A Short and Efficient Synthesis of 3-[2,2,2-Trifluoroethyl]hexahydro-2*H*-1,4-diazepin-2-one

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Abstract: A short, high yielding, five-step synthesis of the pharmaceutically interesting fluorinated heterocycle, 3-[2,2,2-trifluoroethyl]hexahydro-2*H*-1,4-diazepin-2-one, has been developed.

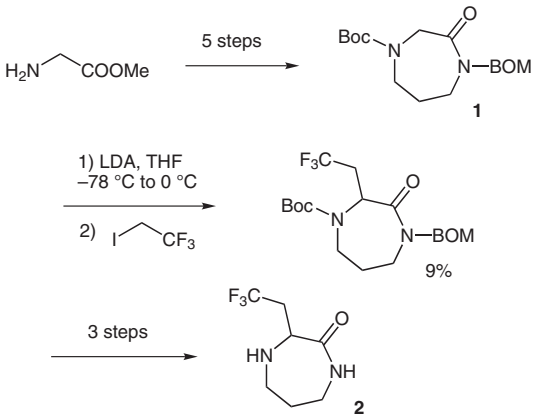
Key words: lactam, fluorine, alkylation, Michael addition, hydrogenation

Substituted hexahydro-1,4-diazepin-2-ones are compounds of pharmaceutical interest as dipeptidyl peptidase inhibitors for the treatment or prevention of diabetes.[1] These heterocyclic compounds have been prepared by a variety of methods including lactamizations,[2] intramolecular reductive amination,[3] or condensations of diamines with glyoxal derivatives.[3b,4] Introduction of substituents at C-3 by alkylation[5] or aldol condensation[6] has also been demonstrated.

We recently required an efficient and scalable synthesis of 3-[2,2,2-trifluoroethyl]hexahydro-2*H*-1,4-diazepin-2-one (**2**, Scheme 1), as part of an ongoing research program to identify dipeptidyl peptidase inhibitors. Compound **2** was first prepared[1] by alkylation of the fully protected hexahydro-2*H*-1,4-diazepin-2-one (**1**) with 2,2,2-trifluoro-1-iodoethane. The synthesis involved nine steps and afforded a very low yield of the desired heterocycle (Scheme 1). A racemic synthesis of **2** was acceptable since the stereogenic center of **2** can be easily epimerized to the desired configuration after preparing an appropriate derivative.[1d]

The 9% yield observed in the alkylation of **1** was attributed to decomposition of CF_3CH_2I in the presence of the highly basic enolate of **1**. Consistent with this observation, high yields were obtained when more stable electrophiles such as ethyl iodide or benzyl iodide, were used in the alkylation of **1**.[1a] Better yields were reported for the alkylation of less basic enolates, such as aminomalonate derivatives, with 2,2,2-trifluoroethyl triflate.[7d]

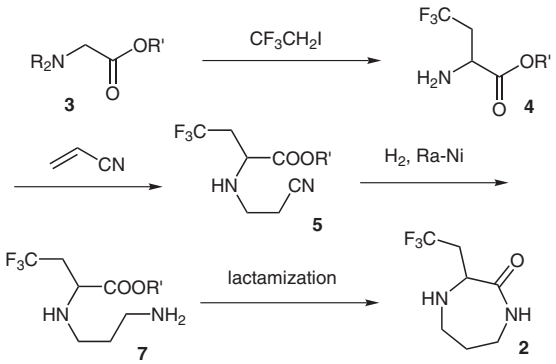
Our strategy for the synthesis of **2** was to install the trifluoroethyl side chain early in the synthesis by alkylation of a more acidic glycine equivalent (Scheme 2). Conjugate addition of the resulting amino acid **4** to acrylonitrile would afford nitrile **5**. The desired heterocycle **2** could then be accessed after nitrile reduction and lactamization.



Scheme 1 Early synthesis of **2**[1a]

Amino acid **4** was previously prepared in moderate yield through multi-step sequences.[7] An alternate, shorter approach, would involve alkylation of ethyl *N*-(diphenylmethylene)glycinate (**3**).[8] This compound is commercially available and would allow the preparation of **4** in an expedient manner. In contrast to the alkylation of **1**, the reaction of **3** with 2,2,2-trifluoro-1-iodoethane afforded the desired product **6** almost quantitatively. Hydrolysis of **6** with HCl afforded amino ester **4** in 90% overall yield after crystallization as its hydrochloride salt (Scheme 3).

Conjugate addition of amino ester **4** to acrylonitrile was examined next. No reaction was observed in aprotic solvents and reactions performed in alcoholic solvents resulted in preferential addition of the solvent to acrylonitrile.



Scheme 2 Proposed synthesis of **2** (compounds **2**–**5** and **7** are depicted with general structures; specific structures are shown in Schemes 3–5)

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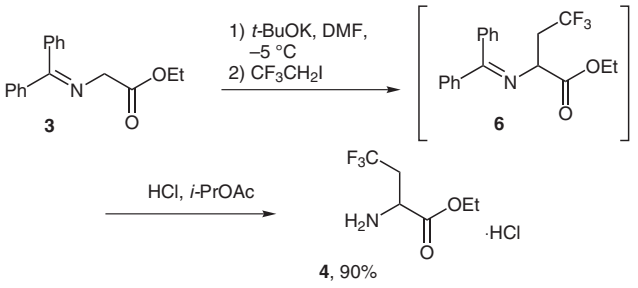
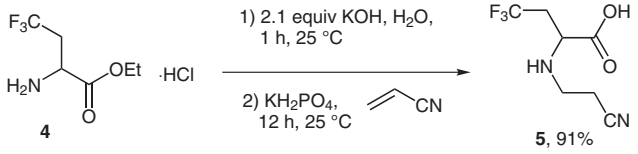


Scheme 3 Alkylation of ethyl *N*-(diphenylmethylene)glycinate (**3**)

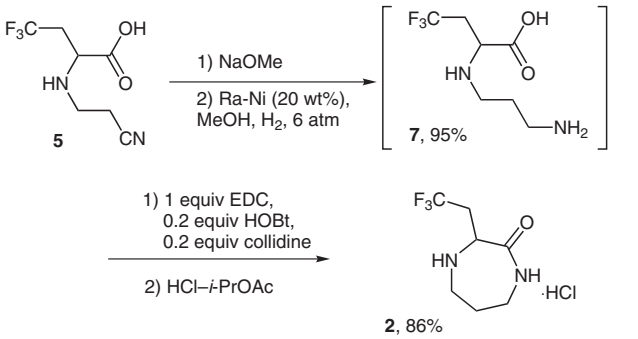
Next, we decided to study the reactivity of a carboxylic salt of **4**. To this end, ester **4** was hydrolyzed at room temperature in aqueous KOH. In contrast to the poor reactivity of ethyl ester **4**, the corresponding potassium carboxylate reacted very efficiently with acrylonitrile (Scheme 4). This two-step sequence can be carried out as a one-pot operation. During the optimization of the reaction, we found that it was important to adjust the pH of the reaction with potassium monophosphate prior to the addition of acrylonitrile in order to suppress basic hydrolysis of the nitrile moiety. After completion of the conjugate addition, HCl was added to the reaction and amino acid **5** crystallized from the reaction mixture. Under our optimized conditions, 91% isolated yield of analytically pure **5** was obtained.



Scheme 4 Conjugate addition of **4** to acrylonitrile

Hydrogenation of nitrile **5** was accomplished using Ra-Ni in methanol (Scheme 5). Sodium methoxide was used as a co-catalyst for the nitrile reduction. Under these conditions, 2-[(3-aminopropyl)amino]-4,4,4-trifluorobutanoic acid (**7**) was obtained in 95% assay yield and carried to the next step without isolation.

Lactamization was accomplished using EDC. Adding catalytic amounts of HOBt and collidine to the reaction mixture increased the reaction rate. The reaction occurred selectively through the primary amine without the need to introduce a protecting group on the secondary amine. Diazepinone **2** was isolated by crystallization of its hydrochloride salt in 86% yield from **7**.



Scheme 5 Hydrogenation and EDC cyclization

In summary, we have developed a high yielding five step synthetic process that does not involve the use of protecting groups or chromatographic purifications to prepare the desired 3-[2,2,2-trifluoroethyl]hexahydro-2*H*-1,4-diazepin-2-one.

All reactions were performed using reagent grade solvents and they were used as received. All reagents were used without prior purification. All manipulations were carried out under an inert atmosphere of nitrogen. ^{1}H NMR and ^{13}C NMR spectra were recorded in CD_3OD, DMSO-d_6 or D_2O on either a Bruker DPX400 (400.13 MHz and 100.62 MHz) or a Bruker DRX500 (500.13 MHz and 125.77 MHz) spectrometer. The chemical shifts (δ) are reported in ppm relative to residual CHD_2OD (δ = 3.31), DMSO-d_5 (δ = 2.50) or HDO (δ = 4.79) for proton and CD_3OD (δ = 49.0) or DMSO-d_6 (δ = 39.5) for carbon. Melting points were determined on a Büchi B-545 apparatus and are uncorrected. Combustion analysis was performed by Quantitative Technologies Inc., Whitehouse, NJ (USA).

Ethyl 2-Amino-4,4,4-trifluorobutanoate Hydrochloride (4)

To DMF (2.0 L) was added *t*-BuOK (176.3 g, 1.57 mol, 1.05 equiv) at 0 °C and the mixture was stirred for 10 min to dissolve the base. Ethyl *N*-(diphenylmethylene)glycinate (**3**; 399.5, 1.49 mol) was added at 0 °C in portions over 10 min. After aging 30 min, 2,2,2-trifluoro-1-iodoethane (362.6 g, 1.73 mmol, 1.16 equiv) was added over 10 min maintaining the temperature at –5 °C to 5 °C. The reaction was aged at this temperature for 6 h and then allowed to warm to r.t. The mixture was partitioned between 5% aq NH_4Cl (2 L) and *i*-PrOAc (4 L). The layers were separated and the organic was washed with aq 2% NaCl (3 × 2 L). Concd HCl (154 mL, 1.9 mol) was added to the organic layer. The resulting solution was concentrated in vacuo and flushed with of fresh *i*-PrOAc (8 L) to azeotropically dry the solution resulting in the precipitation of the HCl salt. The final slurry was concentrated to 2 L. The solid was isolated by filtration, washed with *i*-PrOAc (3 × 500 mL) and dried on the filter under N_2. Ethyl 2-amino-4,4,4-trifluorobutanoate hydrochloride (**4**) was obtained as an off-white solid; yield: 297.4 g (90%); mp 154 °C.

^{1}H NMR (CD_3OD): δ = 1.33 (t, *J* = 7.1 Hz, 3 H), 2.90–3.10 (m, 2 H), 4.34 (q, *J* = 7.1 Hz, 2 H), 4.48 (dd, *J* = 6.7, 5.2 Hz, 1 H), 4.86 (br s, 3 H).

^{13}C NMR (CD_3OD): δ = 12.7, 33.5 (q, *J* = 30 Hz), 47.3, 63.0, 125.1 (q, *J* = 280 Hz), 166.9.

Anal. Calcd for $C_6H_{11}ClF_3NO_2$: C, 32.52; H, 5.00; N, 6.32. Found: C, 32.28; H, 4.83; N, 6.43.

2-[(2-Cyanoethyl)amino]-4,4,4-trifluorobutanoic Acid (5)

2-Amino-4,4,4-trifluorobutanoate hydrochloride (**4**; 20.06 g, 90.5 mmol) was dissolved in aq 1.9 N KOH solution (100 mL) and the mixture aged at r.t. for 4 h giving complete hydrolysis. The pH was adjusted to 9.9 by addition of 1 M KH_2PO_4 solution (11 mL). Acrylonitrile (9.0 mL, 136.7 mmol) was added and the solution aged overnight. Concd HCl (8.4 mL, 101.4 mmol) was added dropwise to the reaction giving a thick, white slurry. The solid was isolated by filtration, washed with H_2O (3 × 35 mL) and MeCN (100 mL), and dried on the filter under N_2. The product **5** was obtained as a white solid; yield: 17.4 g (91%); mp 226 °C (dec.).

^{1}H NMR (DMSO-d_6): δ = 2.50–2.70 (m, 5 H), 2.80–2.85 (m, 1 H), 3.45 (t, *J* = 6.5 Hz, 1 H), 4.10 (br s, 1 H), 7.90 (br s, 1 H).

^{13}C NMR (DMSO-d_6): δ = 18.4, 36.3 (q, *J* = 25 Hz), 43.1, 55.4, 120.2, 126.8 (q, *J* = 275 Hz), 173.9.

Anal. Calcd for $C_7H_9F_3N_2O_2$: C, 40.01; H, 4.32; N, 13.33. Found: C, 40.04; H, 4.09; N, 13.26.

3-[2,2,2-Trifluoroethyl]hexahydro-2*H*-1,4-diazepin-2-one Hydrochloride (2)

A solution of NaOMe in MeOH (417 g, 25% w/w, 1.93 mol) was added to a suspension of nitrile **5** (270 g, 1.28 mol) in MeOH (1.2 L). After all solids had dissolved, Ra-Ni 2800® (62.5 g) was added and the vessel was pressurized with H_2 at 6 atm (90 psi) for 12 h. The catalyst was filtered off, washed with MeOH (600 mL), and the resulting mixture assayed at 1.21 mol of **7** (95% yield). The solution was diluted with MeOH to a final volume of 3.5 L. To this solution was charged concd HCl (182 g, 37% w/w in H_2O, 1.85 mol), HOBt (32.6 g, 0.24 mol), collidine (28.4 g, 0.24 mol), and EDC-HCl (249 g, 1.3 mol). After aging the resulting mixture for 5 h, the batch was concentrated at reduced pressure, diluted with aq 10% NaCl solution (3 L) and extracted with MTBE (4 × 1 L). The organic cuts were combined, dried and concentrated at reduced pressure. Assay showed 1.1 mol of lactam **2** (90% yield). The residue was dissolved in *i*-PrOAc (1.0 L) and HCl (305 mL, 5 N in *i*-PrOAc) was added until pH 2. The resulting slurry was filtered and the solid washed with cold *i*-PrOAc. The hydrochloride of lactam **2** was obtained as a white solid; yield: 242 g (86%); mp 228 °C (dec.).

^{1}H NMR (CD_3OD): δ = 1.90–2.20 (m, 2 H), 2.70–2.90 (m, 1 H), 3.30–3.70 (m, 5 H), 4.53 (dd, *J* = 3.9, 7.8 Hz, 1 H), 4.90 (br s, 3 H).

^{13}C NMR (CD_3OD): δ = 23.9, 32.9 (q, *J* = 30 Hz), 38.6, 48.5, 52.8, 125.3 (q, *J* = 270 Hz), 167.0.

Anal. Calcd for $C_7H_{12}ClF_3N_2O$: C, 36.14; H, 5.20; N, 12.04. Found: C, 35.93; H, 5.01; N, 11.83.

Intermediate Amine 7

An analytical sample of the intermediate **7** was obtained after concentration of the crude hydrogenation mixture and two recrystallizations from MeOH; mp 196 °C (dec.).

^{1}H NMR (D_2O): δ = 1.70–1.80 (m, 2 H), 2.35–2.65 (m, 4 H), 2.99 (t, *J* = 7.2 Hz, 2 H), 3.26 (t, *J* = 6.9 Hz, 1 H), 4.70 (br s, 4 H).

^{13}C NMR (D_2O): δ = 26.2, 36.4 (q, *J* = 30 Hz), 38.3, 44.6, 58.0, 126.2 (q, *J* = 275 Hz), 179.5.

Anal. Calcd for $C_7H_{13}F_3N_2O_2$: C, 39.25; H, 6.12; N, 13.08. Found: C, 38.99; H, 6.21; N, 13.10.

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