

Reaction of trifluoroacetaldehyde with some bromoesters

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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

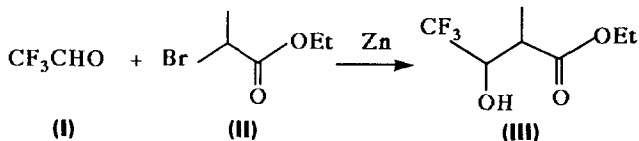
Many preparative methods for introducing perfluoroalkyl groups into carbonyl compounds through organometallic reagents of zinc [1], calcium [2], manganese [3], lithium [4] and trifluoromethyltrimethylsilane [5] are known. However, the method using the Reformatsky reaction of trifluoroacetaldehyde (I)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

Results and discussion

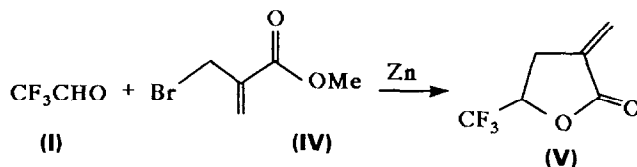
Trifluoroacetaldehyde (I) is available commercially in the form of trifluoroacetaldehyde ethyl hemiacetal. With this in mind, we tried to apply trifluoroacetaldehyde ethyl hemiacetal to the reaction with α -bromoesters in the presence of zinc powder. However, the corresponding adducts were not obtained.

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-bromopentanoate, ethyl 2-bromooc-

tanate and ethyl 3-bromopropionate.



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.



Experimental

General procedures

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

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200 on 60–80 mesh Celite 545. NMR spectra were recorded at 60 MHz or 200 MHz for ^1H 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 ($< -78^\circ\text{C}$). Gaseous trifluoroacetaldehyde was passed into the solution which was maintained at $< -50^\circ\text{C}$. 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 $< -78^\circ\text{C}$ 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, $J_{\text{FH}} = 6.9$ Hz, CF_3) ppm. ^1H 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, $-\text{CHCH}_3$); 2.861, 2.863 [0.5H and 0.5H, each dq, $J = 7.2$ Hz, $J = 4.5$ Hz, $-\text{CH}(\text{CH}_3)$]; 3.10–3.20 (1H, broad s, $-\text{OH}$); 4.201 (2H, q, $J = 7.2$ Hz, CH_3CH_2); 4.38–4.47 [1H, m, $\text{CF}_3\text{CH}(\text{OH})$] ppm. Analysis: Calc. for $\text{C}_7\text{H}_{11}\text{O}_3\text{F}_3$: 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. ^1H NMR δ : 1.30 (3H, t, $J = 7.2$ Hz, CH_3CH_2); 2.70 (2H, d, $J = 7.2$ Hz, $-\text{CH}_2\text{CO}$); 3.75 (1H, broad s, $-\text{OH}$); 4.22 (2H, q,

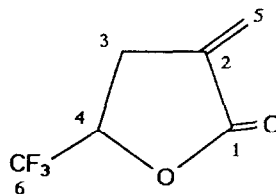
$J = 7.2$ Hz, $-\text{CH}_2\text{CH}_3$); 4.38–4.55 [1H, m, $-\text{CH}(\text{OH})$] ppm.

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

The reaction was performed with 2-bromo-2-methylpropionate (3.88 g, 19.9 mmol), 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. ^1H NMR δ : 1.29 (3H, t, $J = 7.14$ Hz, $-\text{CH}_2\text{CH}_3$); 1.36 [6H, s, $-\text{C}(\text{CH}_3)_2$]; 3.79 (1H, broad s, $-\text{OH}$); 4.11 [1H, q, $J = 7.32$ Hz, $\text{CF}_3\text{CH}(\text{OH})$]; 4.20 (2H, q, $J = 7.14$ Hz, $-\text{CH}_2\text{CH}_3$) 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 $< -50^\circ\text{C}$. 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 $< -78^\circ\text{C}$ 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. ^1H NMR δ : 3.04 (1H, ddt, $J = 2.7$ Hz, 4.7 Hz, 18.0 Hz, $-\text{CH}_2-$); 3.22 (1H, ddt, $J = 2.9$ Hz, 8.8 Hz, 18.0 Hz, $-\text{CH}_2-$); 4.82 (1H, ddq, $J = 4.7$ Hz, 8.8 Hz, 6.2 Hz, $-\text{CHCF}_3$); 5.83 (1H, t, $J = 2.6$ Hz, $=\text{CH}_2$); 6.38 (1H, t, $J = 2.9$ Hz, $=\text{CH}_2$) 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 $\text{C}_6\text{H}_5\text{O}_2\text{F}_3$: 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.

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