Available online at www.sciencedirect.com
SCIENCE DIRECT®
Journal of Fluorine Chemistry 125 (2004) 125–128
JOURNAL OF FLUORINE CHEMISTRY
www.elsevier.com/locate/jfluchem

α-Trifluoroacetyl-δ-valerolactone: synthesis, acyl-lactone rearrangement and unexpected easy decarboxylation of the rearranged product

Dmitri V. Sevenard*, Enno Lork

Institute of Inorganic & Physical Chemistry, University of Bremen, Leobener Strasse, 28334 Bremen, Germany

Received 24 September 2003; received in revised form 18 November 2003; accepted 19 November 2003

Abstract

Claisen condensation of δ-valerolactone and ethyl trifluoroacetate leads to α-trifluoroacetyl-δ-valerolactone, existing completely in $CDCl_3$ solution as an enol. Upon treatment of this cyclic 1,3-ketoester with aqueous HCl, an acyl-lactone rearrangement takes place. The structure of the resulting pyran was confirmed by an X-ray analysis. The ability of the rearrangement product to lose its carboxylic group under unexpected mild conditions was used for the synthesis of the corresponding 3-unsubstituted cyclic *hemi*-ketal.

Keywords: Fluorinated 1,3-ketoesters; Lactones; Enol; Acyl-lactone rearrangement; Pyrans; X-ray analysis

1. Introduction

1,3-Dicarbonyl compounds represent one of the most important classes of polyfunctional organic species due to their interdisciplinary significance and diverse practical uses. Introduction of fluorine into a molecule of 1,3-dicarbonyl derivative changes its electronic density distribution dramatically, resulting in unexpected behaviour in the course of chemical transformations and in peculiar tautomeric (keto–enol, enol–enol) features. Therefore, the fluoroalkyl- and fluoroaryl containing 1,3-dicarbonyl compounds have, over the decades, come to be of considerable interest from theoretical and synthetic points of view. Methods for obtaining such compounds, their structural features (especially with respect to prototropy), chemical properties and practical applications have been reviewed several times [1]. Despite the extensive investigations and significant advances in this area, published data on the 2-polyfluoroacyl substituted lactones are lacking and deal mostly with γ-butyrolactone derivatives [2]. In order to complement this series and as a continuation of our systematic investigation of ring containing 1,3-diketones [3], we undertook a synthesis and study of the structure and chemical properties of such lactones, varying the size of the ring and the degree of fluorination of the acyl moiety. Here, we report the most interesting preliminary results obtained for α-trifluoroacetyl-δ-valerolactone **2**.

2. Results and discussion

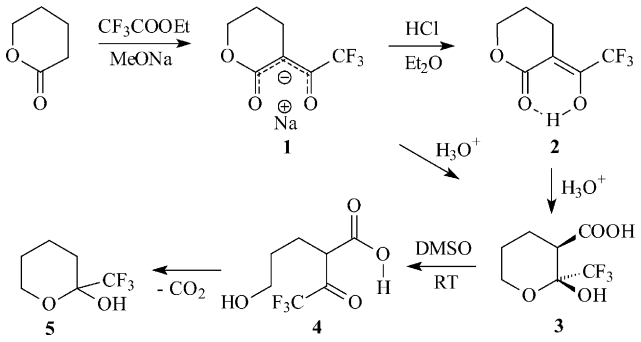
The title compound **2** was synthesized from δ-valerolactone via Claisen condensation using ethyl trifluoroacetate and MeONa as a base. Acidolysis of the initially formed sodium enolate **1** with HCl in diethyl ether gave the desired 1,3-ketoester **2** in 54% isolated yield (Scheme 1).

1,3-Ketoester **2** is a stable colorless crystalline solid, which can be stored at −30 °C for months and handled in air without any discoloration or decomposition. As for the structure of **2**, only *one* set of signals in its ^{1}H and ^{19}F NMR spectra ($CDCl_3$ solution, 20 °C) indicates the presence of only *one* tautomeric form, namely the enol, confirmed by the resonance of the OH-proton at $\delta_H = 13.9$.

After an acidic hydrolysis of the salt **1**, the cyclic *hemi*-ketal **3** was obtained in 82% yield (Scheme 1). Obviously, an acyl-lactone rearrangement [4] takes place in this case, involving an intermediary formation of **2** followed by hydrolytic cleavage of the ester function and recyclization with participation of trifluoroacetyl moiety. In agreement with this assumption, compound **3** was obtained upon treatment of the parent lactone **2** with aqueous HCl in 70% yield (Scheme 1). The reaction proceeds stereospecifically in

* Corresponding author. Tel.: +49-421-218-3435; fax: +49-421-218-4267.
E-mail address: sevenard@chemie.uni-bremen.de (D.V. Sevenard).

0022-1139/$ – see front matter © 2003 Elsevier B.V. All rights reserved.
doi:10.1016/j.jfluchem.2003.11.007



Scheme 1.

both cases; according to the NMR spectroscopic data, only *one* diastereomer was formed. X-ray single crystal investigation of **3** revealed a *trans*-relationship between carboxy- and trifluoromethyl groups (Fig. 1). These groups occupy equatorial positions of the cycle (for the structure of the related compound see [5]). The pyran system shows a ''chair'' conformation with C(2) and C(5) atoms deviating from the plane of other ring atoms by −67.2 and 66.4 pm, respectively. Hydrogen connected to O(2) is bonded via an intramolecular hydrogen bond to the oxygen atom of the carboxylic group [O(2)...O(4) 276.7(2) pm, ∠O–H–O 148(3)°].

It is noteworthy that **3** exists in the cyclic form not only in the solid state but also in $CDCl_3$ and CD_3CN solutions. Ring-chain tautomerism, being typical for related non-fluorinated compounds [6], has not been observed for **3** by NMR spectroscopy in these solvents. Obviously, the stability of the *hemi*-ketal form is caused by the electron-withdrawing influence of trifluoromethyl group; the tendency of highly electrophilic fluorinated ketones to form stable tetrahedral adducts is well known [7]. Surprisingly, by dissolving compound **3** in DMSO-d_6 at ambient temperature, spontaneous decarboxylation occurred to afford the 3-unsubstituted derivative **5** in quantitative ^{19}F NMR yield (Scheme 1). Apparently, the key step of this reaction is the intermediate formation of 1,3-ketoacid **4**, facilitated by the polar solvent. Compound **4** was detected in the reaction mixture by ^{1}H and ^{19}F NMR spectroscopy [characteristic resonances: $\delta_H = 3.39$ (t, 2H, CH_2, $^{3}J_{H-H} = 6.6$ Hz), 5.15 (t, 1H, C*H, $^{3}J_{H-H} = 7.6$ Hz); $\delta_F = -70.5$ s]. It loses CO_2 readily to give, via the subsequent recyclization, the cyclic *hemi*-ketal **5** (Scheme 1). This decarboxylation is a smooth process allowing a reaction on a preparative scale (24 h, 89% isolated yield). On the base of NMR spectroscopy data, pyran **5** exists in $CDCl_3$ as well as in DMSO-d_6 solution in the cyclic *hemi*-ketal form only.

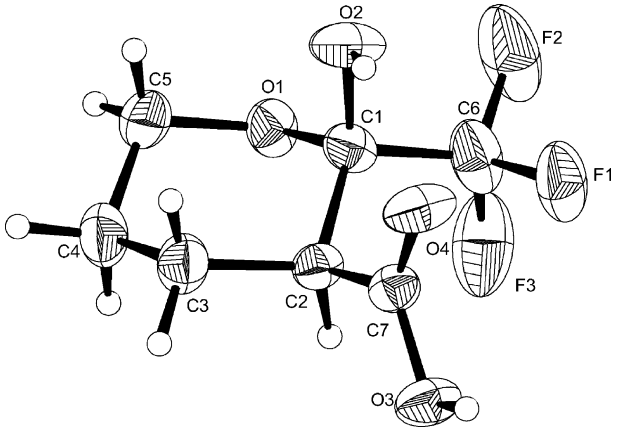


Fig. 1. Molecular structure of **3**. Selected bond lengths (pm): O(1)–C(1) 139.7(2), C(1)–C(2) 153.9(3), C(2)–C(3) 154.0(3), C(2)–C(7) 150.7(3), C(1)–O(2) 139.5(3), C(1)–C(6) 153.3(3); selected bond angles (°): C(6)–C(1)–C(2) 111.0(2), C(7)–C(2)–C(1) 113.3(2), O(2)–C(1)–C(6) 108.6(2).

To summarize, α-trifluoroacetyl-δ-valerolactone **2** was synthesized using Claisen-type trifluoroacetylation of δ-valerolactone. The diastereospecific acyl-lactone rearrangement of compound **2** gave pyran **3**, whose structure was confirmed by X-ray analysis. Under unexpectedly mild reaction conditions this product undergoes decarboxylation to yield the corresponding 3-unsubstituted cyclic *hemi*-ketal **5**. It was found that the reaction mechanism involves a ''ring-opening–decarboxylation–ring-closure'' sequence. A more detailed paper concerning the structure and the properties of α-trifluoroacetyl-δ-valerolactone and other α-polyfluoroacylated lactones is under preparation.

3. Experimental

Melting points are uncorrected. Mass spectra were carried out on a MAT 8200 spectrometer. NMR spectra were recorded in $CDCl_3$ solutions at 20 °C on a Bruker DPX-200 spectrometer operating at 200.1 (^{1}H) and 188.3 MHz (^{19}F). Chemical shifts (δ) are given in ppm relative to TMS for ^{1}H, and relative to $CFCl_3$ for ^{19}F. Diethyl ether was distilled from sodium/benzophenone prior to use. Sodium methoxide was prepared by dissolving sodium metal in dried methanol followed by careful evaporation of the solvent and gradual drying under reduced pressure (20–160 °C, 0.5 Torr). Other compounds are commercially available and were used as purchased.

3.1. 3-Trifluoroacetyltetrahydropyran-2-one (2)

To a stirred suspension of sodium methoxide (5.4 g, 0.1 mol) in dried diethyl ether (40 ml) a solution of δ-valerolactone (10.0 g, 0.1 mol) and ethyl trifluoroacetate (14.2 g, 0.1 mol) in Et_2O (60 ml) was added dropwise within 30 min. The mixture was stirred for 24 h at room temperature, the precipitate (sodium enolate **1**, ca. 17 g) was filtered off and dried in air. Through a stirred suspension of **1** in dried Et_2O (200 ml), dried HCl was bubbled within 2 h, then the NaCl precipitate was filtered off. The filtrate was evaporated under reduced pressure and the solid residue was recrystallized from hexane:toluene (4:1) to afford **2** as colorless

crystals (10.6 g, 54%), mp 43–48 °C. ^{1}H NMR: $\delta = 1.87$–1.99 (m, 2H, CH_2), 2.54–2.69 (m, 2H, CH_2); 4.37 (t, 2H, CH_2, $^3J_{H-H} = 5.4$ Hz), 13.94 (q, 1H, OH, $^4J_{H-F} = 2.1$ Hz). ^{19}F NMR: $\delta = -69.58$ s. MS (EI, 70 eV, *m/z*, species, intensity, %): 196 (M^+, 30), 127 ($[M - CF_3]^+$, 100), 69 (CF_3^+, 25). HRMS: calcd. for $C_7H_7F_3O_3$ (M^+): 196.0347. Found: 196.0354.

3.2. 2-Hydroxy-2-trifluoromethyltetrahydropyran-3-carboxylic acid (*3*)

(a) Starting from **1**: to a stirred suspension of **1** (32.0 g, 0.15 mol) in THF (200 ml) conc. hydrochloric acid (30 ml) was added. After stirring for 24 h at room temperature the precipitated NaCl was filtered off, the filtrate was evaporated on a rotatory evaporator and water (100 ml) was added to the residue. The mixture was extracted with $CHCl_3$ (4 × 20 ml), the combined extracts were dried over $MgSO_4$ and evaporated to dryness. The solid obtained after trituration of the oily residue with hexane (20 ml) was recrystallized from hexane:toluene (1:1) to afford **3** as colorless crystals (25.8 g, 82%), mp 120–124 °C. Anal. Calcd. for $C_7H_9F_3O_4$: C, 39.3; H, 4.2; F, 26.6. Found, %: C, 39.3; H, 4.2; F, 26.6. ^{1}H NMR: $\delta = 1.63$–1.85 (m, 2H, CH_2), 1.89–2.21 (m, 2H, CH_2), 2.91 (dd, 1H, CH, $^3J_{H-H} = 12.0$, $^3J_{H-H} = 5.1$ Hz), 3.82–3.94 (m, 1H, OCH_2), 4.00–4.13 (m, 1H, OCH_2), 5.3 (br.s, 1H, OH), 10.2 (br.s, 1H, COOH). ^{19}F NMR: $\delta = -86.21$ s.

(b) Starting from **2**: to a solution of **2** (1.0 g, 5 mmol) in THF (20 ml) conc. hydrochloric acid (1 ml) was added. After stirring for 20 h at room temperature all volatiles were evaporated under reduced pressure, and the solid residue was recrystallized to afford **3** (0.75 g, 70%).

3.3. X-ray analysis of compound *3*

Colorless needles of **3** suitable for X-ray investigation were obtained from hexane:toluene (1:1) solution. **3**: $C_7H_9F_3O_4$, $M_r = 214.14$, crystal size 0.50 mm × 0.20 mm × 0.15 mm, monoclinic, space group $P2_1/n$, $a = 561.20(10)$, $b = 1473.5(3)$, $c = 1097.9(2)$ pm, $\beta = 101.73(3)^\circ$, $V = 0.8889(3)$ nm^3, $Z = 4$, $d_{calc} = 1.600$ g cm^{-3}, absorption coefficient $\mu = 0.167$ mm^{-1}, $F(000) = 440$. The measurement was performed using a STOE IPDS diffractometer with low temperature device Oxford Cryostream cooler (graphite-monochromated Mo-Kα radiation ($\lambda = 71.073$ pm), $T = -100$ °C). From 8564 reflections measured, 1658 were independent ($R_{int} = 0.0514$). The final discrepancy factors $R1 = 0.0414$ ($I > 2\sigma(I)$), $wR2 = 0.1069$ (F^2, all data), GOF 0.915; $\theta_{max} = 26.1^\circ$, 137 parameters, largest difference peak and hole 0.246/−0.166 e Å^{-3}. The structure was solved by direct methods and refined using the SHELX-97 program package [8]. All non-hydrogen atoms were refined anisotropically (H(2) and H(3) atoms were refined isotropically). The positions of other hydrogen atoms were calculated as a riding model. Crystallographic data have been deposited with Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 220109[1].

3.4. 2-Hydroxy-2-trifluoromethyltetrahydropyran (*5*)

Acid **3** (7.0 g, 33 mmol) was dissolved in DMSO (60 ml) and stirred at room temperature in a sealed flask for 24 h. The solution was poured on ice (ca. 150 g), and then extracted with Et_2O (6 × 30 ml). The combined extracts were additionally washed with water (2 × 15 ml) and dried over $MgSO_4$. The solvent was distilled off (water bath), the residual solvent was evaporated under reduced pressure: first under ca. 15 Torr for ca. 20 min (the flask was cooled with ice), then under 1 Torr for 1.5 h (the flask was cooled to −30 °C) and finally under 1 Torr for ca. 10 min (the flask was cooled with ice). The solid residue was sublimed (1 Torr, temperature of bath ca. 50 °C) to afford **5** as a white powder (5.0 g, 89%), mp 48–51 °C. Compound **5** is considerably volatile at room temperature and should be stored in a sealed flask. ^{1}H NMR: $\delta = 1.55$–1.91 (m, 6H, $3CH_2$), 2.62 (s, 1H, OH), 3.78–4.00 (m, 2H, OCH_2). ^{19}F NMR: $\delta = -88.33$ s. MS (EI, 70 eV, *m/z*, species, intensity, %): 170 (M^+, 2), 153 ($[M - OH]^+$, 4), 101 ($[M - CF_3]^+$, 33), 56 ($C_4H_8^+$, 100), 41 (CH_2=CH–CH_2^+, 68). HRMS: calcd. for $C_6H_9F_3O_2$ (M^+): 170.0555. Found: 170.0550.

Acknowledgements

We thank Dr. K.-H. Hellberg, Solvay Fluor und Derivate GmbH, Hannover, Germany for the generous gift of ethyl trifluoroacetate. D.V.S. is grateful to Prof. Dr. G.-V. Röschenthaler for support.

References

[1] (a) P. Mushak, M.T. Glenn, J. Savory, Fluorine Chem. Rev. 6 (1973) 43–133;
(b) K.I. Pashkevich, V.I. Saloutin, I.Ya. Postovskii, Russ. Chem. Rev. 50 (1981) 180–195 (Usp. Khim. 50 (1981) 325–354);
(c) K.I. Pashkevich, V.I. Saloutin, Russ. Chem. Rev. 54 (1985) 1185–1200 (Usp. Khim. 54 (1985) 1997–2026);
(d) J. Emsley, The composition, structure and hydrogen bonding of the β-diketones, in: Structure and Bonding, vol. 57, Springer-Verlag, Berlin, 1984, pp. 147–191;
(e) K.C. Joshi, R. Joshi, J. Indian Chem. Soc. 78 (2001) 653–661.

[1] Copies of the data can be obtained free of charge via the Internet http://www.ccdc.cam.ac.uk, or on application to the director; CCDC; 12 Union Road, Cambridge CB2 1EZ, UK. Tel.: +44-1223-336-408; fax: +44-1223-336-033; e-mail: deposit@ccdc.cam.ac.uk.

[2] Selected examples (a) R.H. Groth, J. Org. Chem. 24 (1959) 1709–1715;
(b) S. Archer, C. Perianayagam, J. Med. Chem. 22 (1979) 306–309;
(c) J.-P. Bouillon, C. Ates, Z. Janousek, H.G. Viehe, Tetrahedron Lett. 34 (1993) 5075–5078;
(d) J.-P. Bouillon, V. Bouillon, C. Wynants, Z. Janousek, H.G. Viehe, Heterocycles 37 (1994) 915–932;
(e) K.A. Allen, R.H. Abeles, Biochemistry 28 (1989) 8466–8473;
(f) R.C.D. Brown, C.J.R. Bataille, G. Bruton, J.D. Hinks, N.A. Swain, J. Org. Chem. 66 (2001) 6719–6728.

[3] (a) D.V. Sevenard, O.G. Khomutov, M.I. Kodess, K.I. Pashkevich, I. Loop, E. Lork, G.-V. Röschenthaler, Can. J. Chem. 79 (2001) 183–194;
(b) K.I. Pashkevich, D.V. Sevenard, O.G. Khomutov, I.I. Vorontsov, Izv. Ros. AN, Ser. Khim. (2001) 643–646 (Russ. Chem. Bull. 50 (2001) 669–672).;
(c) D.V. Sevenard, O.G. Khomutov, M.I. Kodess, K.I. Pashkevich, I. Loop, E. Lork, G.-V. Röschenthaler, Aust. J. Chem. 54 (2001) 157–163 (and references sited therein);
(d) D.V. Sevenard, G.-V. Röschenthaler, Monatsh. Chem. 132 (2001) 911–918;
(e) D.V. Sevenard, E. Lork, K.I. Pashkevich, G.-V. Röschenthaler, Heteroatom Chem. 13 (2002) 97–107;
(f) D.V. Sevenard, O.G. Khomutov, K.I. Pashkevich, E. Lork, G.-V. Röschenthaler, Helv. Chim. Acta 85 (2002) 1960–1972.

[4] (a) F. Korte, K.H. Büchel, Angew. Chem. 71 (1959) 709–752;
(b) H. Wamhoff, F. Korte, Synthesis (1972) 151–175.

[5] S. Zhu, G. Xu, C. Qin, Q. Chu, Y. Xu, Monatsh. Chem. 130 (1999) 671–680.

[6] Selected examples (a) H. Toshima, Y. Furumoto, S. Inamura, A. Ichihara, Tetrahedron Lett. 37 (1996) 5707–5710;
(b) C. Jin, R.D. Ramirez, A.S. Gopalan, Tetrahedron Lett. 42 (2001) 4747–4750;
(c) H.-D. Gilsing, J. Angerer, D. Prescher, Monatsh. Chem. 133 (2002) 1147–1155.

[7] R.J. Linderman, E.A. Jamois, J. Fluorine Chem. 53 (1991) 79–91.

[8] G.M. Sheldrick, SHELXL-97, Program for Crystal Structure Refinement, University of Göttingen, 1997.