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Fluorinated ketene dithioacetals 6. Synthesis of α-trifluoromethyl-γ-lactams from bis(ethylsulfanyl)(tetrafluoroethylidene)methane

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Abstract

A method is proposed for the synthesis of α-trifluoromethyl-γ-lactams (3-trifluoromethyl pyrrolidin-2-ones) by reductive amination of a γ-keto-α-trifluoromethyl thiol ester. The latter is prepared in high yield from the perfluoroketene dithioacetal obtained from perfluoropropanal hydrate.

Keywords: Organofluorine; Trifluoromethyl; Ketenedithioacetal; γ-Lactam

1. Introduction

Perfluoroketene dithioacetals of the type **1** are versatile building blocks for the synthesis of fluorosubstituted polyfunctional compounds, due to the masked carboxylic function [1], and to the possibility of nucleophilic substitution of the vinylic fluorine [2–4].These perfluoroketenes equivalents may be easily prepared from perfluoroaldehyde hydrates or hemiacetals [1–5], compounds commercially available from C_2 to C_4. A different method consists in a thiophilic organolithium addition on an alkyl perfluorodithiocarboxylate [6]. We recently described an efficient three-step conversion of **1** into α-trifluoromethyl γ-lactone **3** via the γ-oxo intermediate **2** (Scheme 1, path A) [4]. We now report an extension of this chemistry to the synthesis of the corresponding α-trifluoromethyl-γ-lactams.

The strategy is based on the intermediate **2**, which required both reductive amination of the γ-keto group, and acidic releasing of the carboxyl function from the ketene dithioacetal moiety. A subsequent cyclocondensation might lead to the expected lactam. Owing to the acidic conditions required for hydrolysis, we have, in contrast to the lactone preparation, reversed the sequence according to: acid hydrolysis of **2**, then reductive amination. Hence, the key intermediate in the lactam preparation is the γ-oxo-α-trifluoromethyl thiol ester **4** (Scheme 1, path B).

The thiol ester **4** was obtained in almost quantitative yield by hydrolysis of **2** in a 10/1 trifluoroacetic acid–water refluxing mixture. In a qualitative experiment, we first checked that the nucleophilic attack did occur selectively on the ketone function (treatment of **4** by benzylamine in ether in the presence of molecular sieve gave the corresponding imine in high yield). Then our aim was to convert the γ-oxo intermediate **4**, in a *one-pot* reductive amination-cyclocondensation process, into the target lactam **5**.

Some attempts using primary amine and sodium cyanoborohydride [7] or borohydride exchange resin [8] were unsuccessful. On the other hand, the expected lactam was obtained with excellent yield using the borane–pyridine complex as an acid stable reducing reagent [9]. Reactions with aniline and benzylamine are depicted in Scheme 2. It is noteworthy that even if the borane complex was added before significant conversion of **4** into the imine (TLC monitoring), no trace of lactone was detected. The borane–pyridine complex in acetic acid is a highly chemoselective reducing system for our substrate.

The corresponding NH lactam **6** could have been prepared by hydrogenolysis of the *N*-benzyl analogue. However, we have investigated conditions for direct preparation of **6** using the reducing system ammonium acetate–sodium cyanoborohydride [7] (Scheme 3). The expected lactam **6** was obtained as the major product (56% yield), with a minor

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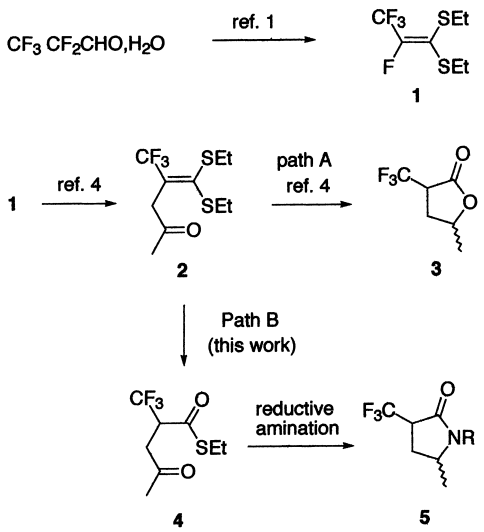
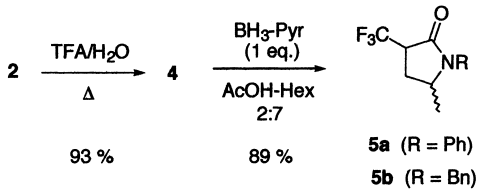


Scheme 1.

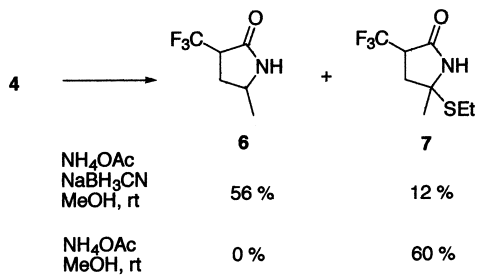


Scheme 2.

amount of the by-product **7** (12%). This by-product probably results from a cyclocondensation of the intermediate imine and a subsequent addition of ethanethiol or ethanethiolate. Indeed the yield of **7** increased to 60%, without any formation of **6**, when the reaction was performed in similar conditions, but without reducing reagent.

Although the reductive amination of γ-keto esters was applied in non-fluorinated series [10], the overall process described here from F-propanal hydrate is not trivial; the few examples of α-trifluoromethyl analogues reported so far were synthesized by different routes [11,12].

In summary, the enolate substitution on F-ketene dithioacetal **1** gives a key versatile building block **2** which can be converted either into α-trifluoromethyl-γ-lactone [4] or, via



Scheme 3.

the γ-keto thiolester **4**, into α-trifluoromethyl-γ-lactams (for a review on γ-lactams and their biological interest: [13]).

2. Experimental

Reaction and extraction were performed with commercial solvents used without further purification. Reactions under anhydrous conditions were performed under argon. All reactions were monitored by TLC (Merck F 254). Flash column chromatography separations were performed on silica gel Merck 9385 (40–63 μm). NMR spectra were recorded in $CDCl_3$ on a BRUCKER AC-250 spectrometer. Tetramethylsilane (^1H and ^{13}C) and $CFCl_3$ (^{19}F) were used as internal standards. Mass spectra were obtained on a Fison VG Autospec spectrometer in the electron impact mode (70 eV). Elemental analyses were performed with a Perkin-Elmer CHN 2400 apparatus.

Compounds **1** [1] and **2** [4] were prepared according to our previously reported procedures.

2.1. S-ethyl-4-oxo-2-(trifluoromethyl)pentanethioate 4

A solution of **2** (0.03 mol) in a 10/1 mixture of trifluoroacetic acid–water (20 ml) is refluxed until complete conversion of **2** (1.5–2 h). After cooling, water (20 ml) is added and product is extracted with dichloromethane. The organic phase is washed with aqueous $NaHCO_3$, water, and dried over $MgSO_4$. Solvent is removed under vacuum and compound **4** is distilled under reduced pressure.

Yield: 93%. bp 65°C/0.75 Torr. ^1H NMR δ 1.25 (t, $J = 7$ Hz, CH_2CH_3), 2.20 (s, $COCH_3$), 2.81 (dd, $J = 18$ and 3 Hz, H-3), 2.96 (q, $J = 7$ Hz, CH_2CH_3), 3.29 (dd, $J = 18$ and 10 Hz, H-3′), 3.8–4.0 (m, H-2); ^{13}C NMR δ 14.0 (CH_2CH_3), 27.1 (SCH_2), 29.5 ($COCH_3$), 39.7 (C-3), 51.7 (q, $J = 27$ Hz, C-2), 126.2 (q, $J = 280$ Hz, CF_3), 192.7 and 203.0 (CO); ^{19}F NMR δ −67.8 (d, $J = 7$ Hz, CF_3), MS *m/z* (%) 167 (M^+ 61, 91), 147 (100), 119 (34).

2.2. Reductive amination with primary amine: general procedure

The amine (2 mmol) is added to the thiol ester **4** dissolved in a mixture hexane (3.5 ml)-acetic acid (1 ml). After stirring 2 h at room temperature, BH_3-pyridine (0.2 ml, 2 mmol) is added slowly (over 10 min). The reaction mixture is stirred 2 h and 5 M HCl (3 ml), then water (10 ml) are added. Extraction with ether (2 × 15 ml), drying over $MgSO_4$, filtration and evaporation of ether give a mixture of diastereomers which is purified (and separated for **5**a), on silica gel (hexane-AcOEt 80/20).

2.3. N-phenyl-5-methyl-3-(trifluoromethyl)pyrrolidin-2-one: 5a

Yield: 89%. Two separated diastereomers 55/45. Major diastereomer: ^1H NMR δ 1.24 (d, $J = 6.5$ Hz, CH_3), 2.07

(ddd, $J = 13.5$, 9.5 and 5 Hz, H-4), 2.57 (ddd, $J = 13.5$, 7.0 and 7.0 Hz, H-4′), 3.43 (m, H-3), 4.36 (m, H-5), 7.3 (m, Ph); ^{13}C NMR δ 20.0 (CH_3), 27.6 (C-4), 45.6 (q, $J = 35$ Hz, C-3), 53.6 (C-5), 125.2 (q, $J = 279$ Hz, **C**F_3), 123.9, 126.4, 129.1 and 136.7 (Ph), 166.0 (CO); ^{19}F NMR δ −69.34.

MS *m/z* (%) 243 (M^+, 75), 228 (100), 208 (35), 119 (34); Anal. Calc. C 59.26, H 4.97, N 5.76; found C 58.76, H 4.64; N 5.68.

Minor diastereomer: ^{1}H NMR δ 1.24 (d, $J = 6.5$ Hz, CH_3), 2.07 (ddd, $J = 13.5$, 9.5 and 5.0 Hz, H-4), 2.57 (ddd, $J = 13.5$, 7.0 and 7.0 Hz, H-4′), 3.43 (m, H-3), 4.36 (m, H-5), 7.3 (m, Ph); ^{13}C NMR δ 20.5 (CH_3), 27.8 (C-4), 46.5 (q, $J = 35$ Hz, C-3), 52.7 (C-5), 124.8 (q, $J = 279$ Hz, **C**F_3), 123.9, 126.4, 129.1 and 136.7 (Ph), 163.3 (CO); ^{19}F NMR δ −69.40.

2.4. N-benzyl-5-methyl-3-(trifluoromethyl)pyrrolidin-2-one: **5***b*

Yield: 89%. Two non-separated diastereomers 55/45. Major diastereomer: ^{1}H NMR δ 1.19 (d, $J = 6.0$ Hz, CH_3), 1.90 (ddd, $J = 13.5$, 10.0 and 5.5 Hz, H-4), 2.60 (ddd, $J = 13.5$, 9.0 and 5.5 Hz, H-4′), 3.23 (m, H-3), 3.55 (m, H-5), 3.97 and 5.06 (2d, $J = 15.0$ Hz, C**H**$_2$Ph), 7.3 (m, Ph); ^{13}C NMR δ 19.2 (CH_3), 27.4 (C-4), 45.4 (q, $J = 28$ Hz, C-3), 50.5 (C-5), 74.8 (**C**H_2Ph), 125.1 (q, $J = 250$ Hz, **C**F_3), 127.4, 127.4, 127.7 and 128.5 (Ph), 166.8 (CO); ^{19}F NMR δ −69.56.

Minor diastereomer: ^{1}H NMR δ 1.23 (d, $J = 6.0$ Hz, CH_3), 1.73 (ddd, $J = 13.5$, 9.5 and 7.5 Hz, H-4), 2.47 (ddd, $J = 13.5$, 9.5 and 7.0 Hz, H-4′), 3.29 (m, H-3), 3.47 (m, H-5), 4.08 and 4.95 (2 d, $J = 15.0$ Hz, C**H**$_2$Ph), 7.3 (m, Ph); ^{13}C NMR δ 19.6 (CH_3), 27.5 (C-4), 45.6 (q, $J = 35$ Hz, C-3), 50.3 (C-5), 74.8 (**C**H_2Ph), 124.8 (q, $J = 279$ Hz, **C**F_3), 123.9, 126.4, 129.1 and 136.7 (Ph), 167.0 (CO); ^{19}F NMR δ −69.40. MS *m/z* (%) 257 (M^+, 100), 172 (36), 166 (33), 146 (45), 105 (35).

2.5. 5-Methyl-3-(trifluoromethyl)pyrrolidin-2-one: **6**

A solution of the thiol ester **4** (1.14 g, 5 mmol), NH_4OAc (3.85 g, 50 mmol) and $NaBH_3CN$ (0.95 g, 15 mmol), in absolute methanol (25 ml), is stirred at room temperature for 24 h. Concentrated HCl is added until pH < 2. After concentration in vacuo, water (5 ml) is added and the crude mixture is extracted with ether (3 × 25 ml). The aqueous phase is neutralized (solid KOH, pH > 10), saturated with NaCl and extracted with ether (5 × 10 ml). After standing over $MgSO_4$ and removal of the solvent under vacuum, the products are separated on silica gel (hexane–AcOEt 75/25). Lactam **6** is isolated as a single diastereomer (single spin system in ^{1}H, ^{13}C and ^{19}F NMR) along with a minor amount of the by-product **7** (12%).

Yield of **6**: 56%. ^{1}H NMR δ 1.28 (d, $J = 6.5$ Hz, CH_3), 1.79 (ddd, $J = 13.5$, 10.0 and 8.0 Hz, H-4), 2.47 (ddd, $J = 13.5$, 9.5 and 7.0 Hz, H-4′), 3.21 (m, H-3), 3.78 (m, H-5); ^{13}C NMR δ 21.9 (CH_3), 30.1 (C-4), 46.3 (q, $J = 32$ Hz, C-3), 47.6 (C-5), 124.6 (q, $J = 272$ Hz, **C**$F_3$170.2 (CO); ^{19}F NMR δ −69.30 (d, $J = 8$ Hz). MS *m/z* (%) 168 ($M^+ + 1$, 100), 167 (M^+, 6), 152 (59), 132 (23).

2.6. 5-Ethylsulfanyl-5-methyl-3-(trifluoromethyl)pyrrolidin-2-one: **7**

A similar procedure, but without $NaBH_3CN$, gave the product **7** (60%), which seems to be a single isomer according to the NMR spectra, and which exhibits a limited stability.

^{1}H NMR δ 1.26 (t, $J = 7.5$ Hz, C**H**$_3$CH$_2$), 1.72 (s, CH_3), 2.28 (dd, $J = 9.5$ and 13.5 Hz, H-4), 2.60 (m, SC**H**$_2$ + H-4′), 3.50 (m, H-3), 7,80 (s, N**H**); ^{13}C NMR δ 14.2, 23.4, 29.6, 37.4, 46.4 (q, $J = 29$ Hz, C-3), 64.8, 124.6 (q, $J = 277$ Hz, **C**F_3), 169.3; ^{19}F NMR δ −69.76.

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