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Scope and mechanism of the electrochemical Reformatsky reaction of α-haloesters on a graphite powder cathode in aqueous anolyte

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ABSTRACT

Six α-haloesters and eighteen carbonyl compounds were submitted to electrochemical coupling on a graphite powder cathode using aqueous anolyte free of organic solvents. Preparative yields of coupling products could be obtained with ethyl 2-bromoisobutyrate and aromatic aldehydes. Ethyl 2-bromopropionate was much less efficient. Extensive variation of applied potential, electrolyte composition, stoichiometry, catalyst, leaving halogen and activating substituents on the carbonyl compound led to the conclusion that the reaction mechanism in most cases proceeds via a radical intermediate generated from the halide reduction. Ethyl chloroacetate produced only trace amounts of coupling product, most probably by a carbanionic mechanism.

1. Introduction

The Reformatsky reaction [1] to obtain β-hydroxy esters from alkyl α-bromoalkanoates and aldehydes or ketones is initiated by an organometallic generated by the insertion of zinc in the carbon-halogen bond [2].

The activation of the zinc is the main problem related to use this methodology, because the acidic condition conducts a highly exothermic process of difficult control [3]. The association of Zn-Ag [4] and Zn-Cu [5,6] or many other metals like a Mg, Cd, Ni, Ce, Mn and In, have been tested to minimize the problem without advantages [7–12].

Alternatively to the classic chemical reactions, electrochemical methodologies in undivided cell, with Mg, Al, Zn and Fe as sacrificial anodes, were used for the preparation of some organometallic intermediates with good results [13–20]. The yields were increased by the use of sub-stoichiometric amounts of $[Ni^{II}(bipy)Br_2]$ along with a Zn anode [21,22].

Bieber and co-workers described in 1997 the Reformatsky reaction in aqueous medium with zinc powder for some aromatic and aliphatic aldehydes and primary, secondary and tertiary α-haloesters, catalyzed by dibenzoyl peroxide, $(BzO)_2$, postulating an evidence of radical mechanism [23]. This proposal of radical mechanism became once again evident, when the Reformatsky reaction in aqueous medium between ethyl 2-bromoisobutyrate (**1**) and benzaldehyde (**2**) to give β-hydroxyester **3**, Scheme 1, was conducted in a metal free electrochemical condition with the potential maintained constant during the electrolysis [24]. In this methodology, the zinc was replaced by carbon fiber electrode of large surface, as electron source excluding any participation of organometallic species.

In 2008, to improve the moderate yield [25], the same reaction was conducted with compacted graphite powder cell to provide a higher active surface. The cell is comparable to a thin-layer cell where the species are adsorbed at the cathode surface and also confined in a thin liquid layer between the grains interstices providing short diffusion pathways [26]. In the following years, the same cell has been successfully applied to the coupling of benzaldehyde with allyl [27], prenyl [28] and benzylhalides [29] as well as with α-haloketones [30]. In all these reactions the mechanism showed characteristics of both radical and carbanionic processes, depending on the halide and reaction conditions.

In the present work we describe the effects of an extensive variation of structural and experimental parameters on the coupling of different α-haloesters and carbonyl compounds aiming at a better evaluation of the synthetic scope and the mechanistic aspects of the reaction.

2. Experimental

All chemicals were of reagent grade and used without further purification. Distilled water was employed in all experiments.

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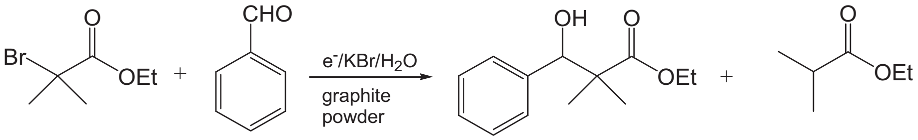


1 **2** **3** **4**

Scheme 1. Electrochemical coupling of ethyl 2-bromoisobutyrate (**1**) with benzaldehyde (**2**) [24].

The cathode materials were graphite Timrex KS44 (9 $m^2 g^{-1}$:GT) from Timcal Group pure as received or mixed with 5 mg of silver sulfate. Voltammetry and controlled-potential electrolyses were carried out using Autolab PGSTAT 30 potentiostat/galvanostat and a home-made three-electrode undivided cell described in a previous work [25]. The cathodic compartment was prepared compressing 150 mg of graphite powder (pure or mixed with silver sulfate under 1.9 kg cm^{-2} during 10 min). In all experiments the organic reagents or their mixtures were impregnated dropwise, without any solvent, on the compressed graphite powder, which was then protected by a filter paper. The anodic compartment was filled with 10 mL of aqueous 0.1 mol L^{-1} KBr. A platinum anode was used and all potentials are referred to the reference electrode Ag/AgCl, KCl (sat'd). The electrolyses were performed at controlled potential over a period of 1 – 4 h until transfer of around 1.7 times the theoretical charge. The aqueous electrolyte was decanted and the cathode cavity was extracted with 5.0 mL of $CHCl_3$ containing 0.1 mmol of 1,3,5-trimethoxybenzene (TMB) as internal quantitative standard. Graphite powder was filtered off and the crude extracts were analyzed by ^1H NMR (Varian Unity-Plus-300) and GC/MS (QP 5050 Shimadzu). All experiments were performed at 25 °C. The reaction products were identified by comparison of their ^1H NMR and EIMS spectra with published data.

3. Results and discussion

In our first communication with a compacted graphite powder cell [25], excellent yields of coupling product **3** had already been obtained with the tertiary halide **1** and benzaldehyde (**2**), whereas its secondary lower homologue, ethyl 2-bromopropionate (**5a**), had shown only moderate reactivity (Scheme 2). For this reason, the latter halide was chosen to initiate a systematic study of the influence of several experimental parameters on the coupling reaction.

Voltammetric analysis at very slow scan rate was performed with the pure reagents and their mixture in the same cavity cell used in previous work. Pure **5a** produced a reduction peak at −0.96 V with a peak current of −9.9 mA (Fig. 1a); the total charge of 31.1 C is situated closer to a two-electron than to a one-electron reaction (theoretical charge for 1 electron: 19.3 C). Under the same conditions, **2** showed a more cathodic peak at −1.31 V and a lower peak current of −7.8 mA; the total charge of 21 C corresponds very well to a one-electron process (Fig. 1b). These peak potentials showed only weak shifts to −0.9 V and −1.32 V, respectively, when an equimolar mixture of both reagents was analyzed (Fig. 1c). At the same time, however, a considerable decrease of the peak current to −6.1 mA and −6.8 mA, respectively, was observed and the separation of both maxima was much less pronounced. The total charge of 43.3 C consumed by the mixture is about 8 C lower than the sum of the values of the pure reagents, indicating a different reduction process.

When the voltammetry of the mixture was repeated using silver doped graphite powder (Fig. 1, line d), a pronounced shift of the first peak from −0.9 V to −0.57 V was observed, whereas the second one was only moved from −1.32 V to −1.27 V; the peak currents increased to −8.2 mA and −9.2 mA, respectively, and the total charge reached 57.6 C, almost exactly the value expected for a three-electron reduction. Similar effects have been observed in earlier reports with benzylic, allylic and alkylic halides on electrodes of pure silver [31–33] or silver doped graphite powder [27,29].

After this voltammetric exploration, a mixture of 0.2 mmol of aldehyde **2** and 0.4 mmol of bromoester **5a** was submitted to electrolyses at constant potentials between −0.6 V and −1.4 V in the absence and presence of catalytic silver (Table 1). The uncatalyzed reaction at the least negative potential (−0.6 V) was extremely slow and most of both reagents remained unchanged; only 6.2% of the expected hydroxyester **6** and 24.3% of ethyl propionate (**7**) were detected in the crude extract (Table 1, entry 1). At a potential of −0.8 V, the halide **5a** was completely consumed and 38.1% of coupling product **6** were obtained (entry 2). More negative potentials of −1.0 V and −1.2 V caused a weak drop in the yields to 35.5% and 33.2%, respectively (entries 3 and 4). Finally, at −1.4 V corresponding to the peak potential of aldehyde **2**, only 11.2% of **6** was formed and 1,2-diphenyl ethan-1,2-diol (**8**) became the main product (52.1%, entry 5).

As could be expected from the increased current in the voltammetric experiments, all silver catalyzed electrolyses occurred much faster. At −0.6 V all starting halide **5a** was consumed, but only 13.3% of coupling product **6** was obtained (entry 6). Also at potentials between −0.8 V and −1.2 V (entries 7 – 9), this yield was always lower than that obtained in the uncatalyzed reaction. At the most negative potential,–1.4 V, both reactions produced almost the same low yield of **6** and, once more, **8** was the main product (entry 10).

In all reactions described so far, the electrolyte was nearly neutral before the electrolysis (pH 5.8), but became weakly acidic at the end (pH 4.0–4.3). This finding can be explained by the different processes occurring at the electrodes. At the anode, both reduction processes to **6** and **7** consume two electrons and one proton; the formation of **8** demands two electrons and two protons, but occurred only at −1.4 V. On the other hand, the only oxidation process at the anode abstracts two electrons from two bromide

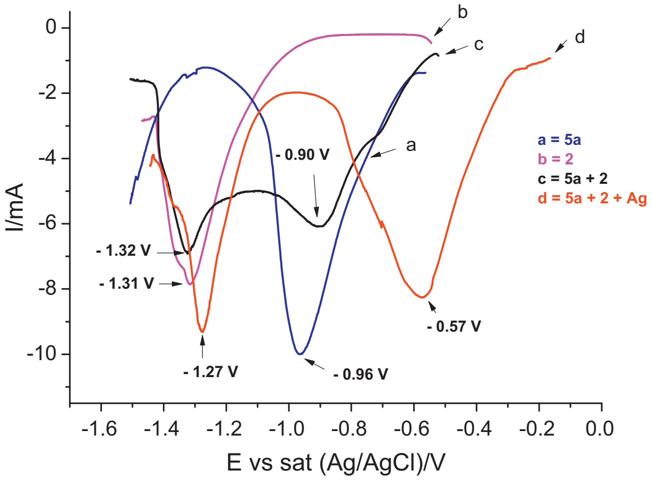
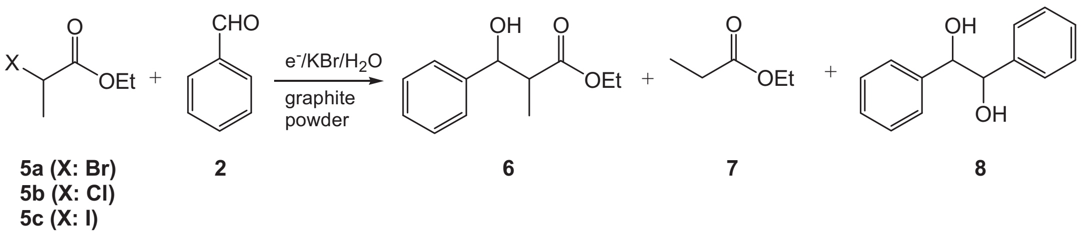


Fig. 1. Voltammograms recorded at 0.1 mV s^{-1} on pure graphite powder of: (a) 0.2 mmol **5a**, (b) 0.2 mmol of **2**, (c) 0.2 mmol of **5a** and 0.2 mmol of **2** and (d) 0.2 mmol of **5a** and 0.2 mmol of **2** on silver doped graphite powder (3.4%).



Scheme 2. Electrochemical coupling of ethyl 2-halopropionates **5a-c** with benzaldehyde (**2**).

ions, producing bromine which hydrolyses partially to bromide and hypobromide generating two protons. As **6** and **7** are the predominant products in all experiments, except in entries 5 and 10, the overall reaction produces more protons than it consumes and turns the electrolyte more acidic. Based on these preliminary considerations, we decided to examine alternative electrolytes of different pH values and buffering capacity under the general conditions of experiment 3 (entries 11–19). As a first result, none of the basic or acidic additives to the aqueous potassium bromide solution improved the yield of **6**, but basic compounds (entries 11 – 15) produced results very close to the reference reaction (entry 3). The same additives, but in the absence of potassium bromide, brought even lower yields of **6** (entries 16 and 17). In all these cases, the electrolysis started at pH values between 7.3 and 12.7 and finished under neutral or weakly basic conditions. On the other hand, addition of acetic acid had a more adverse effect, but this can be explained also by the incomplete conversion of halide **5a** (entry 18). At −1.4 V (entry 19), the negative effect of potassium carbonate, was even more pronounced reducing the yield of **6** to one fourth when compared with entry 5. We conclude from this series of experiments, that any additive or alternative electrolyte decreases the efficiency of the coupling reaction and that the overall pH control is not decisive. Most probably, the local basicity at the hydrophobic cathode is maintained by the cathodic reactions till the total consumption of starting materials.

In the next step, the influence of stoichiometry was examined using a 4-fold excess of halide **5a**. A small, but consistent increase to 40.9 – 43.3% of coupling product **6** was observed at potentials between −1.0 V and −1.3 V (entries 20 – 22).

In the following experiments, the influence of the leaving halogen was studied beginning with a voltammetric comparison of ethyl 2-chloro- and iodopropionate (**5b**,**c**) and the bromo-compound **5a**, all in the presence of benzaldehyde (**2**) (Fig. 2). Based on literature data for alkyl halides [32], we expected a less

Table 1
Electrochemical coupling of ethyl 2-halopropionate **5a,b,c** and acetate **9a,b** with benzaldehyde (**2**)[a].

Entry	Halide	E(V)	Conditions	Product composition/yield (%)[b]			
				2	**6**	**7**	**8**[c]
1	**5a**	-0.6	0.1 mol L^{-1} KBr	88.8	6.2	24.3	0
2	“	-0.8	“	57.6	38.1	44	0
3	“	-1.0	“	45.6	35.5	22.2	0
4	“	-1.2	“	40.8	33.7	6.3	0
5	“	-1.4	“	1.7	11.2	0	52.1
6	“	-0.6	Ag, 0.1 mol L^{-1} KBr	72	13.3	49.7	0
7	“	-0.8	“	50.4	8.5	22.4	0
8	“	-1.0	“	69.6	23.1	39.2	0
9	“	-1.2	“	52.8	23.6	47.5	0
10	“	-1.4	“	1.4	11.5	0	32.8
11	“	-1.0	0.05 mol L^{-1} KBr, 0.05 mol L^{-1} KOH	48.7	36	21	0
12	“	“	0.1 mol L^{-1} KBr, 0.2 mol L^{-1} K_3PO_4	49.1	35.5	24.3	0
13	“	“	0.1 mol L^{-1} KBr, 0.2 mol L^{-1} K_2HPO_4	40.8	29.8	21.6	0
14	“	“	0.1 mol L^{-1} KBr, 0.2 mol L^{-1} K_2CO_3	48	35.7	12	0
15	“	“	0.05 mol L^{-1} KBr, 0.05 mol L^{-1} NaOAc	41.2	33.6	21.1	0
16	“	“	0.1 mol L^{-1} KOH	48	31.1	6.4	0
17	“	“	0.1 mol L^{-1} K_2CO_3	33.6	30.5	14.5	0
18	“	“	0.05 mol L^{-1} KBr, 0.05 mol L^{-1} HOAc	45.6[d]	26.9	28.5	0
19	“	-1.4	0.05 mol L^{-1} KBr, 0.1 mol L^{-1} K_2CO_3	1.4	3.2	0	92.3
20[e]	“	-1.0	0.1 mol L^{-1} KBr	17.5	43.4	81.5	0
21[e]	“	-1.2	“	32	40.9	22.6	0
22[e]	“	-1.3	“	39	43.2	24.3	0
23	**5c**	-0.8	“	23.4	32.7	27.6	0
24	**5b**	-1.0	“	69	5	10	0
25	**5b**	-1.3	“	2.5	8.3	7	27.2
26	**5a**	-1.3	“	6,5	25.3	0	9.1
27	**5c**	-1.3	“	2	12.4	0	0.6
				2	**10**	**11**	**8**
28	**9a**	-0,8	Ag, 0.1 mol L^{-1} KBr	73.4	5.6	0	0
29	**9a**	-1.0	Ag, 0.1 mol L^{-1} KBr	71.2	4	0	0
30	**9b**	-1.0	0.1 mol L^{-1} KBr	62.4	2	0	0
31	**9b**	-1.0	Ag, 0.1 mol L^{-1} KBr	91.5	0.4	0	0

[a] General procedure: 0.4 mmol of haloester and 0.2 mmol of **2** impregnated on 150 mg of graphite powder
bDetermined by GC and ^{1}H NMR relative to internal standard
[c] Mixture of *meso* and *d,l*
[d] 25.8% of **5a** remained also unreacted
[e] Only 0.1 mmol of **2** were applied

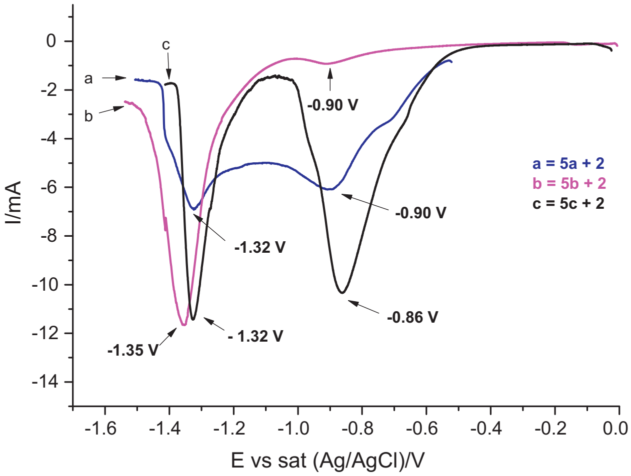


Fig. 2. Voltammograms recorded at 0.1 mV s^{-1} on pure graphite powder of: (a) 0.2 mmol of **5a** and 0.2 mmol of **2**, (b) 0.2 mmol of **5b** and 0.2 mmol of **2** and (c) 0.2 mmol of **5c** and 0.2 mmol of **2**.

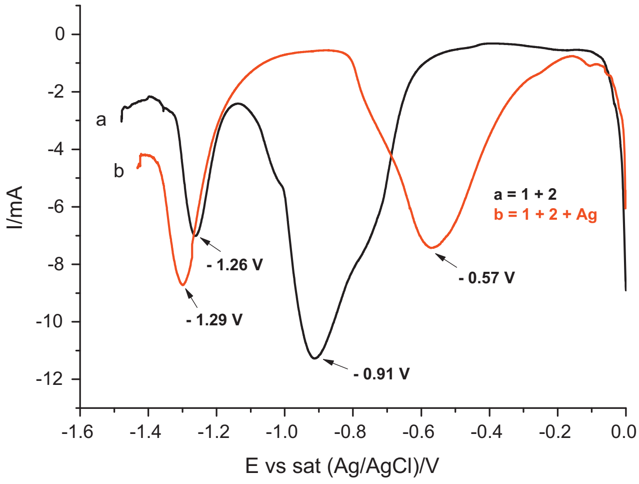


Fig. 3. Voltammograms of a mixture of 0.2 mmol of **1** and 0.2 mmol of **2** on graphite powder recorded at 0.1 mV s^{-1}: (a) in the absence and (b) in the presence of silver (3.4%).

Table 2
Voltamographic data of ethyl chloro- and bromoacetate (**9a,b**) recorded on pure graphite and on silver doped graphite (3.4%) at 0.1 mV s^{-1}.

Entry	Compound	X	Catalyst	E_p(V)	I_p(mA)
1	**9a**	Cl	–	−1.11	4.7
2	**9a**	Cl	Ag	−0.88	13.7
3	**9b**	Br	–	−0.98	4.2
4	**9b**	Br	Ag	−0.77	5.4

negative reduction potential in the order Cl > Br > I. This tendency was not observed in the case of the halopropionates examined here, for all three compounds exhibited almost the same peak potential between −0.86 V and −0.90 V on pure graphite. The peak current, however, increased significantly from chloride to bromide and iodide.

Accordingly, all electrolytic coupling experiments with the chloride **5b** proceeded at a very slow rate and no coupling product at all could be detected at −0.8 V. By contrast, at the same potential, the iodide **5c** produced 32.7% of **6** (entry 23), only 5% less than the bromide **5a** (entry 2). At more negative potentials, −1.0 and −1.3 V, **5b** still produced very modest coupling yields (5 and 8.3%, entries 24 and 25), far away from the results obtained with the bromide **5a** (entry 3 and 26); also the iodide **5c** gave only 12.4% of **6** at −1.3 V (entry 27). Again, at the latter potentials, pinacol **8** was also observed (entries 25 – 27).

From the results presented so far we can deduce that bromoester **5a** has the highest coupling power of all three halides, especially at −0.8 V. The electrolyte composition and the reagent ratio have restricted influence.

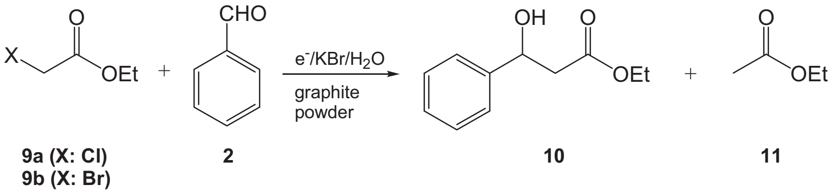
After the extensive investigation with 2-halopropionates under different conditions, we turned our attention to the primary halides ethyl 2-chloro and 2-bromoacetate (**9a,b**, Scheme 3).

Preliminary voltammetric evaluation showed a peak potential for the bromide **9b** of −0.98 V (Table 2, entry 3) on pure graphite, a value in the same range of the other haloesters studied so far, but a more negative peak at −1.11 V for the chloride **9a** (entry 1); the peak currents were also comparable with those of **5a,b**. On silver doped cathode material, both peak potentials became less negative and more intense (entries 2 and 4), but these effects were more pronounced in the case of the chloride **9a** (entry 1).

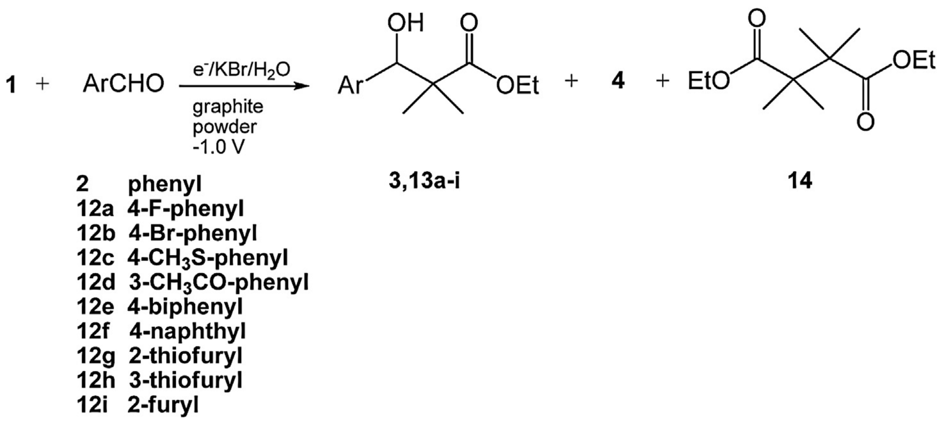
As could be expected, the electrolysis of **9a** in the presence of **2** on pure graphite at −0.8 V and −1.0 V proceeded with very low charge and conversion rate and produced no trace of the coupling product **10**. In the presence of catalytic silver, however, complete conversion even at −0.8 V and 5.6% of coupling to **10** were achieved (Scheme 3, Table 1, entry 28) which decreased to 4% at −1.0 V (Table 1, entry 29). At the latter potential on pure graphite, the bromide **9b** produced only 2% of **10** (Table 1, entry 30); silver catalysis had no positive effect and reduced the yield to nearly undetectable 0.4% (Table 1, entry 31).

In contrast to all other haloesters described so far, we observed in the case of ethyl 2-chloroacetate (**9a**) for the first time a beneficial effect of silver catalysis and higher yields for the chloride than for the bromide. In this aspect, **9a** showed a behavior very similar to allyl [27] and benzylchlorides [29] and this can be related to the primary structure of these three halides.

The experiments described so far confirmed our previous findings that the excellent coupling results with the tertiary bromide **1** cannot be obtained with its secondary and primary analogues even under modified experimental conditions. For this reason, our attention returned to the tertiary bromoester **1** in order to explore its reactivity and synthetic utility with a wide range of structurally and electronically different carbonyl compounds. Once more, we began with a comparative voltammetric assay in the absence and presence of catalytic silver (Fig. 3).The mixture of **1** and **2** on pure graphite reproduced very well the curve published in our previous paper [25] with maxima at −1.26 and −0.91 V. The latter peak, attributed to **1**, was shifted by 0.34 V to less cathodic values when



Scheme 3. Electrochemical coupling of ethyl cloro-, and bromoacetate (**9a,b**) with benzaldehyde (**2**).



Scheme 4. Electrochemical coupling of ethyl 2-bromoisobutyrate (**1**) with aromatic and heteroaromatic aldehydes **2,12a-i**.

silver doped graphite was used, whereas the peak attributed to **2** showed a weak opposite effect. Another striking difference was observed in the relative peak currents: in the absence of catalyst the peak current of **1** was much higher than that of **2** and in the presence of silver the opposite relation was found.

These effects in the voltammetric analysis can be related to the behavior in the electrolyses at −1.0 V. In the uncatalysed reaction, 86% of coupling product **3** was obtained, reproducing our previous results [25] (Scheme 4, Table 3, entry 1). However, in the presence of silver, the yield of **3** decreased considerably and an important sideproduct was formed, identified as the diester **14** previously detected in our first coupling experiments on carbon fiber [9], but not observed so far in the graphite powder cell (entry 2). Consequently, all following reactions were carried out on pure graphite powder under the conditions of entry 1. Benzaldehydes substituted in position 4 by F or Br gave even higher coupling yields of 96.3 and 93%, respectively, than the unsubstituted parent compound **2** (entries 3 and 4). On the other hand, the electron donating thiomethyl group in **12c** caused a net decrease to 65.7% of coupling product **13c** (entry 5). A similar negative effect was observed in the case of a 3-acetyl group (**12d**, 61.5%, entry 6), whereas 4-phenylbenzaldehyde (**12e**, 80%, entry 7) and 2-naphthaldehyde (**12f**, 83.1%, entry 8) gave results very close to that of entry 1. Three heterocyclic aldehydes **12g-i** gave also interesting yields in the range of 65% (entries 9 – 11).

The reactivity of cinnamaldehyde (**15a**) in traditional nucleophilic carbonyl addition is expected to be comparable to benzaldehyde. In the case of an electrochemical coupling, the voltammetric behavior had to be analyzed first. The mixture of **15a** and **1** on pure graphite produced a main reduction peak at −1.23 V with shoulders at −1.40 and −1.07 V (Fig. 4).

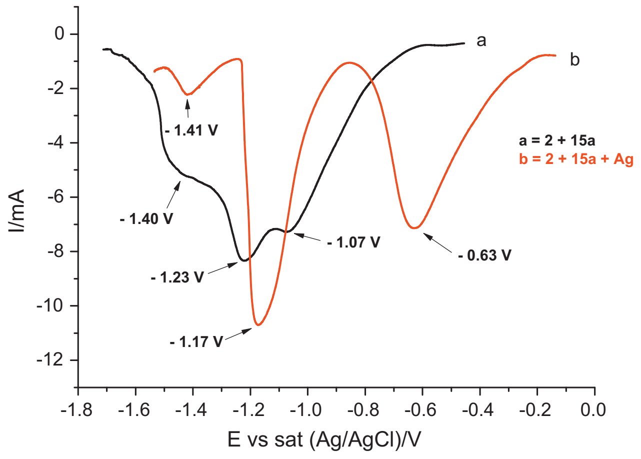


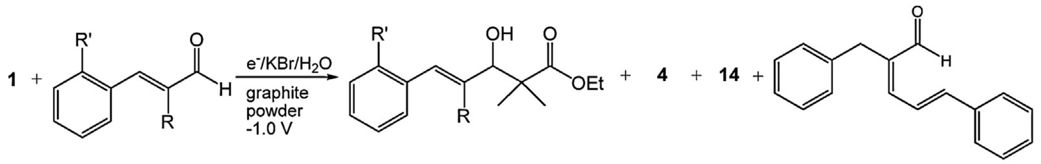
Fig. 4. Voltammograms of a mixture of 0.2 mmol of **1** and 0.2 mmol of **15a** on graphite powder recorded at 0.1 mV s^{-1}: (a) in the absence and (b) in the presence of silver (3.4%).

This broad peak became resolved in three separate maxima at −1.41, −1.17 and −0.63 V when silver doped graphite was used. This proximity or partial superposition of reduction peaks allow no prediction of the coupling behavior. Indeed, a first experiment under the standard conditions of entry 1, gave not only a very satisfying yield of 83% of the expected coupling product **16a**, but also two minor products (Scheme 5, entry 12). The first one can be explained by an electroreductive dimerization of **15a** to **17a**, as already reported in the literature [34,35]. The second side product was the dimeric ester **14** obtained already in entry 2. These two homocoupling products became much more important on silver catalysis and decreased once more the desired heterocoupling to **16a** (entry 13). Introduction of a 2-methoxy group in the aromatic ring (**15b**) or of a methyl group in α to the carbonyl group of the aldehyde (**15c**) resulted in lower yields of adducts **16b,c**, but also in the absence of side products **14** or **17b,c** (entries 14 and 15).

Further decrease in the coupling ability was expected for 3-methyl-2-butenal (**18**) which showed a peak potential of −1.41 V and very low peak current (2 mA) in the voltammetric analysis. In fact, under standard conditions at −1.0 V, only 14.3% of coupling product **19** were observed (Scheme 6a, entry 16). Change of the constant potential to −1.4 V doubled the yield of **19** to 29.3% (entry 17), but silver catalysis reduced it once more and favored instead reductive dimerization to **14** (entry 18).

As an example of an unconjugated aldehyde we chose 3-phenylpropanal (**20**) because of its low volatility and weak tendency to undergo spontaneous aldol-type reactions. Submitted to voltammetry, this compound showed no peak before the reduction of water. Electrolysis in the presence of **2** at −1.0 V produced 10.2% of the expected coupling product **21**, but aldolic condensation to **22** [36,37] was an important side-reaction (Scheme 6b, entry 19). Silver catalysis depressed the heterocoupling severely, had little influence on the condensation and favored reductive dimerization of the halide to the dimeric ester **14** as the major product (entry 20). Also a more cathodic potential of −1.3 V in the absence of silver did not improve the results (entry 21).

Finally, acetophenone (**23a**)–one of the most reactive ketones in nucleophilic additions–was tested in the coupling reaction with **1a** (Scheme 6c). Under standard conditions only 1.2% of the expected product **24a** could be detected (entry 22). A very limited improvement of this extremely low yield was achieved by introduction of F-substituents in the methyl group (**23b**, 1.5%, entry 23) or–more efficiently–in the aromatic ring (**23c**, 3.1%, entry 24).



15a R, R': H
15b R: H, R': CH_3O
15c R: CH_3, R': H

16a-c

17a

Scheme 5. Electrochemical coupling of ethyl 2-bromoisobutyrate (**1**) with cinnamaldehydes **15a-c**.

Summarizing all results reported here, we conclude that only ethyl 2-bromoisobutyrate (**1**) adds efficiently to aromatic and heteroaromatic aldehydes, as well as to cinnamaldehyde **(15a)**. The same substrates react with ethyl 2-bromopropionate (**5a**) only in moderate yields. Ethyl chloro- and bromoacetate (**9a,b**) produce only trace amounts of coupling products. Other α,β-unsaturated and saturated aldehydes and aromatic ketones are not sufficiently reactive for preparative purposes even with **1**.

On the other hand, the effects of experimental and structural parameters observed in the described experiments allow important conclusions on the possible mechanisms involved in the electrochemical Reformatsky reaction. In principle, the cathodic coupling reaction can involve neutral molecules, radicals, radical anions and carbanions and three general pathways can be formulated with these species (Scheme 7).

The first possibility is a transfer of a single electron to a halide **A** producing a radical **C**, most probably in a concerted process [38,39]. A second electron transfer to **C**, still adsorbed on the graphite surface, will generate a carbanion **D**, a powerful nucleophile which will attack adsorbed aldehyde **B** and, after protonation, give the final product **F**.

In the second alternative, radical **C** adds to **B** forming another radical intermediate **E** which can receive a second electron and a proton to produce the same coupling product **F**.

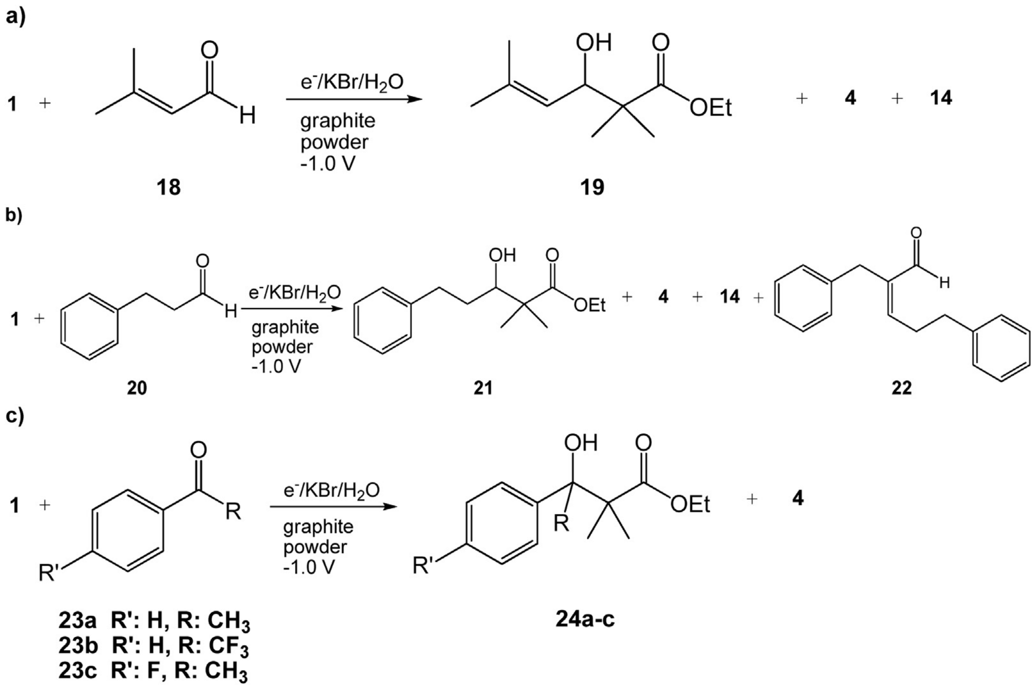
The third pathway starts with a first electron transfer to aldehyde **B** producing initially radical anion **G**, and, after protonation, radical **H**. The latter can combine with a radical **C**, generated from halide **A**, and also give **F**.

The sub-products **I** and **J**, observed in several experiments, result from dimerization of radicals **H** and **C**, and **K** arises from protonation of **D**.

Table 3
Electrochemical coupling of ethyl 2-bromoisobutyrate (**1**) with different carbonyl compounds[a].

Entry	Carbonyl compound	E(V)	Conditions	Product composition/yield (%)[b]				
				2	**3**	**4**	**8**	**14**
1	**2**	−1.0	0.1 mol L^{-1} KBr	9.5	86	47.3	0	0
2	**2**	"	Ag, 0.1 mol L^{-1} KBr	28.5	34	70.2	0	17.1
				12	**13**	**4**		**14**
3	**12a**	"	0.1 mol L^{-1} KBr	4.8	96.3	47.1		0
4[c]	**12b**	"	"	4.7	93	59.2		0
5	**12c**	"	"	34.2	65.8	46.3		0
6[c]	**12d**	"	"	9.7	61.5	64.9		5.6
7[c]	**12e**	"	"	12.3	80	59		0
8[c]	**12f**	"	"	13.4	83.1	52.3		0
9	**12g**	"	"	11.5	68.2	54.6		0
10	**12h**	"	"	20	62.3	35.4		0
11	**12i**	"	"	3.6	65.1	42.3		0
				15	**16**	**4**	**17a**	**14**
12	**15a**	"	"	12.7	83	31.6	1.8	1.6
13	**15a**	"	Ag, 0.1 mol L^{-1} KBr	46.2	46	66	8.2	14.5
14	**15b**	"	0.1 mol L^{-1} KBr	34.4	52.3	66.7		0
15	**15c**	"	"	43	47	47.3		0
					19	**4**		**14**
16	**18**	−1.0	"		14.3	66.2		0
17	**18**	−1.4	"		29.6	37.5		0
18	**18**	−1.4	Ag, 0.1 mol L^{-1} KBr		9.2	45.3		12.6
				20	**21**	**4**	**22**	**14**
19	**20**	−1.0	0.1 mol L^{-1} KBr	55.8	10.2	96.3	5.1	0
20	**20**	−1.0	Ag, 0.1 mol L^{-1} KBr	55.6	0.7	43.3	5.2	30.2
21	**20**	−1.3	0.1 mol L^{-1} KBr	49.1	9	87.2	5.3	0.6
				23	**24**	**4**		**14**
22	**23a**	−1.0	0.1 mol L^{-1} KBr	95.8	1.2	86.3		0
23	**23b**	"	"	21.7	1.5	93.5		0
24	**23c**	"	"	95.8	3.1	97.1		0

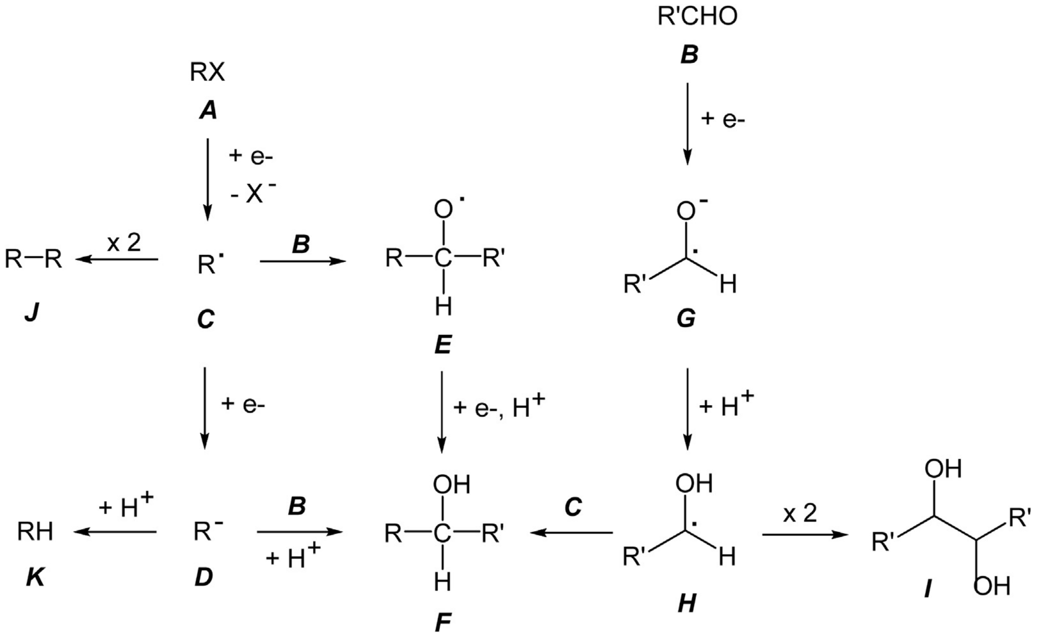
[a] General procedure: 0.4 mmol of haloester and 0.2 mmol of carbonyl compound impregnated on 150 mg of graphite powder
[b] Determined by GC and ^{1}H NMR relative to internal standard
[c] Only 0.1 mmol of carbonyl compound were applied



Scheme 6. Electrochemical coupling of ethyl 2-bromoisobutyrate (**1**) with less reactive carbonyl compounds **18, 20, 23a-c**.

In the following analysis we will try to decide between these three possibilities and the reactive intermediates involved on the basis of thirteen different observations made in the experiments described before (Table 4).

1. The first and most striking observation, already mentioned in our previous publication [23,25] is the sharp decrease of coupling reactivity from the tertiary bromoester **1** to its secondary and primary homologues **5a** and **9b**. This order corresponds exactly to the stability of radicals of type **C** and is opposite to that of carbanions **D** and their reactivity towards carbonyl addition. In other words, the most basic and less nucleophilic tertiary carbanion **D** cannot be responsible for the best results in the coupling reaction, but the most stable radical **C** can, combining either directly with the aldehyde **B** or with the radical **H**.
2. All halides used in this work are reduced at less negative potentials than the carbonyl substrates and the most efficient halide **1** exhibits also a much higher peak current. These differences in the voltammetric data suggest that the first electron transfer occurs to the halide (**A**) and turn an initial formation of radicals **G** and **H** improbable.
3. Although there was only a single peak in the voltammograms of all halides used, a reduction by a single electron to **C** is expected to be favored by a less negative potential and a two – electron transfer to **D** or a reduction of **B** at more negative values. The



Scheme 7. General mechanism of the cathodic coupling of halide with aldehydes.

Table 4
Compatibility of experimental observations and possible reactive intermediates.

Entry	Intermediates	C + E	D	H + C
1	Reactivity order tertiary > secondary > primary	+	–	+
2	Reduction potentials of halide and carbonyl substrate	+	+	–
3	Applied potential	+	–	–
4	Silver catalysis in **1** and **5a**	+	–	–
5	Electrolyte composition	+	–	–
6	Excess of halide	+	+	+
7	Leaving halogen in **5a**,**b**,**c**	+	–	–
8	Substituents in the aromatic ring	+/–	+	+/–
9	Reactivity of carbonyl substrates	+/–	+	+/–
10	Absence of pinacol formation	+	+	–
11	Reductive dimerization of haloester	+	–	–
12	Leaving halogen in **9a**,**b**	–	+	–
13	Silver catalysis in **9a**	–	+	–

best results with halides **1** and **5a** were all obtained at −0.8 or −1.0 V and more negative potentials resulted in lower yields of **F** and increasing formation of pinacol **I**. This gives additional support to the pathway via **C** and **E**.

4. The presence of catalytic silver on the cathode turns the peak potentials of organic halides less negative, thus making a selective one-electron transfer more difficult and favoring the direct formation of **D**. This should enhance the coupling by a carbanionic mechanism as observed recently in the case of allylic and benzylic halides [27,29]. However, in the case of bromoesters **1** and **5a**, the effect of silver catalysis was clearly adverse in all experiments, indicating that no carbanion **D** is involved in the absence of silver, but rather a radical **C**. Intermediates **G** and **H** are also improbable because no effect of silver was observed in the voltammograms.
5. The rather weak effect of changes in the electrolyte composition points also in the direction of radical **C**. Especially the addition of acetic acid should affect severely a process based on highly basic carbanions such as **D**. On the other hand, formation of radical **H** and pinacol **I** even should be favored by acid, but this was not observed.
6. Higher excess of halide as in entries 20–22 caused some improvement in the yield of **F**, but this can be expected for all three mechanisms because of the participation of intermediates derived from **A**.
7. The superiority of bromo- and iodoesters **5a** and **5c** over their chloro-analogue **5b** can be explained by their higher peak current and less negative peak potential. This means that the cathodic cleavage of the C–Cl bond is more difficult to occur, but also to stop at the radical **C**. C–Br and C–I bonds have a better chance for a monoelectronic process producing the radical **C** [40]. A mechanism starting with the radicals **G** and **H** should not be affected by the leaving halogen of **A** and can also be rejected.
8. Our coupling experiments with **1** and substituted benzaldehydes **12a-f** show exactly the trend expected for nucleophilic additions: increase of reactivity by electronegative substituents and decrease by electron donors. Also the activating effect of F-substituents observed in acetophenones 23a-c can be attributed to increased electrophilicity. Both trends seem to support a carbanionic intermediate **D**. However, the effect is less pronounced than in other nucleophilic additions and a similar stabilization of radicals **E**, **G** and **H** cannot be excluded.
9. The reactivity of the carbonyl substrates used in this work follows the order generally observed in nucleophilic additions, decreasing from aromatic aldehydes **12a-i** to cinnamaldehydes **15a-c**, 3-methyl-2-butenal (**18**), 3-phenylpropanal (**20**) and acetophenones **23a-c**, and thus supports an intermediate **D**. However, as in the foregoing point, a similar order can be attributed to decreasing stability of radical intermediates and no preference for one of the three mechanisms is given here.
10. Pinacol formation (**I**) is not an important side reaction except at potentials close to the reduction peak of benzaldehyde. This makes a pathway via radicals **G** and **H** improbable for the coupling reaction to **F** and supports both mechanisms starting with **A**.
11. On pure graphite, reductive dimerization of **A** to **J** is observed only with the tertiary bromide **1** in a few reactions with less reactive carbonyl compounds such as **12d, 15a** and **20**. This is probably due to the high stability of a tertiary radical **C**, whose homocoupling cannot compete with the addition to more reactive aldehydes. This observation is another strong argument in favor of a radical mechanism via **C**. On silver doped graphite, higher amounts of dimeric ester **J** were also found in several experiments and probably cannot be explained by a carbanionic intermediate **D** as postulated in point 4. The reason is rather a special surface effect as found previously in the zinc-promoted dimerization of organic halides [41]. A mechanism via radicals **G** and **H** can also be excluded because in no case both dimers **I** and **J** were detected in the same experiment.

Summarizing these arguments (Table 4), we can conclude that all experimental observations are best conciliated with a predominant mechanism via radicals **C** and **E**, because none of the eleven points is found contrary to it and only two can be considered ambiguous. A carbanionic intermediate **D** is compatible only with five points, but incompatible with six. A pathway starting from **B** via radicals **G** and **H** is even less supported with only two points compatible, two ambiguous and seven incompatible. It must be emphasized that this analysis refers essentially to the results with the tertiary bromoester **1** and its less reactive secondary homologue **5a**. The very low yielding primary halides **9a,b** provided some contradictory results which have to be discussed separately.

12. In sharp contrast to **5a,b**, the chloroacetate **9a** gives better yields than the bromo compound **9b**. This cannot be accounted to an easier formation of radical **C** because the voltammetric data show that the C–Br bond is cleaved at a less negative potential and with a much higher peak current. On the other hand, chlorides are reported to undergo directly a two-electron reduction to carbanion **D**, whereas bromides can stop at the radical stage **C** [40]. Therefore, the higher reactivity of the chloride **9a** can be explained by preferential formation of a carbanion **D** and the low stability of a primary radical **C**. This interpretation is reinforced by the better stabilization and lower basicity of primary enolates in comparison to secondary or tertiary ones.
13. In the same direction points the now beneficial effect of silver catalysis with the chloride **9a**. As already stated before, in the presence of silver the reduction potential is shifted to less cathodic values and the peak current increases significantly, thus favoring the carbanion **D**.

From the last two observations we must conclude that haloacetates **9a,b** prefer an anionic mechanism in the coupling reaction with benzaldehyde. Although this contrasts with the radical process found for the secondary and tertiary homologues, there is a striking parallel with the behavior of benzylic [29] and allylic [27] halides and haloketones [30] which also show higher reactivity of the chlorides, especially in the presence of catalytic silver. All four types of halides have some common characteristics: their primary structure facilitates the formation of a resonance-stabilized carbanion **D** which is less basic–and therefore more stable in aqueous medium–than secondary or tertiary analogues.

4. Conclusions

The electrochemical Reformatsky reaction of structurally different haloesters and carbonyl substrates can be performed on a graphite powder cathode in aqueous medium and in the absence of reactive metals and organic solvents. The preparative interest is restricted to tertiary bromoesters which add in high yield to aromatic aldehydes and cinnamaldehydes. Secondary bromoesters are less efficient and produce only moderate yields. Mechanistic evaluation of the experimental data suggests a radical pathway starting with a one-electron reduction of the halide. By contrast, haloacetates produce only trace amounts of coupling product with benzaldehyde, but probably react via a carbanionic species.

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