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Iron-Mediated Electrochemical Reaction of α-Chloroesters with Carbonyl Compounds

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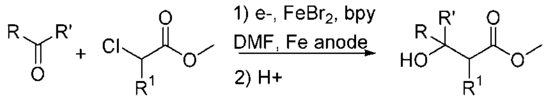
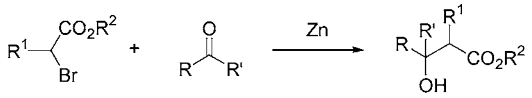
ABSTRACT



Reformatsky-type reactions have been performed efficiently using an electroassisted iron-complex catalysis. Valuable product such as *β*-hydroxyesters, ketones or nitriles are thus prepared with high yields.

The reaction of an α-haloester with an aldehyde or a ketone in the presence of zinc metal to give a *β*-hydroxy-ester,[1] the Reformatsky reaction, is a well-recognized carbon−carbon bond-forming reaction[2] (Scheme 1).

Scheme 1. Reformatsky Reaction.



To extend the scope of this reaction, various parameters have been extensively investigated. Since the reaction is initiated by insertion of zinc into the halogen−carbon bond, most efforts have been focused on the activation of zinc such as Rieke-Zn,[3] Zn−Cu couple,[4] Zn/Ag-graphite,[5] ultrasound,[6] etc. More recently, sonoelectroreduction of zinc powder has given a highly reactive zinc, which reacts with α-bromoesters or allylic compounds.[7] Another process has been performed, in aqueous THF, using BF_3OEt_2 and Zn dust but is limited to aldehydes.[8] Recently, a Reformatsky-type reaction was developed, using $RhCl(PPh_3)_3$ and diethylzinc.[9] Besides the classical zinc method, various other metals have been examined so far, such as chromium,[10] indium,[11] manganese,[12] etc. In our laboratory, we have already described some electrochemical processes for the Reformatsky reaction.[13] More recently, we have reported an electrochemical method, catalytic in both chromium and nickel salts, using a sacrificial stainless steel or iron rod anode.[14] In these conditions, *β*-hydroxyesters are obtained in good yields (60−80%) and

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(1) Reformatsky, S. *Chem. Ber.* **1887**, *20*, 1210.

(2) For recent reviews of the Reformatsky reaction, see: (a) Fürstner, A. *Synthesis* **1989**, 571−590. (b) Rathke, M. W.; Weipert, P. In *Comprehensive Organic Synthesis*; Trost, B. M., I. Fleming, I., Eds.; Pergamon: New York, 1991; Vol. 2, pp 277−299. (c) Fürstner, A. In *Organozinc Reagents*; Knochel, P., Jones, P., Eds.; Oxford University Press: New York, 1999; pp 287−305.

(3) Rieke, R. D.; Uhm, S. J. *Synthesis* **1975**, 452.

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

(5) Csuk, R.; Fürster, A.; Weidmann, H. *J. Chem. Soc., Chem. Commun.* **1986**, 775.

(6) Han, B.; Boudjouk, P. *J. Org. Chem.* **1982**, *47*, 5030.

(7) Durant, A.; Delplanche, J.; Libert, V.; Reisse, J. *Eur. J. Org. Chem.* **1999**, 2845−2852.

(8) Chattopadhyay, A.; Salaskar, A. *Synthesis* **2000**, 561−564.

(9) Kanai, K.; Wakabayashi, H.; Honda, T. *Org. Lett.* **2000**, *2*, 2549−2551.

(10) Wessjohann, L.; Gabriel, T. *J. Org. Chem.* **1997**, *62*, 3772−3774.

(11) (a) Hirashita, T.; Kinoshita, K.; Yamamura, H.; Kawai, M.; Araki, S. *J. Chem. Soc., Perkin Trans. 1* **2000**, *5*, 825−828. (b) Lee, P.; Bang, K.; Sung, S.; Chang, S. *Synth. Commun.* **2001**, *31*, 3781−3789.

(12) (a) Kahiga, H.; Nishimae, S.; Shinokubo, H.; Oshima, K. *Tetrahedron* **2001**, *57*, 8807−8815. (b) Cahiez, G.; Chavant, P.-Y. *Tetrahedron Lett.* **1989**, *30*, 7373−7376.

(13) (a) Rollin, Y.; Gebehenne, C.; Derien, S.; Dunach, E.; Périchon, J.; *J. Orgonomet. Chem.* **1993**, *461*, 9−14. (b) Connan, A.; Sibille, S.; Périchon, J. *J. Org. Chem.* **1991**, *56*, 2018−2024.

(14) Durandetti, M.; Nédelec, J.-Y.; Périchon, J. *Org. Lett.* **2001**, *3*, 2073.

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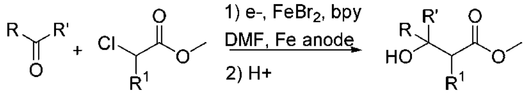
moderate diastereoselectivity (erythro/threo ≈ 60/40 to 70/30). We now report an original version of the Reformatsky reaction, using iron catalysis, associated with an electrochemical reaction (Scheme 2).

Scheme 2. Electrochemical Addition of α-Chloroesters to Carbonyl Compounds Using Iron Catalysis



We have shown that, at first, the electroreduction of a mixture of 3-pentanone and methyl 2-chloropropanoate, in the presence of an iron sacrificial anode, affords the expected β-hydroxyester in 25% and 46% in acetonitrile and DMF, respectively (Table 1, entries 1 and 2). Then, we showed that it was possible to increase the yield to 52% and 74% in acetonitrile and DMF, respectively (Table 1, entries 3 and 4), by using pyridine as cosolvent, to stabilize an electrogenerated low valent compound of iron acting as effective catalyst. In all cases, DMF seems to be the best solvent. Finally, we have tried different ligands of iron in this electrochemical reaction. Results are given in Table 1. Even if the coupling product is always obtained with yields higher than 50%, 2,2′-bipyridine (Table 1, entries 5−8), acac (Table 1, entry 9), and allylic acetate (Table 1, entry 12) are the best ligands. Similarly, reactions are more efficiently performed with 5 mmol of 2,2′-bipyridine than with 1 mmol (Table 1, entries 7 and 8).

Table 1. Electroreductive Cross-Coupling between 3-Pentanone and Methyl 2-Chloropropanoate Using Different Ligands in DMF or Acetonitrile as Solvent

entry	ligand	solvent	yields (%) of coupling product^{a}
1	none	DMF	46
2	none	MeCN	25
3	none	DMF/Pyr 90/10	74
4	none	MeCN/Pyr 90/10	52
5	2,2′-bipyridine^{b}	DMF	83
6	2,2′-bipyridine^{b}	MeCN	75
7	2,2′-bipyridine^{c}	DMF	94
8	2,2′-bipyridine^{c}	MeCN	79
9	acac^{d}	DMF	80
10	1,10-phenanthroline^{b}	DMF	54
11	$CH_3CO_2CH{=}CH_2^{e}$	DMF	61
12	$CH_3CO_2CH_2CH{=}CH_2^{e,f}$	DMF	82
13	$P(OEt)_3^{b}$	DMF	67

[a] Isolated yields, based on initial 3-pentanone. [b] 1 mmol of ligand (0.1 equiv/pentanone). [c] 5 mmol of 2,2′-bipyridine. [d] 1 mmol of Fe(acac)$_3$. [e] 10 mmol of ligand. [f] Reaction conducted with cyclohexanone instead of 3-pentanone.

This led us to employ the following experimental procedure. In a one-compartment electrochemical cell[15] fitted with a nickel sponge as the cathode (20 cm^2) and an iron sacrificial rod as the anode[16] are introduced DMF (40 mL) as solvent, NBu_4BF_4 (0.2 g 0.6 mmol) as supporting electrolyte, and $CH_2Br{-}CH_2Br$ (108 μL 1.25 mmol). A pre-electrolysis is run under argon, at room temperature, at constant current of 0.3 A during 250 C to prepare $FeBr_2$ via the following reactions:

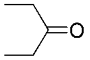
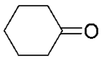
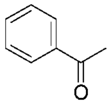
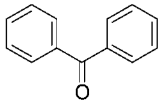
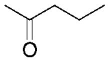
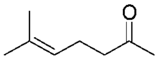
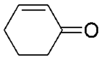
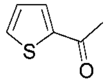
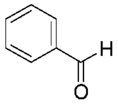
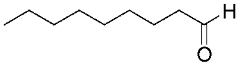
anode: $Fe \rightarrow Fe^{2+} + 2\,e^{-}$

cathode: $CH_2Br{-}CH_2Br + 2\,e^{-} \rightarrow CH_2{=}CH_2 + 2\,Br^{-}$

in solution: $Fe^{2+} + 2\,Br^{-} \rightarrow FeBr_2$

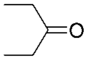
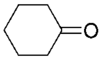
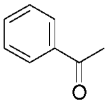
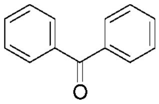
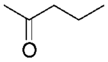
Afterward, 0.78 g of 2,2′-bipyridine (5 mmol) is added along with 10 mmol of carbonyl compounds and a portion of α-chloroester (0.3 mmol). The electrolysis is then conducted at constant current (0.25 A). During this time, the α-chloroester is constantly added in the solution via a syringe pump at a rate of 4 mmol/h, to minimize its condensation. The electrolyses were usually run until the carbonyl compounds were totally consumed. A charge of 3 at 5 F/mol is necessary to consume the carbonyl compounds

Table 2. Iron-Catalyzed Electroreductive Coupling between Methyl 2-Chloropropanoate and Carbonyl Compounds

entry	Carbonyl compounds	$n_{eq.}$ α-chloroester	yields (%) of coupling product^{a}	erythro/threo
1		1.6	94	/
2		1.6	82	/
3		1.4	70	72/28
4		1.5	69	/
5		1.6	84	57/43
6		1.6	64	57/43
7		1.5	48^{b}	50/50
8		1.9	74	61/39
9		1	42	70/30
10		1	29	65/35

[a] Isolated yields, based on initial carbonyl compounds. [b] No 1-4 addition product was detected.

Table 3. Iron-Catalyzed Electroreductive Coupling between Methyl 2-Chloroacetate and Carbonyl Compounds

entry	Carbonyl compounds	$n_{eq.}$ α-chloroester	yields (%) of coupling product[a]
1		2.6	79
2		1.8	87
3		2	72
4		2	49
5		2.5	73

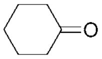
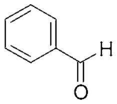
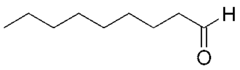
[a] Isolated yields, based on initial carbonyl compounds. All products gave satisfactory analytical data.

because a part of Fe^{II}, released by oxidation of the anode, is reduced to metallic iron at the cathode.

We found that during the electrolysis the potential of the working electrode remained constant at ca. −1.1 V/SCE, which corresponds to the reduction of bipyridine complex of Fe^{II} into Fe^{I}.[17] The subsequent step is certainly an oxidative addition of Fe^{I} to the α-chloroester. The rate constant for the reaction of Fe^{I} (electrogenerated from $FeBr_2bipy_3$) with methyl 2-chloropropanoate was obtained by the method described by Nicholson and Shain[18] and was found to be $k = 31 \pm 3\ M^{-1}\ s^{-1}$.

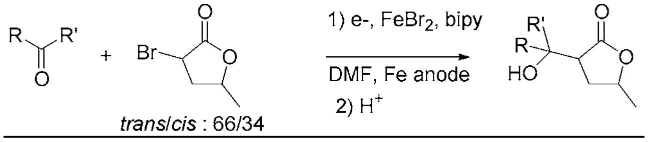
We then applied this method to a large variety of α-chloroester and carbonyl compounds. Results for the electrochemical coupling reaction between methyl 2-chloropropanoate and ketones or aldehydes under the standard reaction conditions defined above are given in Table 2.

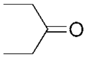
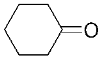
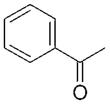
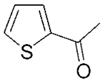
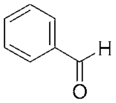
Table 4. Iron-Catalyzed Electroreductive Coupling between Methyl 2-Bromopropanoate and Carbonyl Compounds

entry	Carbonyl compounds	$n_{eq.}$ α-bromoester	yields (%) of coupling product[a]	erythro/threo
1		1.8	90	/
2		1.4	78	71/29
3[b]		1.1	50	63/37

[a] Isolated yields, based on initial carbonyl compounds. All products gave satisfactory analytical data. [b] ArCHO was introduced in five portions to minimize the direct reduction.

Table 5. Iron-Catalyzed Electroreductive Coupling between α-Bromo-γ-valerolactone and Carbonyl Compounds



entry	Carbonyl compounds	$n_{eq.}$ α-bromolactone	yields (%) of coupling product[a]	*trans*/*cis*
1		2	86	73/27
2		1.8	57	75/25
3		2	65	b
4		2	35[c]	c
5		1.6	32[d]	d

[a] Isolated yields, based on initial carbonyl compounds. All products gave satisfactory analytical data. [b] Mixture of four diastereomers in 18/61/20/1 ratio. [c] Mixture of three diastereomers in 20/52/28 ratio, 85% GC. [d] PhCHO was introduced in four portions to minimize the direct reduction, 81% GC.

Aromatic as well as aliphatic or cyclic ketones (Table 2, entries 1−8) gave good yields of β-hydroxyesters. In all of cases, 1.5−2 equiv of α-chloroester are necessary.

In the cases of aldehydes (Table 2, entries 9 and 10), chemical yields are moderate because of the pinacolization of the aldehyde. Lower yields were obtained with 2-cyclohexen-1-one even if the ketone is totally consumed and no other products were detected. No conjugated addition was observed, thus indicating that the reaction is regiospecific. In the case of dissymmetric carbonyl compounds, we obtained the two diastereoisomers with moderate diastereoselectivity (Table 2, entries 3, 5−10), depending on the nature of the carbonyl compounds.

Coupling methyl 2-chloroacetate with the same carbonyl compounds also gave good yields of β-hydroxyesters (50−87% isolated yield, Table 3).

As already observed in the case of electroreductive coupling between aryl halide and α-chloroester with a nickel catalysis,[19] the coupling with chloropropionate is more efficient than with chloroacetate. The excess of α-chloroester, necessary to consume totally the carbonyl compounds, is

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(15) Chaussard, J.; Folest, J. C.; Nédélec, J. Y.; Périchon, J.; Sibille, S.; Troupel, M. *Synthesis* **1990**, *1*, 369.

(16) Iron rod was purchased from Weber (113010007, pur ARMCO), and nickel sponge from Nitech (Mn 110.050.020, grade 110).

(17) (a) Saji, T.; Aoyagui, S. *J. Electroanal. Chem.* **1975**, *58*, 401. (b) Cyclic voltamograms in Supporting Information.

(18) Nicholson, R. S.; Shain, I. *Anal. Chem.* **1964**, *36*, 706.

(19) Durandetti, M.; Nédélec, J.-Y.; Périchon, J. *J. Org. Chem.* **1996**, *61*, 1748.

more important with methyl 2-chloroacetate than with methyl 2-chloropropanoate.

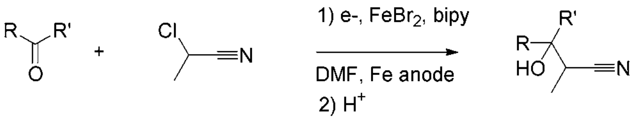
α-Bromoesters were also studied. Results with methyl 2-bromopropanoate are given in Table 4.

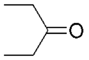
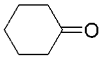
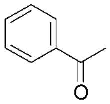
Reactions conducted with ketones gave the same good yields with α-bromoester, as well as α-chloroester, with the same excess of alkyl halide (compare Table 4, entry 1 and Table 2, entry 2). However, with aldehydes, α-bromoesters gave yields twice those with α-chloroester (compare Table 4, entries 2 and 3 and Table 2, entries 9 and 10).

Some natural products have lactone functionalities. We then tried the reaction coupling between the α-bromo-γ-valerolactone and different carbonyl compounds. Results are given in Table 5. Chemical yields are generally good. In the case of acetylthiophene and benzaldehyde, we only obtained an isolated yield of 35%, whereas GC yields are about 80%. The decrease of the chemical yield is probably due to a degradation on the silica column chromatography (β-elimination).

We then extended the process to the coupling with α-chloronitrile. Results with α-chloropropionitrile are given in Table 6. α-Chloronitrile reacts under the same procedure as for α-chloroesters. The method can also be applied to α-chloroketone and α,α′-dichloroester. Thus, as a preliminary study, the coupling between cyclohexanone and sterically hindered α-chloroketone proceeds in good yield (Scheme 3), as well as the direct coupling between 3-pentanone and α,α′-dichloroester (Scheme 4).

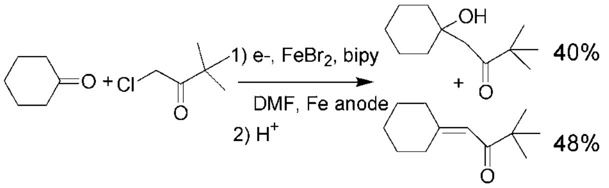
Table 6. Iron-Catalyzed Electroreductive Coupling between α-Chloropropionitrile and Carbonyl Compounds



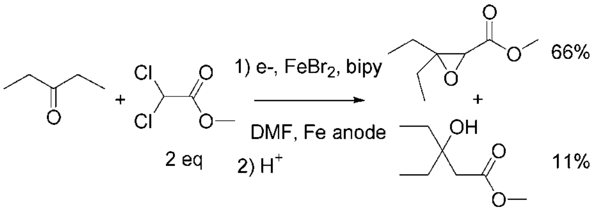
entry	Carbonyl compounds	n_{eq}. α-chloronitrile	yields (%) of coupling product[a]	erythro/threo
1		2	62	/
2		2.5	60	/
3		2.5	81	66/34

[a] Isolated yields, based on initial carbonyl compounds. All products gave satisfactory analytical data.

Scheme 3. Addition of α-Chloroketone to Cyclohexanone via Iron Catalysis



Scheme 4. Addition of α,α′-Dichloroester to Cyclohexanone via Iron Catalysis



In conclusion, we have reported in this paper a method of efficient cross coupling of carbonyl compounds and activated alkyl halides, enabling the preparation of valuable target molecules such as β-hydroxyesters. The scope of the method is wide concerning the type of organic compounds involved: besides α-chloro- or α-bromoesters, α-bromolactone and α-chloronitrile or ketones can also be used. The method is as efficient with ketones as with aldehydes. In addition, because of the use of a simple complex of iron in an undivided cell and sacrificial iron anode, the process is very easy, cheap, nontoxic, and totally original.

This is the first iron-catalyzed Reformatsky-type reaction reported so far to our knowledge. Further investigations are necessary to determine which kind of organoiron species are involved in the mechanism. Results will be reported in due course.

Supporting Information Available: Experimental details, characterization data, and cyclic voltamograms. This material is available free of charge via the Internet at http://pubs.acs.org.

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