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A Novel Route to Dipeptides via Noncondensation of Amino Acids: 2-Aminoperfluoropropene as a Synthon for Trifluoroalanine Dipeptides

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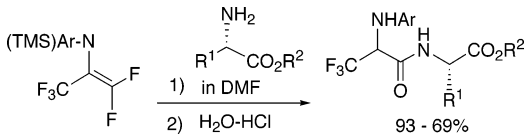
ABSTRACT

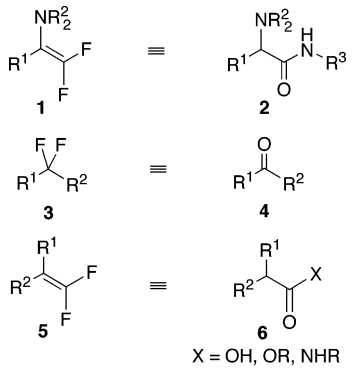


2-Aminoperfluoropropene has been prepared by the Mg-promoted defluorinative *N*-silylation of *N*-*p*-methoxyphenyl hexafluoroacetone imine and has been employed as a synthon of trifluoroalanine for the preparation of trifluoroalanine dipeptides.

The chemistry and science of peptides and their related molecules have been increasingly developed over several decades due to their potential biological activities, and thus, a number of non-natural peptides and peptidomimetics have been designed and synthesized to gain the advantages of increased bioactivity, biostability, and bioselectivity over those of natural peptides.[1] On this basis, highly efficient peptide-bond formations have been increasingly needed to enable the synthesis of more complex, newly functionalized, and/or structurally new peptides. So far, peptide bonds have been prepared mostly by condensation of amino acids. The rational activation of the carboxyl group of one amino acid followed by condensation with another amino ester[2] or ring opening of β-lactams with amino esters[3] has been used. Both enzymatic[4] and chemical[5] activations have been commonly employed for the condensation. But, very few methods for the noncondensation-type peptide synthesis have been known.[6] A novel peptide synthesis method, in which C−N bond formation mechanism is totally different from the conventional condensation of two kinds of amino acids, would open a door into the field of structurally unique and highly functionalized peptides, which would create unique biological activities yet unknown.

Here, we propose β,β-difluoroenamines **1** as general synthons for dipeptides **2** (Scheme 1) and describe, in particular,

Scheme 1



(1) (a) Barrett, G. C., Eds. *Amino Acid Derivatives*; Oxford University Press: Oxford, 1999. (b) Abell, A., Eds. *Advances in Amino Acid Mimetics and Peptidomimetics*; JAI Press, Inc.: Greenwich, 1997.

(2) (a) Jones, J. *Amino Acid and Peptide Synthesis*; Oxford University Press: Oxford, 1992. (b) Kusumoto, S., Eds. *Experimental Chemistry*, 4th ed.; Maruzen: Tokyo, 1990; No. 22. (c) Hodgson, D. R. W.; Sanderson, J. M. *Chem. Soc. Rev.* **2004**, *33*, 422−430.

(3) Ojima, I.; Delaloge, F. *Chem. Soc. Rev.* **1997**, *26*, 377−380.

(4) (a) Schellenberger, V.; Jakubke, H. D.; Fachbereich, B. *Angew. Chem.* **1991**, *103*, 1440−1452. (b) Murakami, Y.; Hirata, A. *J. Biol. Chem.* (in Japanese, *Seibutsu Kogaku Kaishi*) **1998**, *76*, 238−254.

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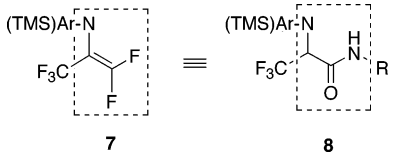
a preparation of 2-aminoperfluoropropene **7** and its transformation to trifluoroalanine dipeptides **8** (Scheme 2).

Scheme 2



7 **8**

Oligopeptides and peptidomimetics of fluorinated amino acids[7] show interesting biological activities as potent enzyme inhibitors, but very limited numbers of these peptides[8] and related mimetics[9] have been prepared due to the lack of a general synthetic method.

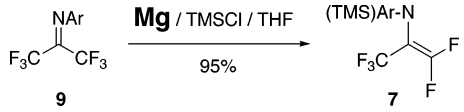
Difluoromethylene group **3** is a potential carbonyl equivalent **4**, and 1,1-difluoroalkenes **5** are synthons for carboester[11] and carboamide[12] groups since they provide the corresponding ketones, carboxylic acids, esters, and amides, respectively, on treating them under hydrolytic conditions.

On this basis, 2-amino-1,1-difluoroalkenes **1**, if available, should react with the amino group of amino esters at the highly activated difluoromethylene site and give, in principle, dipeptides **2** on treating them with amino esters under the addition and the subsequent hydrolytic conditions.

We communicate here a preparation of **7** (Ar = *p*-$MeOC_6H_4$) and its one-pot transformation to trifluoroalanine dipeptides by the reaction with amino esters to demonstrate the enamine **7** as a synthon of trifluoroalanine. The present route, which is totally different from the conventional condensation of two kinds of amino acids, enables the C−N bond formation for peptide synthesis under very mild conditions (Scheme 3 and 4).

The key compound **7** was prepared in an excellent yield (95%, 100 mmol scale) by the magnesium-promoted defluorinative *N*-silylation[13] of imine **9**[14] in an Mg−TMSCl−THF system at 0 °C.[15]

Scheme 3



9 **7**

The enamine **7** is stable enough to be easily handled and can be stored at −5 °C, but it is very reactive even with the less nucleophilic amino group of amino esters due to the strong electron-withdrawing effect of *gem*-difluoromethylene and trifluoromethyl groups. Thus, **7** reacted very smoothly with amino esters in DMF at room temperature within 1.5 h, affording the desired trifluoroalanine dipeptides **11** as a diastereomeric mixture[16] after the subsequent acid-catalyzed hydrolysis of the intermediate imidoyl fluoride (Scheme 4).[17]

Scheme 4

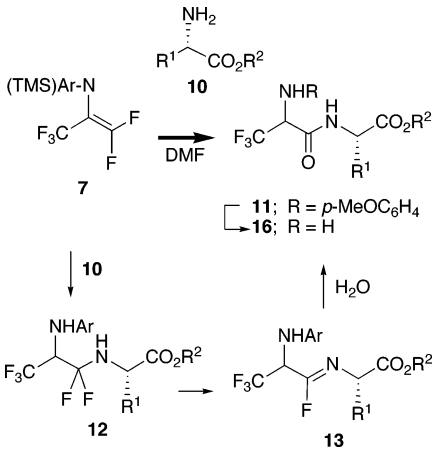


Table 1 summarizes the results of dipeptide synthesis. Most of the amino esters **10** reacted with **7** smoothly, affording dipeptides **11** in good to excellent yields.

Interestingly, serine **10e** and tyrosine **10f** esters reacted exclusively at the amino site rather than the hydroxyl site even when the amino esters were employed without protecting the hydroxyl group. The preferred reactivity of the amino

(5) Bordusa, F.; Dahl, C.; Jakubke, D.-D.; Burger, K.; Koksch, B. *Tetrahedron: Asymmetry* **1999**, *10*, 307−313.

(6) Synthesis of phenylalanine-trifluoroalanine dipeptide via N−H insertion of ketocarbene from methyl 2-azo-3,3,3-trifluoropropionate: Osipov, S. N.; Sewald, N.; Kolomiets, A. F.; Fokin, A. V.; Burger, K. *Tetrahedron Lett.* **1996**, *37*, 615−618.

(7) Welch, J. T.; Gyenes, A.; Jung, M. J. In *Fluorine-containing Amino Acids*; Kukhar, V. P., Soloshonok, V. A., Eds.; John Wiley & Sons: Chichester, 1995; Chapter 9. Sham, H. L. In *Fluorine-containing Amino Acids*; Kukhar, V. P., Soloshonok, V. A., Eds.; John Wiley & Sons: Chichester, 1995; Chapter 10. Kirk, K. L. In *Fluorine-containing Amino Acids*; Kukhar, V. P., Soloshonok, V. A., Eds.; John Wiley & Sons: Chichester, 1995; Chapter 11.

(8) Hoss, E.; Rudolph, M.; Seymour, L.; Schierlinger, C.; Burger, K. *J. Fluorine Chem.* **1993**, *61*, 163−170.

(9) Sani, M.; Bruche, L.; Chiva, G.; Fustero, S.; Piera, J.; Volonterio, A.; Zanda,M. *Angew. Chem., Int. Ed.* **2003**, *42*, 2060−2063.

(10) Ferraris, D.; Cox, C.; Anand, R.; Leckea, T. *J. Am. Chem. Soc.* **1997**, *119*, 4319−4325.

(11) Ishikawa, N.; Takaoka, A.; Iwakiri, H.; Kubota, S.; Kagaruki, S. R. F. *Chem. Lett.* **1980**, 1107−1110.

(12) (a) Bailey, P. D.; Boa, A. N.; Crofts, G. A.; Vandiepen, M.; Helliwell, M.; Gamman, R. E.; Harrison, M. J. *Tetrahedron Lett.* **1989**, *30*, 7457−7460. (b) England, D. C.; Melby, L. R.; Dietrich, M. A.; Lindsey, R. V., Jr. *J. Am. Chem. Soc.* **1960**, *82*, 5116−5122.

(13) (a) Mae, M.; Amii, H.; Uneyama, K. *Tetrahedron Lett.* **2000**, *41*, 7893−7896. (b) Amii, H.; Kobayashi, T.; Hatamoto, Y.; Uneyama, K. *Chem. Commun.* **1999**, 1323−1324.

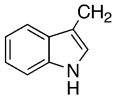
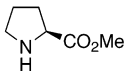
(14) Middleton, W, J.; Krespan, C. G. *J. Org. Chem.* **1965**, *30*, 1398−1402.

(15) 2-*N*-Phenylaminoperfluoropropene was prepared in 43−83% yields by reduction of *N*-phenylacetoneimine with either zinc or alkyl Grignard reagents. (a) Zeifman, Y. V.; Vol'pin, I. M.; Postovoi, S. A.; German, L. S. Y. V. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1987**, 2396−2397; *Chem Abstr.* **1988**, *109*, 54292. (b) Zeifman, Y. V. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1990**, 202−205, *Chem Abstr.* **1990**, *113*, 40035

(16) The absolute stereochemistry (*R*) or (*S*) of the trifluoroalanine site of both major and minor diastereomers has not been determined except for **11c**.

(17) Imidoyl fluoride (R-CF═NAr) was isolated as an intermediate which was easily hydrolyzed to the corresponding amide under the hydrolysis conditions. The trifluoroalanine dipeptides were stable under the acidic conditions employed in the hydrolysis except phenylalanine dipeptide which showed 6% epimerization at the phenyalanine side.

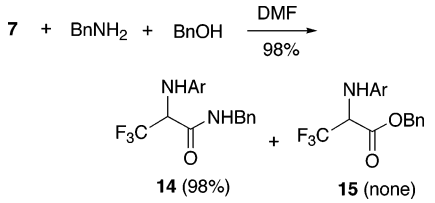
Table 1. Synthesis of Trifluoroalanine Dipeptides by the Reaction of **7** with Amino Esters **10**[a]

amino ester **10**	R^1	R^2	yield **11** (%)	de[a]
10a glycine	H	Bn	91	-
10b Alanine	CH_3	Me	86	14
10c Phenyl alanine	$PhCH_2$	Et	93	28
10d Leucine	$(CH_3)_2CHCH_2$	Me	85	48
10e Serine	$HOCH_2$	Me	80	8
10f Tyrosine	$HOC_6H_4CH_2$	Me	68	18
10g Methionine	$CH_3SCH_2CH_2$	Me	88	21
10h Tryptophan		Me	79	19
10i Proline		—	69	26

[a] Diastereomeric ratios were analyzed by HPLC.

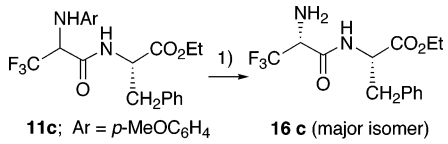
group to **7** over the hydroxyl group is also revealed by the fact that the competitive reaction of **7** with a mixture of equimolar amounts of both benzylamine and benzyl alcohol provided exclusively benzyl amide **14** of trifluoroalanine in 98% isolated yield and none of the corresponding benzyl ester (Scheme 5).

Scheme 5



The *N*-protecting group, *p*-methoxyphenyl, was readily removed by the oxidation of **11** with cerium ammonium nitrate in $MeCN-H_2O$ at room temperature[18] to give the deprotected dipeptides **16** (**16a**; R^1 = H, R^2 = Bn, 83%, **16c**; R^1 = $PhCH_2$, R^2 = Et, 80%). The diastereoisomers of dipeptides **16c** (R^1 = $PhCH_2$, R^2 = Et) could be easily separated and isolated as an enantiomerically pure form by column chromatography. The absolute stereochemistry of the major diastereomer **16c** was clarified by X-ray crystallographic analysis of the single crystal of its hydrochloric acid salt. This is the first example of preparation of the enantiomerically pure (*R*,*S*) and (*S*,*S*) trifluoroalanine−phenylalanine dipeptides (Scheme 6).

Scheme 6



11c; Ar = *p*-$MeOC_6H_4$ **16 c** (major isomer)

1) $Ce(NH_4)_2(NO_3)_6$ / $MeCN-H_2O$

It is suggested the present protocol would be promising for the construction of peptide skeletons and applicable for the preparation of a variety of trifluoroalanine dipeptides in an enantiomerically pure form, although 1,4-asymmetric induction of the chiral center of amine esters to the α-carbon atom in trifluoroalanine moiety has remained unsolved at this moment. Study on the generality for the syntheses of di- and oligopeptides by the present method and 1,4-asymmetric induction are under active investigation.

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Supporting Information Available: Experimental details for the syntheses of compounds **7**, **9**, **11a**−**i**, and **16c** and X-ray crystallographic analysis of compound **16c** hydrochloride. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) Sakai, T.; Yan, F.; Uneyama, K. *Synlett* **1995**, 753−754.