A Simple and Direct Access to Ethylidene Malonates

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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 vicinal 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 salts5) in homogeneous media,6 but organic bases (primary, secondary or tertiary amines, amides, water as reaction medium,7 green alternative in the synthesis of Knoevenagel adducts.8

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 sculled bombs,9 or low temperature conditions and prolonged reaction time.10 Moreover, the high reactivity of the gem-deactivated 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.

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 2a16 using Foucauld’s procedure (Al2O3, 20 °C, 2 min)16a 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).

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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, 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 (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 TiCl₄ and pyridine (method D, 72 h, 74%). 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, which, upon dehydra-
dation 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 (CH₂Cl₂, 20 °C, 48 h, 94%) to afford hydrox-
diesters 4b. However a further dehydration step (MsCl–Et₃N) would be necessary in order to obtain the corre-
sponding ethylidene malonate 2b, since prolonged reac-
tion 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), the combined influence of lithium bromide and acetic anhydride on the Knoevenagel condensa-
tion 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 con-
ducted in the presence of two equivalents of acetic anhy-
dride 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-ad-
duct 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 heat-
ing (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. At this point, we observed that at-
tempts 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.
contrary, a nearly quantitative yield of diphenyl isopropylidene malonate \( \text{6} \) was obtained in one hour from the reaction of isobutyraldehyde with malonate \( \text{1e} \) (LiBr, Ac\(_2\)O, 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 \( \text{1b} \) giving the sensitive diene \( \text{8} \) in good yield (LiBr, Ac\(_2\)O, 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\(_2\)Te, has been reported so far.24

In conclusion, we have successfully developed a simple access to ethylidene malonates \( \text{2} \) based on a Knoevenagel condensation using acetaldehyde and malonates \( \text{1} \). 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 \( \text{2} \) 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 method14 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 \( \text{8} \). Extension of the present methodology to the synthesis of other dienes or polyenes as well as studies dealing with the condensation of these electrophilic alkenes with chiral imines is currently under investigation and will be reported in due course.

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 Büchi capillary melting points apparatus and are uncorrected. \(^1\)H 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).

### Table 1

<table>
<thead>
<tr>
<th>Entry</th>
<th>EWG</th>
<th>MeCHO (equiv)</th>
<th>LiBr (equiv)</th>
<th>Ac(_2)O (equiv)</th>
<th>Conditions</th>
<th>2</th>
<th>Yield (%)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>CN</td>
<td>1</td>
<td>0.2</td>
<td>–</td>
<td>1a, LiBr, MeCHO, 20 °C, 5 min, 80 °C, 10 min</td>
<td>42</td>
<td>0 0 0</td>
</tr>
<tr>
<td>2</td>
<td>CN</td>
<td>2</td>
<td>0.2</td>
<td>–</td>
<td>1a, LiBr, MeCHO, 20 °C, 5 min, 80 °C, 10 min</td>
<td>82</td>
<td>0 0 0</td>
</tr>
<tr>
<td>3</td>
<td>CO(_2)Me</td>
<td>2</td>
<td>0.2</td>
<td>–</td>
<td>1b, LiBr, MeCHO, 20 °C, 5 min, 80 °C, 2 h</td>
<td>0 0 0</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>CO(_2)Me</td>
<td>2</td>
<td>– 2</td>
<td>1b, MeCHO, Ac(_2)O, 20 °C, 5 min, 80 °C, 2 h</td>
<td>0 0 0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>CO(_2)Me</td>
<td>2</td>
<td>0.2</td>
<td>2</td>
<td>1b, LiBr, MeCHO, Ac(_2)O, 20 °C, 5 min, 80 °C, 2 h</td>
<td>73</td>
<td>23 0</td>
</tr>
<tr>
<td>6</td>
<td>CO(_2)Me</td>
<td>6</td>
<td>0.2</td>
<td>2</td>
<td>1b, LiBr, MeCHO, Ac(_2)O, 20 °C, 5 min, 80 °C, 4 h</td>
<td>74</td>
<td>26 0</td>
</tr>
<tr>
<td>7</td>
<td>CO(_2)Me</td>
<td>6</td>
<td>0.2</td>
<td>2</td>
<td>i 1b, LiBr, Ac(_2)O, 80 °C, 4 h, ii) MeCHO, 80 °C, 17 h</td>
<td>47</td>
<td>0 46</td>
</tr>
<tr>
<td>8</td>
<td>CO(_2)Et</td>
<td>3</td>
<td>0.2</td>
<td>2</td>
<td>i 1b, LiBr, Ac(_2)O, 80 °C, 4 h</td>
<td>97</td>
<td>0 0</td>
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<tr>
<td>9</td>
<td>CO(_2)Et</td>
<td>3</td>
<td>0.2</td>
<td>2</td>
<td>i 1c, LiBr, Ac(_2)O, 80 °C, 2 h ii) MeCHO, 80 °C, 1 h</td>
<td>10</td>
<td>0 0</td>
</tr>
<tr>
<td>10</td>
<td>CO(_2)Et</td>
<td>3</td>
<td>0.2</td>
<td>3</td>
<td>i 1c, LiBr, Ac(_2)O, 80 °C, 3 h ii) MeCHO, 80 °C, 17 h</td>
<td>69</td>
<td>0 30</td>
</tr>
<tr>
<td>11</td>
<td>CO(_2)Et</td>
<td>3</td>
<td>0.2</td>
<td>2</td>
<td>i 1c, LiBr, Ac(_2)O, 80 °C, 3 h ii) MeCHO, 80 °C, 4 h</td>
<td>86</td>
<td>0 0</td>
</tr>
<tr>
<td>12</td>
<td>CO(_2)Et</td>
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<td>0.2</td>
<td>3</td>
<td>i 1d, LiBr, Ac(_2)O, 80 °C, 3 h ii) MeCHO, 80 °C, 7 h</td>
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<td>0 0</td>
</tr>
<tr>
<td>13</td>
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<td>6</td>
<td>0.2</td>
<td>2</td>
<td>1e, LiBr, Ac(_2)O, 20 °C, 10 min, 80 °C, 4 h</td>
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<td>15 0</td>
</tr>
<tr>
<td>14</td>
<td>CO(_2)Ph</td>
<td>6</td>
<td>1</td>
<td>2</td>
<td>1e, LiBr, Ac(_2)O, 20 °C, 10 min then 80 °C, 10 min</td>
<td>8</td>
<td>0 84</td>
</tr>
<tr>
<td>15</td>
<td>CO(_2)Ph</td>
<td>3</td>
<td>0.2</td>
<td>2</td>
<td>i 1e, LiBr, Ac(_2)O, 80 °C, 2 h ii) MeCHO, 80 °C, 1 h</td>
<td>20</td>
<td>0 0</td>
</tr>
<tr>
<td>16</td>
<td>CO(_2)Ph</td>
<td>3</td>
<td>0.2</td>
<td>2</td>
<td>i 1e, LiBr, Ac(_2)O, 80 °C, 4 h ii) MeCHO, 80 °C, 1 h</td>
<td>83</td>
<td>0 0</td>
</tr>
</tbody>
</table>

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.

### Scheme 3

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\[
\begin{align*}
\text{1b} & \xrightarrow{1) \text{LiBr, Ac_2O}} \xrightarrow{2) \text{MeCHO}} \text{CHO} \\
\text{CH_3(CH_2)_6CHO} & \xrightarrow{87\%} \text{CO_2Me} \\
\text{1e} & \xrightarrow{1) \text{LiBr, Ac_2O}} \xrightarrow{2) i\text{-PrCHO}} \text{CHO} \\
\text{CO_2Ph} & \xrightarrow{56\%} \text{CO_2Me} \\
\text{1b} & \xrightarrow{1) \text{LiBr, Ac_2O}} \xrightarrow{2) \text{MeCHO}} \text{CHO} \\
\text{CH_3(CH_2)_6CHO} & \xrightarrow{56\%} \text{CO_2Me} \\
\end{align*}
\]```

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via the electrospray ionization technique. Alkyl malonates, anhydrous 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. Microanalyses were performed at the Service de microanalyse, Centre d’Etudes Pharmaceutiques, Châtenay-Malabry, France, with a Perkin-Elmer 2400 analyser.

Synthesis of Ethyldiene Malonates; General Procedure

Ac2O (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 into one portion through the vapor condenser and the solution was stirred at 80 °C until full consumption of malonate (monitored by 1H NMR, see Table 1). The reaction mixture was allowed to cool to r.t. and slowly decomposed in a sat. solution of Na2CO3 (25 mL). The aqueous phase was extracted with Et2O (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-Ethyldiene Malononitrile (2a)16

Yield: 82%; colorless oil.

IR (neat): 3057, 2983, 2238, 2209, 1650, 1614 cm⁻¹.

1H NMR (200 MHz, CDCl 3): δ = 2.26 (d, J = 7.2 Hz, 3 H, CHδ), 7.40 (q, J = 7.2 Hz, 1 H, CHδ).

13C NMR (50 MHz, CDCl 3): δ = 166.2 (CH), 142.8 (C), 141.8 (C), 80.4 (C), 18.4 (CH3).

Anal. Calcd for C6H7 N2 (92.04): C, 73.57; H, 5.93. Found: C, 73.56; H, 5.92.

Diethyl Ethyldiene Malonate (2b)18

Yield: 97%; colorless oil; bp 105 °C (18 mm Hg).

1H NMR (200 MHz, CDCl 3): δ = 1.16 (d, J = 6.7 Hz, 6 H, CHδ), 2.97 (db, J = 6.7, 10 Hz, 1 H, CHCHδ), 7.06–7.39 (m, 11 H, 10 Ar, CHAr). Found: 255.1417.


Diphenyl Ethyldiene Malonate (2c)19

Yield: 84%; mp 51–52 °C (Lit. mp 52 °C).

IR (neat): 3065, 3044, 2945, 1738, 1649, 1591, 1181 cm⁻¹.

1H NMR (200 MHz, CDCl 3): δ = 2.07 (d, J = 7.2 Hz, 3 H, CHδ), 7.05–7.20 (m, 6 H, 5 × Hδ, CHCHδ), 7.23–7.39 (m, 5 H, 5 × Hα).

13C NMR (50 MHz, CDCl 3): δ = 159.8 (CH), 121.4 (4 × CH, CHp-Ar), 126.1 (CHm-Ar), 126.3 (CHp-Ar), 129.4 (C), 129.4 (2 × CH, CHm-Ar), 129.5 (2 × CH, CHp-Ar), 148.9 (CH), 150.4 (2 × C, Cm-Ar), 162.2 (CO), 163.4 (CO).


Ethyldiene Diacetate (5)

Colorless oil; bp 70 °C (18 mm Hg).

IR (neat): 1753, 1709, 1247, 1213 cm⁻¹.

1H NMR (200 MHz, CDCl 3): δ = 1.54 (d, J = 7.2 Hz, 3 H, CHCHδ), 2.11 (s, 6 H, 2 × CH3), 6.93 (q, J = 7.2 Hz, 1 H, CHCHδ).

13C NMR (50 MHz, CDCl 3): δ = 19.0 (CH3), 20.2 (2 × CH3, OCOCH3), 88.3 (CH), 168.8 (C), 176.9 (2 × CO). Found: 265.1417.


Dimethyl 2-Octyldiene Malonate (6)21

Yield: 56%; colorless oil.

The analytical data were in accord with literature values.

Diphenyl 2-Isobutyldiene Malonate (7)

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

IR (neat): 3067, 2970, 2932, 2872, 1737, 1647, 1590 cm⁻¹.

1H NMR (200 MHz, CDCl 3): δ = 1.16 (d, J = 6.7 Hz, 6 H, CHδ), 2.97 (db, J = 6.7, 10 Hz, 1 H, CHCHδ), 7.06–7.39 (m, 11 H, 10 × Hδ, CH=C).

13C NMR (50 MHz, CDCl 3): δ = 21.6 (2 × CH3), 29.7 (CHCHδ), 121.3 (4 × CH, CHp-Ar), 125.4 (C), 126.1 (2 × CHm-Ar), 129.4 (4 × CH, CHp-Ar), 150.4 (2 × C, Cm-Ar), 158.3 (CH=C), 162.2 (CO), 163.5 (CO). Anal. Calcd for C19H19O2: C, 73.53; H, 5.58. Found: C, 73.57; H, 5.93.

Dimethyl 2-Allyldiene Malonate (8)24

Yield: 87%; colorless oil.

IR (neat): 2955, 1719, 1631, 1591, 1437 cm⁻¹.

1H NMR (200 MHz, CDCl 3): δ = 3.53 (s, 3 H, CH3O), 3.58 (s, 3 H, CH3O), 5.41 (dd, J = 1.1, 10.2 Hz, 1 H, CH3O), 5.51 (dd, J = 1.1, 16.8 Hz, 1 H, CH3, 6.50 (ddd, J = 10.2, 11.5, 16.8, 1 H, CH2CH3), 7.07 (d, J = 11.5 Hz, 1 H, CH=C).

13C NMR (50 MHz, CDCl 3): δ = 52.1 (CH2), 52.2 (CH3), 125.8 (C), 129.6 (CH2), 131.6 (CHCHδ), 144.8 (CH), 164.5 (CO), 165.1 (CO). Anal. Calcd for C13H16O3: 70.06; C, 56.47; H, 5.92. Found: C, 56.23; H, 6.11.

Synthesis of Diphenyl 3-Methyl-2,4-bisphenoxy-carbonyl-glutarate (3e)2e

Ac2O (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

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was monitored by 1H NMR). The mixture was filtered over a pad of alumina (1.02 g, 10 mmol), dimethyl malonate (176 mg, 0.22 mL, 4 mmol) in CH2Cl2 (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, 3:1). No trace of ethylidene diacetate could be detected.

**Synthesis of 2-(1-Hydroxyethyl)malonic Acid Dimethyl Ester (4b)**

A suspension of alumina (1.02 g, 10 mmol), dimethyl malonate (264 mg, 2 mmol) and acetaldehyde (1.1 mL, 20 mmol) in Et2O (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) yielding: 84%; colorless solid; mp 110 °C.

IR (neat): 3530, 2958, 2851, 1731 cm–1.

1H NMR (200 MHz, CDCl3): δ = 1.64 (d, J = 6.4 Hz, 3 H, CH3), 3.25 (d, J = 6.9 Hz, 1 H, CHCH3), 3.26 (br s, 1 H, OH), 3.57 (s, 3 H, CH2O), 3.59 (s, 3 H, CH3O), 4.18 (p, J = 6.6 Hz, 1 H, CHCH3)

13C NMR (50 MHz, CDCl3): δ = 20.3 (CH, CH), 52.0 (2 × OCH3), 58.4 (CHCH3), 66.2 (CHOH), 167.9 (CO), 168.5 (CO).


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15. Taken from the web page available at:


