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3-Trifluoromethyl- and 3-difluoromethyl-thalidomides

Sergej N. Osipov,[a] Pavel Tsouker,[b] Lothar Hennig[b] and Klaus Burger[b,*]

[a]*A.N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, Vavilov street 28, GSP-1, RUS 117813 Moscow, Russian Federation*
[b]*Department of Organic Chemistry, University of Leipzig, Johannisallee 29, D-04103 Leipzig, Germany*

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Dedicated to Professor Dr. H.-D. Jakubke on the occasion of his 70th birthday

Abstract—Syntheses of racemic 3-trifluoromethyl- and 3-difluoromethyl-thalidomide starting from 2-(*tert*-butyloxycarbonylimino)-3,3,3-trifluoropropionate or -3,3-difluoropropionate as fluorine-containing building blocks are described.

1. Introduction

Thalidomide (**1**) [2-(2,6-dioxo-3-piperidyl)isoindoline-1,3-dione], a sedativum without the side effects of barbiturates, was introduced into the market by Chemie Grünenthal in 1956 with the trade name Contergan®.[1–3] Thalidomide was withdrawn from the market in 1962,[4] when its use was linked to severe birth defects.[3,5] Unexpected teratogenic side effects produced one of the most notorious medicinal disasters of modern medicinal history.

However, the unique and broad physiological properties discovered during recent years, prompted a reevaluation of its therapeutic potential.[6] Thus, thalidomide is currently applied for treatment of painful inflammations associated with leprosy (recently approved in the USA),[7] rheumatoid arthritis[8] and graft-versus host disease.[9] Furthermore, promising results in the case of treatment of AIDS,[10] Crohn's disease,[11] Behcet's syndrom[12] and cancer related pathologic angiogenesis[13] have been disclosed. Recently, thalidomide was effective in the treatment of high-risk, refractory multiple myeloma.[14]

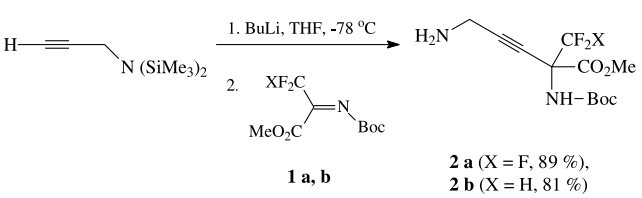
Overproduction of TNF-α is associated with these pathological disorders.[15] The effectivity of thalidomide in these diseases has mostly been attributed to its specific inhibitory activity on TNF-α production. Therefore, based on thalidomide as a lead structure several analogues have been developed.[16] We now report on concise syntheses of racemic 3-trifluoromethyl- and 3-difluoromethyl-thalidomides.

2. Results and discussion

Introduction of fluorine and/or fluoroalkyl groups into strategical positions of target molecules may considerably modify chemical properties, biological activity and selectivity.[17] Numerous fluoro- and fluoroalkyl-substituted pharmaceuticals, agrochemicals, dyes and polymers have been successfully commercialized.[18] The number of patents concerning fluorinated compounds shows growing tendency. Thus, one can anticipate that fluoro-modified compounds will continue to play a significant role in medicinal and agricultural chemistry as well as in material science.[19]

In an effort to improve the biological profile of thalidomide we synthesized new fluoroanalogues of thalidomide by replacing C(3)–H by a trifluoromethyl and a difluoromethyl group, respectively. Key step of the synthesis is the construction of the methyl 2-fluoroalkyl-2-(*tert*-butoxycarbonylamino)-5-aminopent-3-inoates **2**, which we already used as intermediates for the synthesis of α-trifluoromethyl and α-difluoromethyl ornithine[20] and arginine.[21] Compounds **2a** and **2b** are readily obtained in very good yields via addition of bis(trimethylsilyl)propargylamine to the highly electrophilic Boc-protected imines **1**[22] (Scheme 1).

The unsaturated ornithine derivatives **2a**,**b** obtained were subjected to catalytic hydrogenation to give the



Scheme 1.

Keywords: 2-Fluoroalkyl-2,5-diaminopent-3-inoates; 3-Fluoroalkyl-3-aminopiperidin-2-ones; 3-Fluoroalkyl-3-aminopiperidin-2,6-diones.
* Corresponding author. Fax: +49-341-9736599;
e-mail address: burger@organik.chemie.uni-leipzig.de

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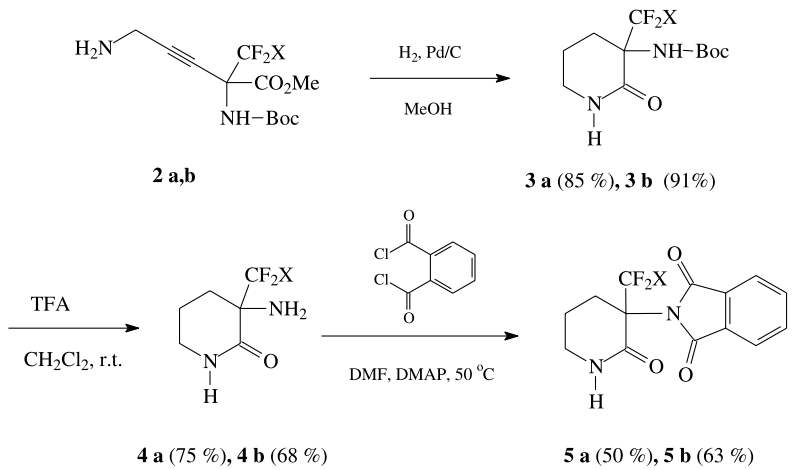
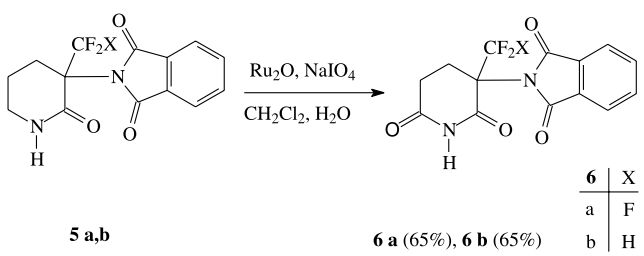


Scheme 2.

Boc-protected 2-fluoroalkyl-ornithine methylesters which spontaneously cyclize to give the Boc-protected 3-amino-3-fluoroalkylpiperidin-2-ones (**3**).[23] Compounds **3** are formed as racemic mixtures. Then the Boc group of **3** was removed on treatment with TFA at room temperature to furnish **4**. The amino group was diacylated with *o*-phthaloyl dichloride in the presence of DMAP (**4→5**)[24] (Scheme 2).

Finally, oxidation of **5** was performed using a catalytic amount of RuO_2 in the presence of excess sodium metaperiodate in a two phase system[25] to give the fluoroalkyl-substituted thalidomides **6a** and **6b** in 65 and 53% yield, respectively (Scheme 3).



Scheme 3.

Biological tests of compounds **5a**,**b** and **6a**,**b** are under current investigation.

3. Experimental

3.1. General

Melting points were determined on a Boetius heating table. IR spectra were obtained with a FTIR spectrometer (Genesis ATI Mattson/Unicam). ^{1}H NMR spectra were recorded with VARIAN Gemini 2000 spectrometers at 200 and 300 MHz. Chemical shifts were reported in ppm relative to tetramethylsilane (TMS, δ=0 ppm); *J* values are given in Hertz (Hz). ^{13}C NMR spectroscopy was performed at 50 and 75 MHz. ^{19}F spectra were recorded at 188 and 282 MHz with trifluoroacetic acid (TFA, δ=0 ppm) as external standard. HRMS spectra were performed at ESI-Mass Spectrometer: 7 T, Bruker Daltronics APEX II ESI-FT-ICR-MS in acetone/methanol solution; ESI ionisation and positive ion detection. For flash chromatography, silica gel (32–63 μm) was used with solvent systems given in text. Organic solvents were dried and distilled prior to use.

3.1.1. 3-Trifluoromethyl-3-(*tert*-butoxycarbonylamino)-piperidin-2-one (3a). A mixture of **2a**[21,22] (4.00 g, 12.9 mmol) and 10% Pd/C (0.80 g) in methanol (70 mL) was stirred under an atmosphere of hydrogen for 48 h. The catalyst was filtered off, and the filtrate was concentrated under reduced pressure. The remaining solid was washed with a hot mixture of ethyl acetate/hexanes (1:10), to give **3a** (3.09 g, 85%). The product was purified by column chromatography (eluent: ethyl acetate/hexanes, 1:1); mp 136 °C; IR (KBr): ν=3295, 3264, 1684, 1172 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ=1.48 (s, 9H, $OCMe_3$), 1.98 (m, 2H, CH_2), 2.56 (m, 1H, CH_2), 2.73 (m, 1H, CH_2), 3.45 (m, 2H, NCH_2), 5.63 (s, 1H, NH), 6.28 (s br, 1H, NH); ^{13}C NMR ($CDCl_3$): δ=19.18 (CH_2), 27.39 (CH_2), 28.47 (3×CH_3), 43.36 (NCH_2), 60.93 (q, $^2J_{CF}$=27.5 Hz, *C*CF_3), 81.03 (O*C*Me_3), 125.35 (d, $^1J_{CF}$=287.9 Hz, CF_3), 154.31 (C=O), 166.20 (C=O); ^{19}F NMR ($CDCl_3$): δ=5.03 (s, 3F, CF_3); HRMS $[M+Na]^+$. Found: *m*/*z*=305.10816; $C_{11}H_{17}F_3N_2NaO_3$ requires *m*/*z*=305.10835.

3.1.2. 3-Difluoromethyl-3-(*tert*-butoxycarbonylamino)-piperidin-2-one (3b). Applying the above protocol **2b**[21,22] (3.30 g, 11.3 mmol) was converted into **3b** (2.71 g, 91%); mp 158 °C; IR (KBr): ν=3389, 3203, 1662, 1063 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ=1.41 (s, 9H, $OCMe_3$), 1.95 (m, 2H, CH_2), 2.28 (m, 1H, CH_2), 2.42 (m, 1H, CH_2), 3.32 (m, 1H, NCH_2). 3.47 (m, 1H, NCH_2), 5.26 (s, 1H, NH), 6.04 (t, 1H, $^2J_{HF}$=57.1 Hz, CF_2H), 6.35 (s br, 1H, NH). ^{13}C NMR ($CDCl_3$): δ=26.98 (CH_2), 28.39 (CH_2), 42.17 (NCH_2), 59.50 (t, $^2J_{CF}$=24.0 Hz, *C*CF_2H), 80.79 (O*C*Me_3), 116.42 (t, $^1J_{CF}$=249.5 Hz, CF_2H), 154.39 (C=O), 167.88 (d, $^3J_{CF}$=5.3 Hz, C=O); ^{19}F NMR ($CDCl_3$): δ=−56.50 (dd_{ABX}, 1F, $^2J_{FF}$=282.3 Hz, $^2J_{FH}$=57.1 Hz, CF_2H); −48.31 (dd_{ABX}, 1F, $^2J_{FF}$=282.3 Hz, $^2J_{FH}$=57.1 Hz, CF_2H); HRMS $[M+Na]^+$. Found *m*/*z*=287.11777; $C_{11}H_{18}F_2NaN_2O_3$ requires *m*/*z*=287.11777.

3.1.3. 3-Trifluoromethyl-3-aminopiperidin-2-one (4a). TFA (10 mL) was added to a solution of **3a** (3.00 g, 10.6 mmol) in CH_2Cl_2 (50 mL) at 0 °C. The mixture was stirred for 6 h at rt. The volatiles were removed under

reduced pressure. The remaining solid was dissolved in ethyl acetate (100 mL), then the solution was treated with a saturated solution of $NaHCO_3$ (50 mL). The organic phase was separated, the aqueous layer was extracted with ethyl acetate (2×30 mL). The combined organic phase was dried over $MgSO_4$ and evaporated in vacuo to give **4a** (1.45 g, 75%); mp 115 °C; IR (KBr): ν=3394, 3319, 1671, 1141 cm^{-1}; ^1H NMR ($CDCl_3$): δ=1.95 (m, 5H, CH_2, NH_2), 2.25 (m, 1H, CH_2), 3.41 (m, 2H, NCH_2), 6.37 (s br, 1H, NH); ^{13}C NMR ($CDCl_3$): δ=18.75 (CH_2), 29.66 (d, $^3J_{CF}$=1.7 Hz, CH_2), 42.40 (NCH_2), 58.92 (q, $^2J_{CF}$=26.3 Hz, CCF_3), 125.45 (q, $^1J_{CF}$=286.3 Hz, CF_3), 169.00 (C=O); ^{19}F NMR ($CDCl_3$): δ=−0.15 (s, 3F, CF_3); MS: HRMS $[2M+Na]^+$. Found m/z=387.12210; $C_{12}H_{18}F_6NaN_4O_2$ requires m/z=387.12262.

3.1.4. 3-Difluoromethyl-3-aminopiperidin-2-one (4b). Applying the above protocol **3b** (1.20 g, 4.45 mmol) was transformed into **4b** (0.51 g, 68%); mp 147 °C; IR (KBr): ν=3389, 3204, 1665, 1063 cm^{-1}; ^1H NMR ($CDCl_3$): δ=1.98 (m, 6H, 2×CH_2, NH_2), 3.39 (m, 2H, NCH_2), 6.00 (t, 1H, $^2J_{HF}$=57.8 Hz, CF_2H), 6.57 (s br, 1H, NH); ^{13}C NMR ($CDCl_3$): δ=18.90 (CH_2), 26.52 (d, $^3J_{CF}$=4.5 Hz, CH_2), 42.55 (NCH_2), 58.14 (t, $^2J_{CF}$=22.6 Hz, CCF_2H), 117.85 (t, $^1J_{CF}$=271.5 Hz, CF_2H), 171.28 (d, $^3J_{CF}$=7.4 Hz, C=O); ^{19}F NMR ($CDCl_3$): δ=−62.85 (dd $_{ABX}$, 1F, $^2J_{FF}$=277.8 Hz, $^2J_{FH}$=57.8 Hz, CF_2H); −45.81 ppm (dd_{ABX}, 1F, $^2J_{FF}$=277.8 Hz, $^2J_{FH}$=57.8 Hz, CF_2H). HRMS $[2M+Na]^+$. Found m/z=351.14097; $C_{12}H_{20}F_4N_4NaO_2$ requires m/z=351.14146.

3.1.5. 3-Trifluoromethyl-3-(phthalimido)piperidin-2-one (5a). To a solution of **4a** (0.20 g, 1.1 mmol) and DMAP (0.27 g, 2.2 mmol) in $CHCl_3$ (50 mL) was added at 0 °C under argon a solution of *o*-phthaloyl dichloride (0.24 g, 1.18 mmol) in $CHCl_3$ (10 mL). The temperature was allowed to rise to rt, then after refluxing for 72 h, the mixture was washed with 1 N HCl (50 mL), then the organic phase was dried with $MgSO_4$ and concentrated in vacuo. The crude phthalimido derivative was purified by column chromatography on silica gel (eluent: ethyl acetate/hexanes, 1:1) to afford analytically pure **5a** (0.17 g, 50%); mp 203 °C; IR (KBr): ν=3402, 1733, 1339, 1334 cm^{-1}; ^1H NMR ($CDCl_3$): δ=1.88 (m, 1H, CH_2), 2.08 (m, 1H, CH_2), 2.41 (m, 1H, CH_2), 2.82 (m, 1H, CH_2), 3.44 (m, 2H, NCH_2), 6.37 (s, 1H, NH), 7.81 (m, 4H arom); ^{13}C NMR (d_6-acetone): δ=19.47 (CH_2), 28.64 (d, $^3J_{CF}$=1.8 Hz, CH_2), 41.61 (NCH_2), 65.54 (q, $^2J_{CF}$=28.0 Hz, CCF_3), 125.35 (q, $^1J_{CF}$=285.6 Hz, CF_3), 124.78, 132.80, 136.38 (C-arom), 164.14 (C=O), 168.25 (2×C=O); ^{19}F NMR ($CDCl_3$): δ=10.38 (s, 3F, CF_3); HRMS $[M+Na]^+$. Found m/z=335.06112; $C_{14}H_{11}F_3NaN_2O_3$ requires m/z=335.06140.

3.1.6. 3-Difluoromethyl-3-(phthalimido)piperidin-2-one (5b). Applying the above described protocol **4b** (0.24 g, 1.46 mmol) was transformed into **5b** (0.27 g, 63%); mp 214 °C; IR (KBr): ν=3377, 1719, 1376, 1066 cm^{-1}; ^1H NMR ($CDCl_3$): δ=1.98 (m, 1H, CH_2), 2.03 (m, 1H, CH_2), 2.30 (m, 1H, CH_2), 2.53 (m, 1H, CH_2), 3.40 (m, 2H, NCH_2), 6.46 (s, 1H, NH), 7.03 (t, 1H, $^1J_{HF}$=54.2 Hz, CF_2H), 7.76 (m, 4H arom); ^{13}C NMR ($CDCl_3$): δ=20.45 (CH_2), 27.95 (d, $^3J_{CF}$=3.6 Hz, CH_2), 42.13 (NCH_2), 63.77 (t, $^2J_{CF}$=25.3 Hz, CCF_2H), 114.36 (t, $^1J_{CF}$=247.3 Hz, CF_2H), 123.58, 131.62, 134.55 (C-arom), 165.93 (C=O), 167.87 (2×C=O); ^{19}F NMR ($CDCl_3$): δ=−44.9 (dd, 1F, $^2J_{FF}$=279.0 Hz, $^2J_{FF}$=54.9 Hz, CF_2H), −46.7 (dd, 1F, $^2J_{FF}$=279.0 Hz, $^2J_{FF}$=53.4 Hz, CF_2H); HRMS $[M+Na]^+$. Found m/z=317.07047; $C_{14}H_{12}F_2NaN_2O_3$ requires m/z=317.07082.

3.1.7. 3-Trifluoromethyl-3-(phthalimido)piperidin-2,6-dione (6a). A mixture of **5a** (0.10 g, 0.32 mmol) and 15 mg of ruthenium dioxide hydrate in CH_2Cl_2 (10 mL) was stirred at rt with 10 equiv. of 10% aqueous solution of $NaIO_4$ for 3 days. The layers were separated; the aqueous layer was extracted with CH_2Cl_2 (3×15 mL). To the combined organic layer methanol (0.1 mL) was added to destroy the excess of the oxidant. The mixture was filtered and the filtrate was washed with 5 mL of 10% aqueous $Na_2S_2O_3$. The solvent was removed under reduced pressure and the remaining solid was purified by column chromatography to give analytically pure **6a** (68 mg, 65%); mp 198 °C; IR (KBr): ν=3436, 3426, 3223, 1743, 1352, 1218 cm^{-1}; ^1H NMR ($CDCl_3$): δ=2.28 (m, 1H, CH_2), 2.65 (m, 1H, CH_2), 2.85 (m, 1H, CH_2), 3.71 (m, 1H, CH_2), 7.85 (m, 4H arom), 7.97 (s, 1H, NH); ^{13}C NMR (d_6-acetone): δ=22.74 (CH_2), 28.37 (CH_2), 64.01 (q, $^2J_{CF}$=28.5 Hz, CCF_3), 124.46, 125.05 (q, $^1J_{CF}$=285.7 Hz, CF_3), 132.00, 136.03 (C arom), 163.92 (C=O), 168.02 (2×C=O), 171.25 (C=O); ^{19}F NMR ($CDCl_3$): δ=3.43 (s, 3F, CF_3). HRMS $[2M+Na]^+$. Found m/z=675.09233; $C_{28}H_{18}F_6NaN_4O_8$ requires m/z=675.09265.

3.1.8. 3-Difluoromethyl-3-(phthalimido)piperidin-2,6-dione (6b). Applying the above protocol **5b** (25 mg, 0.294 mmol) was transformed into **6b** (14 mg, 65%); mp 209 °C; IR (KBr): ν=3434, 2363, 1722, 1375, 1067 cm^{-1}; ^1H NMR (d_6-acetone): δ=2.55 (m, 1H, CH_2), 2.81 (m, 2H, CH_2), 2.92 (m, 1H, CH_2), 7.04 (dd, $^2J_{HF}$=55.0 Hz, CF_2H), 7.95 (m, 4H, arom), 10.25 (s. br, 1H, NH); ^{13}C NMR (d_6-DMSO): δ=19.64 (CH_2), 27.78 (CH_2), 62.61 (t, $^2J_{CF}$=24.8 Hz, CCF_2H), 114.70 (t, $^1J_{CF}$=271.0 Hz, CF_2H), 123.84, 130.87, 135.00 (C arom), 164.01 (C=O), 167.34 (2×C=O), 171.98 (C=O); ^{19}F NMR (d_6-acetone): δ=−45.5 (dd, 1F, $^2J_{FH}$=55.0 Hz, $^2J_{FF}$=284.0 Hz, CF_2H), −49.3 (dd, 1F, $^2J_{FH}$=55.0 Hz, $^2J_{FF}$=284.0 Hz, CF_2H). HRMS $[M+Na]^+$. Found m/z=331.05046; $C_{14}H_{10}F_2NaN_2O_4$ requires 331.05008.

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