An effective synthesis of 2,2-difluoro-3-hydroxy esters

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Abstract

Reformatsky reactions of bromodifluoroacetate with carbonyl compounds and its applications to the synthesis of 2,2-difluoro-3-hydroxy esters as a means of two-carbon homologation with a difluoro moiety under mild conditions in good to excellent yields are described. In the case of aldehydes and aromatic ketones no catalyst was needed, while in the case of aliphatic ketones, 2 mol% of $CeCl_3$ catalyst raises the yields dramatically from 30%–32% to 89%–92%.

Introduction

A Reformatsky reaction of bromodifluoroacetate was first reported by Halliman and Fried [1] as a means of a two-carbon homologation with a difluoro moiety. Since then, its application to the synthesis of fluorinated biologically active compounds has been increasingly reported [2]. However, all examples usually require some type of activation, e.g. reflux [2], ultrasonic irradiation [3] or electrolysis [4]. Although the yields were good in the last two cases, large-scale reaction is impractical and this limitation may restrict further application of this method in organic synthesis [2a]. Therefore, to develop a catalyzed Reformatsky reaction under mild conditions would be valuable.

Results and discussion

In the control reactions, we found that the Reformatsky reagent of bromodifluoroacetate could react with a variety of aldehydes and aromatic ketones without catalyst at room temperature in good to excellent yields. However, in the case of aliphatic ketones, catalyst is needed.

The reaction is as follows:

$$\underset{(1)}{BrCF_2COOEt} + Zn + \underset{(2)}{R^1R^2CO} \xrightarrow[THF,\ r.t.,\ 1\ h]{\text{with or without cat.}} \underset{(3)}{R^1R^2C(OH)CF_2COOEt}$$

Table 1 shows that carbonyl compounds including aromatic (entries 1–4), aliphatic (entries 6–8) and α,β-unsaturated aldehydes (entry 5) and aromatic ketones

TABLE 1. Preparation of 2,2-difluoro-3-hydroxy esters

Entry no.	Compound 3	R^1	R^2	Yield (%)[a]	
				No cat.	Cat. A/B[b]
1	**3a**	C_6H_5	H	94	92(B)
2	**3a**	C_6H_5	H	95[c]	–
3	**3b**	4-$CH_3C_6H_4$	H	93	95(B)
4	**3c**	4-ClC_6H_4	H	93	95(B)
5	**3d**	(*E*)-CH_3CH=CH	H	86	90(B)
6	**3e**	$CH_3(CH_2)_3$	H	90	91(B)
7	**3f**	$CH_3(CH_2)_5$	H	92	92(B)
8	**3g**	$CH_3(CH_2)_2$	H	90	94(B)
9	**3h**	C_6H_5	CH_3	90	92(B)
10	**3i**	C_6H_5	C_6H_5	86	90(B)
11	**3j**	$-(CH_2)_5-$		32	90(A), 89(B)
12	**3k**	$-(CH_2)_4-$		32	90(A), 90(B)
13	**3l**	$CH_3(CH_2)_2$	CH_3	30	92(A), 90(B)

[a]Isolated yields of distilled products pure enough for microanalyses (new compounds) and IR and NMR (^{19}F, ^1H) spectroscopy, and MS (all compounds).
[b]Cat. A, 2 mol% $CeCl_3$; Cat. B, 2 mol% $CeCl_3 \cdot 7H_2O$.
[c]0.1 Molar scale.

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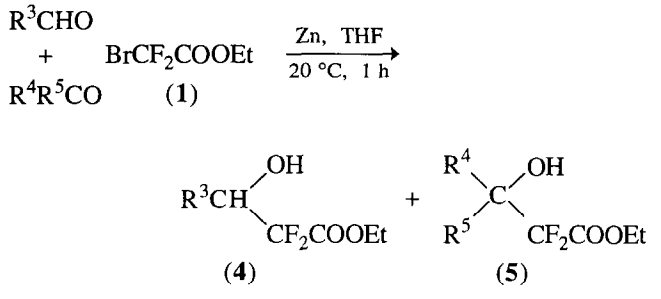
(entries 9 and 10) react with bromodifluoroacetate to give 2,2-difluoro-3-hydroxy esters in the presence of acid-washed zinc without any catalyst at room temperature, the isolated yields being excellent.

In the absence of catalyst, the yields of aliphatic ketones are low (30%–32%, entries 11–13), while in the presence of 2 mol% catalyst the yields can be raised dramatically to 89%–92%. Either anhydrous cerium chloride or its hydrates could be used as catalyst. Since cerium chloride hydrates can destroy some zinc bromodifluoroacetate reagents, 30% excess of bromodifluoroacetate relative to aliphatic ketones was necessary to obtain high yields. The results show that cerium chloride catalyzes the unreactive substrates in the Reformatsky reaction of bromodifluoroacetate.

To extend the application of this reaction, we studied the competitive reaction between aldehydes and ketones as follows:



The results obtained are summarized in Table 2. These show that the chemoselectivity between aromatic aldehydes and ketones is poor, whilst that between aldehydes and aliphatic ketones is good. These results are in accord with the known reactivities of aldehydes and ketones towards nucleophilic reagents.

In this reaction, the Reformatsky reagents of bromodifluoroacetate can be prepared easily in THF, and they are more stable at room temperature than at reflux temperature [1, 5]. The Reformatsky reagents are sufficiently reactive to enable reaction with various aldehydes and aromatic ketones at room temperature via the use of acid-washed zinc. However, the role of catalyst is probably attributable to the fact that lanthanide salts have a strong oxophilicity so that they activate relatively inactive aliphatic ketones towards reaction with Reformatsky reagents.

Thus, this new chemoselective methodology is quite convenient and easy to scale-up. It should be useful in the synthesis of fluorine-containing biologically active compounds.

TABLE 2. Chemoselectivity in the reaction of the Reformatsky reagent[a]

Entry no.	Aldehyde	Ketone	Conversion (%)[b]	4/5[c]
14	C_6H_5CHO	$C_6H_5COCH_3$	97	79:21
15	C_6H_5CHO	$CH_3CH_2CH_2COCH_3$	97(85)	95:5
16	$CH_3CH_2CH_2CHO$	$CH_3CH_2CH_2COCH_3$	95	91:9

[a]Molar ratio of aldehyde/ketone/1 = 1:1:1.
[b]Conversion from 1 to 4 and 5; isolated yield of 4 shown in parentheses.
[c]The 4/5 ratios are based on the ^{19}F NMR spectra of the crude product.

Experimental

All melting and boiling points were uncorrected. The IR spectra of all products were obtained on a Perkin–Elmer 983G spectrometer. ^1H NMR and ^{19}F NMR spectra were recorded on a JEOL FX-90Q FT NMR spectrometer in $CDCl_3$ with TMS and TFA (positive for upfield shifts) as external references, respectively. Mass spectra were measured on a Finnigan GC–MS 4021 spectrometer.

General procedure for the preparation of 2,2-difluoro-3-hydroxy esters (3)

Ethyl bromodifluoroacetate (6.0 mmol) was added slowly to a stirred solution of aldehyde or ketone (5.0 mmol) and acid-washed zinc dust (6.0 mmol) and catalyst (2 mol% $CeCl_3$ or 2 mol% $CeCl_3 \cdot 7H_2O$) if needed in dry THF (5 ml) at room temperature under nitrogen. The reaction mixture was stirred for 1 h and aqueous NH_4Cl (5 ml) and NaCl (5 ml) solutions added. The mixture was filtered, washed with ethyl acetate (10 ml) and the organic layer separated. The aqueous layer was extracted with ethyl acetate (3×10 ml). The combined organic layer was dried. Evaporation of the solvent gave a residue which was fractionally distilled at reduced pressure to give the pure product **3**. (In the case of **3c**, column chromatography was used to purify the crude product.)

Ethyl 2,2-difluoro-3-hydroxy-3-phenylpropionate (**3a**) [1]: B.p. 110 °C/1.5 mmHg. ^1H NMR δ: 7.36–7.46 (m, 5H); 5.15 (dd, 1H, J = 15.5, 8.2 Hz); 4.28 (q, 2H, J = 7.2 Hz); 3.62 (br s, 1H); 1.26 (t, 3H, J = 7.2 Hz) ppm. ^{19}F NMR δ: 36.5 (dd, 1F, J = 259, 8.2 Hz); 43.6 (dd, 1F, J = 259, 15.5 Hz) ppm. IR (neat) (cm^{-1}): 3497; 2983; 1756. MS *m/e*: 230 (M^+); 231 (M+1); 213; 185; 107.

Ethyl 2,2-difluoro-3-hydroxy-3-(4-methyl)phenylpropionate (**3b**): B.p. 104 °C/1.0 mmHg. ^1H NMR δ: 7.34 (d, 2H, J = 8.0 Hz); 7.20 (d, 2H, J = 8.0 Hz); 5.12 (dd, 1H, J = 16.4, 8.2 Hz); 4.25 (q, 2H, J = 7 Hz); 3.44 (br s, 1H); 2.38 (s, 3H); 1.30 (t, 3H, J = 7 Hz) ppm. ^{19}F NMR δ: 36.5 (dd, 1F, J = 259, 8.2 Hz); 42.9 (dd, 1F, J = 259, 16.4 Hz) ppm. IR (neat) (cm^{-1}): 3498; 2984;

1755. MS *m/e*: 244 (M^+); 199; 121. Analysis: Calc. for $C_{12}H_{14}F_2O_3$: C, 59.01; H, 5.73%. Found: C, 58.76; H, 5.75%.

Ethyl 2,2-difluoro-3-hydroxy-3-(4-chloro)phenylpropionate (**3c**): M.p. 45–46 °C. ^{1}H NMR δ: 7.28 (s, 4H); 5.06 (dd, 1H, J=16.3, 8.2 Hz); 4.22 (q, 2H, J=7.0 Hz); 3.38 (br s, 1H); 1.23 (t, 3H, J=7.0 Hz) ppm. ^{19}F NMR δ: 35.98 (dd, 1F, J=263, 8.2 Hz); 43.84 (dd, 1F, J=263, 16.3 Hz) ppm. IR ($CHCl_3$) (cm^{-1}): 3498; 2983; 1756. MS *m/e*: 264 (M^+); 265 (M+1); 247; 219; 141. Analysis: Calc. for $C_{11}H_{11}ClF_2O_3$: C, 49.90; H, 4.16%. Found: C, 49.78; H, 4.24%.

Ethyl 2,2-difluoro-3-hydroxy-4-hexenoate (**3d**): B.p. 66–67 °C/1.0 mmHg. ^{1}H NMR δ: 5.68–6.00 (m, 1H); 5.84 (dd, 1H, J=14.5, 7.0 Hz); 4.42 (m, 1H); 4.28 (q, 2H, J=7.0 Hz); 2.68 (br s, 1H); 1.74 (d, 3H, J=7.0 Hz); 1.26 (t, 3H, J=7.0 Hz) ppm. ^{19}F NMR δ: 37.16 (dd, 1F, J=263, 8.2 Hz); 44.78 (dd, 1F, J=263, 16.5 Hz) ppm. IR (neat) (cm^{-1}): 3486; 2982; 1757. MS *m/e*: 195 (M+1); 177; 149; 71. Analysis: Calc. for $C_8H_{12}F_2O_3$: C, 49.48; H, 6.18%. Found: C, 49.24; H, 6.20%.

Ethyl 2,2-difluoro-3-hydroxyheptanoate (**3e**): B.p. 80–81 °C/3.0 mmHg. ^{1}H NMR δ: 4.32 (q, 2H, J=7.0 Hz); 3.85–4.02 (m, 1H); 3.32 (br s, 1H); 1.38–1.64 (m, 6H); 1.34 (t, 3H, J=7.0 Hz); 0.91 (t, 3H, J=7.0 Hz) ppm. ^{19}F NMR δ: 37.3 (dd, 1F, J=263, 8.2 Hz); 46.00 (dd, 1F, J=263, 12.3 Hz) ppm. IR (neat) (cm^{-1}): 3459; 2957; 2870; 1758. MS *m/e*: 211 (M+1); 193; 185; 87. Analysis: Calc. for $C_9H_{16}F_2O_3$: C, 51.43; H, 7.62%. Found: C, 51.62; H, 7.67%.

Ethyl 2,2-difluoro-3-hydroxynonanoate (**3f**): B.p. 92 °C/1.0 mmHg. ^{1}H NMR δ: 4.32 (q, 2H, J=7.0 Hz); 3.80–4.05 (m, 1H); 2.46 (br s, 1H); 1.28–1.60 (m, 13H); 0.88 (t, 3H, J=7.0 Hz) ppm. ^{19}F NMR δ: 37.40 (dd, 1F, J=263, 8.2 Hz); 46.00 (dd, 1F, J=263, 15.5 Hz) ppm. IR (neat) (cm^{-1}): 3466; 2927; 2857; 1757. MS *m/e*: 239 (M+1); 221; 115. Analysis: Calc. for $C_{11}H_{20}F_2O_3$: C, 55.44; H, 8.40%. Found: C, 55.18; H, 8.54%.

Ethyl 2,2-difluoro-3-hydroxyhexanoate (**3g**): B.p. 66–68 °C/2.0 mmHg. ^{1}H NMR δ: 4.30 (q, 2H, J=7.0 Hz); 3.80–4.05 (m, 1H); 2.53 (br s, 1H); 1.45–1.60 (m, 4H); 1.38 (t, 3H, J=7.0 Hz); 0.96 (t, 3H, J=7.0 Hz) ppm. ^{19}F NMR δ: 37.26 (dd, 1F, J=263, 8.2 Hz); 46.12 (dd, 1F, J=263, 16.5 Hz) ppm. IR (neat) (cm^{-1}): 3454; 2962; 2874; 1757. MS *m/e*: 197 (M+1); 179; 151. Analysis: Calc. for $C_8H_{14}F_2O_3$: C, 48.98; H, 7.14%. Found: C, 49.00; H, 7.04%.

Ethyl 2,2-difluoro-3-hydroxy-3-phenylbutyrate (**3h**): B.p. 82 °C/1 mmHg. ^{1}H NMR δ: 7.20–7.45 (m, 5H); 4.08 (q, 2H, J=7 Hz); 3.58 (s, 1H); 1.65 (s, 3H); 0.98 (t, 3H, J=7 Hz) ppm. ^{19}F NMR δ: 37.4 (s) ppm. IR (neat) (cm^{-1}): 3576; 3057; 1757; 1373. MS *m/e*: 241 (M−3); 227 (M−OH); 155; 121. Analysis: Calc. for $C_{12}H_{14}F_2O_3$: C, 59.01; H, 5.73%. Found: C, 58.79; H, 5.72%.

Ethyl 2,2-difluoro-3-hydroxy-3,3-diphenylpropionate (**3i**): B.p. 115 °C/1.0 mmHg. ^{1}H NMR δ: 7.0–7.47 (m, 10H); 4.02 (s, 1H); 3.95 (q, 2H, J=7 Hz); 0.90 (t, 3H, J=7 Hz) ppm. ^{19}F NMR δ: 31.6 (s) ppm. IR (neat) (cm^{-1}): 3576; 3057; 1761; 1371. MS *m/e*: 303 (M−3); 289 (M−OH); 183; 105. Analysis: Calc. for $C_{17}H_{16}F_2O_3$: C, 66.67; H, 5.22%. Found: C, 66.44; H, 5.22%.

Ethyl 2,2-difluoro-2-(1′-hydroxy-1′-cyclohexyl)acetate (**3j**) [1]: B.p. 77–78 °C/1.0 mmHg. ^{1}H NMR δ: 2.25 (br s, 1H); 4.30 (q, 2H, J=7 Hz); 1.28 (t, 3H, J=7 Hz); 1.52 (m); 1.56 (m); 1.68 (m, 10H) ppm. ^{19}F NMR δ: 42.5 (s) ppm. IR (neat) (cm^{-1}): 3506; 2938; 1757; 1372. MS *m/e*: 220 (M−2); 205 (M−OH); 174; 99.

Ethyl 2,2-difluoro-2-(1′-hydroxy-1′-cyclopentyl)acetate (**3k**): B.p. 70–72 °C/1.0 mmHg. ^{1}H NMR δ: 4.23 (q, 2H, J=7.0 Hz); 2.60 (br s, 1H); 1.60–2.10 (m, 8H); 1.26 (t, 3H, J=7.0 Hz) ppm. ^{19}F NMR δ: 38.5 (s) ppm. IR (neat) (cm^{-1}): 3482; 2965; 2874; 1756. MS *m/e*: 209 (M+1); 191; 163; 85. Analysis: Calc. for $C_9H_{14}F_2O_3$: C, 51.92; H, 6.73%. Found: C, 51.43; H, 6.99%.

Ethyl 2,2-difluoro-3-hydroxy-3-methylhexanoate (**3l**): B.p. 58–59 °C/1.0 mmHg. ^{1}H NMR δ: 4.33 (q, 2H, J=7.0 Hz); 2.53 (br s, 1H); 1.44–1.58 (m, 4H); 1.34 (t, 3H, J=7.0 Hz); 1.26 (s, 3H); 0.93 (t, 3H, J=7.0 Hz) ppm. ^{19}F NMR δ: 40.1 (s) ppm. IR (neat) (cm^{-1}): 3508; 2963; 2874; 1758. MS *m/e*: 211 (M+1); 193; 165; 87. Analysis: Calc. for $C_9H_{16}F_2O_3$: C, 51.43; H, 7.62%. Found: C, 51.15; H, 7.65%.

Competitive reaction. General procedure

The reaction was performed as in the preparation of **3**, except the molar ratio of aldehyde/ketone/**1** was 1:1:1. Before work-up, conversion of bromodifluoroacetate to compounds **4** and **5** was ascertained by ^{19}F NMR spectroscopy. After work-up, the crude product was characterized by ^{19}F NMR spectroscopy, which can gave the ratio of **4**/**5**. Distillation of the crude product gave a mixture of **4** and **5** (entry 14, 16) or the pure product **4** (entry 15) (see Table 2).

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