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Electrochemical activation of zinc in the coupling reaction of α-bromoesters with carbonyl compounds

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Abstract

The Reformatsky reaction has been examined using a mild and effective method of electrochemical zinc activation, based on the cathodic reduction of a catalytic amount of zinc bromide in acetonitrile.

1. Introduction

The Reformatsky reaction of α-bromoesters with zinc and carbonyl compounds constitutes an important synthetic process for the preparation of β-hydroxyesters [1]. Much effort has been devoted to achieving a proper and reproducible method for the necessary activation of the zinc metal [2]. Several procedures, such as washing of zinc with diluted hydrochloric acid [3], reduction of zinc halides [4], the use of Zn/Ag [5] or Zn/Cu [6] couples, or irradiation by ultrasound [7] have been developed. However, the initiation and the control of the reaction (often highly exothermic) still remain a problem. We recently described a new electrochemical zinc activation method [8], based on the cathodic reduction of a catalytic amount of zinc bromide in the presence of a zinc anode. The application of the electrochemical procedure has been proven effective for the preparation of organometallic compounds [9]. Specifically, efficient developments in electrosynthesis have been achieved using sacrificial anodes [10]. Zinc anodes have been utilized in the nickel-catalyzed Reformatsky reaction [11] and in the electrosynthesis of substituted 3-oxo-alkanedioates from cyclic anhydrides [12]. Our electrochemical procedure of zinc activation has been applied to the condensation of activated halides with nitriles (Blaise reaction) [8a], and we present here the extension of this method to the Reformatsky reaction.

2. Results and discussion

2.1. Zinc activation

The electrochemical coupling of α-bromoesters and carbonyl compounds (eqn. (1)) was carried out in a single compartment, undivided cell, fitted with a commercial zinc anode and a zinc or a gold cathode. Under argon, in acetonitrile solutions containing $^{n}Bu_4N^+$ BF_4^-, a catalytic amount of anhydrous $ZnBr_2$ (2 mmol) was first electrolyzed at -0.8 V *vs.* SCE (or at constant current of 80–100 mA), untill 200 Coulomb had passed. This forms within a few minutes at room temperature a grey zinc metal deposit corresponding to 1 mmol of zinc on the cathode surface. Without further electrolysis, the carbonyl compound (10 mmol) and the α-bromoester (10 mmol) were added to the solution. The cathodic zinc deposit disappeared with the addition of the bromide. After hydrolysis, the β-hydroxyesters, **1**, were isolated in good, reproducible yields. The coupling reaction does not need any excess of halide, nor most remarkably, any excess of zinc as reducing agent.

Only a catalytic amount of activated zinc (Zn^*) is formed upon electrochemical reduction. The reaction

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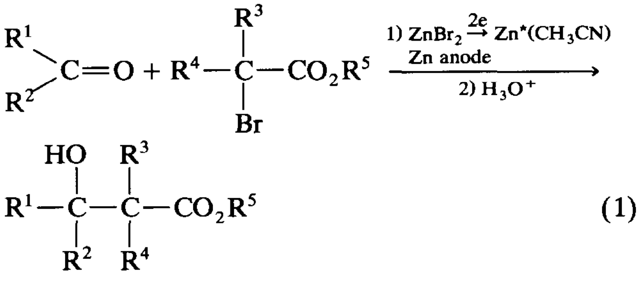
is further mediated by the zinc anode, consumed stoichiometrically, without additional activation.



$$\mathrm{R^1R^2C{=}O} + \mathrm{R^4{-}C(R^3)(Br){-}CO_2R^5} \xrightarrow[\text{2) } H_3O^+]{\text{1) } ZnBr_2 \xrightarrow{2e} Zn^*(CH_3CN)\text{, Zn anode}} \mathrm{R^1{-}C(OH)(R^2){-}C(R^3)(R^4){-}CO_2R^5} \qquad (1)$$

1

2.2. Coupling reaction

The results of the coupling of various α-bromoesters with a series of ketones and aldehydes are collated in Table 1.

Secondary bromoesters ($R^4 = H$) worked efficiently with a variety of ketones and aldehydes. In reactions with methyl 2-bromo-2-phenylacetate (entries 9–11), with a ketone/RBr ratio of 1 : 1, some reductive dimerization and hydrodebromination of the bromide ocurred, thus lowering the yield of the coupled product.

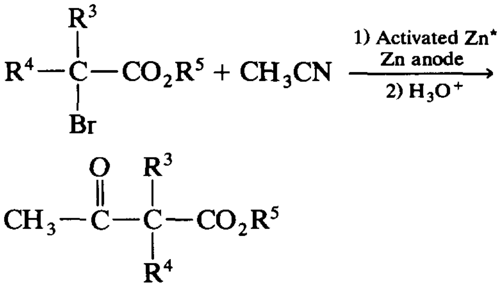
More hindered tertiary bromides (entries 5–8) were also effective and good yields of **1** were obtained, except with ketones containing two bulky substituents ($R^1 = R^2 = Ph$, entry 6). However, low quantities (10–20%) of R–H and R–R could be observed, the main reaction product being the ketoester, **2** (see below).

A primary bromide such as ethyl bromoacetate (entry 12) was less reactive. We found that prolonged electrolysis after the addition of the reactants, at −1.1 V *vs*. SCE during the passage of 600 Coulomb (equivalent to the reduction of 3 mmol of Zn^{2+} to Zn^0), produced a dramatic increase in the yield of the coupled product, to 82%. Without this additional electrolysis, the isolated yield was only 5%. In several other cases, the Reformatsky reaction could be accelerated by further electrolysis of the solution at −1.1 V/100–200 Coulomb.

TABLE 1. Synthesis of β-hydroxyesters **1** (eqn. 1) with electrochemically activated zinc on a zinc or gold cathode.

Entry	R^1	R^2	R^3	R^4	R^5	Isolated yield (%) of **1**
1	Ph	CH_3	CH_3	H	CH_3	80
2	Ph	Ph	CH_3	H	CH_3	92
3	-$(CH_2)_5$-		CH_3	H	CH_3	77
4	C_2H_5	C_2H_5	CH_3	H	CH_3	45
5	Ph	CH_3	CH_3	CH_3	C_2H_5	73
6	Ph	Ph	CH_3	CH_3	C_2H_5	10
7	-$(CH_2)_5$-		CH_3	CH_3	C_2H_5	67
8	C_2H_5	C_2H_5	CH_3	CH_3	C_2H_5	40
9	Ph	CH_3	Ph	H	CH_3	20
10	-$(CH_2)_5$-		Ph	H	CH_3	70
11	C_2H_5	C_2H_5	Ph	H	CH_3	40
12	Ph	Ph	H	H	C_2H_5	82
13	Ph	H	CH_3	H	CH_3	75
14	$(CH_3)_3C$	H	CH_3	H	CH_3	78
15	$C_{11}H_{23}$	H	CH_3	H	CH_3	62

Concerning the reactivity of the electrophile, both aldehydes and ketones led to good results, thus avoiding side-reactions, such as reductive pinacol and aldol coupling, often encountered using electrochemical procedures [13]. The reaction with 3-pentanone (entries 4,8,11) generally led to moderate yields. In these cases, the bromide underwent a side-reaction leading to 3-ketoesters, **2**, in 40–50% yield according to eqn. (2). The 3-ketoesters are derived from the reductive coupling with the solvent acetonitrile, via the Blaise reaction [14].

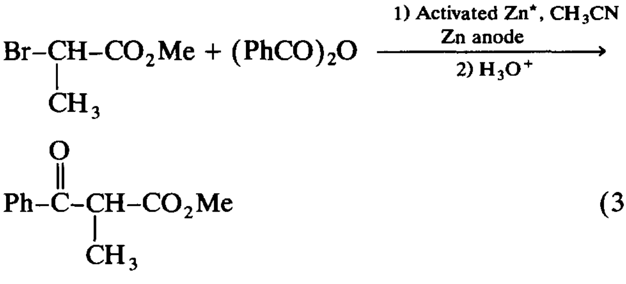


$$\mathrm{R^4{-}C(R^3)(Br){-}CO_2R^5} + \mathrm{CH_3CN} \xrightarrow[\text{2) } H_3O^+]{\text{1) Activated } Zn^*\text{, Zn anode}} \mathrm{CH_3{-}C({=}O){-}C(R^3)(R^4){-}CO_2R^5} \qquad (2)$$

2

We have recently reported [8a] the coupling of α-bromoesters with acetonitrile (or benzonitrile) in the presence of electrochemically activated zinc in the absence of the carbonyl compound. The β-ketoesters, **2**, constituted the main side-products of the Reformatsky reaction carried out in CH_3CN, and their yield increased with the steric bulk of both the bromide and the ketone, as in entry 6.

The reactivity of methyl 2-bromopropionate towards anhydrides using our electrochemical zinc activation method was examined in the case of benzoic anhydride (eqn. (3)). After 1 h reaction with a zinc cathode in CH_3CN, the ketoester **3** was obtained, after hydrolysis, in 80% yield.



$$\mathrm{Br{-}CH(CH_3){-}CO_2Me} + \mathrm{(PhCO)_2O} \xrightarrow[\text{2) } H_3O^+]{\text{1) Activated } Zn^*\text{, } CH_3CN\text{, Zn anode}} \mathrm{Ph{-}C({=}O){-}CH(CH_3){-}CO_2Me} \qquad (3)$$

3 (80%)

We observed a dependence of the reaction time on the nature of the cathodic material. Thus, complete consumption of methyl 2-bromopropionate and acetophenone (entry 1) was effected in 30 min with a zinc cathode, but was complete only in 2 h with a gold cathode. In both cases, the corresponding β-hydroxyester, **1**, was isolated in 80% yield.

2.3. Electrochemical studies

The course of the reaction was followed by cyclic voltammetry. The reduction peak of $ZnBr_2$ in CH_3CN occurs at -0.9 V *vs.* SCE (Fig. 1, curve a), the reoxidation of the "Zn^0" species being observed at -0.2 V. It has already been noted [8a] that nitriles have a great coordination affinity for Zn^{2+} ions, strongly affecting the reduction potential of $ZnBr_2$.

The voltammogram of a CH_3CN solution containing $ZnBr_2$ was not modified by the addition of a carbonyl compound such as acetophenone. However, upon addition of methyl-2-bromopropionate, in a 1 : 1 ratio with respect to $ZnBr_2$ (Fig. 1, curve b), the voltammogram exhibited a new reduction peak at -1.5 V assigned to the reduction of the bromide, and a shift to -1.0 V of the reduction peak of Zn^{2+}. On the anodic scan, a substantial decrease of the peak at -0.2 V was observed. With an $RBr/ZnBr_2$ ratio of 5 : 1 (Fig. 1, curve c), this anodic peak totally disappeared. Consistent with this electrochemical behaviour, we propose the occurrence of a rapid reaction between the electrogenerated "Zn^0" from the cathodic reduction of Zn^{2+} and the bromoester.

On a preparative scale, the addition of methyl 2-bromopropionate to an acetonitrile solution of electrochemically activated Zn^* as the only reducing agent (in the absence of the zinc rod), led to the reduction of RBr to RH. However, if the zinc rod is immersed in the solution, the halide afforded the β-ketoester, **2** in 90% yield.

Similarly, the electrogenerated zinc deposit (Zn^*) in the absence of the zinc rod was not efficient for coupling the bromoester with a carbonyl compound. The presence of the zinc metal rod was necessary to initiate and mediate the coupling reaction (eqn. 1), with the results shown in Table 1.

2.4. Proposed mechanism

The course of the reaction was followed by GC of hydrolyzed aliquots. By relating the relative concentrations of reactants and products, we observed in several reactions that the consumption of the reactants did not follow the rate of formation of the coupled products. Table 2 presents these results for acetophenone and methyl 2-bromopropionate.

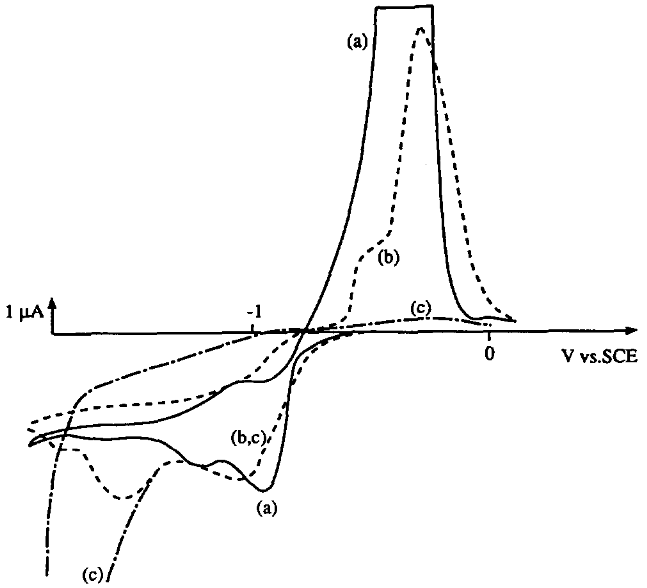


Fig. 1. Cyclic voltammograms obtained with gold microelectrode ($0.05\ mm^2$) at 20°C at a scan rate of $200\ mVs^{-1}$ for a CH_3CN solution (20 ml) containing 0.1 M of tetra-n-butylammonium tetrafluoroborate as supporting electrolyte. a) Anhydrous $ZnBr_2$ (2 mmol). b) After addition of methyl 2-bromopropionate (2 mmol) to solution a). c) After addition of 10 mmol of bromoester.

Between 20 and 50 min, 2.9 mmol of bromide and 2.3 mmol of ketone were consumed. However, the coupling product only increased by 0.9 mmol. Between 50 and 110 min, 1.3 mmol of ketone react, whereas the increase in β-hydroxyester was 2.7 mmol. Thus, the organic halide and the ketone should be quenched by stable zinc intermediates, which are not easily hydrolyzed. Stable functionalized organozinc species have been recently reported [15].

These observations and results led us to a mechanistic scheme (Scheme 1), in which the first step is the cathodic two-electron reduction of 1 mmol of $ZnBr_2$ to Zn^0, to form a solvated species I. In acetonitrile, this zerovalent zinc species has special properties and is active towards the oxidative addition of α-bromoesters, RBr. The resulting organozinc compound RZnBr-

TABLE 2. Concentration of reactants and products during the reaction of $PhCOCH_3$ (10 mmol) with CH_3-$CHBrCOOCH_3$ (10 mmol) (eqn. (1)) [a]

Reaction time (min)	Consumption of halide (mmol)	Consumption of ketone (mmol)	Amount of β-hydroxyester (mmol)
20	6.0	4.6	4.4
50	8.9	6.9	5.3
110	10	8.2	8.0

[a] Reaction under general conditions (see Experimental section), with a gold cathode.

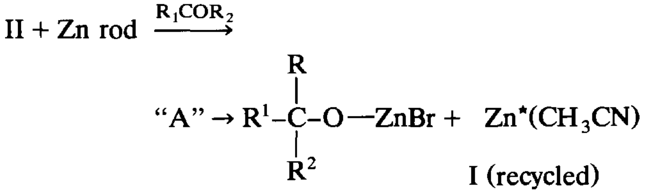
- Electrochemical *in situ* preparation of the catalytic species

$$\text{Anode:}\quad Zn \longrightarrow Zn^{2+} + 2e$$

$$\text{Cathode:}\quad ZnBr_2 + 2e \xrightarrow[CH_3CN]{} \underset{\text{I}}{Zn^*(CH_3CN)} + 2Br^-$$

- Zinc-mediated chemical reaction:

$$\underset{\text{I (catalytic)}}{RBr + Zn^*(CH_3CN)} \longrightarrow \underset{\text{II}}{RZnBr(CH_3CN)}$$



$$\text{II} + \text{Zn rod} \xrightarrow{R_1COR_2} \text{"A"} \rightarrow R^1\text{-}\overset{\displaystyle R}{\underset{\displaystyle R^2}{C}}\text{-O—ZnBr} + \underset{\text{I (recycled)}}{Zn^*(CH_3CN)}$$

Scheme 1.

(CH_3CN), II, should then be reduced chemically by the zinc anode. We propose that this reduced species reacts with the carbonyl compound to give an intermediate "A", which should be stable to hydrolysis (Table 2). Indeed, hydrolyzed aliquots of the reaction mixture do not show any RH compounds. The RZnBr-type intermediate II, was not reactive in the presence of the ketone alone. It needed a further reduction step to effect the coupling with the carbonyl compound, the additional reducing agent being the zinc metal rod. In the case of a less reactive substrate, a partial electrolysis of the solution could also be effective.

A catalytic amount of electrogenerated zinc species I is able to activate the halide; further coupling needs only the function of a commercial zinc rod in a chemical redox reaction, without any further activation, the species I being recycled.

The possibility of a chemical reaction with partial participation of a zinc anode has been recently mentioned for electrochemical halide coupling with cyclic anhydrides [12]. In our case, the presence of the "non-activated" zinc rod allows C–C coupling between the R moiety and the electrophile, and it also regenerates the necessary active Zn^* (CH_3CN) species. The Zn^{2+} alcoholates formed (Scheme 1) are stable under the reaction conditions, and are hydrolyzed to the corresponding β-hydroxyesters, **I** at the end of the reaction.

3. Conclusion

By the electrochemical method of zinc activation, the Reformatsky reaction was mediated by a commercial zinc rod and catalyzed by a Zn^* (CH_3CN) species formed *in situ* by electroreduction of $ZnBr_2$. The coupling reaction was carried out under simple and mild conditions (20°C, a catalytic amount of electricity at -1.1 V *vs.* SCE). Good and reproducible yields of β-hydroxyesters were obtained from α-bromoesters with various ketones and aldehydes. The method is also applicable to the coupling of α-bromoesters with anhydrides. No excess of bromide nor of reducing agent was needed.

4. Experimental section

Acetonitrile was reagent grade (Jansen, SDS). The supporting electrolyte and zinc bromide were dried under vacuum (0.1 mmHg) at 50°C overnight before use. α-Bromoesters and carbonyl compounds were used as supplied.

For preparative-scale coupling reactions, the electrochemical one-compartment cell was a cylindrical glass vessel of *ca.* 50 ml, similar to that described in ref. 16, equipped with a gold gauze or a zinc sheet cathode (20 cm^2) and a zinc rod (immersed to 3 cm) anode.

Cyclic voltammetry experiments were performed with Solea Tacussel conventional equipment and were carried out at 20°C using a gold microelectrode. All potentials are quoted with respect to the saturated calomel electrode (SCE). Intentiostatic zinc electrodeposition and electrolyses were carried out by using a stabilized constant current supply (Sodilec, EDC 36.07).

4.1. General procedure for zinc activation and coupling reaction

A solution of $ZnBr_2$ (2 mmol) in acetonitrile (40 ml) containing tetra-n-butylammonium tetrafluoroborate (1.5 mmol) was electrolyzed under argon with the passage of 200 Coulomb, at either $i = 100$ mA or at -0.8 V. When the electrolysis was stopped, the α-bromoester (10 mmol) and the carbonyl compound (10 mmol) were added and the solution stirred at room temperature until disappearance of the halide (according to GC). The reaction time was of 0.3–4 h, depending on the nature of the cathode (gold or zinc, see text).

The solution was then hydrolyzed (1 N HCl) and extracted with ether. The organic layer was washed with H_2O, dried over $MgSO_4$ and evaporated. The products were purified by column chromatography on silica gel with pentane/ether mixtures as eluent. All compounds had correct spectroscopic and analytical data.

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