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An efficient synthesis of 3-methyl-3-trifluoromethyl azetidin-2-one

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Abstract

The Curtius rearrangement has been used as a key step for the transformation of the unsaturated ester **1** to the 3-trifluoromethylated 2-azetidinone **7** via a six-step synthesis.

Keywords: Trifluoromethyl; Azetidinone; β-Lactam; Curtius rearrangement; Antibiotics

1. Introduction

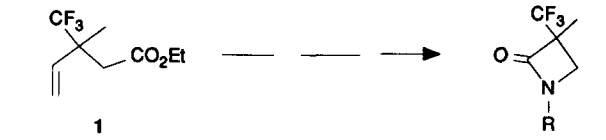
The great number of publications in the field of β-lactam chemistry indicates a current need for more potent β-lactam antibiotics as well as β-lactamase and elastase inhibitors [1]. The introduction of one or more fluorine atoms in natural β-lactams such as penicillin, carbapenam, etc. [2] is an interesting way to fulfil this purpose, since the replacement of hydrogen by fluorine may have a significant effect on the activity of biological molecules [3]. The presence of an electron-withdrawing trifluoromethyl substituent in the α position to the carbonyl group should increase the polarity of the latter, and consequently the reactivity of the β-lactam ring towards enzymatic ring-opening.

2. Results and discussion

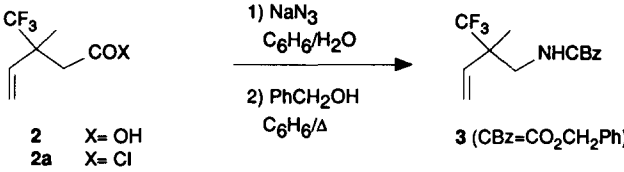
We have recently described the preparation of the ethyl 3-methyl-3-trifluoromethyl-4-pentenoate (**1**) [4], and it appeared to us that it could be used as an intermediate for the synthesis of such a fluorinated β-lactam (Scheme 1).

This transformation implies the removal of two carbon atoms, one at each end of the molecule. Given that the double bond could undergo an oxidative cleavage, the main problem was the ester group.

We first attempted to apply the radical decarboxylative halogenation method of Barton and coworkers [5].



Scheme 1.



Scheme 2.

Compound **1** was therefore saponified to give the acid **2**, and the latter activated as its acid chloride **2a**. Unfortunately, the *N*-hydroxypyridine-2-thione ester formed in situ from **2a** could not be transformed into the halogenated derivative, despite variations in the experimental conditions (solvent and temperature). Only the usual side-product, a pyridyl sulphide, was identified as the main product.

We then turned our attention to the use of the Curtius method [6]. With this aim in mind, **2a** was treated in dry benzene with an excess of sodium azide at 0 °C under phase-transfer conditions [7] to give the corresponding acyl azide. The latter, after careful drying over magnesium sulfphate, was heated under reflux overnight in the presence of benzyl alcohol to afford the benzyl carbamate **3** in 60% overall yield from the acid **2** (Scheme 2).

We then tried to cleave the double bond in **3** in order to obtain either the ester **5** (O_3/MeOH/KOH)

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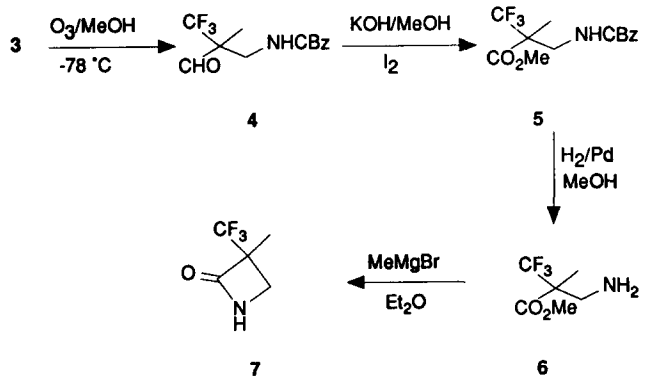

Scheme 3.

[8] or its corresponding acid ($AgNO_3$/NaOH) [9]. However, no satisfactory result was obtained via such direct transformation (low yield in the first case and a purification problem in the second); for this reason, we decided to proceed through the aldehyde intermediate. Aldehyde **4**, which is easily obtained by ozonolysis of **3** in methanol, was treated with iodine in methanolic potassium hydroxide solution [10] to furnish the ester **5** in 68% yield. Deprotection of the amino group was performed under the usual conditions (Pd/C in methanol) to give the amino ester **6** which was cyclized using methyl magnesium bromide in ether [11] to afford the azetidinone **7** in 51% yield (Scheme 3).

It should be pointed out that compound **7** exhibits an IR frequency ($\nu_{C=O}$) at 1770 cm^{-1}, which is a promising value for it may be regarded as a good criterion of the β-lactam ring reactivity [12]. From a synthetic point of view, this monocyclic *N*-unsubstituted β-lactam offers interesting opportunities for the preparation of 3-trifluoromethylated norcardicin and monobactam derivatives, which have a powerful activity against Gram negative micro-organisms [13].

3. Experimental details

IR spectra were recorded on a Perkin-Elmer 1420 spectrometer. NMR spectra were taken in $CDCl_3$ on a Bruker AC-200 E spectrometer. Chemical shifts are expressed in ppm from internal TMS (^1H and ^{13}C) and $CFCl_3$ (^{19}F). Preparative chromatography was performed on a silica gel column (Merck 70–230 mesh). Analytical GC was performed on a Shimadzu GC-14A equipped with a 25 m SE30 column. Bulb-to-bulb distillations were performed on a Büchi GKR-50 Kugelrohr apparatus. Ozonolysis was performed using an ozone generator (Fisher, model 502).

3.1. 3-Methyl-3-trifluoromethyl-4-pentenoic acid (2)

A solution of the ester **1** (6 g, 28.5 mmol) in EtOH (120 ml) and H_2O (30 ml) containing KOH (6.4 g, 114 mmol) was refluxed for 6 h. After cooling, the solvent was removed under vacuum and H_2O (50 ml) was added. The aqueous layer was washed with Et_2O, acidified with 10% HCl and extracted with $CHCl_3$ (2×50 ml). The organic layer was dried over $MgSO_4$, filtered and the solvent evaporated under reduced pressure to afford the crude material which was purified by distillation (Kugelrohr) to give the acid **2** as a colourless oil (4.7 g, 90%), b.p. 150 °C/13 mmHg. (Analysis: Found: C, 46.00; H, 5.05%. $C_7H_9F_3O_2$ requires: C, 46.16; H, 4.97%.) IR (CCl_4) ν_{max} (cm^{-1}): 1710. ^1H NMR δ: 1.42 (s, 3H); 2.64 (AB system, 2H, J=14.3 Hz); 5.27–5.38 (m, 2H); 5.88 (dd, 1H, J=10.9, 17.4 Hz); 10–11 (br, 1H) ppm. ^{19}F NMR δ: −77 (s) ppm.

3.2. Benzyl 2-methyl-2-trifluoromethyl-3-butenylcarbamate (3)

A solution of the acid **2** (4 g, 22 mmol) in $SOCl_2$ (25 ml) and $CHCl_3$ (25 ml) was refluxed for 4 h. The solvent and the excess of $SOCl_2$ were evaporated under reduced pressure to give the acid chloride **2a**. The latter was dissolved in anhydrous benzene (50 ml) and cooled to 0 °C (ice bath). NaN_3 (2.86 g, 44 mmol) and $^nBu_4NBr$ (0.2 g, 0.6 mmol) dissolved in H_2O (20 ml) were added under stirring. The reaction mixture was stirred vigorously for 2 h. The organic phase was separated, washed with brine and dried thoroughly over $MgSO_4$. After filtration, benzyl alcohol (11 ml, 110 mmol) was added and the solution refluxed overnight. After cooling, benzene was evaporated and the residue distilled in a Kugelrohr apparatus to give the benzyl carbamate **3** (3.8 g, 60%), b.p. 170–180 °C/0.2 mmHg. (Analysis: Found: C, 58.71; H, 5.59; N, 4.92%. $C_{14}H_{16}F_3NO_2$ requires: C, 58.53; H, 5.60; N, 4.87%.) IR ($CHCl_3$) ν_{max} (cm^{-1}): 3415; 1710. ^1H NMR δ: 1.23 (s, 3H); 3.33–3.57 (AB part of ABX spectrum, 2H, J_{AB}=14.1 Hz); 4.8 (br, NH); 5.08 (s, 2H); 5.26–5.4 (m, 2H); 5.75–5.9 (dd, 1H, J=10.9, 17.4 Hz); 7.33 (s, 5H) ppm. ^{19}F NMR δ: −74.6 (s) ppm.

3.3. 2-Benzyloxycarbonylamino-2-methyl-2-trifluoromethylpropanaldehyde (4)

A solution of the unsaturated benzyl carbamate **3** (2 g, 6.96 mmol) in MeOH (40 ml) was treated with O_3 (2 g h^{-1}) at −78 °C until a slight blue colour persisted. The solution was degassed with N_2 and brought to 0 °C whereupon Me_2S (1.8 ml, 24.5 mmol) was added. The mixture was stirred at this temperature for 1 h. MeOH was evaporated under reduced pressure and the residue taken up in H_2O (50 ml) and extracted with Et_2O (80 ml). The ethereal layer was washed with brine and dried over $MgSO_4$. Filtration and removal of the solvent under vacuum gave a crude product which was distilled in a Kugelrohr apparatus to afford

the aldehyde **4** (1.82 g, 90%), b.p. 220 °C/0.2 mmHg. (Analysis: Found: C, 53.77; H, 4.95; N, 4.86%. $C_{13}H_{14}F_3NO_3$ requires: C, 53.98; H, 4.87; N, 4.84%.) IR ($CHCl_3$) ν_{max} (cm^{-1}): 3430; 1715. ^1H NMR δ: 1.30 (s, 3H); 3.50–3.76 (AB part of ABX spectrum, 2H, $J_{AB}=14.6$ Hz); 5.07 (s, 3H, CH_2 and NH); 7.32 (s, 5H); 9.63 (s, 1H) ppm. ^{19}F NMR δ: −70.9 (s) ppm.

3.4. Methyl-3-benzyloxycarbonylamino-2-methyl-2-trifluoromethylpropanoate (5)

A solution of 4% (w/v) KOH in MeOH was added dropwise to a solution of the aldehyde **5** (1.8 g, 6.2 mmol) and I_2 (1.73 g, 6.82 mmol) in MeOH (30 ml) at 40–45 °C until no free I_2 remained (the reaction could be monitored by capillary GC). The solution was diluted with H_2O (80 ml) and extracted with Et_2O (80 ml). The ethereal extract was washed with an aqueous 5% $Na_2S_2O_3$ solution, brine and dried over $MgSO_4$. After filtration, the solvent was evaporated and the crude product distilled using a Kugelrohr apparatus to give the ester **6** as an oil (1.35 g, 68%), b.p. 210 °C/0.2 mmHg. (Analysis: Found: C, 52.47; H, 5.15; N, 4.38%. $C_{14}H_{16}F_3NO_4$ requires: C, 52.66; H, 5.04; N, 4.38%.) IR ($CHCl_3$) ν_{max} (cm^{-1}): 3430; 1715. ^1H NMR δ: 1.41 (s, 3H); 3.66 (d, 2H, $J=6.8$ Hz); 3.75 (s, 3H); 5.08 (s, 3H, CH_2 and NH); 7.33 (s, 5H) ppm. ^{19}F NMR δ: −71.6 (s) ppm.

3.5. Methyl 3-amino-2-methyl-2-trifluoromethyl-propanoate (6)

Compound **5** (1 g, 3.13 mmol) in MeOH (30 ml) was catalytically hydrogenated over 10% Pd–C for 12 h (the completion of the reaction was monitored by capillary GC). The mixture was filtered through Celite, the filtrate evaporated and the residue distilled using a Kugelrohr apparatus to give the amine **6** as a colourless liquid (0.49 g, 84%), b.p. 95 °C/13 mmHg. (Analysis: Found: C, 38.68; H, 5.26; N, 7.49%. $C_6H_{10}F_3NO_2$ requires: C, 38.92; H, 5.43; N, 7.56%.) IR ($CHCl_3$) ν_{max} (cm^{-1}): 1725. ^1H NMR δ: 1.24 (s, 2H); 1.35 (s, 3H); 3.05 (AB system, 2H, $J=13.4$ Hz); 3.75 (s, 3H) ppm. ^{19}F NMR δ: −71.2 (s) ppm.

3.6. 3-Methyl-3-trifluoromethyl-2-azetidinone (7)

To a stirred solution of aminoester **6** (0.285 g, 1.54 mmol) in dry ether (30 ml) under argon, was added dropwise via a syringe through a septum a solution of CH_3MgBr in Et_2O (3 M, 1.28 ml, 3.84 mmol). The mixture was stirred for 3 h at room temperature. Saturated aqueous NH_4Cl was added, followed by H_2O (30 ml). The organic phase was separated, washed with brine, dried over $MgSO_4$ and filtered. After removal of the solvent, the crude product was purified by successive column chromatography on silica gel using hexane/AcOEt (55:45) and distillation in a Kugelrohr apparatus affording the azetidinone **7** as a low melting solid (0.12 g, 51%), b.p. 150 °C/13 mmHg. (Analysis: Found: C, 38.94; H, 4.21; N, 8.97%. $C_5H_6F_3NO$ requires: C, 39.22; H, 3.94; N, 9.14%.) IR ($CHCl_3$) ν_{max} (cm^{-1}): 3400; 1770. ^1H NMR δ: 1.55 (s, 3H); 3.33 (AB system, 2H, $J=6.3$ Hz); 6.33 (br, 1H, NH) ppm. ^{19}F NMR δ: −74.6 (s) ppm. ^{13}C NMR δ: 13.63 (q, Me, $^3J=2.4$ Hz); 44.6 (q, C-4, $^3J=2.7$ Hz); 59.1 (q, C-3, $^2J=28.8$ Hz); 125 (q, CF_3, $^1J=278.7$ Hz); 165.4 (q, C-2, $^3J=3.4$ Hz) ppm.

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