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Synthesis of β-amino-α-trifluoromethyl-α-amino acids exhibiting intramolecular interaction of CF_3 with NH_β

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ABSTRACT

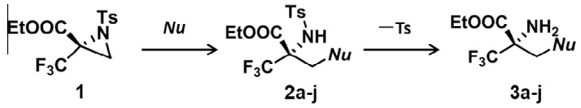
We prepared β-amino-α-trifluoromethyl-α-amino acids through ring-opening reaction of *N*-tosyl-2-trifluoromethyl-2-ethoxycarbonylaziridine with aromatic and benzylic amines, and investigated the intramolecular interaction between the trifluoromethyl (CF_3) group at the α-position and the NH group at the β-position (NH_β). NMR, UV/vis, and circular dichroism measurements indicated that the conformation of these compounds is fixed by intramolecular interaction of CF_3 with NH_β to form a six-membered ring.

Installation of fluorine atom(s) into organic molecules leads to drastic changes in chemical properties, owing to its strongly electron-withdrawing nature.[1,2] For example, fluorine-substituted pharmaceuticals often show increased biological stability due to the high binding energy of the C—F bond (484 kcal mol^{-1}), resulting in greater metabolic stability and bioavailability, and various pharmaceutical candidates containing fluorine, difluoromethyl, or trifluoromethyl (CF_3) moieties have been reported.[3] Indeed, at present approximately 20% of all pharmaceuticals contain fluorine in their molecular structure.[4–6]

Fluorine atom(s) have also found application in the fields of artificial enzymes and peptides.[7–9] For example, trifluoromethylation of leucine and valine improves the thermal stability of coiled-coil structure in artificial peptides containing these amino acids.[10] The high lipophilicity of CF_3 within hydrophobic regions of peptides increases the stability of assembled peptide structures. Thus, trifluoromethylated (CF_3-) amino acid residues can be a powerful tool for protein engineering. However, there are still relatively few biological applications of CF_3-amino acids, even though synthetic methodologies have advanced.[11] Further understanding of the functionality of CF_3 groups in peptides is still required.

Recently, we reported the preparation of α-trifluoromethyl-α-amino acids through ring-opening reaction of *N*-tosyl-2-trifluoromethyl-2-ethoxycarbonyl aziridine (**1**) with nucleophiles and detosylation of the aziridine N-atom (Scheme 1).[12] The reaction of an aziridine with nucleophiles such as amine, alcohol, and thiol gives ring-opened products with various functional groups at the β-position in good to moderate yields.[13] In particular, nucleophilic attack of aniline on the trifluoromethylated (CF_3)-aziridine **1** affords β-phenylamino-α-trifluoromethyl-α-amino acid structure (Scheme 1), in which the NH group at the β-position (NH_β) can function as a proton donor for intramolecular hydrogen bonding with the CF_3 group to form a six-membered ring. Such intramolecular interaction would stabilize the molecular conformation. In this Letter, we describe the synthesis of β-amino-α-trifluoromethyl-α-amino acids through ring-opening reaction of CF_3-aziridine **1** with amines. Intramolecular interaction between the CF_3 and NH_β groups in these molecules was characterized by means of NMR, UV/vis, and circular dichroism (CD) spectroscopic measurements.

As reported previously, the ring-opening reaction selectively proceeds via nucleophilic attack on the aziridine ring.[12] The ring-opened products **2a**–**2j** formed by nucleophilic addition of aromatic amines and benzylic amines were obtained in good to moderate yields, and detosylation by treatment with concentrated H_2SO_4 afforded β-amino-α-trifluoromethyl-α-amino acids **3a**–**3j** as



Scheme 1. Strategy for the synthesis of β-amino-α-trifluoromethylated-α-amino acids.

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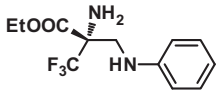
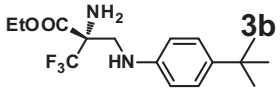
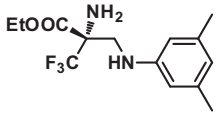
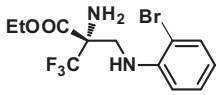
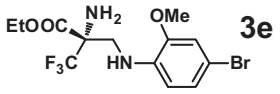
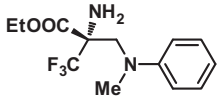
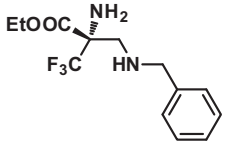
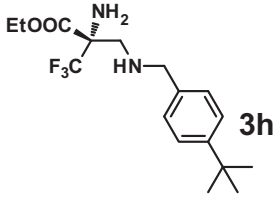
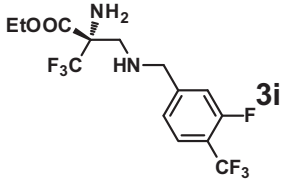
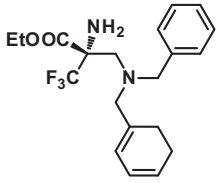
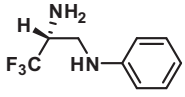
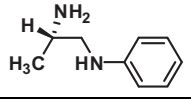
Table 1
Optical properties of β-amino-α-trifluoromethyl-α-amino acids **3a**–**3j** and their analogues **4** and **5**

Compound	^{19}F[a] (ppm)	ε[b] (L mol^{-1}cm^{-1})	λ_{max} (nm)	$[\theta]$[c] (deg cm^2 dmol^{-1})
 **3a**	85.0	1.0×10^4 2.1×10^3	248 291	2.0×10^3
 **3b**	85.1	2.5×10^3	292	1.5×10^3
 **3c**	85.1	9.1×10^4 2.1×10^3	248 292	1.7×10^3
 **3d**	85.0	9.7×10^4 3.0×10^3	245 298	2.5×10^3
 **3e**	85.1	1.2×10^5 4.1×10^3	254 301	N.D.[d]
 **3f**	85.8	1.1×10^5 2.0×10^3	250 295	-3.8×10^3
 **3g**	85.2	2.1×10^2	259	—
 **3h**	85.2	2.8×10^2	263	—
 **3i**	85.1	1.4×10^3	265	—
 **3j**	85.6	6.1×10^2	260	—
 **4**	84.0	9.4×10^4 1.8×10^3	244 293	2.5×10^3
 **5**	—	9.1×10^4 1.7×10^3	248 296	0.58×10^3

[a] Chemical shift based on C_6F_6 as an internal standard.
[b] Reagents and conditions: concentration; 1.2×10^{-4} M, solvent; $CHCl_3$, temperature; 25 °C, light path length; 10 mm.
[c] Reagents and conditions: concentration; 1.0×10^{-3} M, solvent; $CHCl_3$, temperature; 25 °C, light path length; 10 mm.
[d] Not determined.

shown in Table 1. The chirality at the optically active center of the product prepared from optically pure aziridine **1** was retained throughout these reaction processes, as reported previously.[14]

Compounds **4** and **5** were synthesized for comparison of their structural properties with those of β-amino-α-trifluoromethyl-α-amino acids. Analogue **4** lacking the ethyl ester group was

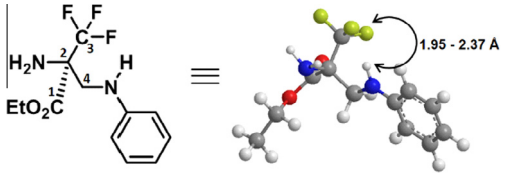


Figure 1. Chemical structure of β-phenylamino-α-trifluoromethyl-α-amino acid **3a**.

prepared by ring-opening reaction of *N*-tosyl-2-(trifluoromethyl)aziridine (**6**) with aniline, followed by detosylation (see Supplementary data). Replacement of F with H atoms afforded methylated (CH_3) analogue **5** from *N*-tosyl-2-methylaziridine (**8**).

A structural model of β-phenylamino-α-trifluoromethyl-α-amino acid **3a** is shown in Figure 1. Intramolecular interaction between the NH_β and CF_3 groups can be anticipated, because weakly hydrogen-bonded six- and five-membered ring formation is known to be favorable.[15] The calculated distance between NH_β and CF in such molecules was estimated to be 1.95–2.37 Å,[16] which is appropriate for the interaction.

NMR measurements were carried out to examine the intramolecular interaction between NH_β and CF_3. The proton signal of NH_β connected to the phenyl group on the β-amino-α-trifluoromethyl-α-amino acids was observed as a broad peak at 4.0–4.5 ppm, but there was no clear coupling signal. In the ^{19}F NMR spectra (Table 1),[17] signals of **3a**–**3e** and **3g**–**3i** were observed at 85.0–85.2 ppm, which can be assigned to interacting fluorine species. These chemical shifts did not appear to be influenced by functional groups on the phenyl ring. On the other hand, *N*-methylated (**3f**) and *N*,*N*-dibenzyl (**3j**) β-amino-α-trifluoromethyl-α-amino acids showed characteristic peaks at 85.8 and 85.6 ppm, respectively, downfield from the other compounds. This may be because fluorine does not interact with nitrogen of the tertiary amine groups of **3f** and **3j**. The ^{19}F NMR spectrum of **4**, which lacks an ester group in its molecular structure, showed a peak at 84.0 ppm due to the CF_3.

UV/vis and CD spectral studies are useful for investigating specific interactions in solution.[18] The UV/vis spectra of β-amino-α-trifluoromethyl-α-amino acids **3a**–**3f** and their analogues **4** and **5** exhibited two absorption bands at around 250 and 290 nm, which were assigned to the π–π* and n–π* transition modes, respectively (see Supplementary data, Figs. S1–S6, S11, and S12). The molar absorption coefficient at 291 nm for **3a** was estimated to be 2.1×10^3 L mol^{-1} cm^{-1} from a Lambert–Beer plot (see Supplementary data, Fig. S1). The fact that the plot obeyed Beer's law indicates that the intermolecular association of **3a** was negligible in this concentration range. Compounds **3b**–**3f**, **4**, and **5** showed similar ε values of 1.7×10^3–4.1×10^3 L mol^{-1} cm^{-1} in this concentration range, irrespective of the presence/absence of ester at the α-position or any functional group on the phenyl ring. The n–π* absorption band of **3a**–**3c** was observed at 291–292 nm, and that of the ethyl ester-lacking compound **4** was also at 293 nm, at shorter wavelength than that (296 nm) of the CH_3-analogue **5**. On the other hand, the absorption peak due to n–π* transition in the spectrum of *N*-methyl β-amino-α-trifluoromethyl-α-amino acid **3f** appeared at 295 nm, which was similar to that of CH_3-analogue **5**. The slight blue-shift of the absorption band for **3a**–**3c** and **4** is attributed to the lower HOMO energy level, which may be due to interaction of the CF_3 group with the NH_β group.[19] It appears that the CF_3 group at the α-position of these amino acids undergoes an intramolecular interaction that stabilizes a particular molecular conformation.

Interestingly, β-phenylamino-α-trifluoromethyl-α-amino acid **3a** showed a positive CD signal in the n–π* absorption region at ca. 290 nm in $CHCl_3$ solution (Fig. 2). This CD signal can be attributed to the chiral conformation of the aromatic moiety, which has an optically active carbon at the α-position. The CD spectra of other

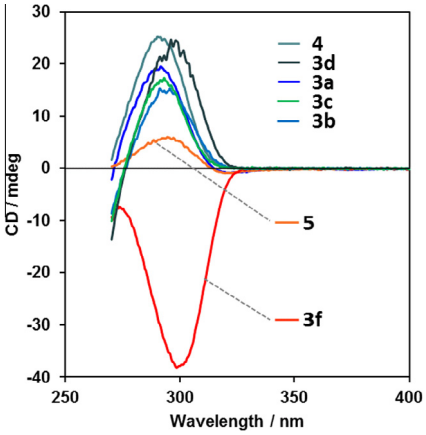


Figure 2. CD spectra of β-amino-α-trifluoromethyl-α-amino acids **3a**–**3d**, **3f**, and their analogues **4** and **5**.

β-amino-α-trifluoromethyl-α-amino acids **3b**–**3d** with various functional groups on the phenyl ring also showed a positive Cotton effect similar to that of **3a**. Compound **4** having no ester group also showed a similar CD spectrum. On the other hand, compound **5**, which contains CH_3 in place of CF_3, showed only a weak signal at the same absorption region (Fig. 2). These results suggested that the phenyl group of β-amino-α-trifluoromethyl-α-amino acids **3a**–**3d** and **4** is fixed in a specific conformation by intramolecular interaction between the CF_3 and NH_β groups, whereas in **5**, in which there is little interaction between NH_β and CH_3, the conformation of the phenyl ring is not fixed. The spectrum of *N*-methylated derivative **3f** showed a negative CD signal, the inverse of that of **3a**. The *N*-methyl group sterically repels the CF_3 group, which presumably flips to the opposite side of the CF_3 group, resulting in the negative CD signal in this absorption range (Fig. 2). On the other hand, β-benzylamino-α-trifluoromethyl-α-amino acids **3g**–**3j** have unique absorption bands at 250–260 nm with the low ε values of 2.1–6.1 $\times 10^2$ L mol^{-1}cm^{-1} due to the benzyl group (see Supplementary data, Figs. S7–S10). The CD spectra of **3g**–**3j** exhibited a very weak Cotton effect in this absorption range (see Supplementary data, Fig. S13), suggesting that the benzyl group has a disordered conformation because it can rotate freely despite the interaction of CF_3 and NH_β. These interpretations of the spectral studies are all consistent with our proposal of intramolecular interaction between CF_3 and NH_β. In future, further support for this proposal will be obtained by additional analysis such as X-ray crystal study and the effort to broaden the scope of substituents on NH_β.

In conclusion, we have synthesized a number of β-amino-α-trifluoromethyl-α-amino acids through ring-opening reaction of CF_3-aziridine. ^{19}F NMR, UV/vis, and CD studies were consistent with stabilization of the structure by intramolecular interaction between CF_3 and NH_β. Application of this interaction is expected to open up new opportunities for the design of functional artificial peptides.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.10.107.

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