Organic LETTERS

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Stereoselective Rearrangement of (Trifluoromethyl)prolinols to Enantioenriched 3-Substituted 2-(Trifluoromethyl)piperidines

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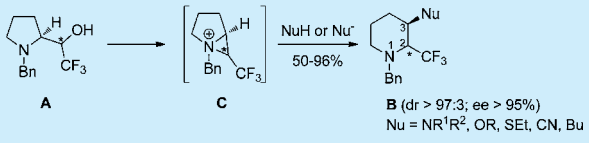
Supporting Information

ABSTRACT: 3-Substituted 2-(trifluoromethyl)piperidines **B** were synthesized by ring expansion of (trifluoromethyl)prolinols **A**, which were obtained from L-proline via an aziridinium intermediate **C**. The ring opening of the (trifluoromethyl)aziridinium intermediate by different nucleophiles is regio- and diastereoselective.



The incorporation of a fluorine atom in compounds can have a profound impact on the physical and chemical properties of the compounds as it can imply the modification of their biological activity.[1] As substituted piperidines are present in a great variety of natural products and bioactive compounds,[2] the search for new methods to prepare CF_3-containing piperidines is of interest.

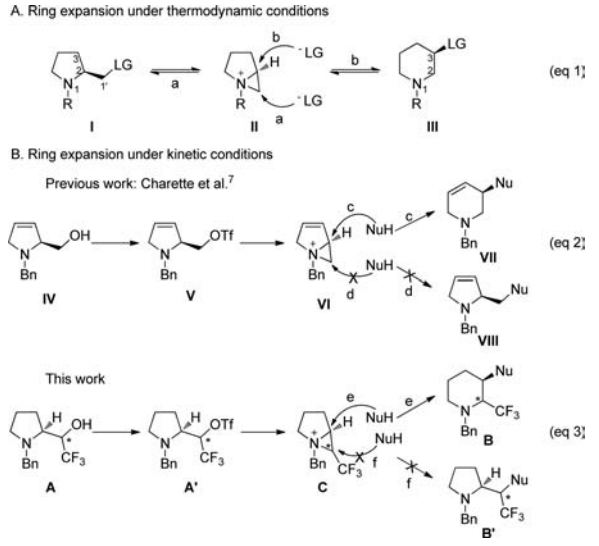
The ring expansion of pyrrolidines to piperidines by attack of a nucleophile on an aziridinium intermediate is well-established.[3] Depending on the nucleophile, the reaction can be under thermodynamic or kinetic control (Scheme 1). When the nucleophile is a good leaving group such as a halide or a trifluoroacetate, a thermodynamic equilibrium is taking place and the formation of the piperidine is favored (Scheme 1, eq 1).[4]

When the nucleophile is a poor leaving group such as azide, cyanide, or alkoxide, the reaction is under kinetic conditions, and a mixture of pyrrolidine and piperidine is observed.[3f,5] However, the ratio of pyrrolidine/piperidine can be modified by appropriate substitution of the pyrrolidine ring. Thus, when a bulky nitrogen protecting group, a bulky substituent at C4, and/or a quaternary center is present at C2 on the pyrrolidine, the formation of the piperidine is favored.[5c,6] In addition, Charette et al. have shown that the ring expansion of unsaturated pyrrolidines such as **IV** can produce unsaturated piperidines **VII**.[7] The ring expansion of the unsaturated pyrrolidine has taken place under kinetic conditions, and the regioselective attack of the nucleophile is governed by the presence of the double bond (attack at the allylic position) (Scheme 1, eq 2).

Based on the regio- and stereoselective ring-opening of monocyclic (trifluoromethyl)aziridinium ions,[8] we have envisaged the access to 3-substituted 2-(trifluoromethyl)piperidine **B** by a regioselective ring expansion of pyrrolidine **A** due to the presence of a CF_3 group at the C1′ position. This ring-opening should be under kinetic control (Scheme 1, eq 3).

Prolinols **A** such as **4** and **5** were prepared from L-proline following a six-step sequence. The synthesis of **4** and **5** started with the preparation of *N*-tritylprolinal **3**. As the presence of an

Scheme 1. Synthesis of Substituted Piperidines by Ring Expansion of Pyrrolidines



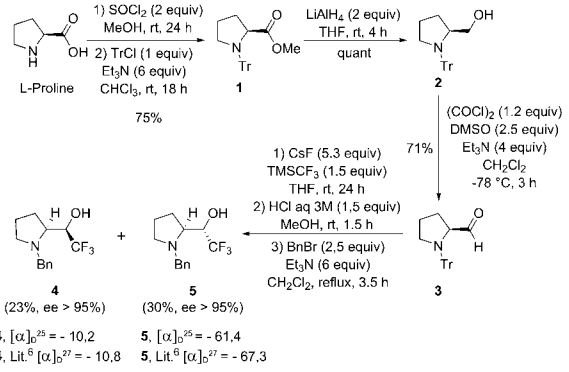
N-trityl group is necessary to avoid the epimerization of the stereogenic center during the transformation of proline **1** to **4** and **5**,[9] the esterification of L-proline ($SOCl_2$, MeOH, rt, 24 h) and *N*-tritylation (TrCl, Et_3N, $CHCl_3$, rt, 18 h) allowed access to ester **1** with a yield of 75%. This ester was then reduced by $LiAlH_4$ (2 equiv) to furnish quantitatively prolinol **2**, which was oxidized to the corresponding prolinal **3** (71%) by using a Swern oxidation.[4e,9] The transformation of **3** to **4** and **5** was realized in a three-step sequence. After treatment of **3** with TMS-CF_3 in the presence of CsF (THF, rt, 24 h), the *N*-trityl group was replaced by a *N*-benzyl group in order to achieve the ring expansion of

Received: April 14, 2015
Published: May 22, 2015

DOI: 10.1021/acs.orglett.5b01084
Org. Lett. 2015, 17, 2916–2919

the prolinol.[5c,4e] After deprotection of the (trifluoromethyl)-prolinol (HCl 3 M, MeOH, rt, 1.5 h) and reprotection using benzyl bromide (Et_3N, refluxing CH_2Cl_2, 3.5 h), compounds **4** and **5** were formed, separated by flash chromatography on silica gel, and isolated in 23% and 30% yield, respectively (Scheme 2).

Scheme 2. Synthesis of (Trifluoromethyl)prolinols 4 and 5

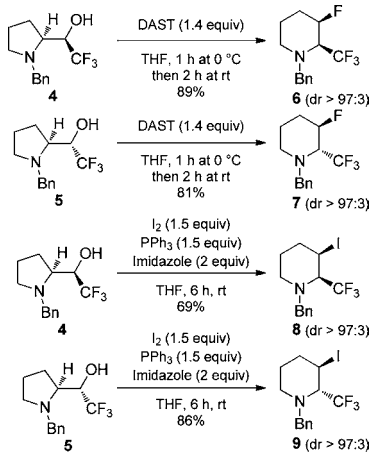


The spectral data of **4** and **5**, as well as their α_D values, matched with those reported in the literature.[10] The enantiomeric excess was determined by SFC and chiral HPLC and proved to be superior to 95% for both of them, showing the preservation of the stereogenic center issued from the L-proline throughout the synthesis.[11]

As the ring expansion of prolinols to 3-fluoropiperidines was achieved with DAST (Et_2NSF_3),[6] trifluoromethylated compounds **4** and **5** were treated with this reagent (1.4 equiv) in THF (1 h, 0 °C then 1 h at rt) to produce piperidines **6** and **7**, respectively, in good yields (89−81%). Compounds **4** and **5** were also transformed to 3-iodopiperidines **8** and **9**, respectively, by using PPh_3 and I_2 in the presence of imidazole.[12] Under these conditions, **8** was isolated in 69% yield and **9** in 86% yield. In each case, an excellent diastereoselectivity was obtained and proved to be superior to 95/5 (measured by NMR) (Scheme 3).

As aziridinium ions can be opened by nucleophiles such as amines, alkoxides, alcohols, and sulfur derivatives as well as carbanions, aziridinium intermediates **C** were formed from **4** and **5** at −15 °C in CH_2Cl_2 using triflic anhydride (Tf_2O) in the presence of *N,N,N′,N′*-tetramethylnaphthalene-1,8-diamine **D**, a proton sponge. After addition of a nucleophile in the reaction

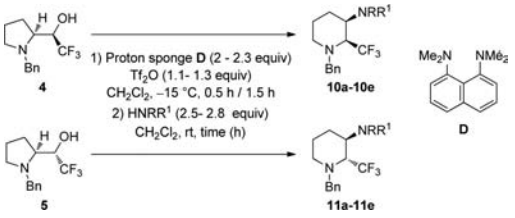
Scheme 3. Synthesis of 3-Fluoro- and 3-Iodo-2-(trifluoromethyl)piperidine by Ring Expansion of 4 and 5



medium, the desired 3-substituted 2-(trifluoromethyl)-piperidines were produced in good yields and with excellent diastereoselectivities (superior to 97/3, measured by NMR and/or GC/MS), whatever the nucleophiles used.[7]

When secondary amines were utilized as the nucleophiles, prolinols **4** and **5** were transformed to the corresponding 3-amino-2-(trifluoromethyl)piperidines **10a−d** and **11a−d** in good to excellent yields and diastereoselectivities (dr >97:3). The enantiomeric excesses of **10d** and **11d** were measured by SFC and chiral HPLC and proved to be excellent (ee >95%).[11] In addition, when aniline was used, **10e** and **11e** were formed, respectively, from **4** and **5** in 96% and 79% yields and with an enantiomeric excess superior to 95%[11] (Table 1).

Table 1. Ring Expansion of (Trifluoromethyl)prolinols 4 and 5 with Amines



entry	amines	time	10a-10e (yield; ee)	time	11a-11e (yield; ee)
1	$HNBn_2$	2 h	**10a** (66%)	2 h	**11a** (67%)
2	HN	2 h	**10b** (80%)	3 h	**11b** (95%)
3	HN O	4 h	**10c** (96%)	5 h	**11c** (84%)
4	Bn HN Et	2,5 h	**10d** (93%; ee > 95%)	2,5 h	**11d** (74%; ee > 95%)
5	H_2NPh	2,5 h	**10e** (96%; ee > 95%)	2,5 h	**11e** (79%; ee > 95%)

It is worth mentioning that the relative configurations of *cis*- and *trans*-piperidines were established by measuring the coupling constant between H2 and H3 and between H3 and H4. For the *cis*-piperidines, the value of the coupling constant between H2−H3 is comprise in between 3 and 5 Hz (4.3 Hz on average), and the value of the coupling constant between H3−H4 is comprise in between 7 and 12 Hz. These values confirmed that, in the *cis*-piperidines, H3 and H4 are in an axial−axial position and, as a consequence, H3 and H2 are axial−equatorial in the *cis*-piperidines. For the *trans*-piperidines, the value of the coupling constant in between H2 and H3 is in between 1 and 3 Hz (2.3 Hz on average). Furthermore, no coupling constant

DOI: 10.1021/acs.orglett.5b01084
Org. Lett. 2015, 17, 2916−2919

with a value of 7−12 Hz was measured for H3−H4, suggesting that H2−H3 are in an equatorial−equatorial position (see the Supporting Information, ^{1}H NMR of **12f** and **13f** as a clear example). As a result, in *trans*-piperidines, the CF_3-group at C2 and the substituent at C3 are axial which can be explained by a possible anomeric effect between the nitrogen of the heterocycle and the CF_3 group (Figure 1).[13]

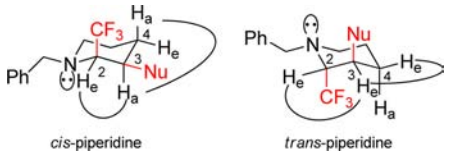


Figure 1. Conformations of *cis*- and *trans*-piperidines.

Water (6 equiv) was the first oxygenated nucleophile tested, and **4** and **5** were transformed to the corresponding 3-hydroxypiperidines **12a** and **13a**, respectively, in 79% and 82% yields. When alcohols were used as the nucleophiles, the corresponding 3-alkoxy-2-(trifluoromethyl)piperidines **12b−d** and **13b−d** were, respectively, obtained from **4** and **5** in 50−88% yield (Table 2, entries 2−4). It is worth mentioning that when 2.5 equiv of alcohol were utilized, the conversion of **4** and **5** was not complete, but by using 5 to 6 equiv of alcohol, a complete conversion of **4** and **5** was observed and piperidines **12b−d** were isolated in good yields (55−65%) as well as piperidines **13b−d** (50−88%).

Due to the low nucleophilicity of phenol, the conversion of **4** and **5** was incomplete even after 72 h (Table 2, entry 5). However, by using sodium phenoxide (2.5 equiv), the conversion of **4** and **5** was total, and **12e** and **13e** were, respectively, isolated in good yields after 3 h. In addition, the enantiomeric excesses were measured and revealed to be superior to 95%.[11]

When **4** and **5** were treated with *n*-Bu_4NOAc, the ring expansion took place, and the corresponding 3-acetoxypiperidines **12f** (86%) and **13f** (78%) were isolated (Table 2, entry 7).

The reactivity of sulfur derivatives such as ethanethiol was examined and 3-(ethylthio)-2-(trifluoromethyl)piperidines **14** and **15** were formed in 73% and 50% yield, respectively, from prolinols **4** and **5** (Scheme 4). The enantiomeric excess of **14** was also determined by SFC and proved to be excellent (ee >95%).[11]

The formation of a carbon−carbon bond was also possible by the attack of the aziridinium intermediate **C** by a carbanion.

Scheme 4. Ring Expansion of (Trifluoromethyl)prolinols 4 and 5 with Ethanethiol

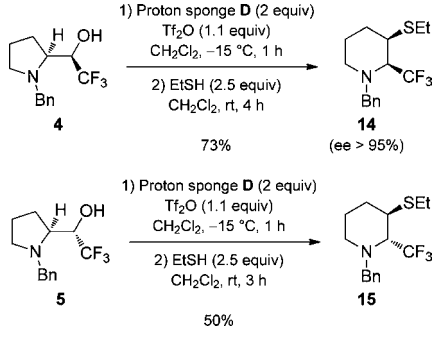
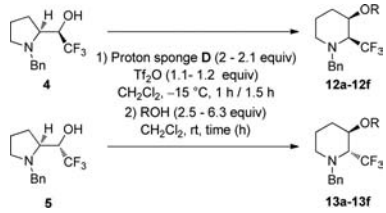


Table 2. Ring Expansion of (Trifluoromethyl)prolinols 4 and 5 with Oxygenated Nucleophiles



entry	ROH	time	12a-12f (yield; ee)	time	13a-13f (yield; ee)
1	H_2O	4 h	**12a** (79%)	18 h	**13a** (82%)
2	MeOH	23 h	**12b** (63%)	5 h	**13b** (50%)
3	EtOH	22 h	**12c** (55%)	5 h	**13c** (88%)
4		23 h	**12d** (65%)	5 h	**13d** (72%)
5	PhOH	72 h	-	23 h	-
6	NaOPh	3 h	**12e** (88%; ee > 95%)	2.5 h	**13e** (94%; ee > 95%)
7[i]	*n*-Bu_4NOAc	1.5 h	**12f** (86%)	1 h	**13f** (78%)

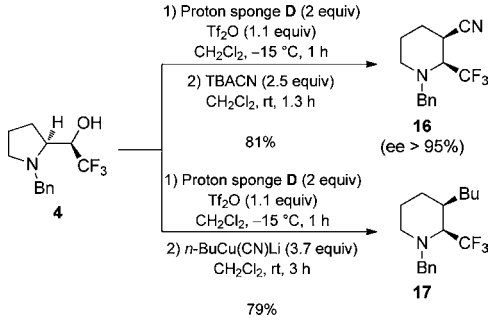
[a] Tf_2O (1.1 equiv), proton sponge **D** (1.25 equiv), 5 min at −15 °C then *n*-Bu_4NOAc (2.5 equiv) at −15 °C for 1−1.5 h. (See the Supporting Information.)

Thus, when **4** and **5** were treated with TBACN, the resulting piperidines **16** and **18** were formed in 81% and 78% yield, respectively, and the enantiomeric excesses measured for **16** and **18** were excellent (ee >95%).[11] When **4** and **5** were treated with *n*-BuCu(CN)Li,[14] the corresponding 3-butyl 2-(trifluoromethyl)piperidines were also obtained in good yields, as **17** was isolated in 79% yield and **19** in 59% yield (Schemes 5 and 6).

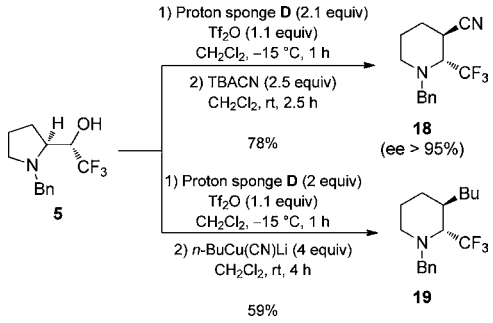
In conclusion, we have developed a straightforward pathway for the synthesis of a great variety of 3-substituted 2-(trifluoromethyl)piperidines by ring expansion of the easily accessible (trifluoromethyl)prolinols. This method is regio- and diastereoselective. It is worth mentioning that all enantiomers of 3-substituted 2-(trifluoromethyl)piperidines are accessible

DOI: 10.1021/acs.orglett.5b01084
Org. Lett. 2015, 17, 2916−2919

Scheme 5. Ring Expansion of (Trifluoromethyl)prolinol 4 with Carbanion



Scheme 6. Ring Expansion of (Trifluoromethyl)pyrrolidinol 5 with Carbanion



depending on whether one uses L- or D-proline as the starting material. This access to 3-substituted 2-(trifluoromethyl)-piperidines should be of interest for medicinal chemists.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data for all compounds, and copies of ^{1}H and ^{13}C NMR spectra for all compounds as well as experimental chromatograms of enantiomeric excess for the products concerned. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01084.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

GlaxoSmithkline is acknowledged for a grant to S. R. and for financial support. Diverchim is acknowledged for its help for the determination of the enantiomeric excess.

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DOI: 10.1021/acs.orglett.5b01084
Org. Lett. 2015, 17, 2916−2919