of compound **18c** as the third fraction. Compound **18c**: IR 1727, 1665, 1615 cm^{-1}; ^{1}H NMR (500 MHz) δ 0.76 (s, 3), 0.83–0.99 (m, 4), 1.12 (s, 3), 1.24 (s (br), 1), 1.25–1.30 (m, 2), 1.32–1.47 (m, 4), 1.56–1.65 (m, 3), 2.23 (dd, 1, J = 14.5, 14.3), 2.26 (m, 1), 2.29 (d (br), 1, J = 19.7), 2.41 (dt, 1, J = 14.4, 6.7), 2.68 (t, 2, J = 7.7), 3.03 (t, 2, J = 7.7), 5.04 (m, 1), 7.31 (m, 1), 7.47 (t, 2, J = 8.1), 7.77 (d, 2, J = 7.0); mass spectrum (FAB, glycerol/thioglycerol) m/z 509 (M + Na), 487 (MH), 471, 255; HRFABMS calcd for $C_{32}H_{39}O_4$ 487.2848, found 487.2854.

Compounds 22c and 23c: IR 1720, 1660, 1605 cm^{-1}; ^{1}H NMR (an approximate 1:1 mixture of **22c** and **23c**) (250 MHz) δ 0.71 (s, 3/2), 0.81 (s, 3/2), 0.81–0.95 (m, 3), 0.96 (s, 3/2), 1.24 (s, 3/2), 1.24–1.78 (m, 12), 2.04 (m, 1/2), 2.06 (d, 1/2, J = 12), 2.22 (m, 1/2), 2.26 (d (br), 1/2, J = 13), 2.54 (dd, 1/2, J = 12, 6), 2.56 (m, 1/2), 2.69 (t, 2, J = 7.5), 3.04 (t, 2, J = 7.5), 5.01 (m, 1/2), 5.14 (m, 1/2), 7.32 (d, 2, J = 8), 7.48 (t, 2, J = 7.5), 7.59 (m, 1), 7.76 (m, 4); mass spectrum (FAB, glycerol/thioglycerol) m/z 509 (M + Na), 487 (MH), 471, 255; HRFABMS calcd for $C_{32}H_{39}O_4$ 487.2848, found 487.2860.

Acknowledgment. This work was supported by a research grant from the United States Public Health Service (CA 21163).

Registry No. 1, 41451-75-6; **5a**, 141396-78-3; **5b**, 91237-33-1; **5c**, 91191-70-7; **6a**, 141396-79-4; **6a** ketone, 141396-80-7; **6b**, 141396-81-8; **6b** ketone, 141396-82-9; **6c**, 141396-83-0; **6c** ketone, 141396-84-1; **7a**, 141396-85-2; **7b**, 141396-86-3; **7c**, 141396-87-4; **8**, 71388-83-5; **9a**, 141396-88-5; **9a** (phosphoproduct, isomer 1), 141396-89-6; **9a** (photoproduct, isomer 2), 141435-17-8; **9b**, 141396-90-9; **9b** (photoproduct, isomer 1), 141396-91-0; **9b** (photoproduct, isomer 2), 141435-18-9; **9c**, 141396-92-1; **9c** (CH12 photoproduct, isomer 1), 141396-93-2; **9c** (C-12 photoproduct, isomer 2), 141435-19-0; **9c** (C-7 photoproduct, isomer 1), 141396-94-3; **9c** (C-7 photoproduct, isomer 2), 141435-20-3; **9c** (C-14 photoproduct, isomer 1), 141396-95-4; **9c** (C-14 photoproduct, isomer 2), 141435-21-4; **11**, 141396-96-5; **12**, 141396-97-6; **13**, 141396-98-7; **14**, 141396-99-8; **15**, 141397-00-4; **16**, 141397-01-5; **17**, 141397-02-6; **18a**, 141397-03-7; **18a** (photo-pinacol, isomer 1), 141397-04-8; **18a** (photo-pinacol, isomer 2), 141435-22-5; **18b**, 141397-05-9; **18c**, 141397-06-0; **19** (isomer 1), 141411-05-4; **19** (isomer 2), 141505-43-3; **20**, 141397-07-1; **21**, 141397-08-2; **22c**, 141397-09-3; **23c**, 141397-10-6; **24**, 141397-11-7.

Supplementary Material Available: ^{1}H NMR spectra for compounds **9b**, **11**, **15**, **16**, **17**, **20**, **18c**, **22c**, and **23c** (8 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and may be ordered from the ACS; see any current masthead page for ordering information.

Notes

Electrochemically Supported Reformatsky Reaction: A Convenient Preparation of 2-Substituted 1-Ethyl 3-Oxoalkanedioates

Karl-Heinz Schwarz, Katharina Kleiner, Ralf Ludwig, and Hans Schick*

Central Institute of Organic Chemistry, Rudower Chaussee 5, O-1199 Berlin-Adlershof, Federal Republic of Germany

Received January 2, 1992

The Reformatsky reaction of ethyl 2-bromoalkanoates with zinc and aldehydes or ketones is an important method for the preparation of various ethyl 3-hydroxyalkanoates.[1] The success of the reaction strongly depends on the reactivity of the zinc. Therefore, much effort has been applied to the activation of the metal.[2] Washing of zinc with diluted hydrochloric acid,[3] reduction of zinc halides with potassium[4] or lithium naphthalenide,[5] preparation of zinc–copper[6] or zinc–silver couples,[7] and ultrasonic irradiation[8] are among the methods that have been employed to achieve a proper activation of the zinc. Even with the use of these methods, the problem remains that Reformatsky reactions are often difficult to control. Usually, the reactions take a highly exothermic course once a critical temperature has been reached.

Electrosynthesis has proven to be an efficient method for the preparation of organometallic compounds.[9] Especially organometallics, generated by sacrificial anodes such as magnesium,[10] aluminum,[11] and zinc,[12] present a useful alternative to purely chemical synthesis in the preparation of nucleophilic intermediates suited for further reactions with electrophiles in order to form new carbon–carbon bonds.[13]

With the application of an electrochemical procedure, we are now able to circumvent both the problems of zinc activation and the difficulties connected with the uncontrolled exothermic course of the Reformatsky reaction of ethyl 2-bromoalkanoates with cyclic carboxylic anhydrides.[14]

Ethyl 2-bromo-2-methylpropanoate (**3a**) was electrolyzed in the presence of succinic anhydride (**1**) in DMF containing tetrabutylammonium bromide as supporting electrolyte. We used a closed undivided cell with a zinc rod as anode and a nickel net as cathode, with an initial external voltage of 50 V. The temperature of the system was maintained at 50 °C by reducing the voltage to about 30 V during the course of the electrolysis. At the end of

---

(1) (a) Fürstner, A. *Synthesis* **1989**, 571. (b) Rathke, M. W. *Org. React.* **1975**, *22*, 423. (c) Gaudemar, M. *Organomet. Chem. Rev. A* 1972, *8*, 183.

(2) (a) Erdik, E. *Tetrahedron* **1987**, *43*, 2203. (b) Rieke, R. D. *Science* **1989**, *246*, 1260.

(3) Hauser, C. R.; Brewlow, O. S. *Organic Syntheses*; Wiley: New York, 1955; Collect. Vol. III, p 408.

(4) (a) Rieke, R. D.; Uhm, S. J.; Hudnall, P. M. *J. Chem. Soc., Chem. Commun.* **1973**, 269. (b) Chao, L. C.; Rieke, R. D. *J. Org. Chem.* **1975**, *40*, 2253. (c) Rieke, R. D.; Uhm, S. J. *Synthesis* **1975**, 452. (d) Rieke, R. D.; Li, P. T.; Burns, T. P.; Uhm, S. T. *J. Org. Chem.* **1981**, *46*, 4323.

(5) Zhu, L.; Wehmeyer, R. M.; Rieke, R. D. *J. Org. Chem.* **1991**, *56*, 1445.

(6) Santaniello, E.; Manzocchi, A. *Synthesis* **1977**, 698.

(7) Bortolussi, M.; Seyden-Penne, J. *Synth. Commun.* **1989**, *19*, 2355.

(8) (a) Han, B. H.; Boudjouk, P. *J. Org. Chem.* **1982**, *47*, 5030. (b) Boudjouk, P.; Thompson, D. P.; Ohrbom, W. H.; Han, B. H. *Organometallics* **1986**, *5*, 1257.

(9) Lehmkuhl, H. *Synthesis* **1973**, 377.

(10) d'Incan, E.; Sibille, S.; Périchon, J.; Moingeon, M.-O.; Chaussard, J. *Tetrahedron Lett.* **1986**, *27*, 4175.

(11) Sibille, S.; Périchon, J.; Chaussard, J. *Synth. Commun.* **1989**, *19*, 2449.

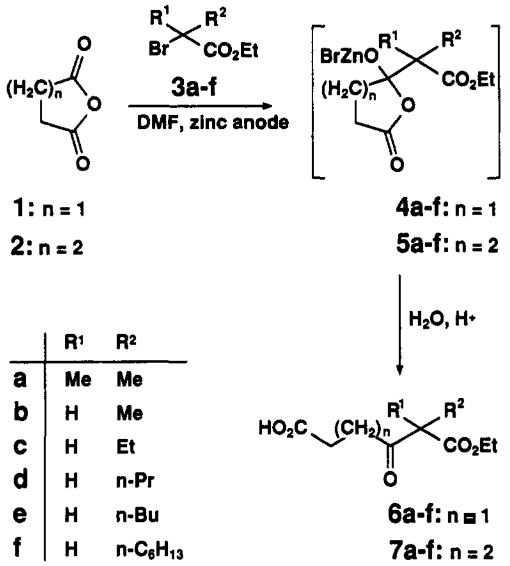
(12) Habeeb, J. J.; Osman, A.; Tuck, D. G. *J. Organomet. Chem.* **1980**, *185*, 117.

(13) Chaussard, J.; Folest, J.-C.; Nedelec, J.-Y.; Périchon, J.; Sibille, S.; Troupel, M. *Synthesis* **1990**, *369*.

(14) Schick, H.; Ludwig, R. *Synthesis* **1992**, 369.

0022-3263/92/1957-4013$03.00/0

Scheme I



	R¹	R²
a	Me	Me
b	H	Me
c	H	Et
d	H	n-Pr
e	H	n-Bu
f	H	n-C_6H_{13}

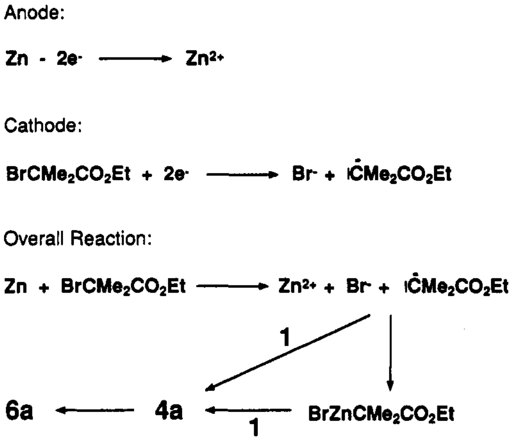
the reaction, the temperature dropped below 50 °C. The reaction was stopped when the loss of weight of the zinc anode corresponded to 1 g atom zinc per mol of ethyl 2-bromo-2-methylpropanoate (**3a**). At this stage the amount of electricity consumed in the electrochemical process was only on the order of 0.2–0.5 F per g atom of dissolved zinc. A usual workup produced 1-ethyl 3-oxo-2,2-dimethylhexanedioate (**6a**) in an isolated yield of 65%.

After we had completed this experiment, a report of Conan, Sibille, and Pĕrichon was published.[15] They showed that methyl 2-chloroacetate forms methyl 3-hydroxyalkanoates when it is electrolyzed at a constant current with an aldehyde or ketone in *N,N*-dimethylformamide (DMF) in the presence of $NiBr_2(bipy)_2$ using zinc as the sacrificial anode. In this process, the Reformatsky reagent $ClZnCH_2CO_2Me$, which reacted with the carbonyl compounds, was formed through a metal-exchange reaction between the corresponding nickel(II) species and zinc chloride. Comparing these results with our findings it is striking that we did not need nickel(II) salts for a successful electroassisted Reformatsky reaction. It must be pointed out, however, that there was not only a difference in the carbonyl compounds used, but also in the experimental conditions. In contrast to ref 15 we did not electrolyze at a constant current of 0.2 A, but at an external voltage of 30–50 V, using a 2-electrode configuration with no reference electrode.

The apparent contradiction in the electroassisted synthesis of **6a** between the applied quantity of electricity (0.2–0.5 F) and the consumed quantity of zinc (1 g atom) can be explained by assuming an overlap of two different reaction sequences. In the first one, anodically generated zinc cations react with the anions created by electroreduction of the bromo ester **3a** forming the Reformatsky reagent $BrZnCMe_2CO_2Et$. This is added to succinic anhydride, producing **4a** or a related intermediate. Alternatively, it is possible that the carbanion formed by electroreduction at the cathode can be added directly to the succinic anhydride, which, after stabilization with electrochemically generated zinc bromide, also yields the addition product **4a**.

This sequence, an electroassisted Reformatsky reaction is assumed to be overlapped by a current-independent second reaction sequence, a normal Reformatsky reaction.

Scheme II



This supposes that the surface of the zinc anode is scoured by the anodic oxidation to zinc cations in such a manner that the bromo ester **3a** can react with the metal, thus producing the Reformatsky reagent. This then forms the addition product **4a** with succinic anhydride.

In order to broaden the application of this electroassisted Reformatsky reaction, experiments with succinic anhydride (**1**) and the 2-bromoalkanoates **3b–f**, as well as with glutaric anhydride (**2**) and the 2-bromoalkanoates **3a–f**, were performed under the same conditions. The yields of the isolated half esters **6b–f** and **7a–f** were in the order of 50–75%. In experiments on a larger scale, it could be demonstrated that problems resulting from the strongly exothermic reaction, under normal Reformatsky conditions,[14] of activated zinc powder with succinic anhydride and the bromo esters **3** could be avoided by regulating the rate of the reaction by a proper choice of the external voltage. Decarboxylative hydrolysis of **6b**, obtained from succinic anhydride and the bromo ester **3b**, produced 4-oxohexanoic acid in an overall yield of 55%. The supporting electrolyte tetrabutylammonium bromide could be substituted with the much cheaper zinc chloride without affecting the yield.

Investigations to determine scope and limitations of this electrochemical process are in progress.

In conclusion, the described electrochemical procedure does not require a troublesome activation of the zinc. By regulating the applied external voltage, even the often vehement course of the Reformatsky reaction in a large-scale preparation can be controlled.

Experimental Section

The electrolysis cell was a beaker with a diameter of 4.5 cm and a height of 4 cm with a Teflon cover. The electrosyntheses were performed without a diaphragm under an atmosphere of dry nitrogen. A commercial dc voltage source (Statron, type 3218) was applied. The cell was equipped with a magnetic stirring bar. A zinc rod (30-mm long, 6-mm in diameter) was used as the anode, a nickel net (40 × 40 mm) as the cathode. The amount of electricity was measured with an electronic coulometer. DMF was purified by azeotropic distillation with water and benzene, fractionated, and redistilled from CaH_2. All other chemicals were purchased from Merck–Schuchardt in good quality and used without further purification. ^1H NMR spectra were determined at 80 MHz on a Tesla BS 587 A spectrometer in $CDCl_3$ with tetramethylsilane as the internal standard ($\delta_{TMS} = 0$). ^{13}C NMR spectra were measured at 75 MHz on a Varian Gemini 300 instrument in $CDCl_3$ with hexamethyldisiloxane as the internal standard ($\delta_{HMDS} = 1.92$). Microanalyses were obtained using a Carlo Erba autoanalyzer 1106.

General Procedure for the Electrosynthesis of the Half Esters 6a–f and 7a–f. A bromo ester **3** (20 mmol), succinic or glutaric anhydride (**1** or **2**, 15 mmol), and tetrabutylammonium

---

[15] Conan, A.; Sibille, S.; Pĕrichon, J. *J. Org. Chem.* **1991**, *56*, 2018.

bromide (645 mg, 2 mmol) were dissolved in DMF (20 mL) and initially electrolyzed at an external voltage of 50 V. When the reaction temperature reached 60 °C, the voltage was reduced to about 30 V in order to maintain the temperature in the range of 50–60 °C. At the end of the electrolysis the temperature dropped below 50 °C. At this point, the loss of weight of the zinc anode amounted to about 1.3 g (20 g atom). The reaction mixture was poured onto a mixture of 5% aqueous HCl (100 mL) and ice (50 g) and extracted with EtOAc (5 × 40 mL). The extract was dried ($MgSO_4$) and concentrated under reduced pressure. The oily residue was purified by flash chromatography on silica gel 60 using hexane/EtOAc/HOAc (66:33:0.5) as the eluent. According to this procedure the following half esters have been obtained.

1-Ethyl 2,2-dimethyl-3-oxohexanedioate (6a): yield 2.11 g (65%); colorless crystals; mp 40–42 °C (*n*-pentane); ^{1}H NMR δ 1.18 (3 H, t, J = 7 Hz), 1.30 (6 H, s), 2.45–2.82 (4 H, m), 4.12 (2 H, q, J = 7 Hz), 10.35 (1 H, s); ^{13}C NMR δ 14.0, 22.0, 28.0, 32.6, 55.3, 61.5, 173.6, 178.3, 206.5. Anal. Calcd for $C_{10}H_{16}O_5$: C, 55.55; H, 7.46. Found: C, 55.68; H, 7.61.

1-Ethyl (±)-2-methyl-3-oxohexanedioate (6b): yield 1.70 g (56%); colorless oil; ^{1}H NMR δ 1.18 (3 H, t, J = 7 Hz), 1.31 (3 H, d, J = 7 Hz), 2.51–2.59 (4 H, m), 3.52 (1 H, q, J = 7 Hz), 4.15 (2 H, q, J = 7 Hz), 9.11 (1 H, s); ^{13}C NMR δ 12.7, 14.0, 27.9, 35.9, 61.1, 61.6, 170.6, 178.0, 204.5. Anal. Calcd for $C_9H_{14}O_5$: C, 53.46; H, 6.98. Found: C, 53.62; H, 7.12.

1-Ethyl (±)-2-ethyl-3-oxohexanedioate (6c): yield 2.17 g (67%); colorless crystals; mp 42–44 °C (pentane); ^{1}H NMR δ 0.86 (3 H, t, J = 7 Hz), 1.20 (3 H, t, J = 7 Hz), 1.83 (2 H, m), 2.41–2.96 (4 H, m), 3.34 (1 H, t, J = 7 Hz), 4.15 (2 H, q, J = 7 Hz), 10.61 (1 H, s); ^{13}C NMR δ 11.8, 14.1, 21.6, 27.7, 36.1, 60.6, 61.4, 169.6, 178.4, 203.4. Anal. Calcd for $C_{10}H_{16}O_5$: C, 55.55; H, 7.46. Found: C, 55.31; H, 7.59.

1-Ethyl (±)-3-oxo-2-propylhexanedioate (6d): yield 2.52 g (73%); colorless oil; ^{1}H NMR δ 0.85 (3 H, t, J = 7 Hz), 1.19 (3 H, t, J = 7 Hz), 1.24 (2 H, m), 1.76 (2 H, t, J = 7 Hz), 2.45–2.91 (4 H, m), 3.42 (1 H, t, J = 7 Hz), 4.14 (2 H, q, J = 7 Hz), 10.85 (1 H, s); ^{13}C NMR δ 13.8, 14.1, 20.6, 27.8, 29.0, 36.1, 58.9, 61.5, 169.9, 178.2, 203.6. Anal. Calcd for $C_{11}H_{18}O_5$: C, 57.38; H, 7.88. Found: C, 57.67; H, 8.01.

1-Ethyl (±)-2-butyl-3-oxohexanedioate (6e): yield 1.83 g (50%); colorless oil; ^{1}H NMR δ 0.84 (3 H, t, J = 7 Hz), 1.17 (3 H, t, J = 7 Hz), 1.09–1.35 (4 H, m), 1.83 (2 H, m), 2.46–2.89 (4 H, m), 3.39 (1 H, t, J = 7 Hz), 4.14 (2 H, q, J = 7 Hz), 10.64 (1 H, s); ^{13}C NMR δ 13.8, 14.1, 22.4, 27.8, 28.0, 29.5, 36.1, 59.1, 61.4, 169.8, 178.4, 203.6. Anal. Calcd for $C_{12}H_{20}O_5$: C, 59.00; H, 8.25. Found: C, 59.29; H, 8.56.

1-Ethyl (±)-2-hexyl-3-oxohexanedioate (6f): yield 2.49 g (61%); colorless oil; ^{1}H NMR δ 0.90 (3 H, t, J = 7 Hz), 1.11–1.39 (8 H, m), 1.21 (3 H, t, J = 7 Hz), 1.80 (2 H, m), 2.41–2.91 (4 H, m), 3.38 (1 H, t, J = 7 Hz), 4.14 (2 H, q, J = 7 Hz), 10.35 (1 H, s); ^{13}C NMR δ 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. Anal. Calcd for $C_{14}H_{24}O_5$: C, 61.74; H, 8.88. Found: C, 61.73; H, 9.07.

1-Ethyl 2,2-dimethyl-3-oxoheptanedioate (7a): yield 2.24 g (65%); colorless liquid; ^{1}H NMR δ 1.04–1.35 (9 H, m), 1.70–2.61 (6 H, m), 4.13 (2 H, q, J = 7 Hz), 10.83 (1 H, s); ^{13}C NMR δ 14.0, 18.9, 21.9, 32.8, 36.8, 55.5, 61.5, 173.7, 179.0, 207.4. Anal. Calcd for $C_{11}H_{18}O_5$: C, 57.38; H, 7.88. Found: C, 57.06; H, 7.79.

1-Ethyl (±)-2-methyl-3-oxoheptanedioate (7b): yield 1.55 g (48%); colorless liquid; ^{1}H NMR δ 1.00–1.44 (6 H, m), 1.72–2.85 (6 H, m), 3.48 (1 H, q, J = 7 Hz), 4.13 (2 H, q, J = 7 Hz), 10.25 (1 H, s); ^{13}C NMR δ 12.7, 14.1, 18.5, 33.0, 40.2, 52.9, 61.6, 171.0, 179.1, 205.7. Anal. Calcd for $C_{10}H_{16}O_5$: C, 55.55; H, 7.46. Found: C, 55.71; H, 7.63.

1-Ethyl (±)-2-ethyl-3-oxoheptanedioate (7c): yield 1.55 g (45%); colorless liquid; ^{1}H NMR δ 0.80 (3 H, t, J = 7 Hz), 1.22 (3 H, t, J = 7 Hz), 1.61–2.76 (8 H, m), 3.28 (1 H, t, J = 7 Hz), 4.13 (2 H, q, J = 7 Hz), 11.30 (1 H, s); ^{13}C NMR δ 11.9, 14.1, 18.5, 21.6, 32.8, 40.7, 60.6, 61.4, 169.9, 178.9, 204.9. Anal. Calcd for $C_{11}H_{18}O_5$: C, 57.38; H, 7.88. Found: C, 57.11; H, 7.65.

1-Ethyl (±)-3-oxo-2-propylheptanedioate (7d): yield 1.83 g (50%); colorless liquid; ^{1}H NMR δ 0.86 (3 H, t, J = 7 Hz), 1.20 (3 H, t, J = 7 Hz), 1.62–2.08 (4 H, m, J = 7 Hz), 2.12–2.80 (6 H, m, J = 7 Hz), 3.40 (1 H, t, J = 7 Hz), 4.15 (2 H, q, J = 7 Hz), 10.82 (1 H, s); ^{13}C NMR δ 13.8, 14.1, 18.4, 20.7, 30.2, 32.8, 40.5, 58.9, 61.3, 169.9, 179.0, 204.7. Anal. Calcd for $C_{12}H_{20}O_5$: C, 59.00; H, 8.25. Found: C, 59.17; H, 8.20.

1-Ethyl (±)-2-butyl-3-oxoheptanedioate (7e): yield 2.01 g (52%); colorless liquid; ^{1}H NMR δ 0.85 (3 H, t, J = 7 Hz), 1.08–1.49 (7 H, m), 1.66–1.98 (4 H, m), 2.13–2.71 (4 H, m), 3.36 (1 H, t, J = 7 Hz), 4.13 (2 H, q, J = 7 Hz); ^{13}C NMR δ 13.8, 14.1, 18.4, 22.5, 28.0, 29.6, 32.8, 40.6, 59.3, 61.5, 170.2, 179.4, 205.1. Anal. Calcd for $C_{13}H_{22}O_5$: C, 60.45; H, 8.59. Found: C, 59.97; H, 8.64.

1-Ethyl (±)-2-hexyl-3-oxoheptanedioate (7f): yield 2.23 g (52%); colorless liquid; ^{1}H NMR δ 0.82 (3 H, t, J = 7 Hz), 1.18 (3 H, t, J = 7 Hz), 1.48–2.64 (16 H, m), 3.18 (1 H, t, J = 7 Hz), 4.08 (2 H, q, J = 7 Hz); ^{13}C NMR δ 14.1, 18.5, 20.7, 22.6, 27.5, 28.3, 29.1, 31.6, 32.8, 40.6, 59.1, 61.4, 170.0, 178.7, 204.8. Anal. Calcd for $C_{15}H_{26}O_5$: C, 62.91; H, 9.15. Found: C, 62.91; H, 9.37.

Typical Procedure for the Synthesis of a 4-Oxoalkanoic Acid (on a Larger Scale). 4-Oxohexanoic Acid.[14] The bromo ester **3b** (36.20 g, 0.2 mol), succinic anhydride (**1**, 15.01 g, 0.15 mol), and tetrabutylammonium bromide (1.61 g, 0.005 mol) were dissolved in DMF (50 mL) and electrolyzed at an external voltage of 50 V. When the reaction temperature reached 60 °C the external voltage was reduced to about 30 V to maintain the temperature between 50 and 60 °C. The electrolysis was stopped as the temperature dropped below 50 °C. The loss of weight of the zinc anode amounted to 13.6 g (0.21 mol). The reaction mixture was poured onto ice (300 g) and 10% aqueous HCl (200 mL) and then extracted with EtOAc (6 × 100 mL). The extract was concentrated under reduced pressure. The residue was refluxed with concentrated HCl (60 mL) and water (60 mL) for 1.5 h. Then the solvent was distilled off. Traces of water were azeotropically removed with toluene. The residue was purified by distillation yielding 4-oxohexanoic acid (10.7 g, 55%) as a colorless crystalline solid: bp 147–150 °C (11 Torr); mp 36–38 °C (lit.[16] mp 37–38 °C).

Acknowledgment. Financial support by FCI (Fonds der Chemischen Industrie) is gratefully acknowledged.

Registry No. **1**, 108-30-5; **2**, 108-55-4; **3a**, 600-00-0; (±)-**3b**, 41978-69-2; (±)-**3c**, 66025-42-1; (±)-**3d**, 79584-43-3; (±)-**3e**, 63927-44-6; (±)-**3f**, 138286-76-7; **6a**, 69527-64-6; (±)-**6b**, 141090-15-5; (±)-**6c**, 141090-16-6; (±)-**6d**, 141090-17-7; (±)-**6e**, 141090-18-8; (±)-**6f**, 141090-19-9; **7a**, 69527-63-5; (±)-**7b**, 141090-20-2; (±)-**7c**, 141090-21-3; (±)-**7d**, 141090-22-4; (±)-**7e**, 141090-23-5; (±)-**7f**, 141090-24-6; Zn, 7440-66-6; $CH_3CH_2C(O)(CH_2)_2CO_2H$, 1117-74-4.

---

[16] Müller, A.; Feld, E. *Monatsh. Chem.* **1931**, *58*, 24.

Synthesis of 1-Propyl-3-(3-hydroxyphenyl)piperidine by Regiocontrolled Palladium-Catalyzed Arylation

Kristina Nilsson and Anders Hallberg*

Department of Organic Pharmaceutical Chemistry, Uppsala Biomedical Center, Uppsala University, Box 574, S-751 23 Uppsala, Sweden

Received December 30, 1991

Dopamine autoreceptor agonists reduce the dopaminergic neurotransmission and are theoretical alternatives to the postsynaptic dopamine D2 antagonists, commonly used in the pharmacotherapy of schizophrenia.[1] Preclamol, (−)-3-PPP, the first example of a dopamine autoreceptor agonist,[2] suppresses neuroleptic induced abnormal

---

[1] Clark, D.; Hjort, S.; Carlsson, A. *J. Neural Transm.* **1985**, *62*, 1 and 171.

[2] Hacksell, U.; Arvidsson, L.-E.; Svensson, U.; Nilsson, J. L. G.; Sanchez, D.; Wikström, H.; Lindberg, P.; Hjorth, S.; Carlsson, A. *J. Med. Chem.* **1981**, *24*, 1475.

0022-3263/92/1957-4015$03.00/0