An Efficient Approach to β-Oxoadipate Derivatives and γ-Oxo Acids by the Reformatsky Reaction of Ethyl α-Bromoalkanoates with Succinic Anhydride

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Dedicated to Prof. Dr. Dr. h. c. mult. Alfred Rieche on the occasion of his 90th birthday

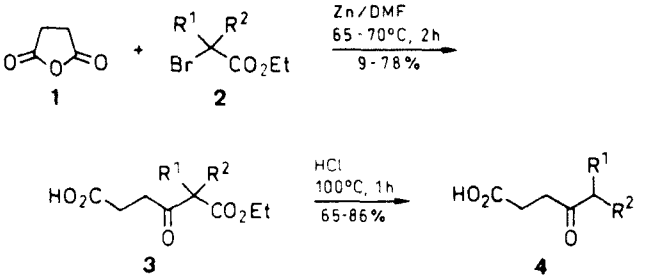
Ethyl 2-bromoalkanoates react with zinc and succinic anhydride in dimethylformamide forming 2-substituted 1-ethyl hydrogen 3-oxoadipates (hexanedioates) isolable in a yield of 56–78%. When subjected to decarboxylative saponification, they afford 4-oxoalkanoic acids in overall yields of 50–72%.

The Reformatsky reaction of alkyl 2-bromoalkanoates with zinc and aldehydes or ketones to 3-hydroxyalkanoates has found widespread application in organic synthesis.[1–4] Although it has been known for a long time that alkylzinc halides add selectively to alkanoyl chlorides forming ketones,[5] the Reformatsky reaction of these reactive carbonyl compounds with alkyl 2-bromoalkanoates has only rarely been taken into consideration as a tool for the synthesis of β-oxo esters so far.[6,7] The same applies to alkanoic anhydrides.[8,9] Being generally interested in the conversion of carboxylic acid derivatives into ketones by selective reactions with suitable organometallics we turned our interest to this problem.

We found that the outcome of the reaction of the ethyl 2-bromoalkanoates **2** with zinc and succinic anhydride (**1**) strongly depends on the substituents R^1 and R^2 and the solvent used for the reaction. The reaction of **2g** in dichloromethane, chloroform, tetrahydrofuran, diethyl ether or toluene proceeded with unsatisfactory yields. However, if dimethylformamide was used as the solvent, the reaction became strongly exothermic and provided 1-ethyl hydrogen 2,2-dimethyl-3-oxoadipate (**3g**) in an isolated yield of 78%. Under the same conditions the ethyl 2-bromoalkanoates **2b–f** afforded the corresponding 1-ethyl hydrogen 2-alkyl-3-oxoadipates **3b–f** in yields between 56 and 68%. Only ethyl 2-bromoacetate (**2a**) strongly deviated by giving **3a** in a yield of only 9%. According to literature,[8] *C*- and/or *O*-acylation of the expected 2-unsubstituted 3-oxoadipic acid derivative by succinic anhydride may be regarded as the reason for the low yield of **3a**. The 2-monosubstituted and, in particular, the 2,2-disubstituted 3-oxoadipic acid derivatives seem to be much less susceptible to such undesired side reactions.

By the described method, 2-mono- and 2,2-disubstituted 1-ethyl hydrogen 3-oxoadipates are accessible in good yields from easily available starting materials in a one-step procedure. In this way, the problems principally connected with the mono- and dialkylation of 2-unsubstituted 3-oxoadipates and with the preparation of 1-monoesters of 3-oxoadipic acids can be circumvented conveniently. Additionally, the esterification of **3b–g** opens an efficient access to 3-oxoadipates with identical or different ester groups.

β-Oxo esters **3b–g** are decarboxylated to 4-oxoalkanoic acids **4b–g** in yields of 65–86% by heating in constantly boiling hydrochloric acid. The access to the 4-oxo acids can be simplified and the overall yield improved by omitting the isolation of the intermediate β-oxo esters.



2–4	R^1	R^2	2–4	R^1	R^2
a	H	H	**e**	H	Bu
b	H	Me	**f**	H	n-C_6H_{13}
c	H	Et	**g**	Me	Me
d	H	Pr			

Ethyl 2-bromoalkanoates **2a–g** were purchased from E. Merck, Darmstadt and used as such. DMF was purified according to Ref. 10. Silica gel 60 (230–400 mesh, E. Merck) was used for flash chromatography.[11] Melting points were determined on a Boëtius micro melting point apparatus and are corrected. ^{1}H NMR spectra were recorded at 80 MHz on a Tesla BS 587 A spectrometer and ^{13}C NMR spectra at 75 MHz on a Varian Gemini 300 instrument.

2-Substituted 1-Ethyl Hydrogen 3-Oxoadipates 3; General Procedure:

Zinc–copper couple[12,13] (1.31 g, 20 mmol) was added to a solution of succinic anhydride (**1**; 1.0 g, 10 mmol) and the appropriate ethyl 2-bromoalkanoate **2** (13 mmol). The temperature of the reaction mixture rose within 1–15 min to 60–80°C. When the strongly exothermic reaction had ceased, the mixture was stirred for 1 h and allowed to stand overnight. The mixture was poured onto ice (50 g) and 5% aq HCl (50 mL) and extracted with EtOAc (5 × 30 mL). The combined extracts were washed with water (2 × 20 mL), dried (Na_2SO_4), and evaporated under reduced pressure. The remaining crude half esters **3a–g** were purified by flash chromatography on silica gel (40 g) using hexane/EtOAc/AcOH (66:33:0.5) as eluent. (Table 1).

4-Oxoalkanoic Acids 4b–g; General Procedure:

Compound **3** (2.0 g) was refluxed for 1 h under vigorous stirring with conc. HCl (4 mL) and water (4 mL). Then the mixture was concentrated under reduced pressure. Traces of water were removed by azeotropic distillation with toluene (2 × 10 mL). The resulting semi-solid residue was purified by flash chromatography on silica gel 60 (35 g) with hexane/EtOAc/AcOH (66:33:0.5) affording the 4-oxoalkanoic acid in pure form (Table 2).

4-Oxopheptanoic Acid (4c); Typical Procedure (for Large-Scale Preparation):

Zinc–copper couple[12,13] (26.2 g, 0.40 mol) was suspended by stirring in a solution of succinic anhydride (20.0 g, 0.20 mol) in DMF (50 mL). To start the reaction, 5 mL of a solution of ethyl 2-bromobutanoate (**2c**; 38.4 mL, 0.26 mol) in DMF (12 mL) was added in one portion. The temperature rose rapidly to about 50°C. The

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Table 1. Compounds **3** Prepared

Product	Yield (%)	mp (°C) (pentane)	Molecular Formula[a] or Lit. mp (°C)	^{1}H NMR ($CDCl_3$/TMS) δ, J (Hz)	^{13}C NMR ($CDCl_3$/TMS) δ
3a	9	oil	55[15]	1.22 (t, 3H, J = 7), 2.50–2.85 (m, 4H), 3.43 (s, 2H), 4.14 (q, 2H, J = 7), 8.31 (s, 1H)	14.0, 27.7, 37.1, 49.2, 61.6, 167.2, 178.0, 201.0
3b	59	oil	$C_9H_{14}O_5$ (202.2)	1.18 (t, 3H, J = 7), 1.31 (d, 3H, J = 7), 2.51–2.59 (m, 4H), 3.52 (q, 1H, J = 7), 4.15 (q, 2H, J = 7), 9.11 (s, 1H)	12.7, 14.0, 27.9, 35.9, 61.1, 61.6, 170.6, 178.0, 204.5
3c	56	42–44	$C_{10}H_{16}O_5$ (216.2)	0.86 (t, 3H, J = 7), 1.20 (t, 3H, J = 7), 1.83 (m, 2H, J = 7), 2.41–2.96 (m, 4H), 3.34 (t, 1H, J = 7), 4.15 (q, 2H, J = 7), 10.61 (s, 1H)	11.8, 14.1, 21.6, 27.7, 36.1, 60.6, 61.4, 169.6, 178.4, 203.4
3d	57	oil	$C_{11}H_{18}O_5$ (230.3)	0.85 (t, 3H, J = 7), 1.19 (t, 3H, J = 7), 1.24 (m, 2H), 1.76 (t, 2H, J = 7), 2.45–2.91 (m, 4H), 3.42 (t, 1H, J = 7), 4.14 (q, 2H, J = 7), 10.85 (s, 1H)	13.8, 14.1, 20.6, 27.8, 29.0, 36.1, 58.9, 61.5, 169.9, 178.2, 203.6
3e	61	oil	$C_{12}H_{20}O_5$ (244.3)	0.84 (t, 3H, J = 7), 1.17 (t, 3H, J = 7), 1.09–1.35 (m, 4H), 1.83 (m, 2H), 2.46–2.89 (m, 4H), 3.39 (t, 1H, J = 7), 4.14 (q, 2H, J = 7), 10.64 (s, 1H)	13.8, 14.1, 22.4, 27.8, 28.0, 29.5, 36.1, 59.1, 61.4, 169.8, 178.4, 203.6
3f	68	oil	$C_{14}H_{24}O_5$ (272.3)	0.90 (t, 3H, J = 7), 1.11–1.39 (m, 8H), 1.21 (t, 3H, J = 7), 1.80 (m, 2H), 2.41–2.91 (m, 4H), 3.38 (t, 1H, J = 7), 4.14 (q, 2H, J = 7), 10.35 (s, 1H)	14.0, 14.1, 22.5, 27.3, 27.8, 28.3, 29.0, 31.5, 36.1, 59.2, 61.4, 169.8, 178.3, 203.5
3g	78	40–42	$C_{10}H_{16}O_5$ (216.2)	1.18 (t, 3H, J = 7), 1.30 (s, 6H), 2.45–2.82 (m, 4H), 4.12 (q, 2H, J = 7), 10.35 (s, 1H)	14.0, 22.0, 28.0, 32.6, 55.3, 61.5, 173.6, 178.3, 206.5

[a] Satisfactory microanalyses obtained: C ±0.29, H ±0.31.

Table 2. 4-Oxoalkanoic Acids **4** Prepared

Product	Yield[a] (%)	mp (°C) (pentane)	Lit. mp (°C)	^{1}H NMR ($CDCl_3$/TMS) δ, J (Hz)	^{13}C NMR ($CDCl_3$/TMS) δ
4b	69 (51)	34–36	37–38[16]	1.02 (t, 3H, J = 7), 2.43 (q, 2H, J = 7), 2.62 (br s, 4H), 10.55 (s, 1H)	7.7, 27.8, 35.8, 36.3, 178.9, 209.4
4c	78 (52)	46–48	48–50[14]	0.86 (t, 3H, J = 7), 1.30–1.80 (m, 2H), 2.36 (t, 2H, J = 7), 2.60 (br s, 4H)	13.7, 17.3, 27.8, 36.8, 44.7, 178.5, 208.8
4d	65 (57)	49–51	52–54[14]	0.85 (t, 3H, J = 7), 1.05–1.75 (m, 4H), 2.40 (t, 2H, J = 7), 2.60 (br s, 4H), 10.45 (s, 1H)	13.8, 22.3, 25.9, 27.8, 36.7, 42.4, 178.9, 209.1
4e	76 (50)	66–67	67–68[17]	0.82 (t, 3H, J = 7), 1.05–1.80 (m, 6H), 2.40 (t, 2H, J = 7), 2.50–2.75 (m, 4H), 11.0 (s, 1H)	13.9, 22.4, 23.5, 27.9, 31.4, 36.8, 42.7, 178.9, 209.1
4f	68 (64)	75–77	78–79[17]	0.82 (t, 3H, J = 7), 1.05–1.75 (m, 10H), 2.38 (t, 2H, J = 7), 2.60 (br s, 4H)	14.0, 22.6, 23.9, 27.8, 29.0, 29.2, 31.7, 36.8, 42.8, 178.5, 208.9
4g	86 (72)	39–41	42–43[18]	1.05 (d, 6H, J = 7), 2.40–2.80 (m, 5H), 10.5 (s, 1H)	18.2, 27.9, 34.5, 40.8, 178.9, 212.6

[a] Yields related to **1** obtained by omitting the isolation of **3** are shown in paranthesis.

remaining solution of **2c** was added carefully within 2 h while the temperature was maintained at 65–70 °C. The mixture was stirred for another 2 h and allowed to stand overnight. Thereafter it was hydrolyzed by the addition of 10% aq HCl (200 mL) and ice (300 g). Extraction with EtOAc (5 × 100 mL) and evaporation of the solvent under reduced pressure afforded crude **4c** as an oil, which was refluxed for 1.5 h with a mixture of conc. HCl (60 mL) and water (60 mL). Then the solvent was evaporated under reduced pressure. Last traces of water were removed by azeotropic distillation with toluene. The semi-solid residue was recrystallized from hexane/Et_2O; yield: 15 g (52%); mp 46–48 °C (Lit.[14] mp 48–50 °C).

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