JOC*Note*

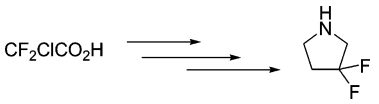
Practical Preparation of 3,3-Difluoropyrrolidine

Feng Xu,* Bryon Simmons, Joseph Armstrong III, and Jerry Murry

Department of Process Research, Merck Research Laboratories, Rahway, New Jersey 07065

feng_xu@merck.com

Received March 23, 2005



A practical and cost-effective synthesis of 3,3-difluoropyrrolidine is reported. The synthesis involves the isolation of two intermediates, which are prepared via two efficient through processes: (1) a Claisen rearrangement followed by a Ru(VIII)-catalyzed oxidation to prepare the 2,2-difluorosuccinic acid and (2) an efficient cyclization to form *N*-benzyl-3,3-difluoropyrrolidinone followed by BH_3·Me_2S reduction.

In recognition of the high electronegativity of fluorine, the strong C−F bond, and its unique capabilities such as increasing lipid solubility and inhibiting the enzymatic recognition process by C−F bonding, etc., it has become popular in the pharmaceutical industry to introduce/incorporate fluorine into an organic molecule in attempts to significantly improve the drug candidates' biological activities and metabolic stability.[1] Although the application of small building blocks containing *gem*-difluoro moieties continues to receive attention,[2] the preparation of these small molecules is not always efficient and practical. Specifically, the 3,3-difluoropyrrolidine moiety has recently been incorporated in pharmacologically active substances;[3] however, the literature synthesis[4] involves DAST fluorination of 3-pyrrolidinone, the latter of which is derived from the expensive chiral 3-hydroxypyrrolidine. Neither of these compounds are ideal for large-scale preparation in terms of cost and safety issues.[5] For our specific research interests, we required a cost-effective, safe synthesis of 3,3-difluoropyrrolidine that was amenable to large-scale preparation.

In this paper, we describe a practical synthesis of 3,3-difluoropyrrolidine (Scheme 1). This synthesis features two efficient through processes: (1) a Claisen rearrangement of **1** followed by a Ru(VIII)-catalyzed oxidation of **2** to prepare 2,2-difluorosuccinic acid (**3**) and (2) an efficient cyclization to form *N*-benzyl-3,3-difluoropyrrolidinone (**5**) followed by BH_3·Me_2S reduction. In comparison to the literature synthesis,[4] this chromatography-free route only requires isolating two crystalline solid intermediates **3** and **6**, employs inexpensive and readily available starting materials, and avoids using expensive and unstable fluorinating reagents such as DAST.

2,2-Difluorosuccinic acid[6] (**3**) is an expensive commercial product (Lancaster, $165/5 g) and is not available in large quantity. The literature-known preparation[7] of 2,2-difluorosuccinic acid is also not suitable for large-scale preparation and requires using 1,1-dichloroethene and 1-chloro-1,2,2-trifluoroethene gas. We envisioned that **3** is a suitable intermediate for the preparation of 3,3-difluoropyrrolidine. As reported, **2** could be prepared from ester **1**.[8]

To overcome the workup issues associated with the volatile intermediates (**1** and 2,2-difluoropent-4-enoic acid from hydrolysis of **2**, vide infra) and avoid isolation of **1** and **2**, we first developed an efficient through process to

(1) For recent reviews, see: (a) Böhm, H.-J.; Banner, D.; Bendels, S.; Kansy, M.; Kuhn, B.; Müller, K.; Obst-Sander, U.; Stahl, M. *ChemBioChem* **2004**, *5*, 637−643. (b) *Houben-Weyl Methods of Organic Chemistry*, workbench edition; Georg Thieme Verlag: Stuttgart, Germany, 2000; Vols. E10a−c. (c) Hiyama, T. *Organofluorine Compounds*; Springer: Berlin, Germany, 2000. (d) Banks, R. E.; Smart, B. E.; Tatlow, J. C. *Organofluorine Chemistry*: *Principles and Commercial Applications*; Plenum Press: New York, 1994.

(2) For recent examples, see: (a) Mae, M.; Hong, J. A.; Hammond, G. B.; Uneyama, K. *Tetrahedron Lett.* **2005**, *46*, 1787−1789. (b) Boydell, A. J.; Vinader, V.; Linclau, B. *Angew. Chem., Int. Ed.* **2004**, *43*, 5677−5679. (c) Suzuki, A.; Mae, M.; Amii, H.; Uneyama, K. *J. Org. Chem.* **2004**, *69*, 5132−5134. (d). Wu, Y.-Y.; Zhang, X.; Meng, W.-D.; Qing, F.-L. *Org. Lett.* **2004**, *6*, 3941−3944. (e) Uneyama, K.; Tanaka, H.; Kobayashi, S.; Shioyama, M.; Amii, H. *Org. Lett.* **2004**, *6*, 2733−2736. (f) Sekiguchi, T.; Sato, K.; Ishihara, T.; Konno, T.; Yamanaka, H. *Chem. Lett*. **2004**, *33*, 666−667.

(3) For recent examples, see: (a) Wilson, D. M.; Termin, A. P.; Neubert, T. D. PCT Int. Appl. WO2005014558, 2005. (b) Hennequin, L. F. A. PCT Int. Appl. WO2005013998, 2005. (c) Nelson, M. L.; Ohemeng, K.; Amoo, V.; Kim, O.; Abato, P.; Assefa, H.; Berniac, J.; Bhatia, B.; Bowser, T.; Chen, J.; Grier, M.; Hohos, A.; Honeyman, L.; Ismail, M. Y.; Mechiche, R.; Nihlawi, M.; Sizensky, E. PCT Int. Appl. WO2005009943, 2005. (d) Kadereit, D.; Defossa, E.; Schoenafinger, K.; Klabunde, T.; Herling, A. German patent DE10335092, 2005. (e) Chan, C. K.; Zhang, M.-Q.; Moinet, C.; Proulx, M.; Reddy, T. J.; Courchesne, M. PCT Int. Appl. WO2005007656, 2005. (f) Caldwell, C. G.; Chen, P.; He, J.; Parmee, E. R.; Leiting, B.; Marsilio, F.; Patel, R. A.; Wu, J. K.; Eiermann, G. J.; Petrov, A.; He, H.; Lyons, K. A.; Thornberry, N. A.; Weber, A. E. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1265−1268. (g) Duffy, J. L.; Mathvink, R. J.; Weber, A. E.; Xu, J. PCT Int. Appl. WO2004050022, 2004. (h) Hulin, B. PCT Int. Appl. WO2004046106, 2004. (i) Colandrea, V. J.; Edmondson, S. D.; Mathvink, R. J.; Mastracchio, A.; Weber, A. E.; Xu, J. PCT Int. Appl. WO2004043940, 2004. (j) Ancliff, R.; Eldred, C. D.; Fogden, Y. C.; Hancock, A. P.; Heightman, T. D.; Hobbs, H.; Hodgson, S. T.; Lindon, M. J.; Wilson, D. M. PCT Int. Appl. WO2004035556, 2004. (k) Churcher, I.; Harrison, T.; Kerrad, S.; Oakley, P. J.; Shaw, D. E.; Teall, M. R.; Williams, S. PCT Int. Appl. WO2004031137, 2004. (l) Shiraishi, M.; Hara, T.; Kusaka, M.; Kanzaki, N.; Yamamoto, S.; Miyawaki, T. PCT Int. Appl. WO2004016576, 2004. (m) Gonzales, J. E., III; Wilson, D. M.; Termin, A. P.; Grootenhuis, P. D. J.; Zhang, Y.; Petzoldt, B. J.; Fanning, L. T. D.; Neubert, T. D.; Tung, R. D.; Martinborough, E.; Zimmermann, N. PCT Int. Appl. WO2004078733, 2004.

(4) Giardina, G.; Dondio, G.; Grugni, M. *Synlett* **1995**, 55−57.

(5) For a recent review, see: Tozer, M. J.; Herpin, T. F. *Tetrahedron* **1996**, *52*, 8619−8683.

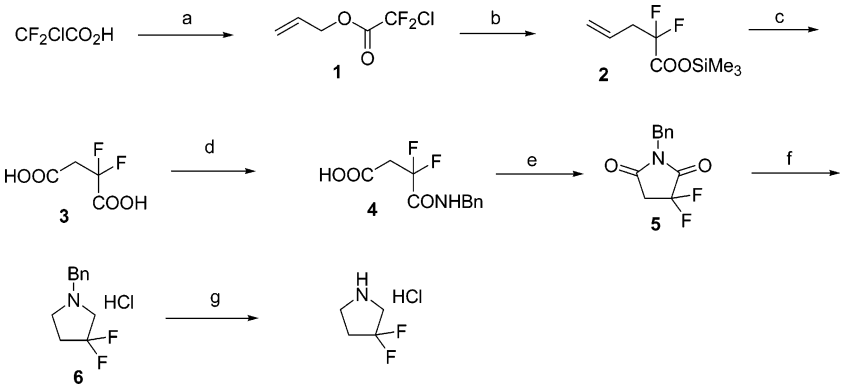
(6) ,2-Difluorosuccinic acid is also a useful building block. For recent applications, see: (a) Boros, E. E.; Samano, V.; Ray, J. A.; Thompson, J. B.; Jung, D. K.; Kaldor, I.; Koble, C. S.; Martin, M. T.; Styles, V. L.; Mook, R. A., Jr.; Feldman, P. L.; Savarese, J. J.; Belmont, M. R.; Bigham, E. C.; Boswell, G. E.; Hashim, M. A.; Patel, S. S.; Wisowaty, J. C.; Bowers, G. D.; Moseley, C. L.; Walsh, J. S.; Reese, M. J.; Rutkowske, R. D.; Sefler, A. M.; Spitzer, T. D. *J. Med. Chem*. **2003**, *46*, 2502−2515. (b) Takeda, S.; Kagawa, H.; Aratani, K.; Miki, S. Jpn. Kokai Tokkyo Koho JP2003201274, 2003. (c) Jorgensen, A. S.; Madsen, P. PCT Int. Appl. WO2002040446, 2002.

(7) (a) Akhtar, M.; Botting, N. P.; Cohen, M. A.; Gani, D. *Tetrahedron* **1987**, *43*, 5899−5908. (b) Rassch, M. S.; Castle, J. E. *Org. Synth*. **1962**, *42*, 44−47. (c) Raasch, M. S.; Miegel, R. E.; Castle, J. E. *J. Am. Chem. Soc*. **1959**, *81*, 2678−2680.

(8) Greuter, H.; Lang, R. W.; Romann, A. J. *Tetrahedron Lett*. **1988**, *29*, 3291−3294.

10.1021/jo050591h CCC: $30.25
Published on Web 06/24/2005

SCHEME 1. Synthesis of 3,3-Difluoropyrrolidine[a]



[a] Reagents and conditions: (a) allyl alcohol, hexane, reflux; (b) TMSCl, Zn dust, MeCN/hexane, 60 °C; (c) 2 mol % of $RuCl_3$, H_5IO_6, MeCN/water, 0−20 °C; (d) $(CF_3CO)_2O$, *i*-PrOAc; then, $BnNH_2$; (e) $SOCl_2$, *i*-PrOAc; (f) $BH_3{\cdot}Me_2S$, THF/toluene, 55 °C; (g) 5% Pd−C, H_2, 45 psi, MeOH.

prepare **3** in high yield. Thus, the ester **1** was efficiently prepared by condensation of 1.3 equiv of allyl alcohol and difluorochloroacetic acid in hexane. Without workup and isolation, the crude ester **1** (bp 110 °C) was directly treated with 1.5 equiv of Zn dust in the presence of 1.5 equiv of TMSCl in MeCN/hexane at 60 °C to afford **2**. The preactivation of Zn dust was not required. In contrast to the reported procedure,[8] the reaction was carried out at much lower reaction temperature to avoid using a sealed tube without diminishing the yield.

Without further purification and isolation, the filtered crude rearrangement product **2** was concentrated to remove hexane as well as the excess TMSCl before oxidation. Removal of hexane improved the efficiency of the subsequent oxidation reaction. Isolation of the corresponding hydrolyzed acid, which is formed as soon as **2** is subjected to aqueous conditions, is not recommended, since this volatile acid can be partially lost during concentration.

After optimization, the crude **2** was directly oxidized with 2 mol % $RuCl_3$ in the presence of H_5IO_6 in aqueous MeCN at 0−20 °C to give the desired diacid **3**. Controlling the reaction temperature below 20 °C and applying only 2 mol % Ru(III) proved to be crucial to achieve a clean oxidation.[9] The use of H_5IO_6 rather than $NaIO_4$ avoided formation of a heavy slurry during the reaction. The water-soluble diacid **3** was best extracted in the organic phase by a mixture of MeCN/*i*-PrOAc (2:3), which provided high efficiency for extraction and clean phase separation. However, part of the iodic acid was also extracted to the organic phase and had to be reduced. Otherwise, a brown to dark color would develop upon storage or during concentration. This was simply overcome by treating the organic phase with thiosulfate. Finally, **3** was isolated as an off-white solid from toluene in 72% overall yield over three steps.

After screening various conditions, the formation of amic acid **4** was best achieved via 2,2-difluorosuccinic anhydride. However, 2,2-difluorosuccinic anhydride is a volatile intermediate and can be easily lost during concentration. After several attempts, we were pleased to find out that formation of 2,2-difluorosuccinic anhydride can be completed cleanly by using 1.2 equiv of $(CF_3CO)_2O$ in *i*-PrOAc. Treatment of the above crude anhydride solution with only 1.5 equiv of $BnNH_2$ gave the desired amic acid **4** in 95% assay yield. In this case, the amide formation can be achieved even in the presence of excess CF_3CO_2H. Although other dehydrating reagents such as $(CF_3CO)_2O$, AcCl, Ac_2O, etc. could be used for formation of the imide **5**, the cyclization of the crude **4** in the presence of 2 equiv of $SOCl_2$ at 60 °C in *i*-PrOAc proceeded very smoothly and cleanly.

After aqueous work up, the crude **5** was reduced with $BH_3{\cdot}Me_2S$ in THF/toluene at 55 °C. The reaction was quenched with dry MeOH followed by HCl(g) to destroy the amine−boron complex as well as convert the volatile free base of **6** to the crystalline HCl salt. The HCl salt **6** was isolated from *i*-PrOH as a white solid in 84% yield over three steps.

Hydrogenolysis of the HCl salt of **6** at room temperature in the presence of 5% Pd−C in MeOH under 45 psi of H_2 gave the desired 3,3-difluoropyrrolidine. However, the use of a catalytic amount of acid such as HOAc or HCl improved the reaction rate and helped to achieve a full conversion. Therefore, in a typical experiment, 0.5 equiv of HOAc was used. Finally, 3,3-difluoropyrrolidine was isolated as its white crystalline HCl salt in 98% yield.

In summary, a practical synthesis of 3,3-difluoropyrrolidine was developed. The overall yield for this chromatography-free synthesis is 59%.

Experimental Section

2,2-Difluorosuccinic Acid (3). A 1-L three-necked round-bottom flask was equipped with a thermometer, a N_2 inlet, a Dean−Stark distillation head, and an overhead stirrer. Chlorodifluoroacetic acid (100 g, 0.766 mol), allyl alcohol (57.8 g, 0.996 mol), and hexane (100 mL) were added at ambient temperature. The reaction solution was heated to 70−75 °C (internal temperature). After 10 h, the reaction solution was allowed to cool to ambient temperature. MeCN (300 mL) and Zn dust (70.1 g, 1.072 mol) were added. TMSCl (600 mL, 1.149 mol) was added dropwise over 30 min. The slurry was stirred at 60 °C (internal temperature) for 3 days. Then, the slurry was cooled to 5 °C. The solid was removed through a Celite plug filtration. The wet cake was washed with cold (5−10 °C) dry MeCN (150 mL). The

(9) Oxidation by using bleach/cat. $RuCl_3$ was tried under various conditions with controlled pH at acidic, or basic, or near neutral conditions. However, the reaction profiles were not as clean as the use of $NaIO_4$ or H_5IO_6.

filtrate was concentrated to about 300 mL and diluted to 400 mL with MeCN.

Water (400 mL) followed by $RuCl_3$ (3.18 g, 15.3 mmol) were added to the above crude reaction solution at ambient temperature. The reaction mixture was then cooled to 5 °C. Periodic acid (627 g, 2.76 mol) was added portion-wise over 2−3 h while the reaction temperature was maintained below 20 °C with external cooling. By ^{19}F and ^1H NMR: >95% conversion was achieved. ^{19}F NMR (d_4-MeOH): 2,2-difluoropent-4-enoic acid, −107.7 ppm; 2,2-difluorosuccinic acid, −106.2 ppm. ^1H NMR (d_4-MeOH): 2,2-difluoropent-4-enoic acid, 2.82 (dt) ppm; 2,2-difluorosuccinic acid, 3.24 (t) ppm. Then, *i*-PrOH (10 mL) was added in one portion and the reaction mixture was aged at ambient temperature for 1 h. *i*-PrOAc (300 mL) was added and the organic phase was separated. The aqueous phase was extracted with a solution of *i*-PrOAc and MeCN (300 mL, *i*-PrOAc/MeCN = 3:2). The combined organic phase was mixed with 20% $Na_2S_2O_3$ (100 mL) until the organic phase turned light yellow. The reaction solution was acidified with concentrated HCl to pH 1 before phase separation. The aqueous phase was back-extracted with a solution of *i*-PrOAc and MeCN (200 mL, *i*-PrOAc/MeCN = 3:2). The combined organic phase was washed with brine (100 mL). Concentration in a vacuum and solvent switch to toluene (300 mL) gave the desired **3** as a slurry before filtration. The wet cake was washed with toluene (2 × 100 mL) to yield 85 g of **3**[7,10] as an off-white crystalline solid; 72% yield over three steps.

***N*-Benzyl-3,3-difluoropyrrolidine (6).** To a solution of 2,2-difluorosuccinic acid (50 g, 0.324 mol) in *i*-PrOAc (500 mL) was added trifluoroacetic anhydride (81.1 g, 0.389 mol) in one portion at ambient temperature. The reaction solution was stirred at 50 °C for 1 h. By ^{19}F NMR: >98% conversion.^{19}F NMR ($CDCl_3$): 2,2-difluorosunnic anhydride, −105.2 ppm. Then, the reaction solution was allowed to cool to 5 °C. $BnNH_2$ (52 g, 0.486 mol) was added dropwise while the reaction temperature was maintained below 20 °C. Then, the slurry was stirred at ambient temperature for 1 h. The reaction was quenched with water (200 mL) followed by saturated Na_2CO_3 to pH 8−9. The separated organic phase was discarded. The aqueous phase was acidified with 5 N HCl to pH 1 and extracted with *i*-PrOAc (2 × 500 mL). The organic phase was washed with 2 N HCl brine (200 mL). The azeotropically dried solution of the crude **4** in *i*-PrOAc (800 mL) was directly used in the next step without further purification. HPLC assay: 95% yield.

$SOCl_2$ (77 g, 0.648 mol) was added to the above solution at ambient temperature. The reaction solution was agitated at 50−55 °C for 4 h. The reaction was cooled to 0−5 °C. Half saturated brine (200 mL) was added slowly to quench the excess $SOCl_2$. The organic phase was washed with brine (200 mL) then brine and 5% Na_2CO_3 (about 300 mL) to pH 8−9. After a final brine wash (200 mL), the organic phase was azeotropically dried and the solvent switched to toluene (150 mL). Any insoluble solids were removed through filtration (Celite). THF (150 mL) and $BH_3{\cdot}Me_2S$ (2.0 M in THF, 648 mL) were added at ambient temperature. The reaction mixture was stirred at 55 °C for 3 h. A light slurry was formed during the reaction. The reaction was then cooled to 0−5 °C and quenched with dry MeOH (200 mL) dropwise followed by saturation with HCl (g). The reaction solution was stirred at 0−10 °C for 1 h and at 55 °C for 1 h. The solvents were switched in a vacuum to *i*-PrOH (about 250 mL), which allowed the product to crystallize as a white solid. The slurry was aged at 0 °C for 2 h before filtration. The wet cake was washed with cold 50% *i*-PrOH in *i*-PrOAc (2 × 100 mL) to yield 64 g of **6** as a white solid; 84% yield over three steps.

2,2-Difluorosunnic anhydride: ^1H NMR ($CDCl_3$, 400 MHz) δ 3.38 (t, J = 12.8 Hz, 2 H). ^{19}F NMR ($CDCl_3$, 376 MHz) δ −105.2.

4: ^1H NMR (d_4-MeOH, 400 MHz) δ 9.16 (s, br, 1 H), 7.35−7.22 (m, 5 H), 4.46 (m, 2 H), 3.27 (t, J = 14.4 Hz). ^{19}F NMR (d_4-MeOH, 376 MHz) δ −105.3. ^{13}C NMR (d_4-MeOH, 100 MHz) δ 168.3 (t, J = 8.0 Hz), 164.4 (t, J = 28.1 Hz), 137.6, 128.2, 127.1, 127.0, 115.5 (t, J = 252.2 Hz), 42.7, 38.7 (t, J = 26.5 Hz). Anal. Calcd for $C_{11}H_{11}F_2NO_3$: C, 54.32; H, 4.56; N, 5.76. Found: C, 54.82; H, 4.15; N, 5.80.

5: ^1H NMR ($CDCl_3$, 400 MHz) δ 7.40−7.32 (m, 5 H), 4.72 (s, 2 H), 3.14 (t, J = 12.6 Hz, 2 H). ^{19}F NMR ($CDCl_3$, 376 MHz) δ −107.44. ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.4 (t, J = 8.0 Hz), 166.0 (t, J = 31.2 Hz), 134.1, 128.9, 128.8, 128.5, 114.0 (t, J = 253.1 Hz), 42.9, 38.9 (t, J = 24.4 Hz). Anal. Calcd for $C_{11}H_9F_2NO_2$: C, 58.67; H, 4.03; F, 16.87; N, 6.22. Found: C, 58.56; H, 3.80; F, 17.16; N, 6.18.

6: ^1H NMR (d_4-MeOH, 400 MHz) δ 7.53 (m, 5 H), 4.05 (s, 2 H), 3.88 (t, J = 11.6 Hz, 2 H), 3.69 (s, br, 2 H), 2.9 (s, br, 2 H). ^{13}C NMR (d_6-DMSO, 100 MHz) δ 131.2, 130.9, 129.8, 129.1, 127,7 (t, J = 241.9 Hz), 57.8 (t, J = 34.4 Hz), 51.2, 33.9 (t, J = 24.8 Hz). Anal. Calcd for $C_{11}H_{14}ClF_2N$: C, 56.54; H, 6.04; N, 5.99. Found: C, 56.45; H, 6.05; N, 5.91.

3,3-Difluoropyrrolidine HCl Salt. A slurry of **6** (50 g, 0.213 mol), 5% Pd−C (contained 50% water, 5.0 g), and HOAc (6.5 g, 0.1065 mol) in MeOH (500 mL) was agitated under 45 psi of H_2 pressure at ambient temperature for 7 h. After filtration through a Celite plug to remove catalysts, the filtrate was solvent switched to toluene (200 mL) in a vacuum. The desired HCl salt was collected through filtration. The wet cake was washed with toluene (2 × 100 mL) to give 30.0 g of 3,3-difluoropyrrolidine HCl salt[4,10] as a white solid; 98% yield. ^1H NMR (d_4-MeOH, 400 MHz) δ 3.73 (m, 2 H), 3.62 (m, 2 H), 2.59 (m, 2 H). ^{19}F NMR (d_4-MeOH, 376 MHz) δ −100.9. ^{13}C NMR (d_4-MeOH, 100 MHz) δ 128.9 (t, J = 247. 5 Hz), 51.8 (t, J = 34.4 Hz), 45.3 (t, J = 4.0 Hz), 34.3 (t, J = 24.8 Hz).

Supporting Information Available: NMR spectra for compounds **3**−**6** and 3,3-difluoropyrrolidine. This material is available free of charge via the Internet at http://pubs.acs.org.

JO050591H

(10) The spectroscopic data and mp were in full agreement with the reported data.