Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Available online: 13 Sep 2010

To cite this article: Shi-Jie Zhang & Wei-Xiao Hu (2010): Method for Regio- and Stereoselective Synthesis of (E)-β,γ-Unsaturated Acids from Aldehydes Under Solvent-Free Conditions, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 40:20, 3093-3100

To link to this article: http://dx.doi.org/10.1080/00397910903370659

Synthetic Communications®, 40: 3093–3100, 2010

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910903370659

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METHOD FOR REGIO- AND STEREOSELECTIVE SYNTHESIS OF (*E*)-β,γ-UNSATURATED ACIDS FROM ALDEHYDES UNDER SOLVENT-FREE CONDITIONS

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Synthesis of (E)-β,γ-unsaturated acids from aldehydes with malonic acid has been explored under solvent-free conditions. The modified Knoevenagel condensation reaction with N-methyl morpholine (NMM) as catalyst exhibits highly β,γ-regioselectivity and exclusively E-stereoselectivity. A mechanism accounting for both regio- and stereoselectivity has been proposed and preliminarily studied.

Keywords: Knoevenagel reaction; regioselectivity; solvent-free; stereoselectivity; β,γ-unsaturated acid

INTRODUCTION

Knoevenagel condensation reactions, involving microwave irradiation, ultrasound irradiation, no solvent, ionic liquids, and dry grinding, have been widely reported.[1] Of these, the reaction with aldehydes and malonic acid is a practical synthetic route to (*E*)-α,β-unsaturated acids with Doebner modification.[2] However, (*E*)-β,γ-unsaturated acids be obtained only in very poor yields from the classical Knoevenagel reactions. The Linstead modification of Knoevenagel reactions suffers from poor yields of β,γ-unsaturated acids (10–37%).[3] Ragoussis and Ragoussis offered a modified Knoevenagel condensation of aldehydes with a straight carbon chain with malonic acid catalyzed by piperidinium acetate, either in dimethylsulfoxide (DMSO) or dimethylformamide (DMF), at 100 °C to afford (*E*)-β,γ-unsaturated aliphatic acids with yields of 86–90% and stereoselectivity of 98%.[4] This was better than that treated in refluxing xylene, which gave 60–85% yields.[5] Zope et al. did the reaction catalyzed by piperidinium acetate in refluxing xylene to obtain 3-nonenoic acid, 3-decenoic acid, and 3-dodecenoic acid from the corresponding aldehydes in 40%, 38% and 45% yields, respectively.[6] Rao et al. discovered that Knoevenagel condensation of long-chain aliphatic aldehydes with malonic acid in triethylamine gave (*E*)-3-alkenoic acids in 80–88% yields, and the synthesis avoided the use of large molar excess of malonic acid.[7] Chen and Li's group found that malonic acid reacted on aliphatic aldehyde catalyzed by a trace of triethylamine supported on zeolite to

Received May 11, 2009.
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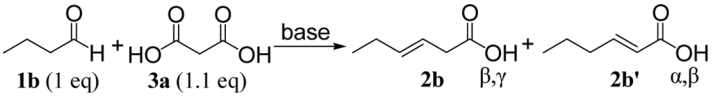
give β,γ-alkenyl carboxylic acids with moderate to good yields, and the β,γ-isomers occupied more than 80%.[8] Kumar et al. presented microwave-promoted, SiO_2-catalyzed Knoevenagel condensation of aldehydes (C_α position unbranched) with malonic acid for the preparation of β,γ-unsaturated acids under solvent-free conditions with yields greater than 80% and stereochemical purity no less than 98%.[9] However, to our knowledge, seldom has the synthesis of (*E*)-β,γ-unsaturated acids been studied comprehensively. Drawbacks have included limited scope of aldehydes, poor yields and poor selectivity, and excessive amounts of reagents.

Herein, we provide a method for regio- and stereoselective synthesis of (*E*)-β,γ-unsaturated acids from aldehydes under solvent-free conditions.

RESULTS AND DISCUSSION

We initiated our study with a screen of several different bases as catalysts for the reaction of n-butyraldehyde with malonic acid (Table 1). To avoid side reactions such as addition and polymerization to the double bond of products at higher temperatures, the reaction temperature was set at 80 °C. Most reactions inevitably led to mixtures of isomeric acids with the α,β-congener as a minor component, as indicated by ^{1}H NMR studies of the crude products. Not unexpectedly, in reactions where pyridine was used as catalyst, the selectivity shifted to α,β-isomer **2b′** (entry 6 in Table 1). In addition, the *E*-stereoselectivity exclusively dominated, and no *Z*-isomer was identified from ^{1}H NMR with slightly different proton shifting and vicinal coupling constants. Moreover, infrared (IR) absorptions of the product at 968 cm^{-1} further supported the identification of *trans*-olefin. Because the yields were poor,

Table 1. Effects for Knoevenagel condensation of n-butyraldehyde with malonic acid



Entry	Base	Base (eq.)	T (°C)	Yield (%)[a]	β,γ:α,β[b]	*E:Z*[c]
1	—	—	80	5.1	68:32	—
2	Et_3N	1.1	80	66.7	94:6	>99:1
3	n-Bu_3N	1.1	80	51.0	95:5	>99:1
4	Morpholine	1.1	80	61.4	81:19	>99:1
5	NMM	1.1	80	68.4	96:4	>99:1
6	Pyridine	1.1	80	61.4	4:96	>99:1
7	Piperidine	1.1	80	73.7	73:27	>99:1
8	DBU	1.1	80	72.0	85:15	>99:1
9	NaOH	1.1	80	43.9	97:3	>99:1
10	Na_2CO_3	1.1	80	40.4	91:9	>99:1
11	NMM	0.1	80	52.6	88:12	>99:1
12	NMM	2.0	80	47.4	94:6	>99:1
13	NMM	1.1	Rt	No reaction	—	—

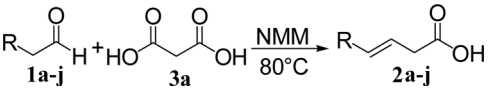
[a]Yields refer to isolated combined product of β,γ- and α,β-hexenoic acids.
[b]Determined by ^{1}H NMR analysis of the crude product.
[c]Ratio of *E*:*Z* refers to β,γ-hexenoic acids, and >99:1 means only one isomer was observed.

we thought that the self-condensation of n-butyraldehyde happened when using strong bases (entry 9 and 10 in Table 1). Although the yields of the reaction with piperidine (entry 7 in Table 1) or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (entry 8 in Table 1) as catalysts were greater than that with N-methyl morpholine (NMM) (entry 5 in Table 1), considering the product yield and the ratio of β,γ/α,β, we choose NMM as the best catalyst. When we conducted the reaction at room temperature with NMM, the reaction did not occur at all, and the mixtures were heterogeneous (entry 13 in Table 1). The catalytic amount of NMM at 10 mol% was not enough to run the reaction smoothly, and apparently 2.0 equivalents of NMM was not rewarding (entries 11 and 12 in Table 1).

With this information in hand, we established the scope of the reaction with different aldehydes in the presence of NMM as catalyst (Table 2). All of the products had exclusively *E*-conformation, except 4-methyl-3-pentenoic acid **2c**, which does not bear such double-bond geometry. Besides, the yield of **2c** starting from the C_α position branched aldehyde **1c** was lowest, and its regioselectivity poorest, but the yield at 42.1% and the selectivity of β,γ at 88% in our results are still much better than those of previous works.[5,9] The regioselectivity of β,γ and α,β for other products was excellent, and the percentage of β,γ-isomer exceeded at least 93%, among which (*E*)-3-eicosenoic acid **2h** had the greatest yield and regioselectivity. It seemed to be the reason for its high lipophilic property, and hence was not easily lost in water washing, whereas the poor yield of **2a** could be explained by the loss from washing with water. This reaction conditions were also feasible for the condensation of long-chain aromatic aldehydes and malonic acid with good yields and excellent selectivity.

Because the performance of Et_3N was quite equal to that of NMM in the reaction with n-butyraldehyde (entries 2 and 5 in Table 1), we repeated the reaction to

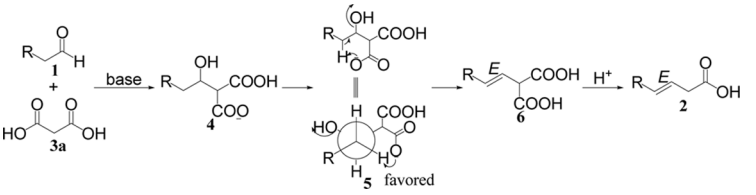
Table 2. Knoevenagel condensation to (*E*)-β,γ-unsaturated acids



1a-j **3a** **2a-j**

Compound	R	Yield (%)[a]	β,γ:α,β[b]	E:Z[c]
2a	CH_3-	56.0	93:7	>99:1
2b	CH_3CH_2-	68.4	96:4	>99:1
2c	$(CH_3)_2-$	42.1	88:12	—
2d	$CH_3(CH_2)_2-$	75.0	96:4	>99:1
2e	$(CH_3)_2CH-$	89.1 (90.6)[d]	98:2 (96:4)[d]	>99:1 (>99:1)[d]
2f	$CH_3(CH_2)_4-$	86.4	96:4	>99:1
2g	$CH_3(CH_2)_5-$	85.2	97:3	>99:1
2h	$CH_3(CH_2)_{15}-$	96.1	>99:1	>99:1
2i	Ph−	75.3	93:7	>99:1
2j	$Ph(CH_2)_2-$	84.2	96:4	>99:1

[a]Yields refer to isolated combined product of β,γ- and α,β-unsaturated acids.
[b]Determined by ^1H NMR analysis of the crude product.
[c]Ratio of *E*:*Z* refers to β,γ-unsaturated acids, and >99:1 means only one isomer was observed.
[d]Data in parantheses refer to the results of reaction with Et_3N instead of NMM.



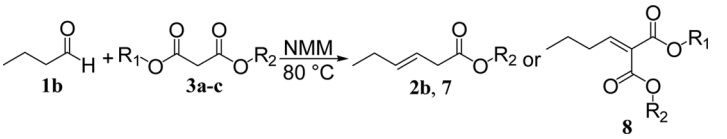
Scheme 1. Plausible mechanism for the formation of (*E*)-β,γ-unsaturated acid.

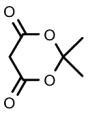
yield **2e** with Et_3N as catalyst, and the results were also quite equal to those with NMM. Only the regioselectivity was seemingly less than that obtained with NMM.

A nucleophic addition of a hydrogen located at active methylene in **3a** to a carbonyl group of **1** gave rise to hydroxymalonic acid **4**. The elimination of water from the intermediate **4** led to two choices: α,β-unsaturated acid or β,γ-unsaturated acid. The mechanism for the formation of the unsaturated acid was proposed by E. J. Corey[10] and is a generally accepted mechanism for Knoevenagel condensation reactions. A plausible mechanism is proposed for the formation of (*E*)-β,γ-unsaturated acid in Scheme 1. We have postulated that the dehydration from β-OH would be preferable with γ-H, as it interacted with one carboxylate ion to form a six-membered ring **5**. A conformational study of the Newman's projection indicated that a *trans* double bond was far more stable during dehydration. The heavily favored (*E*)-β,γ-unsaturated dicarboxylic acid **6,** in a subsequent step, decarboxylated to give (*E*)-β,γ-unsaturated acid **2**.

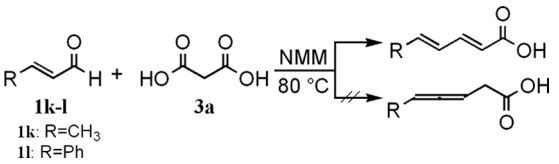
According to the proposed mechanism, it seemed reasonable to assume that one carboxylic acid group linked to active methylene was enough to trigger the reaction. We verified the hypothesis by reaction of n-butyraldehyde with malonic acid **3a**, mono-ethyl malonate **3b**, diethyl malonate **3c**, and Meldrum's acid **3d**, respectively.

Table 3. Knoevenagel condensation of n-butyraldehyde with malonic acid and its derivatives



Compound **3**	R_1	R_2	Product	Yield (%)[a]	β,γ:α,β[b]	***E:Z***[c]
3a	H	H	**2b**	68.4	96:4	>99:1
3b	H	Et	**7**	69.9	93:7	>99:1
3c	Et	Et	**8**	87.9	15:85	—
3d			Complex	—	—	—

[a]Yields refer to isolated combined product of β,γ- and α,β-isomers.
[b]Determined by ^1H NMR analysis of crude product.
[c]Ratio of *E*:*Z* refers to β,γ-isomers, and >99:1 means only one isomer was observed.



Scheme 2. Knoevenagel condensation of α,β-unsaturated aldehydes with malonic acids.

From the results shown in Table 3, when one carboxylic group was masked as ethyl ester, (*E*)-ethyl 3-hexenoate **7** was obtained successfully, accompanied by 7% *E*-ethyl 2-hexenoate. When both carboxylic groups were replaced by ethyl esters, only diethyl butylidenemalonate **8** was found with a yield of 87.9%, the formation of which was probably through the mechanism for classical Knoevenagel condensation reaction rather than what we have proposed. However, a complex mass of by-products was eventually derived from the reaction of n-butyraldehyde with Meldrum's acid.

In addition, the limitation of the reaction was preliminarily studied. In the presence of NMM, α,β-unsaturated aldehydes and malonic acid were transformed to conjugated dienoic acids rather than allenoic acids. We have found that (*E*)-crotonaldehyde **1k** and (*E*)-cinnamaldehyde **1l** reacted with malonic acid **3a**, predominantly resulting in (*E,E*)-2,4-hexadienoic acid and (*E,E*)-5-phenyl-2,4pentadienoic acid, respectively, as shown in Scheme 2. The explanation for the results was that γ-H in a double bond should be difficult to eliminate and conjugated dienoic acids are far more stable, thus classical Knoevenagel condensation took place.

CONCLUSIONS

In conclusion, we have improved a Knoevenagel condensation reaction. The modified reaction with NMM as catalyst is highly β,γ-regioselective and exclusively *E*-stereoselective, and it can be used with aliphatic aldehydes under solvent-free conditions. The mechanism of the reaction was proposed and preliminarily studied. Efforts are under way to disclose the details of the related reactions.

EXPERIMENTAL

Melting points were taken on an XRC-1 apparatus and are uncorrected. IR spectra were obtained on a Thermo Nicolet Avatar 370 Fourier transform (FT)–IR spectrophotometer. ^{1}H NMR spectra were recorded on a Brucker AC-80 spectrometer operating at 400 MHz using tetramethylsilane (TMS) as an internal standard in $CDCl_3$. All the chemicals and solvents were obtained from commercial sources and used as received.

General Procedure for Synthesis of (*E*)-β,γ-Unsaturated Acids (2a–j)

Aldehyde **1a–j** (50 mmol) was added to a mixture of malonic acid **3a** (5.7 g, 55 mmol) and NMM (5.6 g, 55 mmol) with stirring. The reaction mixture was then

heated in an oil bath at 95 °C, and the inner temperature was about 80 ± 5 °C for 8 h. After completion, the mixture was cooled to room temperature, and 11% sulfuric acid (25 mL) was added with continuous stirring for 0.5 h. The mixture was extracted with dichloromethane (20 mL × 3), washed with H_2O (20 mL × 3), dried over $MgSO_4$, and concentrated under reduced pressure to give the crude products **2a–j**, which were pure enough to be characterized.

All spectral data were in agreement with those reported in the literature.[5,11]

Data

(*E*)-3-Pentenoic acid (2a). Colorless oil. IR (liquid film, ν_{max}/cm^{-1}): 2971, 1712, 1417, 1292, 1223, 967. ^1H NMR (400 MHz, $CDCl_3$): δ 11.36 (br, 1H, COOH), 5.66 (dtt, $J = 1.2$, 6.4, 15.2 Hz, 1H, $CH_3-CH=CH-$), 5.57 (dtt, $J = 1.2$, 6.4, 15.2 Hz, 1H, $CH_3-CH=CH-$), 3.11 (dt, $J = 1.2$, 7.2 Hz, 2H, $-CH_2-CO-$), 1.75 (dt, $J = 1.2$, 6.4 Hz, 3H, CH_3-).

(*E*)-3-Hexenoic acid (2b). Colorless oil. IR (liquid film, ν_{max}/cm^{-1}): 2965, 2876, 1712, 1408, 1286, 968. ^1H NMR (400 MHz, $CDCl_3$): δ 9.82 (br, 1H, COOH), 5.66 (dtt, $J = 1.6$, 6.4, 15.6 Hz, 1H, $CH_3-CH_2-CH=CH-$), 5.55 (dtt, $J = 1.6$, 6.8, 15.2 Hz, 1H, $CH_3-CH_2-CH=CH-$), 3.09 (d, $J = 6.8$ Hz, 2H, $-CH_2-CO-$), 2.10 (m, $J = 6.8$ Hz, 2H, CH_3-CH_2-), 0.99 (t, $J = 7.6$ Hz, 3H, CH_3-).

(*E*)-2-Hexenoic acid (2b′). Colorless oil. IR (liquid film, ν_{max}/cm^{-1}): 2964, 2876, 1698, 1654, 1283, 982. ^1H NMR (400 MHz, $CDCl_3$): δ 10.24 (br, 1H, COOH), 7.11 (dt, $J = 7.2$, 15.2 Hz, 1H, $-CH=CH-COOH$), 5.86 (dt, $J = 1.6$, 15.2 Hz, 1H, $-CH=CH-COOH$), 2.25 (dq, $J = 1.6$, 7.2 Hz, 2H, $CH_3-CH_2-CH_2-$), 1.61–1.49 (m, $J = 7.2$ Hz, 2H, $CH_3-CH_2-CH_2-$), 0.98 (t, $J = 7.4$ Hz, 3H, CH_3-).

4-Methyl-3-pentenoic acid (2c). Colorless oil. IR (liquid film, ν_{max}/cm^{-1}): 2969, 1709, 1384, 828. ^1H NMR (400 MHz, $CDCl_3$): δ 5.33–5.29 (m, 1H, $-C=CH-$), 3.10 (d, $J = 7.2$ Hz, 2H, $-CH_2-CO-$), 1.77 (s, 3H, CH_3-), 1.66 (s, 3H, CH_3-).

(*E*)-3-Heptenoic acid (2d). Colorless oil. IR (liquid film, ν_{max}/cm^{-1}): 2960, 2873, 1713, 1415, 1292, 1221, 968. ^1H NMR (400 MHz, $CDCl_3$): δ 11.15 (br, 1H, COOH), 5.64–5.59 (m, 1H, $CH_3-CH_2-CH_2-CH=CH-$), 5.57–5.49 (m, 1H, $CH_3-CH_2-CH_2-CH=CH-$), 3.09 (dd, $J = 1.2$, 6.8 Hz, 2H, $-CH_2-CO-$), 2.03 (q, $J = 6.8$ Hz, 2H, $CH_3-CH_2-CH_2-$), 1.40 (m, $J = 7.2$ Hz, 2H, $CH_3-CH_2-CH_2-$), 0.91 (t, $J = 7.4$ Hz, 3H, CH_3-).

(*E*)-5-Methyl-3-hexenoic acid (2e). Colorless oil. IR (liquid film, ν_{max}/cm^{-1}): 2961, 2872, 1713, 1413, 1287, 1222, 970. ^1H NMR (400 MHz, $CDCl_3$): δ 11.68 (br, 1H, COOH), 5.58 (dtt, $J = 1.6$, 6.4, 15.6 Hz, 1H, $(CH_3)_2-CH-CH=CH-$), 5.48 (dtt, $J = 1.2$, 6.4, 15.6 Hz, 1H, $(CH_3)_2-CH-CH=CH-$), 3.08 (d, $J = 6.4$ Hz, 2H, $-CH_2-CO-$), 2.31 (m, $J = 6.8$ Hz, 1H, $(CH_3)_2-CH-$), 1.00 (d, $J = 6.8$ Hz, 6H, $(CH_3)_2-$).

(*E*)-3-Nonenoic acid (2f). Colorless oil. IR (liquid film, ν_{max}/cm^{-1}): 2958, 2928, 2858, 1712, 1414, 1384, 1288, 1222, 968, 726. ^1H NMR (400 MHz, $CDCl_3$): δ 11.55 (br, 1H, COOH), 5.61 (dt, $J = 6.4$, 15.2 Hz, 1H, $-CH=CH-CH_2-CO$), 5.51 (dt, $J = 6.8$, 15.2 Hz, 1H, $-CH=CH-CH_2-CO$), 3.08 (d, $J = 6.4$ Hz, 2H,

$-C\underline{H}_2-CO-$), 2.04 (q, $J = 6.8$ Hz, 2H, $-C\underline{H}_2-CH=CH-$), 1.34–1.26 (m, 6H, $CH_3-(C\underline{H}_2)_3-$), 0.89 (t, $J = 7.4$ Hz, 3H, $C\underline{H}_3-$).

(*E*)-3-Decenoic acid (2g). Colorless oil. IR (liquid film, ν_{max}/cm^{-1}): 2927, 2856, 1713, 1415, 1384, 1290, 1222, 967, 724. ^1H NMR (400 MHz, $CDCl_3$): δ 11.58 (br, 1H, COO*H*), 5.61 (dt, $J = 6.4$, 15.2 Hz, 1H, $-CH=C\underline{H}-CH_2-CO$), 5.52 (dt, $J = 6.4$, 15.2 Hz, 1H, $-C\underline{H}=CH-CH_2-CO$), 3.08 (d, $J = 6.8$ Hz, 2H, $-C\underline{H}_2-CO-$), 2.05 (q, $J = 6.8$ Hz, 2H, $-C\underline{H}_2-CH=CH-$), 1.33–1.27 (m, 8H, $CH_3-(C\underline{H}_2)_4-$), 0.89 (t, $J = 7.2$ Hz, 3H, $C\underline{H}_3-$).

(*E*)-3-Eicosenoic acid (2h). White solid; mp 54–55 °C. IR (KBr, ν_{max}/cm^{-1}): 2918, 2848, 1711, 1471, 1463, 1242, 1113, 961, 865, 719, 619. ^1H NMR (400 MHz, $CDCl_3$): δ 5.59 (dt, $J = 6.2$, 15.6 Hz, 1H, $-CH=C\underline{H}-CH_2-COOH$), 5.51 (dt, $J = 6.4$, 15.6 Hz, 1H, $-C\underline{H}=CH-CH_2$-COOH), 3.07 (d, $J = 6.8$ Hz, 2H, $-C\underline{H}_2-CO-$), 2.03 (q, $J = 6.8$ Hz, 2H, $-C\underline{H}_2-CH=CH$-), 1.26 (s, 28H, $CH_3-(C\underline{H}_2)_{14}-$), 0.88 (t, $J = 6.6$ Hz, 3H, $C\underline{H}_3-$).

(*E*)-4-Phenyl-3-butenoic acid (2i). Colorless oil. IR (liquid film, ν_{max}/cm^{-1}): 3027, 1709, 1600, 1494, 1384, 966, 750, 699. ^1H NMR (400 MHz, $CDCl_3$): δ 7.37–7.12 (m, 5H, Ar), 6.48 (d, $J = 16.0$ Hz, 1H, Ph$-C\underline{H}=CH-$), 6.26 (dt, $J = 7.2$, 16.0 Hz, 1H, Ph$-CH=C\underline{H}-$), 3.25 (dd, $J = 1.4$, 7.0 Hz, 2H, $-C\underline{H}_2-CO-$).

(*E*)-6-Phenyl-3-hexenoic acid (2j). Colorless oil. IR (liquid film, ν_{max}/cm^{-1}): 3026, 2934, 2858, 1709, 1603, 1496, 1453, 968, 747, 699. ^1H NMR (400 MHz, $CDCl_3$): δ 7.26 (t, $J = 6.6$ Hz, 2H, Ar), 7.18–7.15 (m, 3H, Ar), 5.66–5.50 (m, 2H, $-C\underline{H}=C\underline{H}-$), 3.05 (d, $J = 6.8$ Hz, 2H, $-C\underline{H}_2-CO-$), 2.62 (t, $J = 7.2$ Hz, Ph-$C\underline{H}_2$-), 2.31 (q, $J = 7.2$ Hz, $-C\underline{H}_2-CH=CH-$).

(*E*)-Ethyl 3-hexenoate 7

Compound **7** was prepared from n-butyraldehyde **1b** (2.9 g, 40 mmol) with mono-ethyl malonate **3b** (5.8 g, 44 mmol) following the condensation reaction described for **2a–f**. Colorless oil. IR (liquid film, ν_{max}/cm^{-1}): 2964, 2936, 2875, 1737, 1687, 1463, 1177, 1033, 969. ^1H NMR (400 MHz, $CDCl_3$): δ 5.61 (dtt, $J = 1.6$, 6.0, 15.2 Hz, 1H, $CH_3-CH_2-C\underline{H}=CH-$), 5.52 (dtt, $J = 1.6$, 7.2, 15.2 Hz, 1H, $CH_3-CH_2-CH=C\underline{H}-$), 4.16 (q, $J = 6.8$ Hz, 2H, $-COOC\underline{H}_2CH_3$), 3.02 (dd, $J = 1.2$, 6.8 Hz, 2H, $-C\underline{H}_2-CO-$), 2.06 (m, $J = 7.4$ Hz, 2H, $CH_3-C\underline{H}_2-$), 1.27 (t, $J = 7.2$ Hz, 3H, $-COOCH_2C\underline{H}_3$), 0.99 (t, $J = 7.6$ Hz, 3H, $C\underline{H}_3-$).

Diethyl Butylidenemalonate 8

Compound **8** was prepared from n-butyraldehyde **1b** (3.6 g, 50 mmol) with diethyl malonate **3c** (8.8 g, 55 mmol) following the condensation reaction described for **2a–f.** Colorless oil. IR (liquid film, ν_{max}/cm^{-1}): 2965, 2938, 2875, 1750, 1734, 1465, 1371, 1036. ^1H NMR (400 MHz, $CDCl_3$): δ 7.02 (t, $J = 8.0$ Hz, 1H, $-C\underline{H}=C-$), 4.23 (q, $J = 7.2$ Hz, 4H, $2 \times -COOC\underline{H}_2CH_3$), 1.58–1.52 (m, 2H, $CH_3-CH_2-C\underline{H}_2-$), 1.37–1.29 (m, 8H, $CH_3-C\underline{H}_2-$and $2 \times -COOCH_2C\underline{H}_3$), 0.97 (t, $J = 7.2$ Hz, 3H, $C\underline{H}_3-$).

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