An Easy Access to \((E)\)-Alkylidenedsuccinic Acids¹

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Received 15 October 2002
Dedicated to Dr. B. G. Hazra, OCS, NCL, Pune.

Abstract: A two-step simple, efficient and general approach to \((E)\)-alkylidenedsuccinic acids 1a–e has been demonstrated in 82–88% overall yields via condensation of Wittig adduct of maleimide 2 and triphenylphosphine with aliphatic aldehydes followed by acid-catalyzed hydrolysis pathway.

Key words: maleimide-triphenylphosphine adduct, aliphatic aldehydes, condensations, hydrolysis, alkylidenedsuccinic acids

Alkyl and alkylidenedsuccinic anhydrides have been used as a potential precursors for synthesis of many bioactive natural and synthetic products.²–⁸ Several methods have been reported⁴–¹³ for the preparation of these acids/anhydrides but they do not seem to be of general nature. Very recently Ballini et al have demonstrated¹⁴ an elegant 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)-induced general coupling of nitroalkanes with dimethyl maleate to obtain these acids/anhydrides. Barrett et al. have successfully condensed¹⁵ the maleimide-triphenylphosphine adduct with D-ribose to complete the synthesis of showdomycin and epishowdomycin. The condensation of Wittig adduct 3 with several aromatic aldehydes is also well established,¹⁶ while only the aliphatic aldehyde, propanal has been condensed with 3 in low yields.¹⁶ Since major aliphatic aldehydes are easily available with low costs, we felt that the Wittig reaction of 3 with aliphatic aldehydes will provide an easy access to these alkyl/alkylidene succinic acids/anhydrides and in this context we herein report the simple general two-step approach to \((E)\)-alkylidenedsuccinic acids 1a–e (Scheme 1).

The reaction of maleimide 2 with triphenylphosphine (TPP) furnished the intermediate Wittig adduct 3, which in situ condensed very smoothly with aliphatic aldehydes to afford the alkylidenedsuccinimides 4 in excellent yields. The \(^1\)H NMR spectra of 4 revealed that the present Wittig reaction exclusively furnishes the thermodynamically more stable E-isomers of 4a–e. The alkylidenedsuccinimides 4a–e on hydrolysis under reflux with a mixture of concentrated hydrochloric acid and glacial acetic acid (1:1) gave the corresponding desired \((E)\)-alkylidenedsuccinic acids 1a–e in quantitative yields (Table 1). In both alkylidenedsuccinimides 4a–e and alkylidenedsuccinic acids 1a–e the E-configuration for the trisubstituted double bond was assigned on the basis of the lower field \(^1\)H NMR resonance at \(\delta = ca. 6.95\) for the vinlylic proton in close proximity to the carbonyl and was further confirmed by comparing with similar known compounds.¹⁴,¹⁷ The analytical and spectral data obtained for 1a–e were in complete agreement with the reported data.⁴–¹⁴

The reduction of alkylidenedsuccinic acids 1 to alkysuccinic acids using palladium/charcoal and ring-closure of both the alkyl and alkylidenedsuccinic acids to the corresponding alkyl and alkylidenedsuccinic anhydrides using acetyl chloride as a dehydrating agent is well established.¹⁴

Table 1 Yields of Compounds 1a–e and 4a–e Prepared

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aliphatic Aldehydes</th>
<th>Alkylidenedsuccinimides 4a–e</th>
<th>Alkylidenedsuccinic Acids 1a–e</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Product</td>
<td>Yield (%)</td>
<td>Product</td>
</tr>
<tr>
<td>1</td>
<td>n-butanal</td>
<td>4a</td>
<td>85</td>
</tr>
<tr>
<td>2</td>
<td>n-hexanal</td>
<td>4b</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>n-decanal</td>
<td>4c</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td>n-dodecanal</td>
<td>4d</td>
<td>86</td>
</tr>
<tr>
<td>5</td>
<td>n-tetradecanal</td>
<td>4e</td>
<td>87</td>
</tr>
</tbody>
</table>
In summary, we have demonstrated an efficient two-step easy approach to (E)-alkylidenesuccinic acids. We feel that the present cost effective general method with scale-up potential will be of interest to large number of organic chemists from practical point of view. These (E)-alkylidenesuccinic acids 1 will be potential starting materials for the synthesis of linderanolides. 18

Melting points are uncorrected. 1H NMR spectra were recorded on Bruker AC 200 NMR spectrometer (200 MHz) with TMS as an internal standard. 13C NMR spectra were recorded on Bruker MSL 300 (75 MHz). Mass spectra were recorded on Finnigan Mat 1020 mass spectrometer at 70 eV. Column chromatographic separations were done on ACME silica gel (60–120 mesh). Petroleum ether with a bp range of 60–80 °C was used. Ph3P, maleic anhydride and aliphatic aldehydes were obtained from Aldrich Chemical Co. The N-p-tolylmaleimide (2) was prepared using known procedure. 19

N-p-Tolyl-3-(E)-alkylidenesuccinimides 4a–e; General Procedure

A mixture of N-p-tolylmaleimide (2), 9.35 g (50 mmol) and Ph3P (13.11 g, 50 mmol) in distill THF (125 mL) was stirred at r.t. for 30 min. The appropriate aliphatic aldehyde (75 mmol) was added to the reaction mixture and it was refluxed for 10 h. THF was distilled off in vacuo at 50 °C, and silica gel column chromatographic purification of the residue using petroleum ether–EtOAc mixture (9:1) as eluent gave N-p-tolyl-3-(E)-alkylidenesuccinimides.

N-p-Tolyl-3-(E)-butylidenesuccinic Acid (4a)

Yield: 85%; mp 90–92 °C.

IR (Nujol): 2800–2500, 1703, 1693, 1643 cm–1.

Yield: 97%; mp 147–148 °C.

1H NMR (CDCl3, 200 MHz): δ = 0.99 (t, J = 8 Hz, 3 H), 1.58 (sext, J = 8 Hz, 2 H), 2.32 (q, J = 8 Hz, 2 H), 2.39 (s, 3 H), 3.39 (s, 2 H), 6.95 (t, J = 8 Hz, 1 H), 7.20 (d, J = 8 Hz, 2 H), 7.29 (d, J = 8 Hz, 2 H).

Anal. Calcld for C8H12O4: C, 55.81; H, 7.02; Found: C, 55.70; H, 6.97.

N-p-Tolyl-3-(E)-hexylidenesuccinic Acid (4b)

Yield: 90%; mp 112–113 °C.

IR (Nujol): 1771, 1749, 1712, 1691, 1676 cm–1.

Yield: 96%; mp 169–170 °C.

1H NMR (acetone-6, 200 MHz): δ = 1.20–1.45 (m, 4 H), 1.55 (quint, J = 6 Hz, 2 H), 2.23 (q, J = 8 Hz, 2 H), 2.38 (s, 3 H), 3.38 (s, 2 H), 6.94 (t, J = 8 Hz, 1 H), 7.20 (d, J = 8 Hz, 2 H), 7.30 (d, J = 8 Hz, 2 H).

MS: m/z = 271, 242, 228, 214, 200, 189, 172, 133, 107, 95, 81, 67, 53.


N-p-Tolyl-3-(E)-decyldienesuccinic Acid (4c)

Yield: 90%; mp 106–108 °C.

IR (Nujol): 1771, 1709, 1676, 1466 cm–1.

Yield: 97%; mp 147–148 °C.

1H NMR (acetone-d6, 200 MHz): δ = 1.29 (br s, 12 H), 1.54 (quint, J = 6 Hz, 2 H), 2.25 (q, J = 8 Hz, 2 H), 2.40 (s, 3 H), 3.40 (s, 2 H), 6.96 (t, J = 8 Hz, 1 H), 7.21 (d, J = 8 Hz, 2 H), 7.30 (d, J = 8 Hz, 2 H).


E-Alkylenesuccinic Acids 1a–e; General Procedure

A mixture of succinimide 4a–e (40 mmol), glacial AcOH and concd HCl was refluxed for 60 h. The reaction mixture was allowed to reach r.t., concentrated in vacuo and the residue obtained was dissolved in 5% aq NaHCO3 (60 mL). The aqueous layer was extracted with EtOAc (3 × 50 mL) and acidified with dilute HCl. The acidified aqueous layer was extracted with EtOAc (3 × 50 mL), and the combined organic layers were washed with H2O (50 mL), brine (50 mL), and dried (Na2SO4). Concentration of the organic layer in vacuo gave pure 1a–e. Analytically pure compounds were obtained by recrystallization from EtOAc.

(E)-Butylenesuccinic Acid (1a)

Yield: 96%; mp 169–170 °C.

IR (Nujol): 2800–2500, 1705, 1693, 1640 cm–1.

1H NMR (acetone-d6, 200 MHz): δ = 0.94 (t, J = 8 Hz, 3 H), 1.50 (sext, J = 8 Hz, 2 H), 2.23 (q, J = 8 Hz, 2 H), 3.37 (s, 2 H), 6.97 (t, J = 8 Hz, 1 H).

Anal. Calcld for C4H12O3: C, 55.81; H, 7.80; Found: C, 55.70; H, 6.79.

(E)-Hexylenesuccinic Acid (1b)

Yield: 96%; mp 149–150 °C.

IR (Nujol): 2800–2500, 1704, 1692, 1643 cm–1.

1H NMR (acetone-d6, 200 MHz): δ = 0.88 (t, J = 6 Hz, 3 H), 1.20–1.40 (m, 4 H), 1.49 (quint, J = 6 Hz, 2 H), 2.24 (q, J = 6 Hz, 2 H), 3.35 (s, 2 H), 6.96 (t, J = 8 Hz, 1 H).


(E)-Decylenesuccinic Acid (1c)

Yield: 97%; mp 147–148 °C.

IR (Nujol): 2800–2500, 1703, 1693, 1643 cm–1.

1H NMR (acetone-d6, 200 MHz): δ = 0.88 (t, J = 6 Hz, 3 H), 1.29 (br s, 12 H), 1.49 (quint, J = 6 Hz, 2 H), 2.26 (q, J = 6 Hz, 2 H), 3.36 (s, 2 H), 6.97 (t, J = 8 Hz, 1 H).

Synthesis 2003, No. 3, 343–345 ISSN 0039-7881 © Thieme Stuttgart · New York
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Anal. Calcd for C_{14}H_{24}O_4: C, 65.60; H, 9.44; Found: C, 65.69; H, 9.56.

(E)-Dodecylidenesuccinic Acid (1d)
Yield: 98%; mp 146–147 °C.
IR (Nujol): 2800–2500, 1702, 1692, 1641 cm⁻¹.
1^H NMR (acetone- d_6, 200 MHz): δ = 0.87 (t, J = 6 Hz, 3 H), 1.28 (br s, 16 H), 1.40–1.60 (m, 2 H), 2.25 (q, J = 6 Hz, 2 H), 3.35 (s, 2 H), 6.95 (t, J = 8 Hz, 1 H).

(E)-Tetradecylidenesuccinic Acid (1e)
Yield: 98%; mp 148 °C.
IR (Nujol): 2800–2500, 1705, 1699, 1647 cm⁻¹.
1^H NMR (CDCl₃–DMSO-d_6, 200 MHz): δ = 0.70 (t, J = 6 Hz, 3 H), 1.08 (br s, 20 H), 1.20–1.35 (m, 2 H), 2.01 (q, J = 8 Hz, 2 H), 3.13 (s, 2 H), 6.78 (t, J = 8 Hz, 1 H).
13^C NMR (CDCl₃ + DMSO-d_6, 75 MHz): δ = 12.6, 21.0, 27.0, 27.3, 27.6, 27.7, 28.0 (6 × CH₂), 30.2, 30.8, 125.3, 143.0, 167.1, 170.8. MS: m/z = 312, 294, 276, 266, 206, 192, 178, 139, 126, 113, 95, 81, 67, 55.
Anal. Calcd for C_{18}H_{32}O_4: C, 69.20; H, 10.32; Found: C, 69.07; H, 10.43.

Acknowledgments
S. M. thanks CSIR, New Delhi, for the award of a research fellowship. N. P. A. thanks the Department of Science and Technology, New Delhi, for the financial support. We thank Dr. K. N. Ganesh, Head, Division of Organic Chemistry (Synthesis) for constant encouragement.

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