Synthesis of Monosubstituted Succinic Acids from *tert*-Butylsuccinate

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Abstract: We report the preparation and alkylation of the dianion of *t*-butylsuccinate. This alkylation reaction has proven to be a useful method for the preparation of monosubstituted succinic acids and anhydrides.

Key words: alkylations, carboxylic acids, esters, dianions

Monosubstituted succinic acids and succinic anhydrides are an important class of compounds due to their utility as intermediates in organic synthesis,¹⁻³ as well as being a component of biologically interesting molecules.⁴⁻⁶ As part of our studies for the preparation of different analogs of methyllycaconitine (MLA) as nicotinic antagonists,⁷ we needed to prepare a number of different monosubstituted succinic anhydrides. A number of methods for the preparation of monosubstituted succinic acids have been reported.⁸⁻¹⁶ An attractive synthetic route would be to utilize a monoester of succinic acid. The dianion of monomethyl succinate has previously been generated in liquid NH₃ and alkylated with MeI and BnI.⁸

We report herein, a general and simple method for the synthesis of a series of monosubstituted succinic acids 4a-g and their anhydride derivatives 5a-g. We have successfully applied our procedure to prepare succinic acid and anhydride derivatives bearing a variety of alkyl substituents.



Reagents and conditions: (a) *t*-BuOH, NHS, 77%. (b) LDA (220 mol%), R-I or R-Br, THF, -78 °C. (c) TFA, CH₂Cl₂. (d) AcCl, reflux **Scheme**

We chose to start with *tert*-butylsuccinate (2) as the dianion since it should be more soluble in ethereal solvents and therefore less likely to suffer self-condensation. Additionally, the rapid and facile hydrolysis (TFA or HCl) of the *tert*-butyl ester should provide excellent yields of the diacid. The monoester 2 is readily prepared in 77% yield from succinic anhydride by reaction with *t*-BuOH.¹⁷ Treatment of 2 with 220 mol% of LDA in THF cleanly produced the dianion. The dianion can then be readily alkylated with a variety of alkyl halides to provide the succinate derivatives **3a**–**g** (Table 1). The yields are generally good, ranging from 48% to 72%.

The monoesters **3** can be readily converted to the corresponding diacid **4** in excellent yields by reaction with TFA in CH_2Cl_2 (Table 2). As we were interested in these succinic acid derivatives in the anhydride form, all of the diacids were converted to the anhydrides. Numerous methods have been reported for the synthesis of anhydride from the corresponding acid. Acetyl chloride¹⁸ was used as the dehydrating agent and produced the target anhydrides (**5a**–**g**) in excellent yields (Table 3).

We have demonstrated that the mono-*tert*-butylester of succinic acid can be readily alkylated with a variety of alkyl halides. The resulting monosubustituted succinic acids can either be converted to the corresponding anhydrides or the two carboxylate residues can be differentially functionalized.

Purification of reaction products was carried out by flash column chromatography using a glass column dry packed with silica gel (230–400 mesh) according to the method of Still.²² ¹H and ¹³C NMR spectra referenced to TMS were recorded using a Bruker DX 250 or Bruker DRX 400 spectrometer. All reactions were carried out under Ar atm, unless specified otherwise. Glassware was flame dried under a flow of Ar. THF was distilled from sodium/benzophenone ketyl immediately prior to use. CH₂Cl₂ was distilled from CaH₂ prior to use. Exact mass measurements were determined at The Ohio State University Campus Chemical Instrumentation Center. Combustion analyses were performed at Quantitative Technologies Inc., Whitehouse, New Jersey.

2-Alkyl tert-Butylsuccinate 3a-g; General Procedure

A solution of *n*-BuLi (5.4 mL of 2.3 M solution in hexanes, 12.5 mmol) was added to *i*-Pr₂NH (1.8 mL, 12.5 mmol) in THF (10 mL) at -78 °C. The mixture was stirred at -78 °C for 0.5 h then a solution of *tert*-butylsuccinate (2)¹⁷ (1.0 g, 5.7 mmol) in THF (5 mL) was added. The reaction was warmed to 0 °C and stirred for 2 h, then recooled to -78 °C and the alkyl halide (8 mmol) was

Table 1Yields and Properties of 2-Substituted tert-Butyl Succinates 3a-g

| | R | Yield (%) | Molecular formula Elemental analysis Calcd./Found %C, %H | ¹ H NMR (CDCl ₃ /TMS), δ , <i>J</i> (Hz) | ¹³ C NMR (CDCl ₃ /TMS), δ |
|----|---|--------------|---|---|--|
| 3a | Et | 55 | C ₁₀ H ₁₈ O ₄ 59.37/59.35, 8.96/9.07 | 10.00 (br s, 1 H), 2.80–2.60 (m, 2 H), 2.50–2.35 (m, 1 H), 1.75–1.52 (m, 2 H), 1.45 (s, 9 H), 0.95 (t, 3 H, <i>J</i> = 7.1) | 178.8, 174.3, 77.92, 43.6, 31.9, 28.0, 25.3, 14.5 |
| 3b | <i>i</i> -Pr | 48 | C ₁₁ H ₂₀ O ₄ 61.08/61.12, 9.32/9.23 | 10.50 (br s, 1 H), 2.80–2.59 (m, 2 H), 2.4 (dd, 1 H, <i>J</i> = 12.8, 2.1), 2.09–1.89 (m, 1 H), 1.45 (s, 9 H), 0.95 (app. t, 6 H) | 179.4, 173.7, 80.7, 48.3, 33.2, 30.0, 28.3, 20.4 |
| 3c | <i>n</i> -Bu | 60 | C ₁₂ H ₂₂ O ₄ 62.58/62.26, 9.63/9.94 | 10.80 (br s, 1 H), 2.80–2.61 (m, 2 H), 2.50–2.35 (m, 1 H), 1.73–1.24 (m, 15 H), 0.97–0.82 (t, 3 H, $J = 7.1$) | 178.9, 174.4, 81.0, 42.1, 36.3, 31.9, 29.2, 28.3, 22.8, 14.2 |
| 3d | Allyl | 72 | C ₁₁ H ₁₈ O ₄ 61.66/61.67, 8.47/8.59 | 10.90 (br s, 1 H), 5.85 (m, 1 H), 5.20–5.00 (d, 2 H, <i>J</i> = 9.3), 2.92–2.20 (m, 5 H), 1.45 (s, 9 H) | 178.8, 173.9, 134.7, 118.1, 81.4, 41.7, 36.2, 35.4, 28.6 |
| 3e | Bn | 52 | C ₁₅ H ₂₀ O ₄ 68.16/67.96, 7.62/7.93 | 10.35 (br s, 1 H), 7.35–7.10 (m, 5 H), 3.15–3.00 (m, 2 H), 2.85–2.60 (m, 2 H), 2.50–2.31 (dd, 1 H, $J = 15.0, 3.8$) 1.40 (s, 9 H) | 178.6, 173.6, 138.6, 129.5, 128.8, 127.0, 81.5, 44.0, 38.1, 35.5, 28.5 |
| 3f | Octyl | 66 | C ₁₆ H ₃₀ O ₄ 67.09/67.13, 10.55/10.84 | 10.65 (br s, 1 H), 2.75–2.60 (m, 2 H), 2.49–2.35 (m, 1 H), 1.75–1.52 (m, 2 H), 1.45 (s, 9 H), 1.25 (s, 12 H), 0.88 (t, 3 H, <i>J</i> = 7.1) | 179.0, 174.4, 81.1, 42.2, 36.3, 32.4, 32.2, 29.7, 29.5, 28.3, 27.3, 27.1, 23.0, 14.5 |
| 3g | Cyclo- C ₅ H ₉ | 48 | C ₁₃ H ₂₂ O ₄ 64.43/64.33, 9.15/9.41 | 10.58 (br s, 1 H), 2.95–2.40 (m, 4 H), 1.95 (m, 1 H), 1.90–1.50 (m, 7 H), 1.45 (s, 9 H) | 179.1, 174.2, 81.0, 47.3, 42.7, 35.8, 30.8, 28.3, 25.4, 21.3 |

 Table 2
 Yields and Properties of 2-Substituted Succinic Acids 4a-g

| | R | Yield (%) | Mp (°C) | Molecular formula Elemental analysis Calcd./Found %C, %H | ¹ H NMR (DMSO- d_6), δ , J (Hz) | ¹³ C NMR (DMSO- d_6), δ |
|-------------------------|---|--------------|----------------------------------|---|--|--|
| 4 a | Et | 93 | 96–97 97–98.5 ¹⁹ | C ₆ H ₁₀ O ₄ 49.31/49.51, 6.89/6.75 | 2.68–2.21 (m, 3 H), 1.68–1.42 (m, 2 H), 0.9 (t, 3 H) | 176.1, 173.5, 42.3, 38.8, 24.7, 11.5 |
| 4b | <i>i-</i> Pr | 86 | 110-111 | C ₇ H ₁₂ O ₄ 52.49/52.75, 7.55/7.87 | 2.60–2.22 (m, 3 H), 2.00–1.79 (m, 1 H), 0.86 (app. t, 6 H) | 175.6, 173.9, 47.2, 32.8, 29.6, 20.2, 19.6 |
| 4c ²⁰ | <i>n-</i> Bu | 83 | 82-83 | C ₈ H ₁₄ O ₄ 55.16/55.41, 8.10/8.38 | 2.69–2.24 (m, 3 H), 1.50 (t, 2 H, <i>J</i> = 8.2), 1.35–1.12 (m, 4 H), 0.87 (m, 3 H) | 176.3, 173.5, 40.9, 35.9, 31.3, 28.9, 22.4, 14.1 |
| 4d | Allyl | 80 | 90-91 | C ₇ H ₁₀ O ₄ 53.16/53.20, 6.37/6.21 | 5.90–5.52 (m, 1 H), 5.28–4.82 (m, 2 H), 2.89–2.65 (m, 1 H), 2.64–2.10 (m, 4 H) | 175.6, 173.3, 135.5, 117.6, 40.7, 35.7, 35.1 |
| 4e | Bn | 95 | 160–161 165–166 ²¹ | C ₁₁ H ₁₂ O ₄ 63.45/63.13, 5.80/5.78 | 7.38–7.10 (m, 5 H), 3.10–2.85 (m, 1 H), 2.80–2.60 (m, 1 H), 2.55–2.32 (m, 2 H), 2.3–2.1 (m, 1 H) | 175.5, 173.2, 139.0, 129.3, 128.6, 126.7, 42.8, 37.2, 35.1 |
| 4f | Octyl | 95 | 89-90 | C ₁₂ H ₂₂ O ₄ 62.58/62.53, 9.62/9.43 | 2.65–2.25 (m, 3 H), 1.60–1.35 (m, 2 H), 1.22 (s, 12 H), 0.85 (t, 3 H, <i>J</i> = 7.2) | 175.8, 172.9, 40.4, 35.4, 31.1, 31.0, 28.6, 28.4, 26.4, 21.9, 13.7 |
| 4g | Cyclo- C ₅ H ₉ | 95 | 105-106 | C ₉ H ₁₄ O ₄ 58.05/57.98, 7.57/7.78 | 2.95–2.70 (m, 3 H), 2.68–2.50 (m, 3 H), 2.20–1.30 (m, 6 H) | 176.1, 173.9, 45.8, 42.0, 35.4, 30.3, 29.1, 24.9, 24.8 |

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Table 3Yields and Properties of 2-Substituted Succinic Anhydrides 5a-g

| | R | Yield (%) | Mp (°C) | Molecular Formula HRMS Calc./Found | ¹ H NMR (DMSO- d_6), δ , J (Hz) | ¹³ C NMR (DMSO- d_6), δ |
|----|---|--------------|---------|---|---|--|
| 5a | Et | 96 | Oil | C ₆ H ₈ O ₃ 128.125/128.046 | 3.20–3.03 (m, 2 H), 2.78–2.60 (m, 1 H), 2.10–1.90 (m, 1 H), 1.88–1.67 (m, 1 H), 1.05 (t, 3 H, <i>J</i> = 6.2) | 173.9, 170.6, 42.3, 33.9, 24.5, 11.3 |
| 5b | <i>i</i> -Pr | 87 | Oil | C ₇ H ₁₀ O ₃ 142.152/142.063 | 3.23–2.90 (m, 2 H), 2.85–2.65 (m, 1 H), 2.45–2.20 (br s, 1 H), 1.23–0.90 (m, 6 H) | 173.3, 170.8, 47.2, 31.1, 29.6, 20.1, 18.4 |
| 5c | <i>n</i> -Bu | 96 | 42-43 | C ₈ H ₁₂ O ₃ 156.179/156.078 | 3.25–3.05 (m, 2 H), 2.80–2.50 (m, 1 H), 2.12–1.91 (m, 1 H), 1.75–1.52 (m, 1 H), 1.50–1.22 (m, 4 H), 0.99 (t, 3 H, <i>J</i> = 7.5) | 174.3, 170.8, 41.2, 30.9, 29.1, 24.0, 22.5, 14.4 |
| 5d | Allyl | 85 | Oil | C ₇ H ₈ O ₃ 140.136/140.047 | 5.90–5.65 (m, 1 H), 5.35–5.28 (m, 2 H), 3.40–3.20 (m, 1 H), 3.19–3.00 (m, 1 H), 2.83–2.40 (m, 3 H) | 173.6, 170.5, 132.4, 120.4, 40.5, 34.9, 33.5 |
| 5e | Bn | 95 | 91-92 | C ₁₁ H ₁₀ O ₃ 190.195/190.063 | 7.48–7.10 (m, 5 H), 3.59–3.35 (m, 1 H), 3.32–3.15 (m, 1 H), 3.10–2.82 (m, 2 H), 2.80–2.60 (m, 1 H) | 173.5, 169.9, 136.2, 129.6, 129.3, 128.0, 42.5, 36.3, 33.4 |
| 5f | Octyl | 84 | 60-61 | C ₁₂ H ₂₀ O ₃ 212.285/212.140 | 3.19-3.02 (m, 2 H), 2.75-2.59 (m, 1 H), 2.05-1.85 (m, 1 H), 1.72-1.54 (m, 1 H), 1.45-1.15 (br s, 12 H), 0.88 (t, 3 H, <i>J</i> = 7.3) | 174.0, 170.5, 41.1, 34.5, 32.2, 31.4, 29.6, 29.5, 29.4, 27.0, 23.0, 14.5 |
| 5g | Cyclo- C ₅ H ₉ | 91 | 65-66 | C ₉ H ₁₂ O ₃ 168.189/168.045 | 3.25–2.95 (m, 2 H), 2.95–2.60 (m, 1 H), 2.39–2.15 (m, 1 H), 2.10–1.45 (m, 6 H), 1.45–1.10 (m, 2 H) | 173.5, 170.9, 44.9, 41.4, 33.1, 30.6, 29.7, 25.5, 25.2 |

added dropwise. The reaction was allowed to warm to r.t. and stirred for 24 h. The reaction was quenched with H_2O (3 mL) and concentrated. The residue was partitioned between EtOAc (30 mL) and cold 1 M HCl (20 mL). The organic layer was dried (MgSO₄), filtered, concentrated, and chromatographed (25% EtOAc in hexanes) to afford products **3a**-g as colorless oils (Table 1).

2-Alkylsuccinic Acid 4a-g; General Procedure

Trifluoroacetic acid (3.6 mL, 47.2 mmol) was added to a solution of 2-alkyl *tert*-butylsuccinate 3a-g (1.5 mmol) in CH₂Cl₂ (20 mL). The mixture was stirred at r.t. for 24 h and was then concentrated and chromatographed (50% EtOAc in hexanes) to produce the diacid (4a-g) in good yields as white crystals (Table 2).

2-Alkylsuccinic Anhydride 5a-g; General Procedure

A mixture of 2-alkylsuccinic acid 4a-g (2 mmol) and acetyl chloride (0.9 mL, 12.3 mmol) was refluxed for 3 h. The solution was concentrated to give the desired anhydride 5a-g (Table 3).

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