PERKIN 1 COMMUNICATION

Application of the Ugi four-component condensation reaction for the synthesis of α,α- and α,β-dipeptides substituted with fluoroarylalkyl pendent groups†

Norio Shibata, Biplab Kumar Das and Yoshio Takeuchi*

Faculty of Pharmaceutical Sciences, Toyama Medical and Pharmaceutical University, Sugitani 2630, Toyama 930-0194, Japan. E-mail: takeuchi@ms.toyama-mpu.ac.jp

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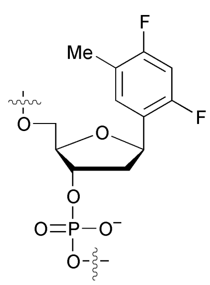
We report a single step synthesis based on the Ugi four-component condensation of previously unknown α,α- and α,β-dipeptides, 2 and 8, having fluoroaromatic groups appended to the nitrogen atom.

Difluorotoluene nucleoside **1** has been developed as a nonpolar shape mimic for natural thymidine and it has been intensively used as a probe of the biological noncovalent interactions of oligonucleotides.[1] Unexpectedly, **1** serves as a template for DNA synthesis even though it lacks standard polar hydrogen bonding. These reports prompted our interest in the synthesis of dipeptides **2** having a difluorotoluene group appended to the nitrogen atom. In this paper, we describe a single step synthesis of previously unknown dipeptides **2**, substituted with fluoroarylalkyl pendent groups using the Ugi four-component condensation.



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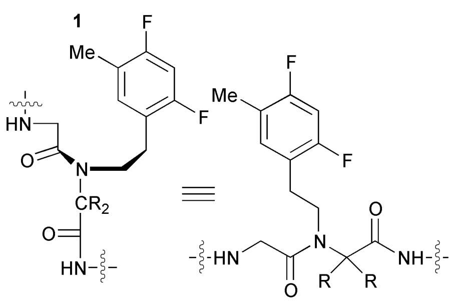

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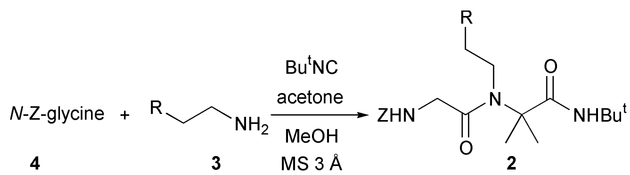
In recent years the synthesis of heterocyclic substituted non-proteinogenic amino acids,[2] especially those amino acids with nucleobases on the side chains,[3] has received much attention. This synthetic activity stems from the biological activity of such analogues, their use as probes to study amino acid–nucleobase interactions, and their utility as polyamide or peptidic nucleic acids.[4] Thus amino acids containing 2,4-difluorotoluene or other fluoroaryl moieties may produce special effects when they are incorporated into peptides. For example, the incorporation of a fluoroaryl moiety could be expected to confer significant changes on the secondary structure of the peptides due to the strong stacking effects of the aromatic rings,[5] now functioning as nucleobase surrogates. Moreover, the introduction of a fluorine atom into amino acids and peptides,[6] in general, should induce interesting new chemical and physiological properties.[7]

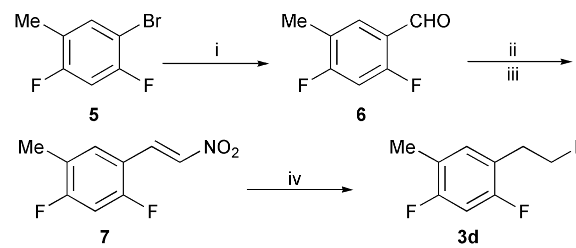
The preparation of the target compound **2** undoubtedly could be accomplished by conventional peptide synthesis procedures. However, this would require multi-step syntheses. The Ugi four-component coupling reaction has recently been shown to be a powerful method for the synthesis of amino acids, peptides and nucleobase–peptide chimeras.[8,9] We applied this method for the preparation of our dipeptides substituted with fluorophenethyl pendent groups. We first examined the Ugi reaction using readily available fluorophenethyl amines **3a–c**.‡ *N*-Z-Glycine (**4**) was stirred with **3a–c**, acetone and *tert*-butyl isocyanide in methanol in the presence of molecular sieves 3 Å at −78 °C for 2 h. Then the reaction mixture was allowed to warm to room temperature over 1 h and stirred for 1 week. The solvent was removed and the mixture was purified by silica-gel column chromatography to furnish **2a–c** in 42–50% yield (Table 1, entry 1–3). We then performed the Ugi reaction using

Table 1 Synthesis of *N*-fluorophenethyl appended α,α-dipeptides **2**



Entry	Amine **3**	R	Product **2**	Yield (%)[a]
1	**3a**	*p*-Fluorophenyl	**2a**	42
2	**3b**	2,4-Difluorophenyl	**2b**	50
3	**3c**	Pentafluorophenyl	**2c**	45
4	**3d**	2,4-Difluoro-5-methylphenyl	**2d**	43

[a] Yields were based on the amines **3** employed.



Scheme 1 *Reagents and conditions*: i, Mg, DMF, THF, 0 °C, 45%; ii, $MeNO_2$, KOH–MeOH, 53%; iii, MsCl, Et_3N, CH_2Cl_2, 61%; iv, $LiAlH_4$, THF–Et_2O, reflux, 63%.

† Experimental procedures and data for characterization of new compounds **2** and **8** (^{1}H NMR and HPLC spectra) are available as supplementary data. For direct electronic access see http://www.rsc.org/suppdata/p1/b0/b007455l/

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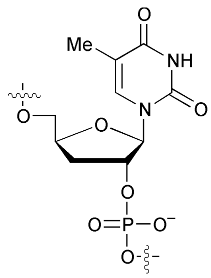
the amine **3d** with a difluorotoluene moiety as a steric mimic for thymine. The amine **3d** was prepared from 5-bromo-2,4-difluorotoluene (**5**) in 4 steps *via* formylation, nitroaldol reaction, dehydration, and reduction in good yield (Scheme 1). The Ugi reaction of **3d** with **4**, acetone and *tert*-butyl isocyanide gave the target α,α-dipeptide **2d** in 43% yield (Table 1, entry 4).

We next focused our attention on the synthesis of fluoroarylmethyl appended α,β-dipeptides **8**. This is designed based on the structure of 2′,5′-linked isoDNA **9**.[10] The constituent elements of **8** are an α-amino acid, a β-homoamino acid and a fluoroarylmethyl unit. This arrangement was chosen because a seven atom spacing can be found between the nucleobases in **9**,



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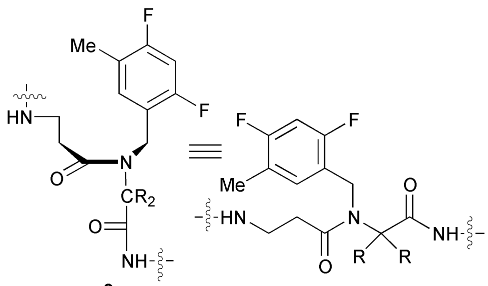

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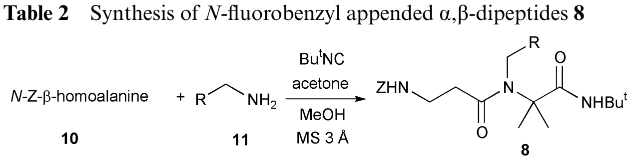
and because the optimal number of bonds between the nucleobases and the backbone was found to be one.

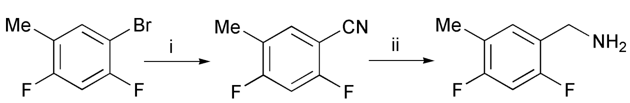
The target α,β-dipeptides **8** were also synthesized in the same manner. The Ugi condensation of the four components, *N*-Z-β-homoalanine (**10**), fluorobenzylamine derivatives **11a–d**, acetone, and *tert*-butyl isocyanide, successfully produced the dipeptides **8a–d** in a single step in moderate yields. The results are summarized in Table 2. The starting amines **11a–c** are readily available and **11d** was prepared from **5** in two steps (Scheme 2).

Table 2 Synthesis of *N*-fluorobenzyl appended α,β-dipeptides **8**



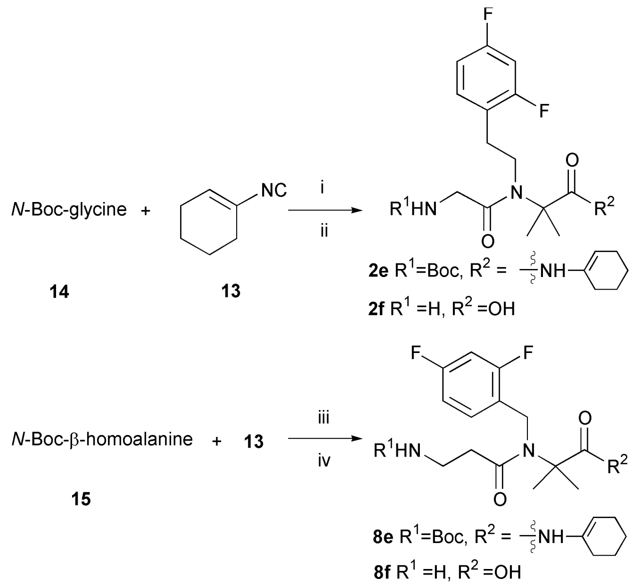
Entry	Amine **11**	R	Product **8**	Yield (%)[a]
1	**11a**	*p*-Fluorophenyl	**8a**	59
2	**11b**	2,4-Difluorophenyl	**8b**	66
3	**11c**	Pentafluorophenyl	**8c**	43
4	**11d**	2,4-Difluoro-5-methylphenyl	**8d**	42

[a] Yields were based on the amines **11** employed.



Scheme 2 *Reagents and conditions*: i, CuCN, DMF, 160 °C, 50%; ii, BH_3–THF complex, THF, reflux, 2.6 M HCl, reflux, 67%.

1-Isocyanocyclohexene (**13**) is quite useful for the Ugi reaction because the cyclohexenamide moiety in the product can be converted to a variety of functional groups.[11] We then used **13** in our Ugi reaction to obtain free dipeptides. *N*-Boc-Glycine (**14**) was treated with **13**, **3b**, and acetone in methanol to furnish corresponding α,α-dipeptide **2e**, which was deprotected readily by 3 M HCl in THF to give the free dipeptide **2f** in excellent yield. *N*-Boc-β-Homoalanine (**15**) was also coupled with **13**, **11b** and acetone followed by hydrolysis to give free α,β-dipeptide **8f** (Scheme 3).



Scheme 3 *Reagents and conditions*: i, **3b**, acetone, MeOH, MS 3 Å, −78 °C, then rt, 45%; ii, 3 M HCl, THF, 100%; iii, **11b**, acetone, MeOH, MS 3 Å, −78 °C, then rt, 43%; iv, 3 M HCl, THF, 98%.

In summary, we have demonstrated single step syntheses of α,α- and α,β-dipeptides having fluoroaromatic groups appended to the nitrogen atom as isosteric replacements for thymine. Of particular note regarding our method is its applicability to those peptides containing a variety of amino acids (not only α- and β-, but also γ-amino acids) attached to a diverse series of fluoroarylalkyl groups. Incorporation of **2** and **8** into oligopeptides is now under investigation.

Acknowledgements

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Notes and references

‡ *Typical experimental procedure*: the amine **3a** (200 mg, 1.52 mmol) and acetone (176 mg, 3.04 mmol) were dissolved in distilled methanol in a flask containing 3 Å molecular sieves. The mixture was allowed to stir for 1 h and then **4** (635 mg, 3.04 mmol) was added directly into the flask in one portion. A solution of *tert*-butyl isocyanide (252 mg, 3.04 mmol) in methanol was added to the flask at −78 °C in one portion. The resulting solution was allowed to stir at room temperature for a week. When the reaction was complete by TLC (5–10% MeOH in CH_2Cl_2), the reaction mixture was filtered and the solvent was removed *in vacuo*. The residue was chromatographed on silica gel to give **2a** (301 mg, 42%) as colourless solid.

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