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Synthesis of 4-Trifluoromethylated 2-Alkyl- and 2,3-Dialkyl-Substituted Azetidines

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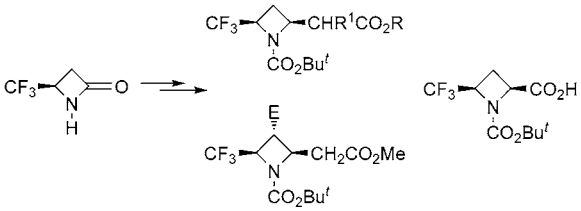
ABSTRACT



A diastereoselective approach to the synthesis of 4-trifluoromethylated 2-alkyl- and 2,3-dialkylazetidines, including BOC-protected 4-trifluoromethylazetidin-2-ylcarboxylic acid, was developed via Wittig reaction of 4-trifluomethylated β-lactam followed by alkylation and hydrogenation.

Selective introduction of a trifluoromethyl group into heterocyclic compounds at a strategic position has become an important aspect of pharmaceutical research due to the unique physical and biological properties of fluorine.[1] The strong covalent bonding of the C−F bond (116 kcal/mol) versus that of the C−H bond (100 kcal/mol)[2] often avoids unwanted metabolic transformations. The high electronegativity of fluorine enables a trifluoromethyl group to decrease the electron density of the neighboring functional groups within the molecule. Moreover, substituting a methyl group with a trifluoromethyl group in many systems results in added lipophilicity ($\pi_{CF3} = 1.07$ versus $\pi_{CH3} = 0.6$).[3] This may lead to easier absorption and transportation of the molecules within biological systems, thereby improving the overall pharmacokinetic properties of drug candidates.

Synthesis of monotrifluoromethyl-substituted heterocycles has created a significant challenge for synthetic chemists.[4] Direct trifluorination of the nonfluorinated compounds is less applicable due to poor selectivity.[1f] The more general method is to incorporate a trifluoromethylated synthetic building block into the molecules via chemical reaction processes. However, trifluoro substitution significantly impacts the characteristics of functional groups and frequently results in unexpected reactivity of this class of compounds. As previously noted,[5] there are often surprises that emerge from what should be the simplest transformation of fluorine substrates.

Cyclic amines such as azetidines and piperidines are an important class of saturated aza-heterocyclic compounds with remarkable biological activities. Although several trifluoromethylated cyclic amines were reported in the literature, few examples of cyclic amines with a trifluoromethyl group α to the amine are known.[1f] In the previous communication, we reported on the syntheses of 2-alkyl-6-trifluoromethylated piperidines and decahydroquinolines.[6] The 6-trifluoromethyl

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(2) McAtee, J. J.; Schinazi, R. F.; Liotta, D. C. *J. Org. Chem.* **1998**, *63*, 2161−2167 and references therein.

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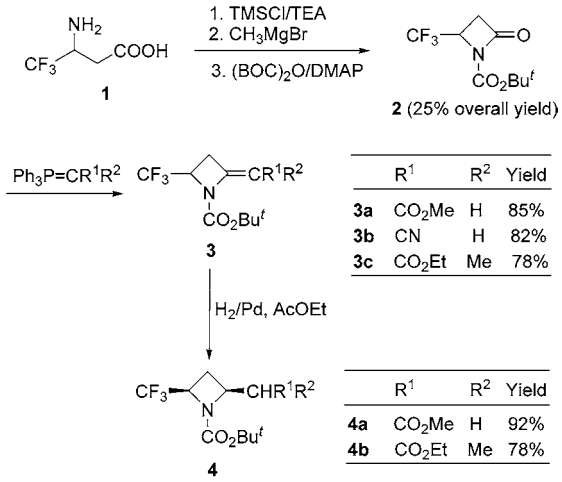
group reduced the basicity of the piperidine approximately 1000-fold and improved the pharmacokinetic profile of quinolone derivatives that contained a trifluoromethylated piperidine substituent.[7] 2-Alkyl-4-trifluoromethyl azetidines were not previously reported.

The most important method for the synthesis of nonfluorinated azetidines is cyclization of the open-chain compounds by formation of the C−N bond.[8] A few azetidine derivatives were prepared by cycloaddition and rearrangement of other heterocycles. We now describe the first synthesis of 4-trifluoromethyl-substituted azetidine derivatives by alkylation and hydrogenation of Wittig reaction adducts of 4-trifluoromethyl-substituted β-lactam.

Scheme 1 shows the procedure for the preparation of lactam **2** and azetidines **3** and **4**. 4-Trifluoromethyl-β-lactam

Scheme 1



	R^1	R^2	Yield
3a	CO_2Me	H	85%
3b	CN	H	82%
3c	CO_2Et	Me	78%

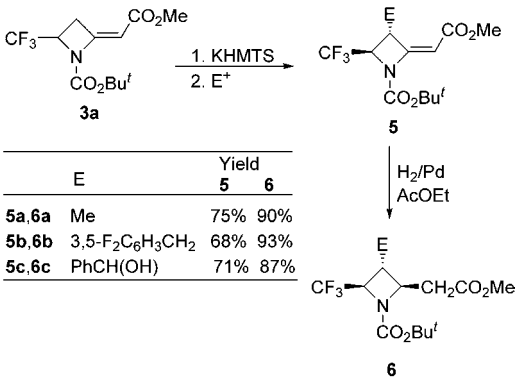
	R^1	R^2	Yield
4a	CO_2Me	H	92%
4b	CO_2Et	Me	78%

was prepared from the commercially available β-amino acid according to the literature procedure.[9] Without purification, the lactam thus obtained was treated with di-*tert*-butyl dicarbonate in the presence of 10% mol DMAP at 20 °C for 2 h to afford *N*-Boc-protected β-lactam **2** in 25% overall yield from acid **1**. Treatment of lactam **2** with stabilized Wittig reagents in refluxing toluene for 12−48 h afforded adducts **3a**−**c** in 75−90% yield. Wittig reaction of nontrifluoromethylated lactams similar to compound **2** was previously reported in the literature.[10] Ethyl and *tert*-butyl (triphenylphosphoranylidene)acetate gave the Wittig adducts in high yield. However, ethyl 1-(triphenylphosphoranylidene)-propionate and (triphenylphosphoranylidene)acetonitrile resulted in only moderate yields of the adducts. In contrast, all the present Wittig reactions of trifluoromethylated lactam **2** with stabilized ylids afforded adducts of type **3** in high yield, presumably due to the strong electron-withdrawing trifluoromethyl group that enhances the electrophilicity of the lactam carbonyl group.

The utility and further transformations of adducts **3**, including the corresponding nonfluorinated lactams, were not found in the literature. Catalyzed hydrogenation of the C=C bond of derivatives **3a**,**c** afforded corresponding azetidines **4a**,**b** in high yield (Scheme 1). The diastereoselectivity of the hydrogenation depends on the catalyst and solvent used. Hydrogenation of **3a** over catalyst Pd/C in ethyl acetate gave exclusive cis-2,4-disubstituted azetidine **4a**, while in ethanol and over the same catalyst, a mixture of cis and trans isomers obtained in a 2:1 ratio. When platinum oxide was used as the catalyst, hydrogenation of **3a** in ethyl acetate resulted in an 1:1 ratio of the two diastereomers.

Treatment of *N*-(*t*-butoxylcarbonyl)-2-(methoxycarbonylmethylene)-4-trifluoromethylazetidine (**3a**) with potassium bis(trimethylsilyl)amide at −78 °C followed by reaction with an alkyl halide or an aldehyde afforded 3-alkyl-substituted derivatives **5a**−**c** in 75−85% yield (Scheme 2). Compounds

Scheme 2



E	Yield 5	6
5a,**6a** Me	75%	90%
5b,**6b** 3,5-$F_2C_6H_3CH_2$	68%	93%
5c,**6c** PhCH(OH)	71%	87%

5a,**b** are single diastereomers with the 3-substituent added trans to the 4-trifluoromethyl group. This procedure is of particular importance to synthesis of azetidines with an alkyl substituent at the 3-position. As noted in the literature,[10] 3-substitution in the nonfluorinated β-lactam similar to **2** (Scheme 2) tended to lower the yield of the Wittig adduct (∼20% yield). On the other hand, our attempts to add a methyl group at the 3-position of the lactam **2** by alkylation under basic conditions resulted in decomposition of the lactam **2**.

Hydrogenation of the Wittig adducts **5a**−**c** over Pd/C in ethyl acetate gave compounds **6a**−**c** as single isomers with the 3-alkyl substituent trans and the 2-alkyl substituent cis to the 4-trifluoromethyl group (Scheme 2). The structures were characterized by NMR spectra and confirmed by CHN microanalysis. The relative stereo configuration of the 3-alkyl, 2-alkyl, and trifluoromethyl group was determined by NOEs ^{1}H NMR spectra (see Supporting Information).

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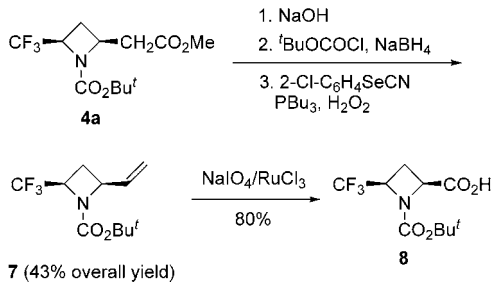
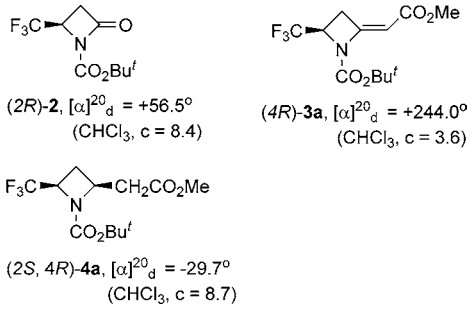
The azetidine ring of compound **4a** is stable during a variety of chemical transformations. This allowed for the synthesis of trifluoromethylated azetidines with various 2-substituents by simple functional group transformations. For example, 4-trifluoromethylazetidin-2-yl olefin **7** and carboxylic acid **8** were readily prepared from ester **4a** (Scheme 3).

Scheme 3



Chiral, nonracemic (*R*)-3-amino-4,4,4-trifluorobutyric acid **1** was synthesized according to a literature method[11] and transformed into an optically pure lactam (4*R*)-**2a** (>98 % ee based on chiral HPLC), using the procedure described above and recrystallizing from hexane. Wittig reaction of (4*R*)-**2a** followed by hydrogenation afforded chiral nonracemic azetidines (2*S*,4*R*)-**4a**.



In summary, we reported the first synthesis of 4-trifluoromethyl-substituted 2-alkyl and 2,3-dialkylazetidines, including 4-trifluoromethyl-substituted amino acid **8**. Both alkylation of adduct **3a** and hydrogenation of adducts **3a**,**c** and **5a**−**c** were diastereoselective, producing only single diastereoisomers.

Supporting Information Available: Experimental procedures and full characterization for compounds **2**−**8**, including copies of their ^{1}H NMR and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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