldehyde products.[29] To our surprise, *Z* isomers were received as the major products, and the ratio of *Z* and *E* was shown in the note of Table 4. However, all the products of *p*-nitrobenzoylacetic acid ethyl ester and benzoylacetic acid ethyl ester were obtained selectively as *E* isomers. The structure of product **p16** was further confirmed by single-crystal x-ray analysis as depicted in Fig. 1.

Table 4. L-Lysine–catalyzed Knoevenagel condensations of α,β-unsaturated aldehydes and 1,3-dicarbonyl compounds



Entry	a	b	Time (h)	Yield (%)[a]	Product number
1			2.5	97	**p1**
2			1	97[b]	**p2a, p2b**
3			2	97	**p3**
4			3	55	**p4**
5			2	90	**p5**
6			2	80	**p6**
7			4	98	**p7**
8			3	92[b]	**p8a, p8b**
9			12	89	**p9**
10			21	70	**p10**
11			8	90	**p11**

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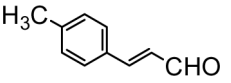
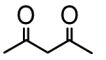
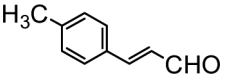
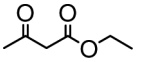
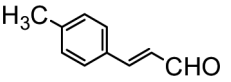
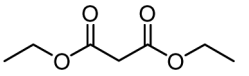
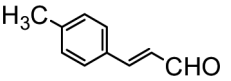
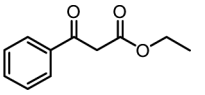
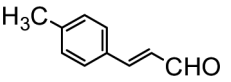
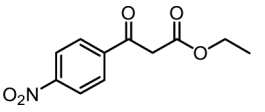
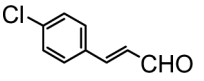
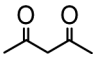
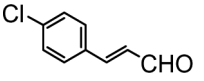
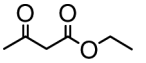
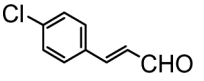
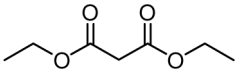
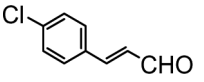
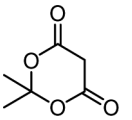
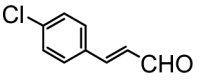
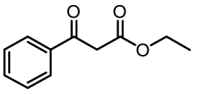
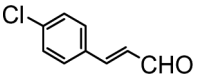
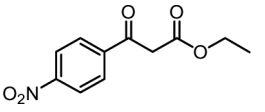
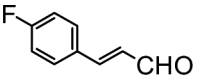
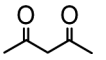
12			4	96	**p12**
13			24	79[b]	**p13a, p13b**
14			18	77	**p14**
15			24	86	**p15**
16			18	96	**p16**
17			18.5	95	**p17**
18			6	72[b]	**p18a, p18b**
19			23	90	**p19**
20			6	47	**p20**
21			24	72	**p21**
22			18	60	**p22**
23			2	79	**p23**

(*Continued*)

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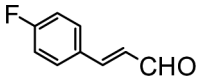
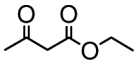
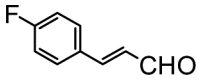
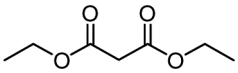
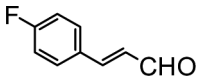
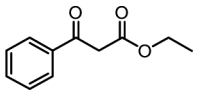
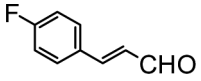
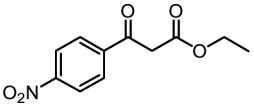
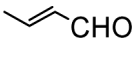
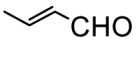
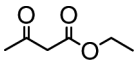
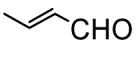
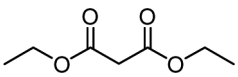
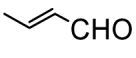
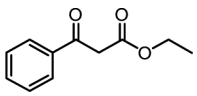
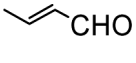
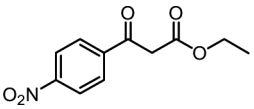
Table 4. Continued

Entry	a	b	Time (h)	Yield (%)[a]	Product number
24			3	56[b]	**p24a, p24b**
25			24	79	**P25**
26			12	76	**p26**
27			24	51	**p27**
28			5	88	**p28**
29			4	96	**p29**
30			4	80	**p30**
31			4	33	**p31**
32			4	52	**p32**

[a]Refers to yield of isolated product after flash chromatography.

[b]Refers to the total yield of two isomers. The ratio of two isomers: $Z/E = 2.1$ for entries 2 and 8; $Z/E = 2.2$ for entries 13 and 18; $Z/E = 3.2$ for entry 24. Z and E refer to the newly formed double bond between α-C and β-C.

In addition, aliphatic α,β-unsaturated aldehyde crotonaldehyde also performed well. Crotonaldehyde reacting with acetyl acetone, ethyl acetoacetate, and diethyl malonate respectively furnished good yields (Table 4, entries 28–30), but when it reacted with benzoylacetic acid ethyl ester (Table 4, entry 31), poor yield was obtained and a side reaction was observed. The possible reason may be that the δ-carbon (Table 4) of the product from crotonaldehyde is less hindered than the product from aromatic α,β-unsaturated aldehyde, which makes it easy to further react with benzoyl acetic acid ethyl ester. However, crotonaldehyde reacting with *p*-nitrobenzoylacetic acid ethyl ester (Table 4, entries 32) also gave poor yield

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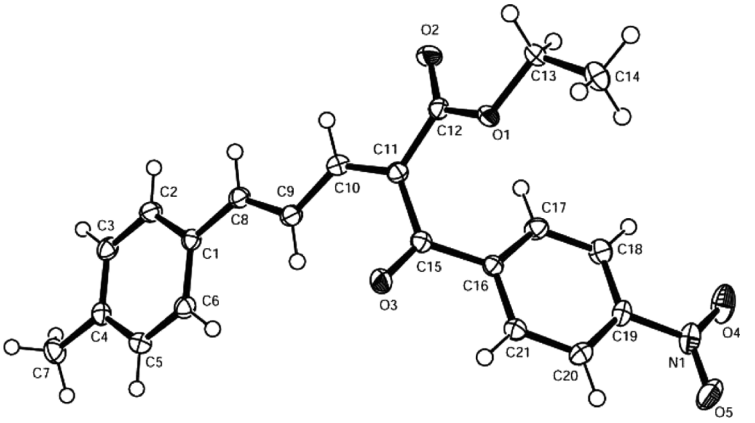

Figure 1. X-ray crystal structure of (2E,4E)-ethyl(2-*p*-nitrobenzoyl-5-*p*-tolyl)-2,4-pentadienoate (**p16**).

because of the incomplete reaction. This reaction gave two isomers, but we could not distinguish them by column chromatography. The ratio of two isomers was about 3.3:1 by NMR.

CONCLUSION

In summary, the present procedure provides a convenient and efficient method for the synthesis of α,β,γ,δ-unsaturated dicarbonyl compounds by Knoevenagel condensations of aliphatic and aromatic α,β-unsaturated aldehydes with 1,3-dicarbonyl compounds. The reaction was carried out at room temperature. It employs amino acid L-lysine as a green and efficient catalyst. This report also successfully expanded the use of primary amino acids in Knoevenagel condensations. With those significant advantages, this method has great potential for future application.

EXPERIMENTAL

General Procedure for L-Lysine-Catalyzed Knoevenagel Condensation

A catalytic amount of L-lysine (0.2 mmol, 20 mol%) was added to a vial containing α,β-unsaturated aldehyde (1 mmol), 1,3-dicarbonyl compounds (1 mmol) and DMSO (2 mL). The mixture was stirred at room temperature and monitored by thin-layer chromatography (TLC). After completion, the mixture was diluted with CH_2Cl_2 (20 ml) and washed with H_2O (10 ml × 2). The mixture was concentrated in vacuo and purified by silica-gel column chromatography (EtOAc/petrol mixtures).

Data of New Compounds

(2E,4E)-Ethyl(2-(*p*-nitrobenzoyl)-5-phenyl)-2,4-pentadienoate (p6). Yellow solid, mp 94–98 °C. ^{1}H NMR spectrum, δ, ppm: 8.33 d (2H, *p*-nitrophenyl, $J = 8.6$ Hz), 8.04 d (2H, *p*-nitrophenyl, $J = 8.6$ Hz), 7.79 d (1H, $R_3CH{=}CR_4R_5$,

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$J = 11.7$ Hz), 7.41 d (2H, Ph, $J = 1.9$ Hz), 7.34–7.33 m (3H, Ph), 7.14 d (1H, PhCH=, $J = 15.4$ Hz), 6.90 dd (1H, PhCH=CH-CH, $J_1 = 11.8$ Hz, $J_2 = 15.3$ Hz), 4.18 q (2H, OCH_2, $J = 7.1$ Hz), 1.13 t (3H, CH_3, $J = 7.1$ Hz). ^{13}C NMR spectrum, δ_C, ppm: 192.7, 164.7, 150.3, 146.1, 145.8, 142.1, 135.1, 130.1, 129.8, 129.6, 128.8, 127.8, 123.8, 122.3, 61.4, 13.9. HRMS-ESI: m/z $[M + Na]^+$ calcd. for $C_{20}H_{17}NO_5Na$ 374.0999; found 374.1001.

(2E,4E)-Ethyl(2-(*p*-nitrobenzoyl)-5-(*p*-methoxyphenyl))-2,4-pentadienoate (p11). Yellow solid, mp 143–145 °C. ^1H NMR spectrum, δ, ppm: 8.32 d (2H, *p*-nitrophenyl, $J = 8.1$ Hz), 8.02 d (2H, *p*-nitrophenyl, $J = 8.2$ Hz), 7.78 d (1H, $R_3CH=CR_4R_5$, $J = 11.8$ Hz), 7.38 d (2H, *p*-methoxyphenyl, $J = 8.2$ Hz), 7.10 d (1H, PhCH=, $J = 15.3$ Hz), 6.87–6.77 m (3H, *p*-methoxyphenyl and PhCH=CH-CH), 4.17 q (2H, OCH_2, $J = 6.9$ Hz), 3.82 (3H, s, OCH_3), 1.12 t (3H, CH_3, $J = 7.0$ Hz). ^{13}C NMR spectrum, δ_C, ppm: 192.9, 165.0, 161.4, 150.3, 147.0, 145.9, 142.5, 129.8, 129.6, 128.1, 123.8, 123.6, 120.4, 114.4, 61.3, 55.4, 14.0. HRMS-ESI: m/z $[M + Na]^+$ calcd. for $C_{21}H_{19}NO_6Na$ 404.1105; found 404.1107.

Diethyl-2-((E)-3-*p*-tolylallylidene) malonate (p14). Yellow solid, mp 61–66 °C. ^1H NMR spectrum, δ, ppm: 7.53 d (1H, $R_3CH=CR_4R_5$, $J = 11.5$ Hz), 7.40 d (2H, *p*-tolyl, $J = 7.8$ Hz), 7.34–7.22 m (1H, *p*-tolylCH=CH-CH), 7.18 d (2H, *p*-tolyl, $J = 7.2$ Hz), 7.02 d (1H, *p*-tolylCH=, $J = 15.4$ Hz), 4.37 q (2H, OCH_2, $J = 7.1$ Hz), 4.28 q (2H, OCH_2, $J = 7.0$ Hz), 2.37 s (3H, *p*-tolylCH_3), 1.38 t (3H, CH_3, $J = 7.1$ Hz), 1.33 t (3H, CH_3, $J = 7.0$ Hz). ^{13}C NMR spectrum, δ_C, ppm: 165.4, 164.8, 145.6, 144.7, 140.2, 132.9, 129.5, 127.8, 124.2, 122.3, 61.2, 21.4, 14.2. HRMS: m/z $[M + Na]^+$ calcd. for $C_{17}H_{20}O_4Na$ 311.1254; found 311.1255.

(2E,4E)-Ethyl(2-benzoyl-5-*p*-tolyl)-2,4-pentadienoate (p15). Yellow solid, mp 71–75 °C. ^1H NMR spectrum, δ, ppm: 7.91 d (2H, phenyl, $J = 8.0$ Hz), 7.70 d (1H, $R_3CH=CR_4R_5$, $J = 11.7$ Hz), 7.59–7.45 m (3H, phenyl), 7.28 d (2H, *p*-tolyl, $J = 8.1$ Hz), 7.11 d (2H, *p*-tolyl, $J = 7.7$ Hz), 7.02 d (1H, *p*-tolylCH=, $J = 15.4$ Hz), 6.78 dd (1H, *p*-tolylCH=CH-CH, $J_1 = 11.8$ Hz, $J_2 = 15.1$ Hz), 4.18 q (2H, OCH_2, $J = 7.1$ Hz), 2.32 s (3H, *p*-tolylCH_3), 1.13 t (3H, CH_3, $J = 7.1$ Hz). ^{13}C NMR spectrum, δ_C, ppm: 194.4, 165.2, 144.4, 144.1, 140.0, 137.2, 133.5, 132.7, 130.6, 129.5, 129.1, 128.6, 127.6, 121.9, 61.0, 21.4, 13.9. HRMS-ESI: m/z $[M + Na]^+$ calcd. for $C_{21}H_{20}O_3Na$ 343.1305; found 343.1307.

(2E,4E)-Ethyl(2-*p*-nitrobenzoyl-5-*p*-tolyl)-2,4-pentadienoate (p16). Yellow solid, mp 131–134 °C. ^1H NMR spectrum, δ, ppm: 8.32 d (2H, *p*-nitrophenyl, $J = 8.5$ Hz), 8.03 d (2H, *p*-nitrophenyl, $J = 8.4$ Hz), 7.78 d (1H, $R_3CH=CR_4R_5$, $J = 11.7$ Hz), 7.32 d (2H, *p*-tolyl, $J = 7.8$ Hz), 7.13 d (2H, *p*-tolyl, $J = 7.3$ Hz), 7.09 (1H, *p*-tolylCH=), 6.87 dd (1H, *p*-tolylCH=CH-CH, $J_1 = 11.9$ Hz, $J_2 = 14.9$ Hz), 4.17 q (2H, OCH_2, $J = 7.0$ Hz), 2.34 s (3H, *p*-tolylCH_3), 1.12 t (3H, CH_3, $J = 7.1$ Hz). ^{13}C NMR spectrum, δ_C, ppm: 192.8, 164.8, 150.2, 146.6, 146.0, 142.2, 140.6, 132.4, 129.7, 129.6, 128.8, 127.8, 123.8, 121.4, 61.3, 21.4, 13.9. HRMS-ESI: m/z $[M + Na]^+$ calcd. for $C_{21}H_{19}NO_5Na$ 388.1155; found 388.1148.

Diethyl-2-((E)-3-*p*-chlorophenylallylidene)malonate (p19). White solid, mp 75–76 °C. ^1H NMR spectrum, δ, ppm: 7.50 d (1H, $R_3CH=CR_4R_5$, $J = 11.5$ Hz), 7.43 d (2H, *p*-chlorophenyl, $J = 8.4$ Hz), 7.34 d (2H, *p*-chlorophenyl, $J = 8.4$ Hz), 7.23

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dd (1H, *p*-chlorophenylCH=CH-CH, $J_1 = 11.6$ Hz, $J_2 = 15.3$ Hz), 6.98 d (1H, *p*-chlorophenylCH=C, $J = 15.4$ Hz), 4.37 q (2H, OCH_2, $J = 7.1$ Hz), 4.28 q (2H, OCH_2, $J = 7.1$ Hz), 1.38 t (3H, CH_3, $J = 7.1$ Hz), 1.33 t (3H, CH_3, $J = 7.1$ Hz). ^{13}C NMR spectrum, δ_C, ppm: 165.1, 164.5, 144.7, 142.8, 135.5, 134.0, 129.0, 128.8, 125.4, 123.7, 61.3, 14.1. HRMS-ESI: m/z $[M + Na]^+$ calcd. for $C_{16}H_{17}ClO_4Na$ 331.0708; found 331.0708.

(2E,4E)-Ethyl(2-benzoyl-5-*p*-chlorophenyl)-2,4-pentadienoate (p21). Yellow solid, mp 99–102 °C. ^1H NMR spectrum, δ, ppm: 7.90 d (2H, phenyl, $J = 7.8$ Hz), 7.68 d (1H, $R_3CH{=}CR_4R_5$, $J = 11.6$ Hz), 7.62–7.58 m (1H, phenyl), 7.51–7.46 m (2H, phenyl), 7.32–7.28 m (4H, *p*-chlorophenyl), 6.99 d (1H, *p*-chlorophenylCH=C, $J = 15.4$ Hz), 6.83–6.78 m (1H, *p*-chlorophenylCH=CH-CH), 4.18 q (2H, OCH_2, $J = 7.1$ Hz), 1.13 t (3H, CH_3, $J = 7.1$ Hz). ^{13}C NMR spectrum, δ_C, ppm: 194.1, 165.0, 143.5, 142.2, 137.2, 135.4, 134.0, 133.6, 131.9, 129.1, 129.0, 128.7, 128.7, 123.4, 61.2, 13.9. HRMS-ESI: m/z $[M + Na]^+$ calcd. for $C_{20}H_{17}ClO_3Na$ 363.0758; found 363.0753.

(2E,4E)-Ethyl(2-*p*-nitrobenzoyl-5-*p*-chlorophenyl)-2,4-pentadienoate (p22). Yellow solid, mp 151–153 °C. ^1H NMR spectrum, δ, ppm: 8.33 d (2H, *p*-nitrophenyl, $J = 8.5$ Hz), 8.03 d (2H, *p*-nitrophenyl, $J = 8.5$ Hz), 7.76 d (1H, $R_3CH{=}CR_4R_5$, $J = 11.6$ Hz), 7.36 d (2H, *p*-chlorophenyl, $J = 8.4$ Hz), 7.30 d (2H, *p*-chlorophenyl, $J = 8.4$ Hz), 7.08 d (1H, *p*-chloroCH=, $J = 15.4$ Hz), 6.87 dd (1H, *p*-chlorophenylCH=CH-CH, $J_1 = 11.7$ Hz, $J_2 = 15.1$ Hz), 4.18 q (2H, OCH_2, $J = 7.1$ Hz), 1.13 t (3H, CH_3, $J = 7.1$ Hz). ^{13}C NMR spectrum, δ_C, ppm: 192.6, 164.6, 150.4, 145.8, 144.2, 142.0, 136.0, 133.7, 130.2, 129.8, 129.1, 129.0, 123.9, 122.9, 61.5, 13.9. HRMS: m/z $[M + Na]^+$ calcd. for $C_{20}H_{16}ClNO_5Na$ 408.0609; found 408.0607.

Diethyl-2-((E)-3-*p*-fluorophenylallylidene)malonate (p25). White solid, mp 63–65 °C. ^1H NMR spectrum, δ, ppm: 7.52–7.45 m (3H, *p*-fluorophenyl and $R_3CH{=}CR_4R_5$), 7.19 dd (1H, *p*-fluorophenylCH=CH-CH, $J_1 = 11.6$ Hz, $J_2 = 15.3$ Hz), 7.09–6.97 m (3H, *p*-fluorophenyl and *p*-fluorophenylCH=), 4.37 q (2H, OCH_2, $J = 7.1$ Hz), 4.28 q (2H, OCH_2, $J = 7.1$ Hz), 1.38 t (3H, CH_3, $J = 7.1$ Hz), 1.33 t (3H, CH_3, $J = 7.1$ Hz). ^{13}C NMR spectrum, δ_C, ppm: 165.3, 164.7, 163.5 d ($J = 249.6$ Hz), 145.0, 143.1, 131.8, 129.5 d ($J = 8.2$ Hz), 125.0, 123.0, 115.9 d ($J = 21.8$ Hz), 61.3, 14.2. HRMS-ESI: m/z $[M + Na]^+$ calcd. for $C_{16}H_{17}FO_4Na$ 315.1003; found 315.1005.

(2E,4E)-Ethyl(2-benzoyl-5-*p*-fluorophenyl)-2,4-pentadienoate (p26). White solid, mp 107–108 °C. ^1H NMR spectrum, δ, ppm: 7.91 d (2H, phenyl, $J = 7.2$ Hz), 7.70–7.66 m (1H, phenyl), 7.59 d (1H, $R_3CH{=}CR_4R_5$, $J = 7.2$ Hz), 7.48 dd (2H, phenyl, $J_1 = 7.2$ Hz, $J_2 = 7.3$ Hz), 7.35 d (2H, *p*-flurophenyl, $J = 5.4$ Hz), 7.02–6.97 m (3H, *p*-flurophenyl and *p*-flurophenylCH=), 6.78–6.73 m (1H, *p*-fluorophenylCH=CH-CH), 4.18 q (2H, OCH_2, $J = 7.1$ Hz), 1.13 t (3H, CH_3, $J = 7.1$ Hz). ^{13}C NMR spectrum, δ_C, ppm: 194.2, 165.0, 163.3 d ($J = 250.3$ Hz), 143.8, 142.5, 137.1, 133.6, 131.7, 131.3, 129.4 d ($J = 8.2$ Hz), 129.1, 128.6, 122.6, 115.8 d ($J = 21.8$ Hz), 61.1, 13.9. HRMS-ESI: m/z $[M + Na]^+$ calcd. for $C_{20}H_{17}FO_3Na$ 347.1054; found 347.1051.

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(2E,4E)-Ethyl(2-*p*-nitrobenzoyl-5-*p*-fluorophenyl)-2,4-pentadienoate (p27). Yellow solid; mp 121–123 °C. ^{1}H NMR spectrum, δ, ppm: 8.32 d (2H, *p*-nitrophenyl, $J = 8.1$ Hz), 8.03 d (2H, *p*-nitrophenyl, $J = 8.0$ Hz), 7.76 d (1H, $R_3CH{=}CR_4R_5$, $J = 11.7$ Hz), 7.44–7.39 m (2H, *p*-fluorophenyl), 7.13–7.00 m (3H, *p*-fluorophenyl and *p*-fluorophenylCH=), 6.83 dd (1H, *p*-fluorophenylCH=CH-CH, $J_1 = 12.0$ Hz, $J_2 = 15.0$ Hz), 4.18 q (2H, OCH_2, $J = 7.0$ Hz), 1.13 t (3H, CH_3, $J = 7.0$ Hz). ^{13}C NMR spectrum, δ_C, ppm: 192.7, 164.7, 163.7 d ($J = 250.3$ Hz), 150.4, 146.1, 144.4, 142.1, 131.5, 129.8, 129.7, 123.9, 122.2, 116.2, 115.9, 61.4, 14.0. HRMS-ESI: m/z $[M + Na]^+$ calcd. for $C_{20}H_{16}FNO_5Na$ 392.0905; found 392.0907.

(4E)-Ethyl(2-*p*-nitrobenzoyl)-2,4-hexadienoate (p32). The spectroscopy showed that the product is a mixture of two isomers. Data of the major isomer are listed. Yellow oil. ^{1}H NMR spectrum, δ, ppm: 8.31 d (2H, *p*-nitrophenyl, $J = 8.5$ Hz), 8.01 d (2H, *p*-nitrophenyl, $J = 8.6$ Hz), 7.58 d (1H, $R_3CH{=}CR_4R_5$, $J = 11.6$ Hz), 6.43 dd (1H, methylCH=CH-CH, $J_1 = 7.1$ Hz, $J_2 = 19.7$ Hz), 6.37–6.15 m (1H, methylCH=), 4.16 q (2H, OCH_2, $J = 7.2$ Hz), 1.86 d (3H, methyl, $J = 6.7$ Hz), 1.11 t (3H, CH_3, $J = 7.1$ Hz). ^{13}C NMR spectrum, δ_C, ppm: 192.8, 164.8, 149.0, 147.8, 146.1, 145.8, 141.9, 129.8, 126.5, 123.8, 61.3, 19.1, 13.9. HRMS: m/z $[M + Na]^+$ calcd. for $C_{15}H_{15}NO_5Na$ 312.0842; found 312.0837.

Supplementary Material: The ^{1}H NMR, ^{13}C NMR and HRMS spectra of new compounds are given as Supplementary Material (available online).

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