# Synthesis of carbonyl-bridged peptides containing an α-fluoroglycine residue†

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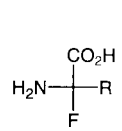
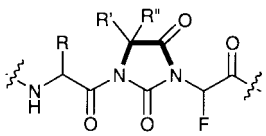
***Received (in Cambridge, UK) 15th February 2000, Accepted 29th March 2000***

**Gabriel reaction of hydantoins with bromofluoroacetate provides a general method for the synthesis of carbonyl-bridged peptides containing an α-fluoroglycine residue.**

Introduction of fluorine atoms into amino acids is a powerful and reliable strategy for the design of potent biologically active amino acid and peptide derivatives.[1] Numerous fluorinated analogues encompassing essentially every class of amino acid have been synthesized and examined for biological activity. As part of an ongoing research program committed to preparation of multifunctional carbon compounds,[2] we have selected the α-fluoro α-amino acids **1** as synthetic targets. Fluorine substitution at the α-position of α-amino acids is of great interest because of the profound influence this has on the chemical properties of the carbonyl carbon and, in particular, the α-amino group, and the expected accompanying consequences on biological activity. However, there are few reports for the synthesis of α-fluoro α-amino acids. Bailey *et al.* developed pioneering work for this study in 1989.[3] They carried out an asymmetric synthesis of protected α-fluoroglycines utilizing the Gabriel reaction of chiral fluoroiodoacetamides with potassium phthalimide. We also independently reported the synthesis of a protected α-fluoroglycine in the following year[4] and recently applied our method to the preparation of protected α-fluoroglycine containing dipeptides.[5] Despite considerable effort, however, neither free α-fluoroglycine nor free fluorine-containing dipeptides have ever been isolated because of rapid dehydorofluorination under ambient conditions. Whereas we recognized the importance of a more recent report by Bailey *et al*. on the first isolation of a free α-fluoroglycine derivative, α-fluorobetaine,[6] it is obviously impossible to incorporate this structure into peptides. We herein disclose a general method for a synthesis of carbonyl-bridged peptides containing the α-fluoroglycine residue **2** using the Gabriel reaction of hydantoins **3** with bromofluoroacetate.

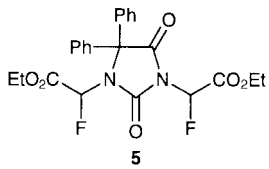


**1**



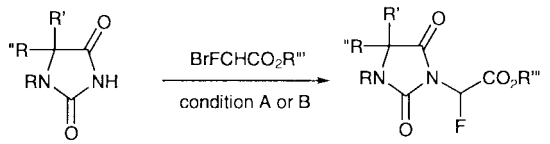
**2**

The design of the target carbonyl-bridged peptides **2** was based on the following strategies. First, the carbon–fluorine bond of **2** is stabilized to loss of fluoride by virtue of the electron attracting effect of the imide carbonyl groups. Second, peptides in a conformationally restricted environment are important structural features used in the field of peptidomimetics.[7] In addition, hydantoins are known to possess a broad range of biological activities, including antiviral, antibacterial, antifungal and herbicidal activity.[8] We first examined the synthesis of hydantoin-α-fluoroglycine-containing dipeptides **4** that are the key component parts of **2**. The Gabriel-type reaction of the commercially available diphenylhydantoin **3a** was performed by deprotonation, using NaH in DMF, followed by the addition of ethyl bromofluoroacetate (Table 1, entry 1). Although the desired **4a** was the predominant product, obtained in moderate yield, this procedure resulted in the formation of a mixture of **4a** and bis-alkylated product **5** along with recovered starting material **3a**. In an attempt to overcome this problem of selectivity in the alkylation reaction, optimization of the



**5**

**Table 1** Synthesis of hydantoin-fluoroglycine-containing dipeptides



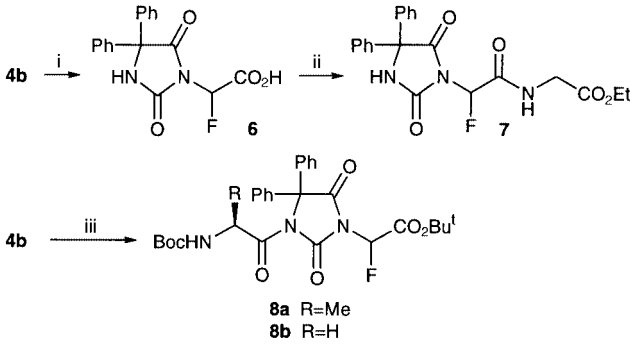
**3** **4**

| Entry | 3 | R | R' | R" | Condition | R"' | 4 | Yield[a] (%) |
|---|---|---|---|---|---|---|---|---|
| 1 | **3a** | H | Ph | Ph | A | Et | **4a** | 46 |
| 2 | **3a** | H | Ph | Ph | B | Et | **4a** | 53 |
| 3 | **3a** | H | Ph | Ph | C | Et | **4a** | 91 |
| 4 | **3a** | H | Ph | Ph | C | $Bu^t$ | **4b** | 67 |
| 5 | **3b** | H | Me | Me | C | Et | **4c** | 42 |
| 6 | **3c**[b] | | | | C | Et | **4d**[c] | 74 |
| 7 | **3c**[b] | | | | C | $Bu^t$ | **4e**[c] | 65 |
| 8 | **3d**[b] | H | Ph | H | C | $Bu^t$ | **4f**[c] | 31 |
| 9 | **3e**[b] | H | Bn | H | C | Et | **4g**[c] | 51 |
| 10 | **3f**[b] | H | $Pr^i$ | H | C | Et | **4h**[c] | 20 |
| 11 | **3g**[b] | H | H | H | C | Et | **4i**[c] | 32 |
| 12 | **3h**[b] | Boc | Ph | H | C | Et | **4j**[c] | 97 |
| 13 | **3i**[b] | Boc | Bn | H | C | Et | **4k**[c] | 69 |
| 14 | **3j**[b] | Boc | $Pr^i$ | H | C | Et | **4l**[c] | 57 |
| 15 | **3k** | Boc | H | H | C | Et | **4m** | 55 |

Condition A: NaH, DMF 80 °C, 1 h; B: NaH, $NBu_4Br$, DMF, room temp., 12 h; C: NaH, $NBu_4Br$, THF, room temp., 12 h. [a] Isolated yield. [b] Racemic hydantoins **3c**–**j** used. [c] Mixture of diastereoisomers (1 : 1).

† Part 4 of series: Synthetic studies for novel structure of α-nitrogenousyl functionalized α-fluorocarboxylic acids.

DOI: 10.1039/b001265n



**Scheme 1** *Reagents and conditions*: i, TFA, $CH_2Cl_2$, room temp. (quant.); ii, H-Gly–OEt, DCC, HOBT, $Et_3N$, DMF, room temp. 12 h (76%); iii, isobutyl chloroformate, $Et_3N$, DMAP, DMF, THF, then Boc-Ala–OH or Boc-Gly–OH, −15 °C to room temp., 3 h (91% for **8a**, 79% for **8b**).

conditions was investigated by examining several bases and additives in several solvents at different temperatures. The best result was obtained in the reaction of **3a** with NaH, $NBu_4Br$ and ethyl bromofluoroacetate in THF at room temperature to give **4a** in 91% yield (entry 3).[9] Other hydantoins **3b**,**c** having different substituents at the 5 position were treated with ethyl or *tert*-butyl bromofluoroacetate under the same conditions to give **4b**–**d** in moderate to good yields (entries 4–7). Lower yields (31–51%) of **4** were observed when unsubstitutued or 5-mono-substituted hydantoins **3d**–**g** derived from naturally occurring α-amino acids were used as starting materials (entries 8–11). However, the yields using these substrates were improved to 55–97% by the use of Boc protected hydantoins **3h**–**k** (entries 12–15) (Table 1).[10]

With the development of a general method for the synthesis of hydantoin-α-fluoroglycine-containing peptides **4**, we next demonstrated that **4** could be incorporated into the oligopeptide **2** by normal peptide coupling techniques. Deprotection at the *C*-terminus of **4b** was nicely achieved with TFA–$CH_2Cl_2$ to give free dipeptide **6** quantitatively. As expected, the free acid **6** is sufficiently stable for subsequent chemical manipulation under ambient conditions. Coupling of the carboxylic acid **6** obtained with glycine ethyl ester in the presence of DCC/HOBT furnished the tripeptide **7** in 76% yield. Furthermore, *N*-terminal chain elongation was achieved by coupling **4b** with Boc-Ala–OH or Boc-Gly–OH using the mixed anhydride method to give the tripeptides **8** in good yield (Scheme 1).

In summary, we have described the design and synthesis of fluoroglycine-containing peptides.[2] Neither free α-fluoroglycine nor free fluorine-containing dipeptides have been previously isolable.[3–6] The carbonyl-bridged strategy employed in the present work offers one solution to this problem.[11] Oligomerization of hydantoin-α-fluoroglycine-containing dipeptides **4** will be presented in the near future.

We thank the Ministry of Education, Science, Sports and Culture, Japan for a Grant-in Aid for Scientific Research and for Encouragement of Young Scientists. Y. T. thanks the Grant from Asahi Glass Foundation.

## Notes and references

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9 General procedure; to a stirred mixture of **3a** (100 mg, 0.40 mmol) and $NBu_4Br$ (129 mg, 0.48 mmol) in THF (1.0 ml) was added NaH (60%, 19 mg, 0.48 mmol) at 0 °C. After 30 min stirring at room temperature, ethyl bromofluoroacetate (73.4 mg, 0.40 mmol) was added to the mixture which was stirred for 12 h. The reaction was stopped by addition of a saturated solution of $NH_4Cl$ (1 ml) and the mixture was diluted with ethyl acetate (100 ml). The organic phase was washed with water (20 ml), brine (20 ml) and dried over $MgSO_4$. The solvent was removed under reduced pressure to give an oil that was purified by column chromatography on silica gel eluting with 60% ethyl acetate in hexane to give **4a** (128 mg, 91%) as a colorless oil.
10 Dipeptides **4d–l** were the 1 : 1 mixtures of diastereomers, which were not separated.
11 A recent publication of similar types of bridged compounds; P. D. Bailey, A. N. Boe, S. R. Baker, J. Clayson, E. J. Murray and G. M. Rosair, *Tetrahedron Lett.*, 1999, **40**, 7557.