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Reaction of α-trifluoromethylacrylic acid with various unsaturated Grignard reagents

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Abstract

The reactions of 2-(trifluoromethyl)propenoic acid (I) with unsaturated Grignard reagents have been examined. Vinylmagnesium bromide with I gave 2-difluoromethylene-4-pentenoic acid (II) and analogous acids were obtained from propenyl and butenyl magnesium halides. The iodolactonization of **II** gave 2-difluoromethylene-4-iodomethyl-γ-lactone (III). 2-Monofluoromethylene-4-penten-1-ol (IV) was obtained by the reduction of **II** with lithium aluminium hydride.

Introduction

It has been reported that fluorinated acrylic acids and their esters, $F_2C=C(R')COOR''$, are produced from the reaction of Grignard reagents with the trimethylsilyl or benzyl ester of 2-(trifluoromethyl)propenoic acid (I) below −40 °C [1–3]. The reaction of sodium 2-trifluoromethylacrylate with ethylmagnesium bromide or phenylmagnesium chloride gives 2-propyl- or 2-benzyl-3,3-difluoro-acrylic acid, respectively [2]. However, the reaction of **I** with unsaturated Grignard reagents has not been studied in detail, and on examination of this reaction we have found that 2-difluoromethylene unsaturated carboxylic acids were obtained. These carboxylic acids are useful intermediates for α-difluoromethylene-γ-lactones.

Results and discussion

The reaction of **I** with unsaturated Grignard reagents at temperatures up to −30 °C did not give products from attack at the –COOH group. We have found that the reaction of an α,β-unsaturated Grignard reagent with **I**

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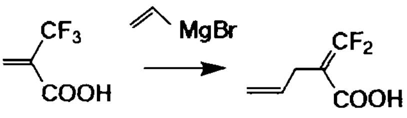
below −60 °C gave their adducts from attack at the $=CH_2$ group. For example, from the reaction of vinylmagnesium bromide with **I**, 2-difluoromethylene-4-pentenoic acid (**II**) was obtained in 30% yield.



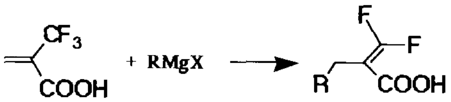
(**I**) (**II**)

The reactions of 1-propenylmagnesium bromide and allylmagnesium halides with **I** gave similar one-to-one adducts. From the reaction of 2-butenylmagnesium halides with **I**, 2-difluoromethylene-4-methyl-5-hexenoic acid was obtained. In these reactions, it is essential to keep the temperatures below −60 °C. The results obtained are given in Table 1.

A variety of γ-lactones are widely used as perfumes and synthetic intermediates. However, convenient ways of preparing difluoromethylene γ-

TABLE 1

Reaction of α-trifluoromethyl acrylic acid with various unsaturated Grignard reagents



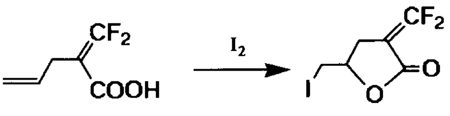
Grignard reagent		Product **II**[a,b]			
R	X	Yield[c] (%)	B.p. (°C/mmHg)	^{19}F NMR	
				δ (ppm)	J_{FF} (Hz)
$H_2C=CH-$	Br	30.0	90–91/25	+12.93(d) +8.46(d)	13.77 13.77
$H_2C=CH-$	Cl	38.5	–	–	–
$CH_3CH=CH_2-$	Br	12.9	134–140/18	+11.25(d) +10.52(d)	15.05 15.05
$H_2C=CHCH_2-$	Br	20.3	82–84/6	+10.177(d) +6.324(d)	13.78 13.78
$H_2C=CHCH_2-$	Cl	35.0	–	–	–
$CH_3CH=CHCH_2-$	Br	15.0	111–116/24	+12.75(d) +9.78(d)	12.41 12.41
$CH_3CH=CHCH_2-$	Cl	18.9	–	–	–

[a] The microanalyses were in satisfactory agreement with the calculated values: C, ±0.30%; H, ±0.05%.

[b] All compounds were separated by vacuum distillation. All these compounds were liquid.

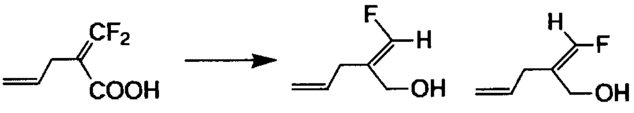
[c] The yield was calculated as isolated yield.

lactones have not been investigated, except via a Wittig-type reaction. We report herein the synthesis of a γ-lactone carrying a difluoromethylene group. Iodolactonization [4, 5] of **II** proceeded by an exocyclic mode of ring closure, producing 2-difluoromethylene-4-iodomethyl-γ-lactone (**III**). The structure of **III** was determined by IR, ^{1}H NMR and ^{19}F NMR spectroscopy and by mass spectrometry. It is known that the reaction pathway proceeds as shown in refs. 4 and 5. The iodolactonization of the other difluoromethylene carboxylic acids was unsuccessful.



(II) (III)

Reduction of compound **II** using lithium aluminium hydride was carried out in the usual way to give a mixture of 1-fluoro-2-hydroxymethyl-(*E*)-1,4-pentadiene (**IV$_A$**) and 1-fluoro-2-hydroxymethyl-(*Z*)-1,4-pentadiene (**IV$_B$**). It is suspected that the fluorine atom of 1-fluoro-2-hydroxymethyl-(*Z*)-1,4-pentadiene (**IV$_B$**) forms a hydrogen bond with the hydrogen atom of the hydroxy group, so that **IV$_B$** is more stable than **IV$_A$** and hence **IV$_B$** is the main component. The ratio of **IV$_A$** to **IV$_B$** was 1.0:5.1. Similarly, the reduction of 2-difluoromethylene-5-hexenoic acid with lithium aluminium hydride gave a mixture of 1-fluoro-2-hydroxymethyl-(*E*)-1,5-hexadiene (**V$_A$**) and 1-fluoro-2-hydroxymethyl-(*Z*)-1,5-hexadiene (**V$_B$**) in the molar ratio of 1.0:6.2.



(II) (IV$_A$) (IV$_B$)

Experimental

The reaction products were analyzed by GLC methods on a Shimadzu model GC-3BF chromatographic apparatus using a 3 m×3 mm column of 15% silicone DC 200 on 60–80 mesh Celite 545. ^{1}H NMR and ^{19}F NMR spectra were obtained using $CDCl_3$ as a solvent on a Hitachi model R-24 spectrometer. The chemical shift (ppm) values are quoted relative to external CF_3COOH (^{19}F NMR) (positive value downfield). ^{1}H NMR spectra (δ value) were recorded using tetramethylsilane as an internal standard. IR spectra were obtained on a JASCO model IR-G infrared spectrophotometer. 2-Trifluoromethyl-2-propenoic acid (**I**) was provided by the Japan Halon Co. Ltd.

Reaction of 2-trifluoromethyl-2-propenoic acid (I) with vinylmagnesium bromide

To a solution of compound **I** (3.5 g, 0.025 mol) in tetrahydrofuran (35 ml), vinylmagnesium bromide prepared from magnesium (2.4 g, 0.10 mol) and vinyl bromide (10.7 g, 0.10 mol) in tetrahydrofuran (100 ml) was added drop-by-drop under an atmosphere of nitrogen gas at a temperature of -60 °C. The reaction mixture was stirred for 5 h and left overnight. It was quenched with NH_4Cl solution and extracted with diisopropyl ether. The ether extracts were washed with water, dried over sodium sulphate and distilled to give a pale yellow oil. This was distilled under reduced pressure to give 1.11 g of 2-difluoromethylene-4-pentenoic acid (II) (yield 30.0%), b.p. 90–91 °C/25 mmHg. It exhibited the following physical properties: IR (cm^{-1}): 3000–3400; 1710; 990; 910. ^1H NMR δ: 2.98 (2H, dt, $J_{HH}=7.44$ Hz, $J_{HF}=2.2$ Hz, $-CH_2-$); 5.10 (2H, m, CH_2–CH–); 5.80 (1H, m, $CH_2=CH-$); 12.2 (1H, s, –COOH) ppm. ^{19}F NMR δ: $+8.461$ (1F, dt, $J_{FF}=13.77$ Hz, $J_{FH}=2.2$ Hz); $+12.93$ (1F, dt, $J_{FF}=13.77$ Hz, $J_{FH}=2.2$ Hz) ppm. MS (*m/e*): M^+ (observed), 148.0340. Calcd. for $C_6H_6F_2O_2$, 148.0335.

Similarly, the reactions of vinylmagnesium chloride and 1-propenylmagnesium bromide with **I** were studied and the results obtained are also listed in Table 1.

Reaction of 2-trifluoromethyl-2-propenoic acid (I) with allylmagnesium chloride

To a solution of compound **I** (3.5 g, 0.025 mol) in tetrahydrofuran (35 ml), allylmagnesium chloride prepared from magnesium (2.4 g, 0.10 mol) and allyl chloride (7.65 g, 0.10 mol) in tetrahydrofuran (100 ml) was added drop-by-drop under nitrogen gas at a temperature of -60 °C. The reaction mixture was treated in a similar manner to the case of vinylmagnesium bromide to give 1.42 g of 2-difluoromethylene-5-hexenoic acid (yield 35.0%), b.p. 82–84 °C/6 mmHg. It exhibited the following physical properties: IR (cm^{-1}): 3000–3500; 1710; 1620; 990; 910. ^1H NMR δ: 2.23 (4H, broad s, $-CH_2CH_2-$); 4.8–5.2 (2H, m, $-CH=CH_2$); 5.4–6.0 (1H, m, $-CH=CH_2$); 12.0 (1H, s, –COOH) ppm. ^{19}F NMR δ: $+10.177$ (1F, d, $J_{FF}=13.78$ Hz); $+6.324$ (1F, d, $J_{FF}=13.78$ Hz) ppm. MS (*m/e*): $M^+=162$; 142; 141; 97.

The reactions of crotylmagnesium halides with **I** were performed similarly and the results are also listed in Table 1.

Iodolactonization of 2-difluoromethylene-4-pentenoic acid (II)

A mixture of compound **II** (0.815 g, 0.0055 mol), iodine crystals (4.14 g, 0.0163 mol) and acetonitrile (30 ml) was agitated for 24 h under nitrogen at a temperature of 0 °C. The mixture was dissolved in 200 ml of diisopropyl ether. The ether solution was washed with sodium thiosulphate solution and water, and dried over anhydrous sodium sulphate. The solvent was removed to give a pale yellow oil. It was chromatographed through a silica gel column using benzene containing 20% dichloromethane as the solvent to give 0.340

g (yield 22.5%) of pure 2-difluoromethylene-4-iodomethyl-γ-lactone (**III**), showing the following spectral data: IR (cm^{-1}): 1780; 1730; 1040. ^1H NMR δ: 2.80 (1H, m, ring CH_2); 3.20 (1H, m, ring CH_2); 3.42 (2H, m, $-CH_2I$); 4.61 (1H, m, –O–C*H*–) ppm. ^{19}F NMR δ: +10.488 (1F, dt, $J_{FF}=12.4$ Hz, $J_{FH}=3.76$ Hz); +11.269 (1F, dt, $J_{FF}=12.4$ Hz, $J_{FH}=3.76$ Hz) ppm. MS (*m/e*): M^+ (observed), 273.9320. Calcd. for $C_6H_5F_2O_2I$, 273.9303.

*Reduction of 2-difluoromethylene-4-pentenoic acid (**II**) with lithium aluminium hydride*

To a freshly dried suspension of lithium aluminium hydride (0.76 g, 0.02 mol) in anhydrous diethyl ether (20 ml), compound **II** (1.48 g, 0.01 mol) in diethyl ether (20 ml) was added dropwise under nitrogen gas at a temperature of 0 °C. The reaction mixture was stirred for 5 h, quenched with methanol containing a small amount of hydrochloric acid and extracted with diisopropyl ether. The ether extracts were treated in the usual way to give 1.20 g of 1-fluoro-2-hydroxymethyl-1,4-pentadiene (**IV**). The microanalysis was in satisfactory agreement with the calculated values (C_6H_9FO): C, ±0.30%; H, ±0.05%; F, ±0.03%. The minor component, 1-fluoro-2-hydroxymethyl-(*E*)-1,4-pentadiene ($\mathbf{IV_A}$) and main component, 1-fluoro-2-hydroxymethyl-(*Z*)-1,4-pentadiene ($\mathbf{IV_B}$) were obtained by gas-chromatographic trapping. The $\mathbf{IV_A}/\mathbf{IV_B}$ molar ratio was 1.0:5.1.

Compound $\mathbf{IV_A}$ showed the following data. IR (cm^{-1}): 3300 (–OH); 1630 (–C=C–); 1100 (–OH); 910 and 990 ($-CH=CH_2$). ^1H NMR δ: 1.906 (1H, s, OH); 2.80 (2H, m, $=C-CH_2-C=$); 4.25 (2H, d, $J_{HH}=2.64$ Hz, $-CH_2OH$); 5.02 (2H, m, $-CH=CH_2$); 5.05–5.20 (1H, m, $-CH=CH_2$); 6.43 (1H, d, $J_{HF}=86.45$ Hz, –C=CHF) ppm. ^{19}F NMR δ: −59.20 (1F, d, $J_{FH}=86.45$ Hz) ppm.

Compound $\mathbf{IV_B}$ showed the following spectral data. IR (cm^{-1}): 3300 (–OH); 1630 (–C=C–); 1100 (–OH); 910 and 990 ($-CH=CH_2$). ^1H NMR δ: 1.906 (1H, s, OH); 2.96 (2H, d, $J_{HH}=6.24$ Hz, $=C-CH_2-C=$); 4.02 (2H, d, $J_{HH}=4.00$ Hz, $-CH_2OH$); 5.05–5.20 (2H, m, $-CH=CH_2$); 5.70–5.91 (1H, m, $-CH=CH_2$); 6.67 (1H, d, $J_{FH}=84.55$ Hz, –C=CHF) ppm. ^{19}F NMR δ: −60.05 (1F, d, $J_{FH}=84.55$ Hz) ppm.

Reduction of 2-difluoromethylene-5-hexenoic acid (1.134 g, 0.007 mol) with lithium aluminium hydride (0.53 g, 0.014 mol) was similarly carried out to give 0.80 g of 1-fluoro-2-hydroxymethyl-1,5-hexadiene (**V**). The minor component, 1-fluoro-2-hydroxymethyl-(*E*)-1,5-hexadiene ($\mathbf{V_A}$) and the main component, 1-fluoro-2-hydroxymethyl-(*Z*)-1,5-hexadiene ($\mathbf{V_B}$) were obtained by gas-chromatographic trapping. The $\mathbf{V_A}/\mathbf{V_B}$ molar ratio was 1.0:6.2.

Compound $\mathbf{V_A}$ showed the following data. IR (cm^{-1}): 3300 (–OH); 1615 (–C=CF); 910 and 990 ($-CH=CH_2$). ^1H NMR δ: 2.03 (1H, s, OH); 2.13 (4H, m, $-CH_2CH_2-$); 4.26 (2H, d, $J_{HH}=3.4$ Hz, $-CH_2OH$); 4.95–5.08 (2H, m, $-CH=CH_2$); 5.75–5.85 (1H, m, $-CH=CH_2$); 6.42 (1H, d, $J_{FH}=86.45$ Hz, –CHF) ppm. ^{19}F NMR δ: −58.391 (1F, d, $J_{FH}=86.45$ Hz) ppm.

Compound $\mathbf{V_B}$ showed the following data. IR (cm^{-1}): 3300 (–OH); 1615 (–C=CF); 910 and 990 ($-CH=CH_2$). ^1H NMR δ: 2.03 (1H, s, OH); 2.23 (2H, m, $-CH_2-$); 2.31 (2H, m, $-CH_2-$); 4.03 (2H, d, $J_{HH}=4.0$ Hz, $-CH_2OH$);

4.95–5.08 (2H, m, $-CH{=}C\mathit{H}_2$); 5.75–5.85 (1H, m, $-C\mathit{H}{=}CH_2$); 6.63 (1H, d, $J_{FH}=84.55$ Hz, $=CHF$) ppm. ^{19}F NMR δ: -58.448 (1F, d, $J_{FH}=84.55$ Hz) ppm.

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