Reaction of trifluoroacetaldehyde with some bromoesters

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(Received May 11, 1993; accepted September 27, 1993)

Abstract

Reformatsky reactions of trifluoroacetaldehyde with lower bromoesters gave their corresponding adducts. The reaction of trifluoroacetaldehyde with methyl 2-(bromomethyl)acrylate gave γ-trifluoromethyl-α-methylene-γ-butyrolactone.

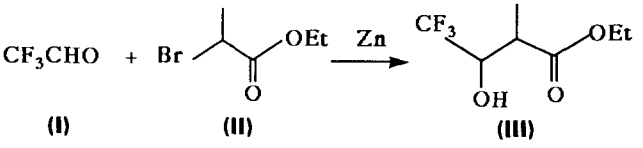
Introduction

Many preparative methods for introducing perfluoroalkyl groups into carbonyl compounds through organometallic reagents of zinc [1], calcium [2], manganese [3], lithium [4] and trifluoromethyltrimethylsilane [5] are known. However, the method using the Reformatsky reaction of trifluoroacetaldehyde (**I**) with bromoesters is not well known. In this study we examined the reaction of compound **I** with some α-bromoesters.

Results and discussion

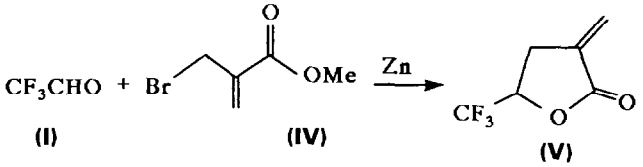
Trifluoroacetaldehyde (**I**) is available commercially in the form of trifluoroacetaldehyde ethyl hemiacetal. With this in mind, we tried to apply trifluoroacetaldehyde ethyl hemiacetal to the reaction with α-bromoesters in the presence of zinc powder. However, the corresponding adducts were not obtained.

We have found, however, that trifluoroacetaldehyde (**I**) itself reacts with α-bromoesters in the presence of zinc powder at the reflux temperature of the aldehyde to give the corresponding adducts. For example, the reaction of **I** with ethyl 2-bromopropionate (**II**) in dry tetrahydrofuran gave ethyl 4,4,4-trifluoro-3-hydroxy-2-methylbutyrate (**III**) in 25.0% yield. The reaction of ethyl 2-bromoacetate and ethyl 2-bromo-2-methylpropionate with **I** also gave their corresponding products. However, similar products were not obtained from the reaction of **I** with higher esters, such as ethyl 2-bromobutyrate, ethyl 2-bromopentanate, ethyl 2-bromooctanate and ethyl 3-bromopropionate.



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

In recent years, there has been considerable interest in the development of new methods for the synthesis of α-methylene-γ-butyrolactone[dihydro-3-methylene-2(3*H*)-furanones], since such compounds possess remarkable biological activities [6–8]. Among the numerous possible syntheses of α-methylene-γ-butyrolactones, an attractive one is the one-step Reformatsky reaction of methyl(2-bromomethyl)acrylate (**IV**) with trifluoroacetaldehyde (**I**). Using our method, γ-trifluoromethyl-α-methylene-γ-butyrolactone (**V**) was obtained from the reaction of **I** with **IV** as described below in the Experimental section. At present, we are examining the biological activities of compound **V**.



(**I**) (**IV**) (**V**)

Experimental

General procedures

The reaction products were analyzed by GC methods using a 3 mm i.d.×3 m column of 15% silicone DC

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SSDI 0022-1139(93)02986-O

200 on 60–80 mesh Celite 545. NMR spectra were recorded at 60 MHz or 200 MHz for ^{1}H NMR and 56.4 MHz for ^{19}F NMR in $CDCl_3$. ^{19}F chemical shift are reported in parts per million (ppm) relative to trifluoroacetic acid (δ 0.00) as an external standard with the upper field positive.

Ethyl 4,4,4-trifluoro-3-hydroxy-2-methylbutyrate (III)

A mixture consisting of 1.19 g (18.2 mmol) of zinc powder and 20 ml of anhydrous tetrahydrofuran was placed in a 100 ml three-necked flask equipped with a magnetic stirrer, reflux condenser cooled at −78 °C and a gas inlet tube. The flask was surrounded with a Dry Ice/acetone freezing mixture (< −78 °C). Gaseous trifluoroacetaldehyde was passed into the solution which was maintained at < −50 °C. Trifluoroacetaldehyde (**I**) was generated by dropping 3.03 g (21.0 mmol) of trifluoroacetaldehyde ethyl hemiacetal into concentrated sulphuric acid (50 ml) maintained at 140 °C. Ethyl 2-bromopropionate (**II**) (1.89 g, 10.5 mmol) was added drop-by-drop to the reaction mixture while maintaining the temperature at −78 °C. While the temperature of the reflux condenser was kept at < −78 °C with Dry Ice/acetone, the mixture was refluxed for 4 h. It was then quenched with 1 N hydrochloric acid (50 ml) and extracted with ether. The extracts were washed with saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulphate and evaporated to give a yellow oil. The oil was purified by column chromatography with silica gel using a mixture of hexane and benzene (3:7 v/v) as an eluant to give ethyl 4,4,4-trifluoro-3-hydroxy-2-methylbutyrate (**III**) [0.522 g; yield, 25.0% based on **II**]. The spectral data are as follows. IR (cm^{-1}): 1710; 3420. ^{19}F NMR δ: 2.51 (3F, d, J_{FH}=6.9 Hz, CF_3) ppm. ^{1}H NMR δ: 1.288 (3H, t, J=7.2 Hz, CH_3CH_2); 1.325, 1.327 (1.5H and 1.5H, each d, J=7.2 Hz, $-CHCH_3$); 2.861, 2.863 [0.5H and 0.5H, each dq, J=7.2 Hz, J=4.5 Hz, $-CH(CH_3)$]; 3.10–3.20 (1H, broad s, −OH); 4.201 (2H, q, J=7.2 Hz, CH_3CH_2); 4.38–4.47 [1H, m, CF_3CH(OH)] ppm. Analysis: Calc. for $C_7H_{11}O_3F_3$: C, 41.96; H, 5.54%. Found: C, 41.90; H, 5.51%.

Ethyl 4,4,4-trifluoro-3-hydroxybutyrate

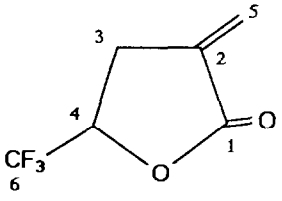
The reaction was performed in a similar manner with ethyl bromoacetate (5.83 g, 34.9 mmol), zinc (6.06 g, 92.7 mmol) and trifluoroacetaldehyde [which was obtained from trifluoroacetaldehyde ethyl hemiacetal (5.19 g, 36.0 mmol)] to give ethyl 4,4,4-trifluoro-3-hydroxybutyrate (1.175 g; yield, 18.1%, based on ethyl bromoacetate). IR (cm^{-1}): 1730; 3490. ^{19}F NMR δ: 2.51 (3F, d, J=6.9 Hz, CF_3) ppm. ^{1}H NMR δ: 1.30 (3H, t, J=7.2 Hz, CH_3CH_2); 2.70 (2H, d, J=7.2 Hz, $-CH_2CO$); 3.75 (1H, broad s, −OH); 4.22 (2H, q, J=7.2 Hz, $-CH_2CH_3$); 4.38–4.55 [1H, m, $-CH$(OH)] ppm.

Ethyl 4,4,4-trifluoro-3-hydroxy-2,2-dimethylbutyrate

The reaction was performed with 2-bromo-2-methylpropionate (3.88 g, 19.9 mol), zinc (2.77 g, 42.3 mmol) and trifluoroacetaldehyde [prepared from trifluoroacetaldehyde ethyl hemiacetal (5.86 g, 40.7 mmol)] to give ethyl 4,4,4-trifluoro-3-hydroxy-2,2-dimethylbutyrate (0.455 g; yield, 10.7%). IR (cm^{-1}): 3400; 1708. ^{19}F NMR δ: 6.06 (3F, d, J=7.32 Hz, CF_3) ppm. ^{1}H NMR δ: 1.29 (3H, t, J=7.14 Hz, $-CH_2CH_3$); 1.36 [6H, s, $-C(CH_3)_2$]; 3.79 (1H, broad s, −OH); 4.11 [1H, q, J=7.32 Hz, CF_3CH(OH)]; 4.20 (2H, q, J=7.14 Hz, $-CH_2CH_3$) ppm.

γ-Trifluoromethyl-α-methylene-γ-butyrolactone (V)

To a mixture consisting of 0.54 g (8.2 mmol) of zinc powder and 20 ml of anhydrous tetrahydrofuran, gaseous trifluoroacetaldehyde was passed, the temperature being held at < −50 °C. Trifluoroacetaldehyde (**I**) was generated from 1.96 g (13.6 mmol) of trifluoroacetaldehyde ethyl hemiacetal. Methyl 2-bromoacrylate (**IV**) (0.975 g, 0.40 mmol) was added dropwise to the reaction mixture while maintaining the latter at −78 °C. The mixture was refluxed, while the temperature of the reflux condenser was kept at < −78 °C by Dry Ice/acetone. The mixture was quenched with 1 N hydrochloric acid (50 ml) and treated as for compound **III** to give a yellow oil. This was purified by column chromatography with silica gel using a mixture of hexane and ethyl acetate (2:1 v/v) as an eluant to give 4-trifluoromethyl-2-methylene-γ-butyrolactone (**V**) (0.294 g; yield, 32.6%). The spectra data are as follows. IR (cm^{-1}): 1784; 1666; 970. ^{19}F NMR δ: 4.60 (3F, d, J=6.1 Hz, CF_3) ppm. ^{1}H NMR δ: 3.04 (1H, ddt, J=2.7 Hz, 4.7 Hz, 18.0 Hz, $-CH_2-$); 3.22 (1H, ddt, J=2.9 Hz, 8.8 Hz, 18.0 Hz, $-CH_2-$); 4.82 (1H, ddq, J=4.7 Hz, 8.8 Hz, 6.2 Hz, $-CHCF_3$); 5.83 (1H, t, J=2.6 Hz, $=CH_2$); 6.38 (1H, t, J=2.9 Hz, $=CH_2$) ppm. ^{13}C NMR δ: 27.12 (3C, q, J=2.0 Hz); 77.08 (4C, q, J=34.8 Hz); 123.30 (6C, q, J=279.5 Hz); 124.76 (2C, s); 130.33 (5C, s); 168.04 (1C, s) ppm. Analysis: Calc. for $C_6H_5O_2F_3$: C, 43.4; H, 3.03%. Found: C, 43.1; H, 3.00%.



A small amount of methyl 5,5,5-trifluoro-4-hydroxy-2-methylenepentanoate (28 mg) was obtained as a minor

component. IR (cm^{-1}): 1722; 1666; 3550. ^{19}F NMR δ: 4.30 (3F, d, $J=7.6$ Hz, CF_3) ppm.

Acknowledgement

We are grateful to Ms Chika Nakajima of Chiba University for her technical assistance.

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