CHEMISTRY OF α-FLUORO-α-AMINO ACIDS: THE FIRST SYNTHESIS OF α-FLUOROGLYCINE-CONTAINING DIPEPTIDES

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The Gabriel reaction was used as a key step in the first synthesis of protected α-fluoroglycine-containing dipeptides **10**.

KEY WORDS α-fluoro-α-amino acid; fluorinated peptide; Gabriel reaction; ruthenium tetroxide oxidation

Examples of important classes of fluorinated amino acids include α-trifluoromethyl, α-difluoromethylene, or α-fluoromethylene group-containing α-amino acids, as well as aromatic and heteroaromatic α-amino acids having ring-fluorine substituents. As a part of our research program directed toward the preparation of multifunctional carbon compounds,[1] we became interested in a class of fluorinated amino acids previously unreported, the α-fluoro-α-amino acids (**1**). The compounds **1** not only incorporate the multifunctional carbon structure but also likely would alter significantly the biological properties of peptides, if incorporated as constituents. In this regard, there is continuing and growing interest in the design and synthesis of analogues of biologically active peptides that contain fluorine-substituted amino acids.[2]

Prior to our work, no examples of the synthesis, or attempted synthesis, of protected α-fluoro-α-amino acids had been reported. This is probably due both to the lack of a method for selective fluorination of amino acids under mild conditions[3] and recognition of the well-established chemical lability of α-bromo- and α-chloro-α-amino acids.[4] Previously, we reported the results of our study on the attempted synthesis of α-fluoroglycine (**1**, R = H) using the Gabriel reaction of imidodicarboxylates with ethyl bromofluoroacetate.[5] From this work, we confirmed our expectation that **1** cannot exist under ambient conditions because of rapid dehydrofluorination. Since protection of the amino group by amide formation should stabilize the C–F unit, we next considered as target molecules the dipeptides **2** that incorporate the α-fluoroglycine moiety at the C-terminus. In this paper, we present a novel, general method for the preparation of fully protected dipeptides containing an α-fluoroglycine moiety.

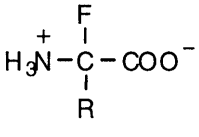

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Fig. 1

Dipeptides containing α-bromo- and α-chloroglycine have been prepared by direct halogenation of dipeptides.[6] However, this method is not applicable to the preparation of **2** because of the difficulty of site-selective monofluorination of peptides.[7] Moreover, the conventional method for peptide coupling shown in Chart 1 cannot be applied since **1** has eluded synthesis to date.[5] Our strategy for the preparation of **2** relied on the recognition that the amido derivatives **3** could be utilized as intermediates for the Gabriel reaction. The *tert*-butoxycarbonyl (Boc) group was chosen for protection of the dipeptides based on both the reactivity of the amido nitrogen in the Gabriel reaction[8]

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and on the ease of its removal at the final stage. While we experienced problems with selective mono-Boc protection of the amide under general conditions,[9] amide **3** was successfully prepared from the diamine **4** using the ruthenium tetroxide oxidation developed by Tanaka *et al.*[10]

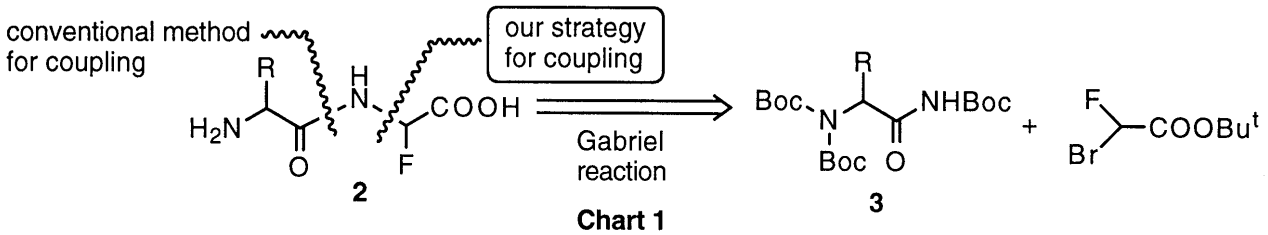
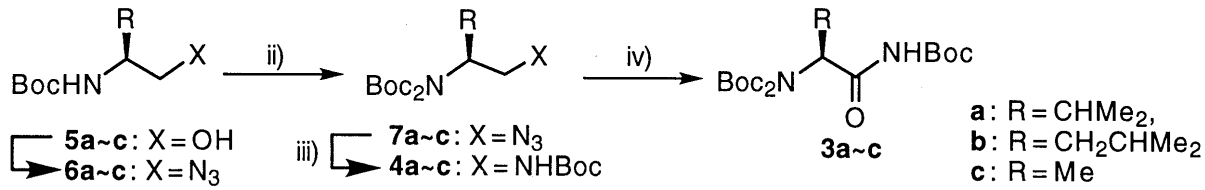


Chart 1

Mesylation of the hydroxyl group of *N*-Boc amino alcohols **5** with methanesulfonyl chloride/TEA followed by nucleophilic substitution with sodium azide under phase transfer conditions afforded **6**.[11] Introduction of the second Boc group into **6** was accomplished by employing Boc_2O/DMAP/THF.[12] The azides **7** were hydrogenated in the presence of Boc_2O to afford the intermediate **4** protected with three Boc groups. Finally, oxidation of **4** at the methylene position using ruthenium tetroxide[10] gave **3** in moderate yields.



i) MsCl, Et_3N , toluene then NaN_3, Bu_4NBr, H_2O (16~67%) ii) Boc_2O, DMAP, MeCN (68~96%)
iii) H_2, Pd-C, Boc_2O, AcOEt (65~84%) iv) RuO_2/ $NaIO_4$, AcOEt / H_2O (39~80%)

Chart 2

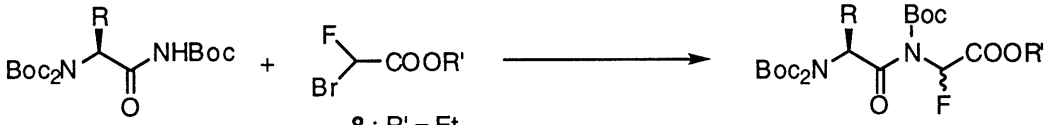
We next examined the Gabriel reaction of **3** with bromofluoroacetates. Treatment of the potassium salt of **3a** with ethyl bromofluoroacetate (**8**) in DMF at room temperature gave **10a** in 29% yield as a mixture of diastereomers. However, condensation of **3a** with *tert*-butyl bromofluoroacetate (**9**) under normal conditions did not proceed. When the reaction was carried out in the presence of 18-crown-6, the corresponding dipeptide **11a** was produced in 8% yield. Other results are shown in Table 1. Although the isolated yields of the dipeptides **10** and **11** are generally low, we have established here the first method for the synthesis of α-fluoroglycine-containing dipeptides.

Finally, we attempted the removal of the Boc groups of the dipeptides **10** by treatment with TFA in CH_2Cl_2 at 0 ℃. As soon as the starting material **10** or **11** had disappeared, as monitored by TLC, the resulting mixture was concentrated in vacuum without heating to give a solid. However, no fluorine signals were observed in the ^{19}F NMR spectra. We therefore examined the deprotection reaction of **10c** with TFA in $CDCl_3$ as monitored by ^{19}F NMR spectroscopy. Upon careful addition of TFA into the $CDCl_3$ solution of **10c**, several new fluorine signals gradually appeared (–151.8, –151.9, –154.8, –154.9 ppm [each d, *J*=48 Hz], –161.7, –161.6 ppm [each d, *J*=46 Hz]). However, none of these signals persisted, and no product could be identified.[13]

In summary, the first synthesis of protected derivatives of α-fluoroglycine-containing dipeptides **10** and **11** was accomplished by extension of the Gabriel reaction for peptide synthesis. The chiral amido derivatives **3** can be utilized as new substrates for preparation of peptides having other

unnatural amino acids at the C-terminus. The free form of the dipeptides, however, is too unstable to be isolated or identified, in contrast to the corresponding α-chloro and α-bromo analogues.[4, 6)]

Table 1. The Gabriel Reaction of 3 with Bromofluoroacetates 8, 9



3	R	Conditions	Product[a]	R'	Yield (%)	δ(^{19}F, $CDCl_3$) ppm[c,d]
3a	$CHMe_2$	i) $KOBu^t$, THF ii) **8**, DMF, rt	**10a**	Et	29	−157.2, −158.2
3a	$CHMe_2$	$KOBu^t$, 18-crown-6, **9**, THF, rt	**11a**	Bu^t	8	−157.4, −159.2
3b	CH_2CHMe_2	i) $KOBu^t$, THF ii) **8**, DMF, rt to 70°C	**10b**	Et	13	−157.8, −158.3
3b	CH_2CHMe_2	$KOBu^t$, 18-crown-6, **9**, THF, rt	**11b**	Bu^t	18 (68)[b]	−158.3, −159.3
3c	Me	i) $KOBu^t$, THF ii) **9**, DMF, rt	**11c**	Bu^t	24	−158.9, −159.7

a) Mixture of diastereomers (1:1). b) Conversion yield. c) The fluorine chemical shifts are referenced with respect to $CFCl_3$. d) Each signal is a doublet (J=47~50 Hz).

ACKNOWLEDGMENT This work was supported by a Grant-in Aid for Scientific Research (09044277) from the Ministry of Education, Science, Sports and Culture, Japan.

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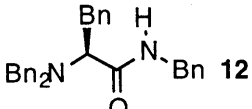
7) Although the direct fluorination of dipeptides using several fluorinating agents was attempted in our laboratory, no successful examples have been found yet.
8) The Gabriel type reaction of benzylamido derivative **12** with α-bromo-α-fluoroacetate **8** or **9** failed using the conditions indicated in Table 1.
9) Reaction of an amide **13** with $(Boc)_2O$ under various conditions gave a mixture of **14** and **15**, along with **13**.
10) Tanaka K., Yoshifuji S., Nitta Y., *Chem. Pharm. Bull.*, **35**, 364—369 (1987).



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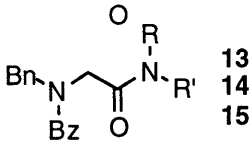

13: R = R' = H
14: R = H, R' = Boc
15: R = R' = Boc

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13) A peak of doublet of doublets should have been observed in the ^{19}F NMR spectra if **2** existed in the solution.

(Received April 16, 1998; accepted May 19, 1998)