Preparation of β-Bromodifluoromethyl-functionalized Esters, Nitrile and Ketones *via* Addition of Dibromodifluoromethane to Electron-deficient Alkenes Initiated by a $CrCl_3$/Fe Bimetal Redox System

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The addition of dibromodifluoromethane to electron-deficient alkenes proceeds smoothly in the presence of a $CrCl_3$/Fe bimetal redox system, giving various β-bromodifluoromethyl-functionalized esters, nitriles and ketones in good yields.

The addition of CF_2Br_2 to alkenes gives bromodifluoromethyl-containing compounds, which are useful precursors for the syntheses of molecules bearing a difluoromethylene fragment.[1] Such reactions usually involve a radical mechanism and can be promoted by benzoyl peroxide,[2] light,[3] CuCl/2-aminoethanol[4] or BEt_3,[5] but its additions are restricted to electron-rich alkenes. The addition of CF_2Br_2 to electron-deficient alkenes like ethyl acrylate is not possible under these conditions owing mainly to the electrophilic nature of fluorinated radicals and the ready polymerisation of the acrylate before the addition occurs. The fact that electron-deficient alkenes such as ethyl acrylate could not be used as substrates has limited the scope of the reaction. Recently, as our previous reports have demonstrated, the addition of per(poly)fluoroalkyl iodides or bromides to acrylates could be realized by a Co^{III}/Zn redox couple.[6] However, with zinc, the reactive dibromodifluoromethane is readily debrominated to form CF_2: so a search was made for an efficient catalyst to initiate the addition of CF_2Br_2 to electron-deficient alkenes.

In our continuing study of organofluorine chemistry initiated by redox systems, we have found that $CrCl_3$ could be slowly reduced to Cr^{II} by iron powder. Subsequent experiments showed that a catalytic amount of $CrCl_3{\cdot}6H_2O$ (20 mol%) and iron powder (1.5 equiv.) could efficiently initiate the addition of CF_2Br_2 to electron-deficient alkenes in one-pot giving the corresponding 1:1 hydrobromodifluoromethylation products (Scheme 1).

$$\underset{\mathbf{1}}{CF_2Br_2} + \underset{\mathbf{2}}{CHR^1{=}CR^2R} \xrightarrow{i} \underset{\mathbf{3}}{BrCF_2CHR^1CHR^2R}$$

Scheme 1 *Reagents and conditions*: R = electron-withdrawing group; i, $CrCl_3{\cdot}6H_2O$ (20 mol%), Fe (1.5 equiv.), EtOH, 60 °C

A typical procedure is as follows: A mixture of iron powder (0.84 g, 15 mmol), $CrCl_3{\cdot}6H_2O$ (0.53 g, 2 mmol), CF_2Br_2 (2.1 g, 10 mmol) and ethyl acrylate (1.2 g, 12 mmol) in EtOH (20 ml) was stirred at 60 °C for 20 h. The mixture was then poured into ice-water (10 ml) and the residue filtered off. The filtrate was extracted with diethyl ether (3 × 20 ml), and the combined ethereal layers were washed (water and brine), then dried (Na_2SO_4). After removal of the diethyl ether, the residue was distilled under reduced pressure to give 2.66 g (72%) of ethyl 4-bromo-4,4-difluorobutyrate. Volatile colourless oil; b.p. 78–80 °C at 3.3 kPa; ^{19}F NMR (CCl_4/CF_3CO_2H), positive at upper field. δ −32.0 (s); ^1H NMR ($CCl_4/SiMe_4$): δ 4.15 (q, $^3J_{HH}$ 7 Hz, 2H), 3.2–2.2 (m, 4H) and 1.25 (t, $^3J_{HH}$ 7 Hz, 3H); IR (neat): ν_{max}/cm^{-1} 1740s, 1180s, 1100s and 1020br; MS: *m/z* 230 (M^+, 2.61), 232 (M^+, 2.94), 151 (M − Br, 100%).

With such a bimetal redox system, no polymerized or telomerized product was found. Neither debromination to give CF_2: nor hydrodebromination to give CF_2BrH product was detected even in a protic solvent (ethanol) and in the presence of water ($CrCl_3{\cdot}6H_2O$). This redox-couple-catalysed reaction proved to be quite general for various electron-deficient alkenes. Representative results are summarized in Table 1. When acrylates were used as substrates, good yields of the corresponding adducts were obtained. In ethanol, no exchange of methyl to ethyl acrylic ester was found (run 3). Ethyl methacrylate gave a satisfactory result, while ethyl crotonate gave a lower yield (43%), this was attributed to steric effects. Acrylic acid and amide were also available. In tetrahydrofuran, 4-bromodifluorobutyric acid **3c** was obtained in 64% isolated yield (run 4). In addition, this reaction also worked well with acrylonitrile and α,β-unsaturated ketones.

Table 1 Addition of **1** to **2** initiated by the $CrCl_3$/Fe redox system[a]

Run No.	Alkenes **2**	T/°C (t/h)	Adducts **3**	Yield[b] (%)
1	CH_2=$CHCO_2Et$ **2a**	60 (20)	$BrCF_2CH_2CH_2CO_2Et$ **3a**	72
2	**2a**	60 (20)	No reaction	[c]
3	CH_2=$CHCO_2Me$ **2b**	60 (20)	$BrCF_2CH_2CH_2CO_2Me$ **3b**	75
4	CH_2=$CHCO_2H$ **2c**	65 (20)	$BrCF_2CH_2CH_2CO_2H$ **3c**[d]	64
5	CH_2=$CHCONH_2$ **2d**	70 (20)	$BrCF_2CH_2CH_2CONH_2$ **3d**	72
6	CH_2=$C(Me)CO_2Et$ **2e**	60 (24)	$BrCF_2CH_2C(Me)HCO_2Et$ **3e**	80
7	MeCH=$CHCO_2Et$ **2f**	75 (28)	$BrCF_2C(Me)HCH_2CO_2Et$ **3f**	43
8	CH_2=CHCN **2g**	60 (18)	$BrCF_2CH_2CH_2CN$ **3g**	62
9	CH_2=CHCOMe **2h**	60 (20)	$BrCF_2CH_2CH_2COMe$ **3h**	60
10	Cyclohex-2-en-1-one **2i**	75 (20)	3-Bromodifluoromethylcyclohexan-1-one **3i**	18

[a] The solvent used was EtOH unless otherwise indicated. Molar ratio **1**:**2**:$CrCl_3{\cdot}6H_2O$:Fe = 1:1.2:0.2:1.5. [b] Isolated yield based on **1**. All new compounds were characterized by MS, IR, ^1H NMR, ^{19}F NMR spectroscopy and microanalyses. [c] Iron powder alone was used. [d] The solvent used was tetrahydrofuran.

Although the mechanism of this new redox-couple-catalysed reaction is not yet confirmed, certain facts are noteworthy: (*a*) iron powder alone cannot initiate this reaction in the parallel experiment (run 2) and (*b*) $Cr^{II}Cl_2$ freshly prepared could initiate the same addition reaction at room temp. in low conversion (20%). These facts might imply that the *in situ* generated Cr^{II} species is the real initiator.

In conclusion, a new, useful and practical hydrobromodifluoromethylation reaction of electron-deficient alkenes has been discovered. The ready availability of catalyst and alkenes bearing various electron-withdrawing functionalities, the simplicity of the experimental procedures, the absence of debromination with dibromodifluoromethane and the good yields obtained make this approach a useful route to syntheses of a variety of β-bromodifluoromethyl functionalized esters, nitriles and ketones. Furthermore, these adducts bearing a reactive centre CF_2Br^- and a variety of functionalities like esters are potentially useful building blocks in organic synthesis.

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