A Simple and Direct Access to Ethylidene Malonates

Maité Sylla, Delphine Joseph, Emilie Chevallier, Cheikhou Camara, Françoise Dumas*

Laboratoire de Synthèse de Composés d'Intérêt Biologique, BioCIS, Unité associée au CNRS, Centre d'Etudes Pharmaceutiques, Université Paris Sud, 5 rue Jean-Baptiste Clément, 92296 Châtenay-Malabry Cedex, France
Fax +33(1)46835752; E-mail: francoise.dumas@cep.u-psud.fr

Received 29 June 2005; revised 7 November 2005

Abstract: The condensation of active methylene compounds **1** with acetaldehyde was efficiently promoted by a catalytic amount of lithium bromide in the presence of acetic anhydride to give ethylidene malonates **2** in 77–97% yield.

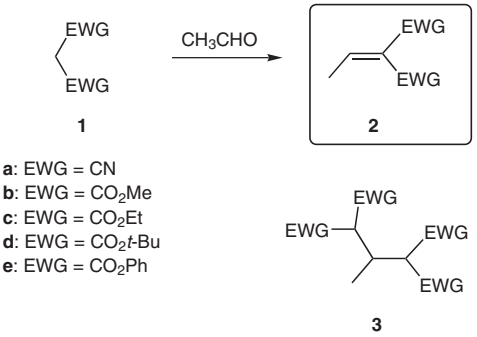
Key words: Knoevenagel condensations, catalysis, aldol reactions, aldehydes, substituent effects

As a part of our program directed toward the synthesis of highly substituted optically active synthons bearing vicinally substituted quaternary and tertiary carbon centers,[1] we faced the problem of the low reactivity of alkyl and aryl crotonates in the Michael reaction of chiral imines.[2] In this respect, we selected the corresponding ethylidene malonates **2** (Scheme 1)[3] as synthetic equivalents of alkyl crotonates possessing an enhanced reactivity. Indeed, alkylidene malonates are well-known intermediates in organic synthesis, mainly due to the reactions of their double bond which is activated by conjugation with two electron-withdrawing groups. However, despite numerous published routes to aryl- and alkylidene malonates,[4] the synthesis of the ethylidene derivatives remains delicate.

The introduction of a carbon–carbon double bond carrying one or two electron-withdrawing groups is a cornerstone of synthetic organic chemistry in the form of numerous reactions including Perkin, Knoevenagel, Stobbe, Claisen and Wittig condensations, and dehydration products of Reformatsky and aldol reactions. After examination of the available options, the Knoevenagel condensation process involving acetaldehyde and the appropriate malonic derivatives **1** was deemed to be the most expedient approach. The reaction is usually catalyzed by weak organic bases (primary, secondary or tertiary amines, ammonia and ammonium salts[5]) in homogeneous media,[4] but numerous synthetic conditions for the Knoevenagel reaction are described in the literature.[6] After more than a century, this typically base-catalyzed process is still an active research area, in the context of environmentally friendly routes including reactions in the absence of solvent,[7] adsorption on inorganic solids,[8] water as reaction medium,[9] microwave[10] or high pressure activations,[11] or through the combined use of [6-mim]PF_6 and supercritical CO_2[12] as a green alternative in the synthesis of Knoevenagel adducts.

SYNTHESIS 2006, No. 6, pp 1045–1049
Advanced online publication: 27.02.2006
DOI: 10.1055/s-2006-926344; Art ID: T09405SS

Knoevenagel condensation is effective for aromatic aldehydes since the obtained electrophilic olefins are less prone to side reactions, due to the delocalization of the electrons in the aromatic system. In fact, the above-described methods did not allow the preparation of alkenes **2** and proved to be suitable only in the case of aromatic or branched aliphatic aldehydes. Using acetaldehyde, this approach is complicated by its low boiling point, below the ambient temperature, which dictates the use of either scelled bombs,[13] or low temperature conditions and prolonged reaction time.[14] Moreover, the high reactivity of the *gem*-diactivated olefinic products **2**, which can easily condense in turn with nucleophiles such as the parent active methylene compound leading to bis-adduct **3**,[4] is reinforced by the relative absence of steric crowding at the β-position of the activated ethylidene derivatives **2**. The objective of the work presented here was then to develop an efficient and practical alternative method for the synthesis of these geminal activated electrophilic alkenes **2**.

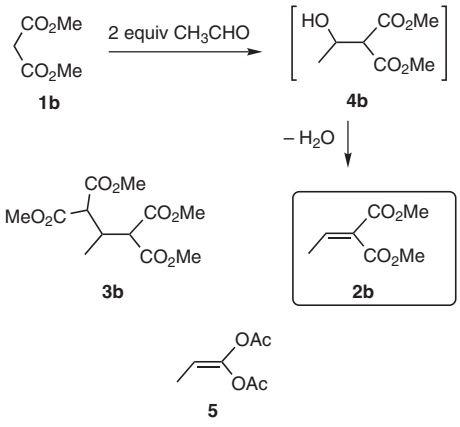


Scheme 1

The condensation between acetaldehyde and malononitrile **1a** was attempted first, owing to its higher acidity (^{DMSO}pKa 11.1) relative to dimethyl malonate **1b** (^{DMSO}pKa 15.9) and related esters.[15] The synthesis of ethylidene malononitrile **2a**[16] using Foucauld's procedure (Al_2O_3, 20 °C, 2 min)[8a] proved to be unsatisfactory in our hands, with a huge amount of polymeric material being formed. As recently reported by Prajapati and coworkers,[17] heterogeneous catalysis by lithium bromide promotes the stoichiometric condensation of acetaldehyde with malononitrile **1a**, allowing a rapid access to the corresponding ethylidene derivative **2a**, however, in only 42% yield (Table 1, entry 1). The yield was improved to 82% when a twofold excess of acetaldehyde was used under the same conditions (Table 1, entry 2).

We then turned our attention to the synthesis of the dimethyl derivative **2b**. While Foucaud and Prajapati's methods were proven successful for the synthesis of a series of cyanoacetic esters,[8a,17] we found that these conditions were fruitless with the less acidic methyl malonate **1b**. Prolonged heating did not improve the yield of the desired adduct **2b**[18] (method A, Scheme 2). Most of the classical Knoevenagel methods failed to work properly in this case (for example method B using piperidine acetate or method C, Scheme 2). The most satisfying condensation of acetaldehyde with active methylene function **1b** was achieved in the presence of $TiCl_4$ and pyridine (method D, 72 h, 74%).[14] However alkene **2b** was contaminated with various amounts of the bis-adduct **3b** as well as some polymeric material, and thus had to be further purified. The Knoevenagel reaction is a multistep process involving an aldol type intermediate, e.g. **4b**[19] which, upon dehydration led to the observed ethylidene derivative, e.g. **2b** (Scheme 2). Thus, the addition of methyl malonate **1b** to acetaldehyde has been efficiently promoted using alumina[20] (CH_2Cl_2, 20 °C, 48 h, 94%) to afford hydroxydiester **4b**.[21] However a further dehydration step (MsCl–Et_3N) would be necessary in order to obtain the corresponding ethylidene malonate **2b**, since prolonged reaction time in these conditions led to extensive degradation of the reaction mixture. A method affording pure ethylidene derivative **2b** was thus needed.

Since diethyl ethylidene malonate **2c** has been previously obtained, along with ethylidene diacetate **5**, by the reaction of acetaldehyde and diethyl malonate **1c** in the presence of excess acetic anhydride (sealed bomb, 100 °C, 20 h, 79% yield),[13] the combined influence of lithium bromide and acetic anhydride on the Knoevenagel condensation of malonates **1** with acetaldehyde was then studied (Scheme 2, methods F and G, Table 1). As a matter of fact, when the reaction of dimethyl malonate **1b** was conducted in the presence of two equivalents of acetic anhydride and 0.2 equivalent of LiBr for two hours at 80 °C (Table 1, entry 5), ethylidene derivative **2b** was obtained in 73% yield, accompanied by the corresponding bis-adduct **3b** in 23% yield. A similar result was obtained on using twice as much acetaldehyde and maintaining the heating for four hours (Table 1, entry 6). Prolonged heating (17 h) resulted in the formation of equimolar amounts of adduct **2b** and ethylidene diacetate **5** (Table 1, entry 7), as previously described in the synthesis of diethyl ethylidene malonate **2c**.[13] At this point, we observed that attempts to purify the crude reaction mixture by vacuum distillation led to increased amounts of ethylidene diacetate **5**. Chromatographic purification was therefore the method of choice to get the pure ethylidene derivatives **2**. To our delight, the yield of ethylidene compound **2b** could be improved to 97%, simply by heating dimethyl malonate **1b**, lithium bromide and acetic anhydride up to four hours at 80 °C prior to the addition of acetaldehyde (Table 1, entry 8). No purification was required in this case.



Methods:

A: 0.2 equiv LiBr, 80 °C, 2–5 h
B: piperidine, AcOH, benzene, reflux
C: piperidine, EtOH, 0 °C
D: $TiCl_4$, pyridine, THF, –78 °C then 20 °C, 72 h, 74%
E: Al_2O_3, CH_2Cl_2, 20°C, 1–24 h
F: 0.2 equiv LiBr, 2 equiv Ac_2O, 80 °C, 2 h, 73%
G: see Table 1 (entry 8), 1 h, 97%

Scheme 2

Owing to their unique properties, e.g. high hydrogen-bonding donor ability, low nucleophilicity, high ionizing power and ability to solvate water, fluorinated solvents such as hexafluoroisopropanol (HFIP) and trifluoroethanol (TFE) play a growing role in organic reactions.[22] It has been demonstrated that the course of reactions which usually require the use of added reagents or metal catalysts can be modified and carried out under neutral and mild conditions. However, replacing acetic anhydride by such solvents, HFIP or TFE, prove to be inefficient, with the reaction returning only the starting materials (80 °C, 4 h).

The synthesis of ethylidene derivatives **2c**–**2e** was next investigated by using the optimized condition for the synthesis of **2b** (Table 1, entry 8).

For obvious reasons, the malonates **1c** and **1d** are less reactive than their dimethyl counterpart **1b** (Table 1, compare entry 8 with entries 11 and 12). Nevertheless, the ethylidene malonates **2c** and **2d** were obtained in good yields. A 86% yield of pure **2c**[13,21] was obtained in four hours (Table 1, entry 11). Di-*tert*-butyl malonate **1d** reacted more slowly, yielding the corresponding ethylidene derivative **2d** in 77% yield after seven hours at 80 °C (Table 1, entry 12). Finally, diphenyl malonate **1e** cleanly afforded the corresponding ethylidene product **2e**[3] in 83% yield (Table 1, entry 16).

Although there is no peculiar problem in synthesizing Knoevenagel adducts from aromatic, long chain or branched aliphatic aldehydes and malonates using the appropriate previously described methods, we tested the LiBr–Ac_2O conditions with a few representative aldehydes. Compared to acetaldehyde, the condensation of *n*-octanaldehyde with dimethyl malonate **1b** proved to be more difficult, since consumption of all the malonate **1b** occurred after 18 hours at 80 °C. Alkylidene derivative **6**[23] was obtained in this case in 56% yield (Scheme 3). On the

Table 1 Knoevenagel Condensation of Acetaldehyde and Malonates in the Presence of LiBr

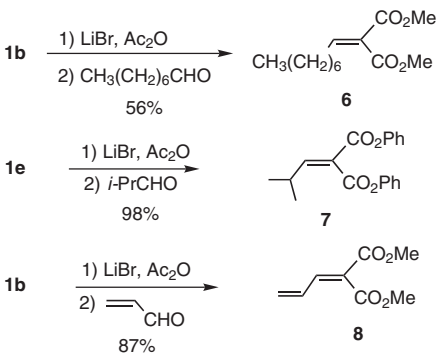
Entry	EWG	MeCHO (equiv)	LiBr (equiv)	Ac_2O (equiv)	Conditions[a]	Yield (%) 2	3	5
1	CN	1	0.2	–	**1a**, LiBr, MeCHO, 20 °C, 5 min, 80 °C, 10 min	42	0	0
2	CN	2	0.2	–	**1a**, LiBr, MeCHO, 20 °C, 5 min, 80 °C, 10 min	82	0	0
3	CO_2Me	2	0.2	–	**1b**, LiBr, MeCHO, 20 °C, 5 min, 80 °C, 2 h	0	0	0
4	CO_2Me	2	–	2	**1b**, MeCHO, Ac_2O, 20 °C, 5 min, 80 °C, 2 h	0	0	0
5	CO_2Me	2	0.2	2	**1b**, LiBr, MeCHO, Ac_2O, 20 °C, 5 min, 80 °C, 2 h	73	23	0
6	CO_2Me	6	0.2	2	**1b**, LiBr, MeCHO, Ac_2O, 20 °C, 5 min, 80 °C, 4 h	74	26	0
7	CO_2Me	6	0.2	2	i) **1b**, LiBr, Ac_2O, 80 °C, 4 h, ii) MeCHO, 80 °C, 17 h	47	0	46
8	CO_2Me	3	0.2	2	i) **1b**, LiBr, Ac_2O, 80 °C, 4 h ii) MeCHO, 80 °C, 1 h	97	0	0
9	CO_2Et	3	0.2	2	i) **1c**, LiBr, Ac_2O, 80 °C, 2 h ii) MeCHO, 80 °C, 1 h	10	0	0
10	CO_2Et	3	0.2	3	i) **1c**, LiBr, Ac_2O, 80 °C, 3 h ii) MeCHO, 80 °C, 17 h	69	0	30
11	CO_2Et	3	0.2	2	i) **1c**, LiBr, Ac_2O, 80 °C, 3 h ii) MeCHO, 80 °C, 4 h	86	0	0
12	CO_2t-Bu	3	0.2	3	i) **1d**, LiBr, Ac_2O, 80 °C, 3 h ii) MeCHO, 80 °C, 7 h	77	0	0
13	CO_2Ph	6	0.2	2	**1e**, LiBr, Ac_2O, 20 °C, 10 min, 80 °C, 4 h	77	15	0
14	CO_2Ph	2	1	2	**1e**, LiBr, Ac_2O, 20 °C, 10 min then 80 °C, 10 min	0	84	0
15	CO_2Ph	3	0.2	2	i) **1e**, LiBr, Ac_2O, 80 °C, 2 h ii) MeCHO, 80 °C, 1 h	20	0	0
16	CO_2Ph	3	0.2	2	i) **1e**, LiBr, Ac_2O, 80 °C, 4 h ii) MeCHO, 80 °C, 1 h	83	0	0

[a] Entries 1–6: acetaldehyde and malonate were mixed with the other component(s) at the beginning of the reaction. Entries 7–16: acetaldehyde was added at step ii.

contrary, a nearly quantitative yield of diphenyl isopropylidene malonate **6** was obtained in one hour from the reaction of isobutyraldehyde with malonate **1e** (LiBr, Ac_2O, 80 °C, 2 h then *i*-PrCHO, 80 °C, 1 h, 98% yield).

Last but not least, these conditions were also suitable for the condensation of acrolein with malonate **1b** giving the sensitive diene **8**[24] in good yield (LiBr, Ac_2O, 80 °C, 2 h then acrolein, 80 °C, 8 h, 87%). Surprisingly, to our knowledge, only one preparation of this diene, based on a stabilized telluronium ylide prepared from a toxic organotelluride reagent, Bu_2Te, has been reported so far.[24]

In conclusion, we have successfully developed a simple access to ethylidene malonates **2** based on a Knoevenagel condensation using acetaldehyde and malonates **1**. The results thus far obtained show that this condensation proceeded smoothly when conducted in acetic anhydride in the presence of a catalytic amount of lithium bromide, producing the desired ethylidene malonates **2** in good to excellent yield. This convenient method avoided the use of a sealed bomb.[13] Another decisive advantage compared to the $TiCl_4$–pyridine method[14] is that neither solvent nor low temperature were required, making this method more cursory. Moreover, we have extended this protocol to the synthesis of dimethyl 2-allylidene-malonate **8**. Extension of the present methodology to the synthesis of other dienes or polyenes as well as studies dealing with the condensation of these electrophilic alkene with chiral imines is currently under investigation and will be reported in due course.



Scheme 3

All reactions were carried out under nitrogen. Acetic anhydride was purified by fractional distillation over sodium carbonate. Flash column chromatography was performed on Merck silica gel 60 with particle size 0.040–0.063 mm (230–400 mesh, flash). Analytical TLC was carried out on Merck silica gel 60 F_{254} plates. IR spectra were taken on a Bruker FT/IR Vector 22 spectrometer. Melting points were determined on a Tottoli type S Büchi capillary melting points apparatus and are uncorrected. ^1H NMR (200 MHz) and ^{13}C NMR (50 MHz) spectra were recorded on a Bruker ARX 200 spectrometer with $CDCl_3$ as solvent and as internal standard. Mass spectra were recorded on a Navigator LC–MS instrument (source AQA)

via the electrospray ionization technique. Alkyl malonates, anhyd lithium bromide and acetaldehyde are commercially available and were used as received. Diphenyl malonate was prepared from malonic acid, phenol and phosphorus oxychloride according to the literature.[3] Microanalyses were performed at the Service de microanalyse, Centre d'Etudes Pharmaceutiques, Châtenay-Malabry, France, with a Perkin-Elmer 2400 analyser.

Synthesis of Ethylidene Malonates; General Procedure

Ac_2O (1.6 mL, 20 mmol), anhyd LiBr (170 mg, 2 mmol) and malonate (10 mmol) were placed in a round-bottomed flask (10 mL) equipped with a magnetic stirrer and a vapor condenser fitted with a septum-held gas-inlet tube. The resulting mixture was stirred for 10 min to 4 h (see Table 1) at 80 °C under nitrogen. Then, acetaldehyde (1.7 mL, 30 mmol) was added in one portion through the vapor condenser and the solution was stirred at 80 °C until full consumption of malonate (monitored by ^{1}H NMR, see Table 1). The reaction mixture was allowed to cool to r.t. and slowly decomposed in a sat. solution of Na_2CO_3 (25 mL). The aqueous phase was extracted with Et_2O (2 × 15 mL) and the combined organic phases were washed with brine and, after drying, were evaporated under reduced pressure. The residue was purified using flash chromatography (eluent: EtOAc–cyclohexane, 15:85).

2-Ethylidene Malononitrile (2a)[16]

Yield: 82%; colorless oil.

IR (neat): 3057, 2985, 2238, 2209, 1650, 1614 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.26 (d, J = 7.2 Hz, 3 H, CH_3), 7.40 (q, J = 7.2 Hz, 1 H, CH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 166.2 (CH), 142.8 (C), 141.8 (C), 80.4 (C), 18.4 (CH_3).

Anal. Calcd for $C_5H_4N_2$ (92.04): C, 65.21; H, 4.38; N, 30.42. Found: C, 65.12; H, 4.20; N, 30.68.

Dimethyl Ethylidene Malonate (2b)[18]

Yield: 97%; colorless oil; bp 97 °C (15 mm Hg) (Lit.[18] 105 °C, 18 mm Hg).

IR (neat): 2999, 2956, 1721, 1649, 1437, 1383, 1262, 1221 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.90 (d, ^3J = 7.3 Hz, 3 H, CH_3CH), 3.70 (s, 3 H, CH_3O), 3.80 (s, 3 H, CH_3O), 7.10 (q, ^3J = 7.3 Hz, 1 H, CHCH$_3$).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.8 (CH_3CH), 51.6 (OCH_3), 128.8 (C), 144.8 (CH), 163.5 (CO), 164.9 (CO).

HRMS (ESI): m/z [M -+ Na^+] calcd for $C_7H_{10}O_4Na$: 181.0477; found: 181.0484.

Diethyl Ethylidene Malonate (2c)

Yield: 86%; colorless oil.[13]

The analytical data were in accord with the literature values.

HRMS (ESI): m/z [M + Na^+] calcd for $C_9H_{14}O_4Na$: 209.0790; found: 209.0784.

Di-*tert*-butyl Ethylidene Malonate (2d)

Yield: 77%; colorless oil.

IR (neat): 1720, 1652, 1219 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.48 [s, 9 H, C$(CH_3)_3$], 1.52 [s, 9 H C$(CH_3)_3$], 1.80 (d, ^3J = 7.2 Hz, 3 H, CHCH_3), 6.80 (q, ^3J = 7.2 Hz, 1 H, CHCH$_3$).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.7 (CHCH$_3$), 27.8 [6 × CH_3, C$(CH_3)_3$], 44.1 (2 × C, CCH$_3$), 132.3 (C), 141.1 (CH), 164.8 (CO), 165.9 (CO).

HRMS (ESI): m/z [M + Na^+] calcd for $C_{13}H_{22}O_4Na$: 265.1416; found: 265.1417.

Diphenyl Ethylidene Malonate (2e)[3]

Yield: 80%; mp 51–52 °C (Lit.[3] mp 52 °C).

IR (neat): 3065, 3044, 2945, 1738, 1649, 1591, 1491, 1181 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.07 (d, ^3J = 7.2 Hz, 3 H, CH_3), 7.05–7.20 (m, 6 H, 5 × H_{Ar}, CHCH$_3$), 7.23–7.39 (m, 5 H, 5 × H_{Ar}).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 15.9 (CH_3), 121.4 (4 × CH, $CH_{o\text{-}Ar}$), 126.1 ($CH_{p\text{-}Ar}$), 126.2 ($CH_{p\text{-}Ar}$), 128.4 (C), 129.4 (2 × CH, $CH_{m\text{-}Ar}$) 129.5 (2 × CH, $CH_{m\text{-}Ar}$), 148.9 (CH), 150.4 (2 × C, C_{Ar}), 162.2 (CO), 163.4 (CO).

HRMS (ESI): m/z [M + Na^+] calcd for $C_{17}H_{14}O_4Na$: 305.0790; found: 305.0775.

Ethylidene Diacetate (5)

Colorless oil; bp 60 °C (18 mm Hg).

IR (neat): 1753, 1709, 1247, 1213 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.54 (d, ^3J = 7.2 Hz, 3 H, CHCH_3), 2.11 (s, 6 H, 2 × CH_3), 6.93 (q, ^3J = 7.2 Hz, 1 H, CHCH$_3$).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 19.0 (CH_3), 20.2 (2 × CH_3, OCOCH_3), 88.3 (CH), 168.8 (C), 176.9 (2 × C, CO).

HRMS (ESI): m/z [M + Na^+] calcd for $C_7H_{10}O_4Na$: 181.04777; found: 181.0509.

Dimethyl 2-Octylidene Malonate (6)[23]

Yield: 56%; colorless oil.

The analytical data were in accord with literature values.

Diphenyl 2-Isobutylidene Malonate (7)

Yield: 98%; colorless waxy solid; mp 43 °C.

IR (neat): 3067, 2970, 2932, 2872, 1737, 1647, 1590 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.16 (d, ^3J = 6.7 Hz, 6 H, CH_3), 2.97 (dh, ^3J = 6.7, 10 Hz, 1 H, CHCH$_3$), 7.06–7.39 (m, 11 H, 10 × H_{Ar}, CH=C).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.6 (2 × CH_3), 29.7 (CHCH$_3$), 121.3 (4 × CH, $CH_{o\text{-}Ar}$), 125.4 (C), 126.1 (2 × $CH_{p\text{-}Ar}$), 129.4 (4 × CH, $CH_{m\text{-}Ar}$), 150.4 (2 × C, C_{Ar}), 158.3 (CH=C), 162.2 (CO), 163.5 (CO).

Anal. Calcd for $C_{19}H_{18}O_4$ (92.04): C, 73.53; H, 5. 58. Found: C, 73.57; H, 5.93.

Dimethyl 2-Allylidene Malonate (8)[24]

Yield: 87%; colorless oil.

IR (neat): 2955, 1719, 1631, 1591, 1437 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.53 (s, 3 H, CH_3O), 3.58 (s, 3 H, CH_3O), 5.41 (dd, J = 1.1, 10.2 Hz, 1 H, CH_2), 5.51 (dd, J = 1.1, 16.8 Hz, 1 H, CH_2), 6.50 (ddd, J = 10.2, 11.5, 16.8, Hz, 1 H, CH_2CH), 7.07 (d, J = 11.5 Hz, 1 H, C=CH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 52.1 (CH_3), 52.2 (CH_3), 125.8 (C), 129.6 (CH_2), 131.6 (CHCH$_2$), 144.8 (CHC), 164.5 (CO), 165.1 (CO).

Anal. Calcd for $C_8H_{10}O_4$ (170.06): C, 56.47; H, 5.92. Found: C, 56.23; H, 6.11.

Synthesis of Diphenyl 3-Methyl-2,4-bisphenoxycarbonylglutarate (3e)

Ac_2O (1.6 mL, 20 mmol), anhyd LiBr (850 mg, 10 mmol) and diphenyl malonate (**1e**; 10 mmol) were placed in a round-bottomed flask (10 mL) equipped with a magnetic stirrer and a vapor condenser fitted with a septum-held gas-inlet tube. The resulting mixture

was stirred for 10 min at 20 °C under N_2. Then, acetaldehyde (1.1 mL, 20 mmol) was added in one portion through the vapor condenser and the solution was stirred at 80 °C for 10 min. The reaction mixture was allowed to cool at r.t. and slowly decomposed in a sat. solution of Na_2CO_3 (25 mL). The aqueous phase was extracted with Et_2O (2 × 15 mL) and the combined organic phases were washed with brine and, after drying, were evaporated under reduced pressure. The residue was purified using flash chromatography (eluent: EtOAc–cyclohexane, 15:85); yield: 84%; colorless solid; mp 110 °C.

IR (neat): 1744, 1590, 1484, 1158, 1130, 815, 734, 684, cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.64 (d, ^3J = 7.0 Hz, 3 H, CH_3), 3.57 (q, ^3J = 7.0 Hz, 1 H, $CHCH_3$), 4.44 (d, ^3J = 7.0 Hz, 2 H, CH_2CHCH_3), 7.22–7.52 (m, 20 H, H_{Ar}).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.8 (CH_3), 33.1 ($CHCH_3$), 54.3 (2 × CH, CH_2CHCH_3), 121.3 (8 × CH, $CH_{o\text{-}Ar}$), 126.4 (4 × CH, $CH_{p\text{-}Ar}$), 129.6 (8 × CH, $CH_{m\text{-}Ar}$), 150.3 (4 × C, C_{Ar}), 166.3 (2 × C, CO), 166.8 (2 × C, CO).

Anal. Calcd for $C_{32}H_{26}O_8$ (538.54): C, 71.37; H, 4.87. Found: C, 71.15; H, 4.95.

Synthesis of 2-(1-Hydroxyethyl)malonic Acid Dimethyl Ester (4b)[21]

A suspension of alumina (1.02 g, 10 mmol), dimethyl malonate (264 mg, 2 mmol) and acetaldehyde (176 mg, 0.22 mL, 4 mmol) in CH_2Cl_2 (4 mL) was stirred at 20 °C for 24 h (the reaction progress was monitored by ^1H NMR). The mixture was filtered over a pad of celite, the filtrate was concentrated in vacuo and the residue was purified by flash chromatography on alumina (cyclohexane–EtOAc, 8:2); yield: 81%; colorless oil.

IR (neat): 3530, 2958, 2851, 1731 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.09 (d, ^3J = 6.4 Hz, 3 H, CH_3CH), 3.25 (d, ^3J = 6.9 Hz, 1 H, $CHCH_3$), 3.26 (br s, 1 H, OH), 3.57 (s, 3 H, CH_3O), 3.59 (s, 3 H, CH_3O), 4.18 (p, ^3J = 6.6 Hz, 1 H, $CHCH_3$)

^{13}C NMR (50 MHz, $CDCl_3$): δ = 20.3 (CH_3CH), 52.0 (2 × OCH_3), 58.4 ($CHCH_3$), 66.2 (CHOH), 167.9 (CO), 168.5 (CO).

HRMS (ESI): *m/z* [M + Na^+] calcd for $C_7H_{12}O_5Na$: 199.0582; found: 199.0576.

Acknowledgment

This work was supported by the CNRS and the MENRT. We thank Michèle Ourevitch (CNRS, BioCIS, Châtenay-Malabry, France) for NMR assistance and Sophie Mairesse-Lebrun (CNRS, BioCIS, Châtenay-Malabry, France) for elemental analyses.

References

(1) (a) d'Angelo, J.; Desmaële, D.; Dumas, F.; Guingant, A. *Tetrahedron: Asymmetry* **1992**, *3*, 459. (b) d'Angelo, J.; Cavé, C.; Desmaële, D.; Dumas, F. In *Trends in Organic Chemistry*, Vol. 4; Pandalai, S. G., Ed.; Trivandrum: India, **1993**, 555.

(2) (a) Camara, C.; Joseph, D.; Dumas, F.; d'Angelo, J.; Charoni, A. *Tetrahedron Lett.* **2002**, *42*, 1445. (b) de Oliveira, E. R.; Miet, C.; d'Angelo, J.; Dumas, F. In *Chemical Processes and Reactions under Extreme or Non-Classic Conditions*; Luche, J. L.; Balny, C.; Benefice, S.; Denis, J. M.; Pétrier, C., Eds.; Office for Official Publications of the European Communities: Luxembourg, **1998**, 97. (c) Camara, C.; Keller, L.; Jean-Charles, K.; Joseph, D.; Dumas, F. *High Pres. Res.* **2004**, *24*, 149.

(3) Also see: Jabin, I.; Revial, G.; Monnier-Benoit, N.; Netchitailo, P. *J. Org. Chem.* **2001**, *66*, 256.

(4) (a) For a review, see: Jones, G. In *Organic Reactions*, Vol. 15; Wiley: New York, **1967**, 204. (b) Brettle, R. In *Comprehensive Organic Chemistry*, Vol. 1; Stoddart, J. F., Ed.; Pergamon Press: Oxford UK, **1979**, 943; see page 967. (c) Tiezte, L. F.; Beifuss, U. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford UK, **1991**, 341.

(5) Chodroff, S.; Whitmore, W. F. *J. Am. Chem. Soc.* **1950**, *72*, 1073.

(6) See for example: Cardillo, G.; Fabbroni, S.; Gentilucci, L.; Gianotti, M.; Tolomelli, A. *Synth. Commun.* **2003**, *33*, 1587.

(7) (a) Kaupp, G.; Naimi-Jamal, M. R.; Schmeyers, J. *Tetrahedron* **2003**, *59*, 3753. (b) McCluskey, A.; Robinson, P. J.; Hill, T.; Scott, J. L.; Edwards, J. K. *Tetrahedron Lett.* **2002**, *43*, 3117.

(8) (a) Texier-Boulet, F.; Foucaud, A. *Tetrahedron Lett.* **1982**, *23*, 4927. (b) Cooke, G.; Palmer, H. M.; Schultz, O. *Synth. Commun.* **1996**, 2549. (c) Cabello, J. A.; Campelo, J. M.; Garcia, A.; Luna, D.; Marinas, J. M. *J. Org. Chem.* **1984**, *49*, 5195. (d) Angeletti, E.; Canapa, C.; Martinetti, G.; Venturello, P. *Tetrahedron Lett.* **1993**, *34*, 7437.

(9) Brufola, G.; Fringuelli, F.; Piernatti, O.; Pizzo, F. *Heterocycles* **1997**, *45*, 1715.

(10) (a) Mitra, A. K.; De, A.; Karchaudhuri, N. *Synth. Commun.* **1999**, *29*, 2731. (b) Cherouvrier, J. R.; Boisset, J.; Carreaux, F.; Bazureau, J. P. *Green Chem.* **2001**, *3*, 165.

(11) Jenner, G. *Tetrahedron Lett.* **2001**, *42*, 243.

(12) Morrisson, D. W.; Forbes, D. C.; Davis, J. H. Jr. *Tetrahedron Lett.* **2001**, *42*, 6053.

(13) (a) Liu, H. N.; Auchus, R.; Walsh, C. T. *J. Am. Chem. Soc.* **1984**, *106*, 5335. (b) Ishida, A.; Yamashita, S.; Takamuku, S. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 2229.

(14) (a) Lehnert, W. *Tetrahedron Lett.* **1970**, *34*, 4723. (b) Lehnert, W. *Tetrahedron* **1972**, *28*, 663. (c) Lehnert, W. *Tetrahedron* **1973**, *29*, 635. (d) Compare: Jones, G. *Org. React. (N.Y.)* **1967**, *15*, 204.

(15) Taken from the web page available at: http://daecr1.harvard.edu/pdf/evans_pKa_table.pdf.

(16) Weir, M. R. S.; Hyne, J. B. *Can. J. Chem.* **1965**, *43*, 772.

(17) Prajapati, G.; Lekhok, K. C.; Sandhu, J. S.; Ghosh, A. C. *J. Chem. Soc., Perkin Trans 1* **1996**, 959.

(18) (a) Wingler, F.; Reiff, H. *Liebigs Ann. Chem.* **1967**, *705*, 96. (b) Yamamoto, Y.; Nishii, S. *J. Org. Chem.* **1988**, *53*, 3597. (c) Bogdanov, V. S.; Ugrak, B. I.; Krasnaya, Z. A.; Stytsenko, T. S. *Bull. Acad. Sci. USSR, Div. Chem. Sci. (Engl. Transl.)* **1990**, 298.

(19) For a synthesis and reactivity of aldol **4c**, see for example: (a) Roesch, A. *Bull. Soc. Chim.* **1937**, *4*, 1643. (b) Brink, M.; Schjanberg, E. *J. Prakt. Chem.* **1980**, 685. (c) Ref. 13b.

(20) Lopez Giral, A.; Mahuteau-Betzer, F.; Gateau-Olesker, A.; Marazano, C. *Eur. J. Org. Chem.* **2003**, 1859.

(21) Doleschall, G. *Acta Chim. Hung.* **1991**, *128*, 823.

(22) Bégué, J.-P.; Bonnet-Delpon, D.; Crousse, B. *Synlett* **2004**, 18.

(23) (a) A partial conversion was observed after 12 h at 80 °C (**1a**:**7** = 3:1). No trace of ethylidene diacetate **5** could be detected in the crude. (b) Cardillo, G.; Gentilucci, L.; Gianotti, M.; Perciaccante, R.; Tolomelli, A. *J. Org. Chem.* **2001**, *66*, 8657. (c) Tsuboi, S.; Wada, H.; Murakana, K.; Takeda, A. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 2917.

(24) (a) Matsuki, T.; Hu, N. X.; Aso, Y.; Otsubo, T.; Ogura, F. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 2105. (b) Niwayama, S.; Houk, K. N.; Kusumi, T. *Tetrahedron Lett.* **1994**, *35*, 527.