Notiz / Note

Reactions of Electrochemically Generated Organometallics, 2[1]

The Use of Zinc, Tin, Aluminium, Indium, and Iron as Sacrificial Anodes in the Electrochemically Assisted Reformatsky Reaction of Ethyl 2-Bromoalkanoates with Succinic Anhydride☆

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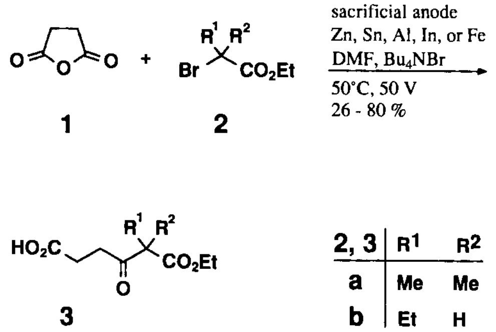
Zinc, tin, aluminium, indium, and iron were applied as sacrificial anodes in the electrochemically assisted Reformatsky reaction of succinic anhydride (**1**) with ethyl 2-bromoalkanoates **2**. In all cases the expected 1-ethyl 3-oxohexanedioates **3** were abtained in good to moderate yields. However, the amount of current consumed for the dissolution of one equivalent of anode metal strongly depends on the kind of metal. Whereas aluminium and iron require 1 Faraday per equivalent (Faraday val^{-1}), tin demands only 0.9 Faraday val^{-1}, and zinc and indium require an even smaller amount of current. It is assumed that in the case of the last three metals the electrochemical Reformatsky reaction is overlapped by a current-independent normal Reformatsky reaction, in which the anode acts as activated metal.

The Reformatsky reaction of alkyl 2-bromoalkanoates and zinc with aldehydes and ketones is a well-documented process for the preparation of alkyl 3-hydroxyalkanoates[2–4]. Instead of zinc, a variety of other metals, such as magnesium[5], cadmium[6], nickel[7], indium[8,9], and cerium[10], have also been occasionally applied. The success of the reaction depends strongly on the proper activation of the metal[11,12] and upon the application of a suited halogen compound[2] for the preparation of the nucleophilic organometallic intermediate. Only recently it has been shown that instead of the commonly used aldehydes and ketones, cyclic carboxylic anhydrides can also be used successfully as electrophiles in the Reformatsky reaction, giving rise to 3-oxoalkanedioic acid derivatives[13–15]. In connection with the synthesis of a series of 2-substituted 1-ethyl 3-oxoalkanedioates by the Reformatsky reaction of 2-bromoalkanoates with succinic or glutaric anhydride, we have found that the problems with the zinc activation could be circumvented by performing the reaction in an electrolysis cell with a sacrificial zinc anode[1]. In order to broaden the scope of this electrochemical variant of the Reformatsky reaction, we then were interested in the application of other metals as sacrificial anodes in this process[16].

Results and Discussion

In a series of experiments, succinic anhydride (**1**) and a 2-bromoalkanoate **2** were electrolyzed at an external voltage of 30–50 V in an undivided cell with a nickel net as cathode and a rod or lump of zinc, tin, aluminium, indium, and iron as sacrificial anode. The process was performed under nitrogen by using dry DMF as solvent and tetrabutylammonium bromide as supporting electrolyte. The reaction was conducted at a temperature of 50°C and stopped after consumption of 2 equivalents of metal per mol of 2-bromoalkanoate. Isolated yields of the obtained monoesters **3** and the required amount of current are listed in Table 1.

Scheme 1. Transformation of succinic anhydride (**1**) into 2-substituted ethyl 3-oxohexanedioates **3** by an electochemically assisted Reformatsky reaction



2, 3	R1	R2
a	Me	Me
b	Et	H

With zinc as anode the half esters **3a** and **3b** were obtained in a yield of 71 and 65% (entries 1 and 6 in Table. 1). Best results were reached with indium (entries 4 and 9). The use of tin, aluminium, and iron gave lower yields.

The formation of the 3-oxohexanedioates **3a** and **3b** is assumed to proceed via the carbanions **4** or corresponding organometallic equivalents, such as **5** and **6**[17]. The electrochemical generation of **4** by cathodic reduction theoretically requires 2 Faraday per mol of 2-bromoalkanoate **2**. Simultaneously, at the anode 1 gram atom of the divalent metals zinc and tin or 2/3 gram atoms of the trivalent metals aluminium, indium, and iron have to be dissolved. Therefore, the electrolysis was stopped after this amount of metal had been

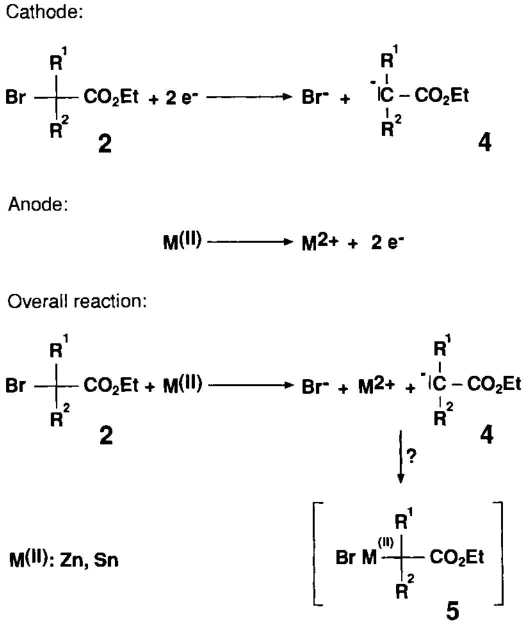
Table 1. 2-Substiuted 1-ethyl 3-oxohexanoates **3** prepared from succinic anhydride (**1**) and bromo esters **2** by the use of various metals as sacrificial anodes

En- try	Product	Sacri- ficial anode	Amount of current[a] (Faraday val^{-1})	Product yield (%)
1	**3a**	Zn	0.4	71
2	**3a**	Sn	0.9	34
3	**3a**	Al	1.0	62
4	**3a**	In	0.6	80
5	**3a**	Fe	1.0	59
6	**3b**	Zn	0.6	65
7	**3b**	Sn	0.9	26
8	**3b**	Al	1.0	57
9	**3b**	In	0.7	74
10	**3b**	Fe	1.0	49

[a] Amount of current per val of dissolved metal.

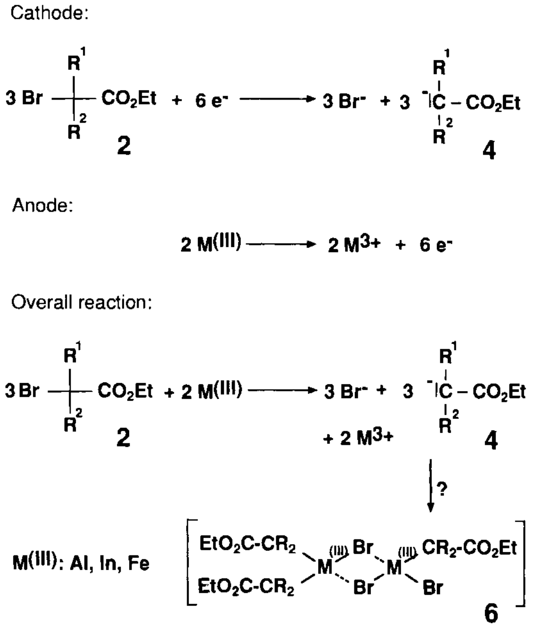
consumed. The expected amount of current, however, was reached only in the cases of aluminium and iron. With zinc, tin, and indium, the consumed amount of current was significantly lower. The first-mentioned group of metals seems to react exclusively by an electrochemical generation of the nucleophilic carbanions as shown in Schemes 2 and 3. The lower amounts of current observed for zinc, indium, and tin may best be explained by assuming that in these cases the electrochemical Reformatsky reaction competes with a current-independent normal Reformatsky reaction, in which the bromo ester **2** reacts directly with the compact anode metal.

Scheme 2. Electrochemical generation of Reformatsky reagents from divalent metals



It is known that the Reformatsky reaction can principally be performed as a two-step procedure. In the first step, the Reformatsky reagent is prepared from zinc and an alkyl 2-bromoalkanoate in a solvent like diethyl ether[18] or dimethoxymethane[19,20] and is then allowed to react in a subsequent step with a corresponding electrophile. This caused us to measure the amount of current in the course of the electrolysis of 20 mmol of the bromo ester **2a** in DMF in the absence of succinic anhydride (**1**) under the conditions

Scheme 3. Electrochemical generation of Reformatsky reagents from trivalent metals



of the foregoing described experiments. The ratio between the amount of current and the equivalents of metal dissolved at the anode was determined up to a consumption of 23.3 mFaraday, which corresponds to 58% of the theoretical amount of current. The obtained data show that aluminium and iron exhibit during the whole course of the electrolysis a constant ratio of approximately 1 Faraday val^{-1}. The same applies to tin. However, especially at the beginning of the electrolysis, zinc and indium exhibit a ratio much smaller than 1 Faraday val^{-1} (Figure 1).

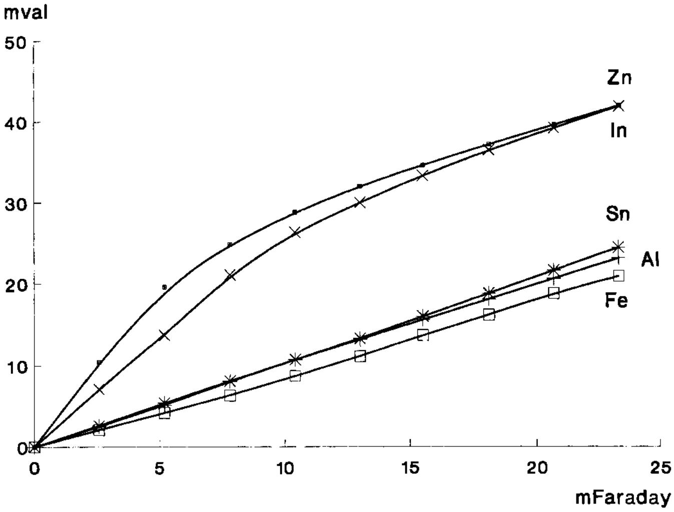


Figure 1. Ratio between the amount of current and the equivalents of dissolved metal in the electrochemically assisted generation of a Reformatsky reagent from bromo ester **2a** by means of various sacrificial anodes

The behavior of zinc and indium clearly shows that the dissolution of these metals by anodic oxidation is superimposed by a current-independent metal-consuming process. The rate of this process slows down with the decreasing concentration of **2a**, as can be seen from the inclination of the curves for zinc and indium in Figure 1.

Conclusion

The electrochemical generation of the carbanions **4** or organometallic species like **5** or **6** from the bromo esters **2** by application of various metals as sacrificial anodes allows a one-step transformation of succinic anhydride (**1**) into 2-substituted 1-ethyl 3-oxohexanedioates **3**. With zinc, and especially with indium, good yields are obtained. In the case of indium this process allows a high-yielding Reformatsky reaction, which does not require the preparation of activated indium[8] or the use of the more reactive ethyl 2-iodoalkanoates[9].

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Experimental

The electrolysis cell was a beaker with a diameter of 4.5 cm and a height of 4 cm, equipped with a Teflon cover and a magnetic stirring bar. The electrosyntheses were performed without a diaphragm under dry nitrogen. A commercial dc voltage source (Statron, type 3218) was applied. The amount of electricity was measured with an electronic coulometer. A nickel net (40 × 40 mm) was used as cathode. Rods or lumps of zinc, tin, aluminium, indium, and iron were applied as anodes. The purity of the metals purchased from Johnson Matthey Alpha Products was in all cases higher than 99%. DMF, dried with molecular sieve, and the bromo esters **2** were purchased from Fluka. — ^{13}C NMR: 75 MHz, Varian Gemini 300 instrument, solvent $CDCl_3$ with hexamethyldisiloxane as the internal standard ($\delta_{HMDS} = 1.92$).

1-Ethyl 3-Oxohexanedioates **3** *by Electrochemically Supported Reformatsky Reaction with Various Sacrificial Anodes. — General Procedure:* A solution of succinic anhydride (**1**, 1.50 g, 15 mmol), a bromo ester **2** (3.90 g, 20 mmol), and tetrabutylammonium bromide (2 mmol, 644 mg) in dry DMF (20 ml) was initially electrolyzed with 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 sacrificial anode amounted to about 20 mval. The reaction mixture was poured onto a mixture of 5% aqueous HCl (100 ml) and ice (50 g) and extracted with ethyl acetate (5 × 40 ml). The combined extracts were dried with magnesium sulfate and concentrated under reduced pressure. The oily residue was purified by flash chromatography on silica gel 60 with hexane/ethyl acetate/acetic acid (66:33:0.5) as eluent. Yields of half esters **3a** and **3b** obtained with the different anodes are given in Table 1. The spectral data are identical with those reported earlier[14].

1-Ethyl 2,2-Dimethyl-3-oxohexanedioate (**3a**): M.p. 40–42°C (pentane) (ref.[14] 40–42°C). — ^{13}C NMR ($CDCl_3$): $\delta = 13.96, 22.01, 28.01, 32.62, 55.33, 61.53, 173.6, 178.3, 206.5$.

1-Ethyl (±)-2-Ethyl-3-oxohexanedioate (**3b**) M.p. 42–44°C (pentane) (ref.[14] 42–44°C). — ^{13}C NMR ($CDCl_3$): $\delta = 11.82, 14.07, 21.65, 27.68, 36.09, 60.59, 61.38, 169.6, 178.4, 203.4$.

Determination of the Ratio between the Amount of Current and the Equivalents of Dissolved Metals in the Absense of Succinic Anhydride. — General Procedure: Tetrabutylammonium bromide (2 mmol, 644 mg) and the bromo ester **2a** (3.90 g, 20 mmol) were dissolved in dry DMF (20 ml), and the solution was electrolyzed with sacrificial zinc, tin, aluminium, indium, and iron anodes, initially at an external voltage of 30 V. During the course of the experiment the voltage was regulated in such a manner that the temperature of the reaction mixture did not exceed 60°C. Up to a current amount of 2250C (23.3 mFaraday, 58% of the theoretical current amount) the electrolysis was interrupted at intervals of 250C in order to determine the weight loss of the anode. The obtained data are presented in Figure 1.

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