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Electrochemical, nickel-catalyzed Reformatsky reaction with methyl chlorodifluoroacetate

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Abstract

2,2-difluoro-3-hydroxyesters are readily obtained from methyl chlorodifluoroacetate and carbonyl compounds by electrolysis in a one-compartment cell with use of a sacrificial zinc anode and a nickel-complex catalyst.

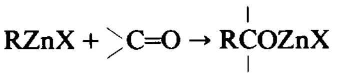
Introduction

We recently described [1] an electrochemical Reformatsky reaction which advantageously uses α-chloroesters instead of the corresponding bromo-compounds to give high yields of β-hydroxyesters in coupling with various carbonyl compounds. The main features of the process are the use of a sacrificial zinc anode in a one-compartment electrolysis cell and catalytic amounts of nickel-2,2′-bipyridine complex, with DMF as the solvent. The catalytic cycle (Eq. 1–4) involves the reduction of the Ni^{II} complex to a zerovalent one, the oxidative addition of the chloroester to Ni^0, followed by a metal exchange between the organonickel(II) species and Zn^{II}, and addition of the organozinc species to the carbonyl compound.

$$Ni^{II} + 2e \rightarrow Ni^0 \qquad (1)$$

$$Ni^0 + RX \rightarrow RNiX \qquad (2)$$

$$RNiX + ZnX_2 \rightarrow RZnX + NiX_2 \qquad (3)$$



$$RZnX + {>}C{=}O \rightarrow R\overset{|}{\underset{|}{C}}OZnX \qquad (4)$$

The Reformatsky reaction using iodo-, bromo- or chloro-difluoroacetate has been recently reported [2–4] and its synthetic utility in the field of fluoroorganic chemistry has been outlined. In the case of the less expensive chlorodifluoroacetate however, the reaction requires relatively severe conditions (DMF, 70 ° C, 20 h), and only applies to non-enolizable aldehydes. This prompted us to examine the suitability of our method for the synthesis of 2,2-difluoro-3-hydroxyesters.

Results and discussion

As shown in Table 1, electrolyses performed in DMF containing a four-fold excess of methyl chlorodifluoroacetate relative to the carbonyl compound gave high yield of the β-hydroxyester in the case of benzaldehyde, but much lower yields with heptanal or various ketones. Unchanged ketone was mostly recovered, but not heptanal. The main by-products were CHF_2CO_2Me and a Claisen condensation product isolated in the hydrated form $ClCF_2C(OH)_2CF_2CO_2CH_3$ (I). Near the end of the electrolysis the latter was formed almost exclusively, and the ketone was no longer consumed. In the absence of carbonyl compound, (I) was obtained in 75% yield.

In the reaction of non fluorinated α-chloroesters, DMF can be replaced by a 90:10 CH_2Cl_2–DMF mixture, with essentially the same yield of β-hydroxyesters [1]. Interestingly, with chlorodifluoroacetate, the use of CH_2Cl_2–DMF as solvent led to substantial improvements in the synthesis of 2,2-difluoro-3-hydroxyesters, in respect of both the required amount of chlorodifluoroacetate (2–2.5 eq. relative to the carbonyl) and the yield of the product (Table 2).

High yields were obtained in this way even with ketones and enolizable aldehydes. A lower yield in the case of 5-methylfurfural was due to the polymerization of the substrate, but no conjugate addition was detected.

There are noteworthy differences between the reactions carried out in CH_2Cl_2–DMF and those in DMF. The ^{19}F NMR monitoring of the electrolysis indicated that the major by-product was CHF_2CO_2Me, formed in the same amount as in DMF, but that the formation of $ClCF_2COCF_2CO_2CH_3$ was far less important. When the electrolysis was performed in the absence of carbonyl compound, a singlet at −115 ppm ($CFCl_3$), which was not detected in DMF was observed. It can be assigned to an organometallic species which reacts rapidly with water or acetophenone to give CHF_2CO_2Me or $PhC(OH)(CH_3)CF_2CO_2CH_3$, respectively, and slightly more slowly (in 10–30 min) with an excess of methyl chlorodifluoroacetate to give the Claisen condensation product (I). This organometallic species, although not very stable could be kept in CH_2Cl_2–DMF solution during the electrolysis at concentrations of up to 0.15 *M* (as judged by ^{19}F NMR spectroscopy with CF_3SO_3Li as internal standard), much higher than that of the nickel catalyst (0.025 M). It must be an organozinc species, its NMR signal then being in agreement with literature data [2,5].

Table 1

Electrosynthesis of 2,2-difluoro-3-hydroxyesters in DMF

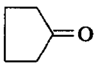
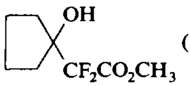
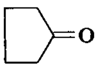
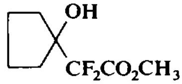
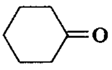
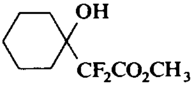
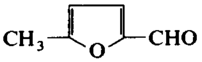
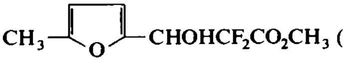
Carbonyl compound	Product	Isolated yield (%)
PhCHO	$PhCHOHCF_2CO_2CH_3$ (II)	79
$C_6H_{13}CHO$	$C_6H_{13}CHOHCF_2CO_2CH_3$ (III)	35
$PhCOCH_3$	$PhC(OH)(CH_3)CF_2CO_2CH_3$ (IV)	34
	 (V)	20

Table 2

Electrosynthesis of 2,2-difluoro-3-hydroxyesters in 90 : 10 CH_2Cl_2–DMF

Carbonyl compound	Product	Isolated yield (%)
$PhCOCH_3$	$PhC(OH)(CH_3)CO_2CH_3$ (IV)	72
PhCOPh	$Ph_2C(OH)CF_2CO_2CH_3$ (VI)	54
	 (V)	63
	 (VII)	62
$n\text{-}C_3H_7COCH_3$	$n\text{-}C_3H_7C(OH)(CH_3)CF_2CO_2CH_3$ (VIII)	77
$C_2H_5COC_2H_5$	$(C_2H_5)_2C(OH)CF_2CO_2CH_3$ (IX)	64
PhCHO	$PhCHOHCF_2CO_2CH_3$ (II)	70
	 (X)	45
$n\text{-}C_6H_{13}CHO$	$n\text{-}C_6H_{13}CHOHCF_2CO_2CH_3$ (III)	56

This evidence for an organozinc intermediate strengthens the case for the suggestion that nickel zinc exchange is the key-step in the catalytic cycle [1]:

$ClNiCF_2CO_2CH_3 + ZnBr_2 \rightarrow ClZnCF_2CO_2CH_3 + NiBr_2$

In DMF the intermediate will react rapidly with the excess of chlorodifluoroacetate to give the Claisen product (I) in high yield. In CH_2Cl_2 as solvent this side-reaction will be slower, and the condensation with the carbonyl compound thus favoured.

In conclusion, this simple, easy to scale-up electrosynthetic process enables preparation of reactive organometallic species under milder conditions and from cheaper reagents than classical organometallic chemistry, and provides an efficient synthesis of valuable 2,2-difluoro-3-hydroxyesters.

Experimental

General procedure for the electrolyses

A solution in 40 ml of the relevant solvent (DMF or 90 : 10 CH_2Cl_2–DMF) of $NiBr_2$-2,2′-bipyridine (1 mmol), $ZnBr_2$ (5 mmol), the carbonyl compound (10 mmol), and an excess $ClCF_2CO_2CH_3$ was introduced into an electrolysis cell fitted with a zinc rod as the anode and a carbon fiber cathode (20 cm^2 area). The solution was kept under argon at room temperature and a constant current intensity (0.3 A) applied. The electrolysis was stopped when the product concentration, as monitored by GC, became constant. Acid hydrolysis, diethyl-ether extraction, and evaporation of the extract, followed by preparative column chromatography (silica gel, 90 : 10 pentane–ether as eluant) gave the pure product. Yields are relative to the initial carbonyl compound.

Products analysis

^1H NMR (δ, ppm from TMS) and ^{19}F NMR (δ, ppm from $CFCl_3$) spectra were obtained from an AC200 Bruker spectrometer ($CDCl_3$ solution). IR spectra were recorded on a Perkin Elmer 577 spectrometer.

Methyl 4-chloro-3,3-dihydroxy-2,2,4,4-tetrafluorobutanoate (I). ^1H NMR: 5.4 (s, 2 OH) 3.8 (s, 3H). ^{19}F NMR: − 66.3 (t, J(FF) = 13.6 Hz), −117.2 (t, J(FF) = 13.6 Hz). IR: 3440, 1760, 1445, 1330, 1160, 1065 cm^{-1}. Found: C: 24.78; H: 2.31; Cl: 13.97; F: 30.75. $C_5H_5ClF_4O_4$ calc.: C: 24.96; H: 2.10; Cl: 14.70; F: 31.50%.

Methyl 2,2-difluoro-3-hydroxy-3-phenylpropanoate (II). ^1H NMR: 7.25 (s, 5H), 5.1 (dd, 1H), 3.75 (s, 3H), 3.1 (OH). ^{19}F NMR: −112.8 (dd, J(FF) = 271Hz, J(HF) = 7.4 Hz), −120.8 (dd, J(FF) = 271, J(HF) = 16.8 Hz). Found: C: 55.63; H: 4.92; F: 17.4. $C_{10}H_{10}F_2O_3$ calc.: C: 55.56; H: 4.66; F: 17.58%.

Methyl 2,2-difluoro-3-hydroxynonanoate (III). ^1H NMR: 4.0 (m, 1H), 3.9 (s, 3H), 2.75 (s, OH), 1.65–1.5 (m, 2H), 1.45–1.2 (m, 8H), 0.9 (t, 3H). ^{19}F NMR: −114.1 (dd, 1F, J(FF) = 254, J(HF) = 6 Hz), −125.5 (dd, 1F, J(FF) = 254, J(HF) = 15.2 Hz). The alcohol III could not be obtained very pure. Acetylation (acetyl chloride, pyridine in CH_2Cl_2) gave the acetate: n-$C_6H_{13}CH(OCOCH_3)CF_2CO_2CH_3$. ^1H NMR: 5.35 (m, 1H), 3.85 (s, 3H), 2.1 (s, 3H) 1.7 (m, 2H), 1.3–1.25 (m, 8H), 0.9 (t, 3H). ^{19}F NMR: −114.1 (dd, 1F, J(FF) = 263, J(HF) = 8.4 Hz), −118.4 (dd, 1F, J(FF) = 263, J(HF) = 13.9 Hz). Found: C: 54.47; H: 7.52; F: 14.36. $C_{12}H_{20}F_2O_4$ calc: C: 54.13; H: 7.57; F: 14.27%.

Methyl 2,2-difluoro-3-hydroxy-3-phenylbutanoate (IV). ^1H NMR: 7.5 (m, 2H), 7.3 (m, 3H), 3.6 (s, 3H), 3.4 (OH), 1.8 (s, 3H). ^{19}F NMR: −114.7 (s, 2F). IR: 3500, 1760, 1450, 1315, 1130, 1070, 1040 cm^{-1}. Found: C: 57.19; H: 5.31; F: 15.5. $C_{11}H_{12}F_2O_3$ calc: C: 57.39; H: 5.25; F: 16.5%.

Methyl 2,2-difluoro-2(1-hydroxycyclopentyl)-ethanoate (V). ^1H NMR: 3.9 (s, 3H), 2.4 (OH), 2.2–1.8 (m, 8H). ^{19}F NMR: −116 (s, 2F). IR: 3480, 2960, 1760, 1440, 1320, 1130, 1090 cm^{-1}. Found: C: 49.60; H: 6.38; F: 18.66. $C_8H_{12}F_2O_3$ calc: C: 49.48; H: 6.23, F: 19.57%.

Methyl 2,2-difluoro-3,3-diphenyl-3-hydroxypropanoate (VI). ^1H NMR: 7.4 (m, 10H), 4.5 (OH), 3.7 (s, 3H). ^{19}F NMR: −101.5 (s, 2F). VI could not be obtained free from benzophenone.

Methyl 2,2-difluoro-2-(1-hydroxycyclohexyl)-ethanoate (VII). ^1H NMR: 3.8 (s, 3H), 2.5 (OH), 1.8–1.4 (m, 10H). ^{19}F NMR: −119.4 (s, 2F). IR: 3500, 2940, 1760, 1450, 1320, 1200, 1125 cm^{-1}. Found: C: 51.92; H: 6.66; F: 16.75. $C_9H_{14}F_2O_3$ calc: C: 51.92; H: 6.78; F: 18.25%.

Methyl 2,2-difluoro-3-hydroxy-3-methylhexanoate (VIII). ^1H NMR: 3.65 (s, 3H), 2.5 (OH), 1.5–1.2 (4H), 1.1 (m, 3H), 0.8 (t, 3H). ^{19}F NMR: −117 (s, 2F). IR: 3480, 2960, 1760, 1440, 1320, 1120, 1040 cm^{-1}. Found: C: 48.82; H: 7.24; F: 19.26. $C_8H_{14}F_2O_3$ calc: C: 48.98; H: 7.19; F: 19.37%.

Methyl 2,2-difluoro-3-ethyl-3-hydroxypentanoate (IX). ^1H NMR: 3.9 (s, 3H), 2.3 (OH), 1.7 (m, 4H), 0.9 (m, 6H). ^{19}F NMR: −114 (s, 2F). IR: 3500, 2980, 1760, 1450, 1310, 1200, 1120 cm^{-1}. Found: C: 48.92; H: 7.27; F: 18.66. $C_8H_{14}F_2O_3$ calc: C: 48.96; H: 7.19; F: 19.37%.

Methyl 2,2-difluoro-3-hydroxy-3-(2-(5-methylfuryl))-propanoate (X). ^1H NMR: 6.55 (d, 1H, J(HH) = 3.5 Hz), 6.2 (d, 1H, J(HH) = 3.5 Hz), 5.3 (m, 1H), 4.1 (s, 3H), 3.6 (OH), 2.5 (s, 3H). ^{19}F NMR: −113.7 (dd, J(FF) = 268.8, J(HF) = 8.2Hz), −119.6 (dd, J(FF) = 268.8, J(FH) = 16Hz). IR: 3460, 1760, 1560, 1445, 1310, 1220, 1080 cm^{-1}. Found: C: 48.04; H: 4.44; F: 16.04. $C_9H_{10}F_2O_4$ calc: C: 49.1; H: 4.58; F: 17.26%.

Acknowledgements

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